Clinical Trial Protocol

Clinical Trial Protocol Number	EMR700461-023
Title	A Phase IIb, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multidose, 24-Week Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With Systemic Lupus Erythematosus (SLE)
Trial Phase	Phase IIb
IND Number	11584
EudraCT Number	2013-002773-21
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Clinical Trial Protocol Version	28 August 2013/Version 1.0

- Confidential -

Signature Page

Protocol Lead responsible for designing the clinical trial:

I approve the design of the clinical trial.

29 Aug 2013

Signature Date of Signature

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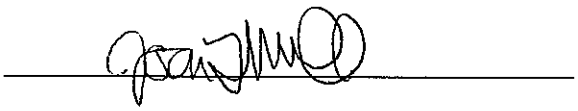
Coordinating Investigator

I agree to conduct the clinical trial in accordance with this clinical trial protocol and in compliance with Good Clinical Practice and all applicable regulatory requirements.



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8/29/13 (Aug 29 2013)

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Trial Title	A Phase II, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multidose, 24-Week Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With Systemic Lupus Erythematosus (SLE)
EudraCT Number	2013-002773-21
Clinical Trial Protocol Version/Date	28 August 2013/Version 1.0
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 Conference of Harmonisation (ICH) Good Clinical Practice (ICH Topic E6 GCP) and all applicable Health Authority requirements and national laws.
- I will not deviate from the clinical trial protocol without prior written permission from the sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent immediate danger to the subject.

I understand that some health authorities require the sponsors of clinical trials to obtain and supply, when required, details about the investigators' ownership interests in the sponsor or Investigational Medicinal Product and information regarding any financial ties with the sponsor. The sponsor will use any such information that is collected 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.

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List of Abbreviations

ACR	American College of Rheumatology
AE(s)	adverse event(s)
ANA	anti-nuclear antibody(ies)
Anti-dsDNA	anti-double-stranded deoxyribonucleic acid
Anti-La	an antinuclear antibody associated with autoimmune diseases including Sjögren syndrome (also called "SSB")
Anti-ribosomal P	an antibody associated with systemic lupus erythematosus, and in particular with neuropsychiatric manifestations of the disease
Anti-RNP	an antibody to ribonucleoprotein, associated with autoimmune diseases including Sjögren's syndrome and systemic lupus erythematosus
Anti-Ro	an antinuclear antibody associated with autoimmune diseases including Sjögren's syndrome and systemic lupus erythematosus (also called "SSA")
Anti-Sm	anti-Smith antibody, an antinuclear antibody associated with autoimmune diseases including systemic lupus erythematosus
APRIL	a proliferation-inducing ligand
APRIL-SLE	Clinical trial 27646 in systemic lupus erythematosus
β-hCG	beta-human chorionic gonadotropin
BICLA	BILAG-based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLyS	B lymphocyte stimulator (also called B-cell activating factor or BAFF)
BP	blood pressure
C3, C4, and C4d	complement proteins C3, C4, and C4d
eCRF	electronic case report form
CRO	contract research organization

CRP	C-reactive protein
CS	corticosteroid(s)
C-SSRS	Columbia-Suicide Severity Rating Scale
CTP	clinical trial protocol
CTR	clinical trial report
DBPC	double-blind placebo-controlled
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
EQ-5D	EuroQoL 5 Dimension
ET	early termination
FACIT	Functional Assessment of Chronic Illness Therapy
Fc	fragment crystallizable
FDA	Food and Drug Administration (United States)
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GMP	Good Manufacturing Practice
Ig	immunoglobulin
IgA, G, M, G1	immunoglobulins A, G, M, G1
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	investigational medicinal product

IRB	Institutional Review Board
ISR	injection site reaction
ITT	intent-to-treat
mITT	modified intent-to-treat
IWRS	Interactive Web Response System
LN	lupus nephritis
LTBI	latent TB infection
LTE	long-term extension
LupusQoL	Lupus Quality of Life
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MPA	mycophenolic acid or mycophenolate
MPS	mycophenolate sodium
MS	multiple sclerosis
NK	natural killer
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
PCS	Physical Component Summary
PD	pharmacodynamic(s)
PGx	pharmacogenetics
PGA	Physician's Global Assessment
PGIC	Patient Global Impression of Change
PK	pharmacokinetics

PP	per protocol
PRO	patient-reported outcome
QA	quality assurance
QoL	quality of life
RF	rheumatoid factor
RNA	ribonucleic acid
RNP	ribonucleoprotein
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SF-36	Medical Outcomes Study 36-item Short Form Health Survey
SFI	SELENA SLEDAI Flare Index
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index-2000
SLICC	Systemic Lupus International Collaborating Clinics
SoC	standard of care
SRI	SLE Responder Index
SRI-50	SLEDAI-2K Responder Index-50
SSA	see “Anti-Ro”
SSB	see “Anti–La”
SUSAR	suspected unexpected serious adverse reaction
TACI	transmembrane activator and calcium-modulator and cyclophilin ligand interactor
TB	tuberculosis

TNF	tumor necrosis factor
TNF-R	tumor necrosis factor receptor
UPCr	urine protein:creatinine ratio
UPEP	urine protein electrophoresis
US	United States
VAS	visual analog scale
WOCBP	women of childbearing potential

1 Synopsis

Trial title	A Phase IIb, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multidose, 24-Week Study to Evaluate the Efficacy and Safety of Atacicept in Subjects With Systemic Lupus Erythematosus (SLE)
Trial number	EMR-700461-023
EudraCT number	2013-002773-21
Sponsors	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt Germany EMD Serono, Inc. (USA only) One Technology Place Rockland, MA 02370 USA
Phase	IIb
Trial under IND	☒ yes ☐ no
FDA "covered trial"	☒ yes ☐ no
Trial center(s)/country(ies)	Approximately 100 sites in about 25 countries in Europe, Asia, North America, Latin and Central America. Approximately 30 sites are anticipated to participate in the United States.
Planned trial period **(first enrollment-last subject out)**	November 2013 through April 2016
Trial objectives	**Primary:** 1. Evaluate the efficacy of atacicept compared to placebo in reducing SLE disease activity in subjects treated with standard of care (SoC) therapy and to investigate the dose-response relationship. **Secondary:** 1. Evaluate the effect of atacicept in reducing corticosteroid (CS) usage.

	2. Evaluate the effect of atacicept on changes in disease activity over time. 3. Evaluate the safety, tolerability and immunogenicity profiles of atacicept in SLE subjects. 4. Evaluate the pharmacokinetics (PK) and pharmacodynamic (PD) profiles of atacicept in SLE subjects. 5. Evaluate the effect of atacicept on patient-reported outcomes (PROs). **Exploratory objectives** 1. Identify potential associations of genetic variations and gene expression with atacicept response, efficacy and safety. 2. Identify potential associations of the profiles of circulating proteins with atacicept response, efficacy and safety. 3. Evaluate the effect of atacicept in reducing damage accrual from SLE (Systemic Lupus International Collaborating Clinics [SLICC]/American College of Rheumatology [ACR] Damage Index).
Trial design and plan	This is a Phase IIb, multicenter, double-blind, placebo-controlled (DBPC) parallel-arm trial in which subjects are planned to be randomized in a ratio of 1:1:1 to receive placebo, or atacicept 75 mg or 150 mg, given as once weekly subcutaneous (SC) injections for 24 weeks. The trial is composed of a screening period, a DBPC treatment period, and a safety follow-up (FU) period. The trial will be conducted on an outpatient basis and treatment duration will be 24 weeks. A long-term extension (LTE) trial will be offered to completers of the 24-week treatment period as part of a separate protocol.
Planned number of subjects	279 subjects (93 per treatment arm)
Schedule of visits and assessments	**Screening Period:** The first visit will be a screening visit. The screening visit will be considered the baseline for disease activity (i.e., British Isles Lupus Assessment Group [BILAG] 2004 Disease Activity Index, SLE Disease Activity Index-2000 [SLEDAI-2K], Physician's

	Global Assessment [PGA] and SLEDAI-2K Responder Index-50 [SRI-50]). Duration will be up to 4 weeks to determine the subject's eligibility; however, subjects should undergo the Day 1 visit procedures as soon as possible after eligibility for the trial has been confirmed. **DBPC Treatment Period**: Duration will be 24 weeks starting at randomization. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be reviewed again at the site on Day 1 prior to randomization. Following confirmation of eligibility for the trial, subjects will be randomized in a ratio of 1:1:1 to receive placebo, or atacicept 75 mg or 150 mg. These will be given as once weekly SC injections for 24 weeks. Subjects will be monitored at trial visits at Weeks 1, 2, 4, and every 4 weeks thereafter. Subjects will receive the last dose at Week 23 and complete the last treatment visit at the following Week 24. Day 1 procedures will be performed up to at most 4 weeks after the screening visit. The first dose of the investigational medicinal product (IMP; atacicept or placebo) will be given while the subject is still on site for Day 1. Four additional blood samples for PK will be collected from a PK subset of subjects. The PK subset is planned to include 40 subjects from all dose groups (placebo=8, atacicept 75 mg=16, atacicept 150 mg=16). **Safety Follow-up Period:** Duration will be 24 weeks. Subjects will enter this period directly from the DBPC period after the Week 24/ET visit. Safety visits are scheduled at 4, 12, and 24 weeks after the last IMP dose. This includes subjects who stop treatment prematurely and those who complete the DBPC period but do not enter the LTE. Follow-up Week 24 is the last scheduled visit for subjects not entering the LTE trial. **LTE Trial:** Subjects who complete the 24-week DBPC period will be offered participation in the LTE trial, which will be conducted under a separate protocol. Subjects continuing in the LTE trial will not attend the safety FU period.

Diagnosis and main inclusion and exclusion criteria	Eligible male and female subjects, aged 18 years or older, must have at least moderately active SLE, as defined by SLEDAI-2K score ≥6, at least 4 of the 11 ACR classification criteria for SLE (diagnosed ≥6 months prior to the screening visit), and be seropositive for anti-nuclear antibodies (ANA) and/or anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies. Subjects are not eligible for this study if they have a demyelinating disorder, severe central nervous system SLE, use of cyclophosphamide within 3 months of the screening visit or a urine protein:creatinine ratio (UPCr) ≥2 mg/mg per day.
Oral corticosteroid (CS) restrictions during study	CS must not be increased to a dose >40 mg/day for 2 weeks prior to the screening visit. CS may be initiated during the screening period, increased or decreased until the Week 4 visit. The initiated or increased dose should not be >40 mg/day. At Week 4, the dose has to be ≤30 mg/day. The dose must also be ≤screening visit dose; however, subjects taking <7.5 mg/day at Day 1 (Week 0) can have a dose of up to 7.5 mg/day at Week 4. Between Weeks 5 to 16, the CS dose must always be ≤Week 4 dose. The CS dose must be maintained at the Week 16 dose between Weeks 17 and 24; no increases or decreases are allowed.
Investigational Medicinal Product: dose/mode of administration/dosing schedule	Atacicept 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 treatment duration per subject	24 weeks
Primary endpoint(s)	The proportion of subjects with the SLE Responder Index (SRI) response at Week 24 compared to the screening visit. The SRI response, a measure of reduced SLE disease activity, is defined by meeting all the following conditions: 1. ≥4 point reduction in SLEDAI-2K score. 2. No significant worsening in PGA score (<10% increase).

	3. No new BILAG A organ domain scores and ≤1 new BILAG B organ domain score. 4. No protocol-prohibited medication/treatment.
Secondary endpoint(s)	**Key Secondary Endpoints:** 1. Proportion of subjects at Week 24 whose prednisone-equivalent CS dose has been reduced from screening visit by ≥25% and to a dose of ≤7.5mg/day, and have no BILAG A or 2B flare in disease activity during Weeks 16 through 24. A BILAG A or 2B flare is defined by ≥1 new BILAG A organ domain score and/or ≥2 new BILAG B organ domain scores compared to screening visit. 2. Proportion of subjects in the Patient Global Impression of Change (PGIC) categories of 1 or 2, 3 or 4 or 5, 6 or 7 at Week 24. **Corticosteroid dosing:** 3. Proportion of subjects at each visit whose prednisone-equivalent CS dose has been reduced from screening visit by ≥25% and to a dose of ≤7.5mg/day, and have no BILAG A or 2B flare in disease activity (at that visit). 4. Change from screening visit to Week 24 in prednisone-equivalent CS daily dose. 5. Proportion of subjects at Week 24 with a decrease from screening visit in prednisone-equivalent CS daily dose of 0-<25%, 25%-50%, >50%, or an increase. 6. Cumulative prednisone-equivalent CS dose from the screening visit until completion of the treatment period. **Disease activity (induction of response):** 7. Proportion of subjects with a SRI response at each trial visit. 8. Time to first SRI response during the treatment period. 9. Proportion of subjects with a confirmed SRI response

	at each trial visit. A confirmed response is defined as having at least 2 consecutive assessments (4 weeks apart) meeting the SRI response criteria at each time point of interest. 10. Time to first confirmed SRI response during the treatment period. 11. Proportion of subjects with ≥4 point reduction from screening visit in SLEDAI-2K score at each trial visit. 12. Proportion of subjects with no significant worsening of the PGA, defined as <10% increase from screening visit at each time point. 13. Proportion of subjects with no new BILAG A organ domain scores and ≤1 new BILAG B organ domain score at each time point compared to screening visit. 14. Proportion of subjects responding to treatment according to the BILAG-based Combined Lupus Assessment (BICLA), at each trial visit. The BICLA response is defined as meeting all of the following conditions compared to screening visit: a) BILAG-2004 improvement (all screening visit BILAG A improving to B/C/D, all screening visit BILAG B to C/D, and ≤1 new BILAG B and no new BILAG A), b) no deterioration in SLEDAI total score, c) PGA increase by <10%, and d) no protocol-prohibited medication/treatment. 15. Change from screening visit in total and in organ specific SLEDAI-2K scores at each time point. 16. Change from screening visit in PGA score at each time point. 17. Change from screening visit in total and in organ specific BILAG score (using validated numerical score) at each time point. 18. Absolute values and change from screening visit in UPCr, at each time point (in subjects with UPCr >0.5 mg/mg at screening visit).

	19. SRI-50 scores at each time point. 20. Change from Day 1 in Medical Outcomes Study 36-item Short Form Health Survey (SF-36) Physical Component Summary (PCS), Mental Component Summary (MCS) and total score at each time point. 21. Change from Day 1 in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and EuroQoL 5 Dimension (EQ-5D) at each time point. 22. Proportion of subjects in the PGIC categories of 1 or 2, 3 or 4 or 5, 6 or 7 at each time point. **Disease activity (analysis of worsening/flares):** 23. Proportion of subjects with at least one BILAG A flare at each time point. A BILAG A flare is defined by ≥1 new BILAG A organ domain score compared to screening visit. 24. Time from screening visit to first BILAG A flare. 25. Proportion of subjects with at least one BILAG A or 2B flare at each time point. A BILAG A or 2B flare is defined by ≥1 new BILAG A organ domain score and/or ≥2 new BILAG B organ domain scores compared to screening visit. 26. Time to first BILAG A or 2B flare. 27. Proportion of subjects with any flare per the SELENA SLEDAI Flare Index (SFI) at each time point. 28. Time to first SFI severe flare. **Safety Endpoints** 1. The nature, incidence, severity, and outcome of adverse events (AEs). 2. Columbia-Suicide Severity Rating Scale (C-SSRS) outcome. 3. Changes in standard laboratory parameters and vital signs. 4. Antibodies to atacicept, both binding and neutralizing.

Pharmacokinetics endpoint	Atacicept concentrations.
Pharmacodynamic endpoints	1. Absolute values and change from screening visit in serum complement C3, C4, and C4d levels at each time point, in subjects with low levels of C3 or C4 and/or elevated levels of C4d at screening visit, respectively. 2. Change from screening visit in anti-dsDNA antibodies (in subjects with anti-dsDNA antibodies ≥30 IU/mL at baseline) and proportion of subjects with positive ANA levels (in subjects with human epithelial cell (Hep)-2 ANA ≥1:80 at baseline) at each time point. 3. Absolute values and change from screening visit in levels of total immunoglobulin (Ig) classes (IgG, IgA, and IgM) at each time point. 4. Absolute values and change from Day 1 in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid. 5. Absolute values and change from Day 1 in total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and plasma cells, plasmablasts, and natural killer (NK) cells by flow cytometry analysis at each time point. 6. Absolute values and change from screening in free BLyS and free APRIL if an appropriate assay is available.
Other assessments	**Exploratory Endpoints** 1. Change in Lupus Quality of Life (LupusQoL) domain scores at each time point. 2. Health resource utilization: (a) number of emergency room visits and (b) number of inpatient admissions. 3. Genetic variants, and gene expression variations associated with subjects' responses to atacicept therapy. 4. Change in levels of circulating proteins (e.g., cytokines, chemokines, and additional autoantibodies).

	5. Change from Day 1 in SLICC/ACR Damage Index score at Week 24. 6. Absolute values and change from Day 1 in anticardiolipin, anti-Smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), anti-La and anti-Ro antibodies, rheumatoid factor (RF) and lupus anticoagulant (recorded as absent or present) at each time point, in subjects with abnormal values at Day 1.
Statistical methods (includes sample size calculation)	In order to have 80% power to detect 20% absolute difference in proportion of subjects achieving a response defined by SRI, 93 subjects per arm are required, assuming a placebo response rate of 30% and a 2-sided α=0.05. The total sample size is thus planned to be 279 subjects with a randomization ratio of 1:1:1. The intent-to-treat **(**ITT) population consists of all randomized subjects. The modified ITT **(**mITT) population is defined as all randomized subjects who have received at least 1 dose of the IMP. The per protocol **(**PP) population consists of all randomized and treated subjects who do not have any major protocol deviations. The safety population consists of all randomized subjects who receive at least 1 dose of IMP. Subjects in the ITT, mITT and PP populations will be analyzed according to their randomized treatment and subjects in the safety population will be analyzed according to the actual treatment received during the trial. The primary efficacy analysis will be performed using the mITT population. A step-down sequential testing procedure will be used to control for multiplicity in atacicept doses. The atacicept 150 mg arm will first be compared with the placebo arm (2-sided α=0.05) and if statistically significant, the atacicept 75 mg arm will be compared with the placebo arm (2-sided α=0.05). If the primary endpoint is met for both atacicept doses, the key secondary endpoints for both atacicept doses will also be tested hierarchically in a pre-specified order to control the overall type I error rate (2-sided α=0.05). If the primary endpoint is not met for either atacicept dose, the analysis of the key secondary endpoints will become exploratory.

	The analysis of other secondary endpoints is exploratory. 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. Binary endpoints will be analyzed using logistic regression adjusted for the stratification factors in the randomization. Continuous endpoints will be analyzed using analysis of covariance adjusted for the stratification factors in the randomization. An independent Data Safety Monitoring Board will be formed to monitor interim safety and disease activity data on a regular basis to ensure the safety of the subjects in this trial.

2 Sponsor, Investigators and Trial Administrative Structure

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USA

Dr. Merrill will work in conjunction with the principal investigators and investigative sites to provide medical input and advice relating to the trial design and execution and will be responsible for review and sign-off of the clinical trial report (CTR).

The sponsor will enlist the support of Quintiles, a contract research organization (CRO), to conduct the clinical part of the trial including trial set up, coordination, monitoring, data capture, data management and statistical analysis. The sponsor will supervise all outsourced activities.

This trial will be conducted at 100 sites in 25 countries in Europe, Asia, North America, Latin and Central America. Approximately 30 sites are anticipated to participate in the United States (US).

Investigational medicinal product (IMP) supply and distribution will be the responsibility of the Clinical Trial Supply Department at Merck KGaA, Darmstadt, Germany.

An independent Data Safety Monitoring Board (DSMB) will be formed to monitor interim safety and disease activity data on a regular basis to ensure the safety of the subjects in this trial (see Section 8.7).

3 Background Information

3.1 Medical Need

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple organ systems and is unpredictable in disease severity, with periods of illness or flares alternating with periods of remission. The diverse presentation of lupus can range from rash and arthritis, to anemia and thrombocytopenia, to serositis, nephritis, seizures, and psychosis. At its onset, SLE may involve one or more organ systems, including the musculoskeletal, cutaneous, vascular, renal, pulmonary, hematological, and nervous systems. Additional manifestations may occur over time. Disease prevalence is approximately 1 in 1000 individuals overall, but varies with race and ethnicity. SLE is more common in women than in men (i.e., up to 10 times more common) and onset typically occurs in women during their childbearing years. Patients with moderate to severe SLE consider their health-related quality of life (QoL) to be poor, and they are chronically exposed to medication with significant side effects, such as, corticosteroids (typically prednisone or prednisolone) and immunosuppressive agents [1, 2].

Although the pathogenesis of SLE is not fully understood, B cells are believed to play a central role, through both antibody-dependent and independent mechanisms. A hallmark of SLE is production of autoantibodies to a variety of nuclear antigens that account for some of its pathological findings [1, 3]. Serologically, a series of these autoantibodies are used routinely in clinical practice to further characterize the disease and risk for potential manifestations. These include anti-nuclear antibodies (ANA) as well as anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-Ro (SSA), anti–La (SSB), anti-Smith (anti-Sm), anti-ribonucleoprotein (anti-RNP), and anti-ribosomal P antibodies [1, 2, 4]. Histological results have shown association between the presence of autoantibodies and tissue damage [4, 5, 6, 7]. Levels of anti-dsDNA antibodies have been shown to correlate with disease activity, are highly specific for the disease, and may be correlated with renal involvement. Analysis of the relationship between the

immunoglobulin (Ig) classes IgG, IgA, and IgM anti-dsDNA antibody isotypes and clinical manifestations showed a significant association of the IgM isotype with cutaneous involvement and of the IgG isotype with lupus nephritis (LN) [7, 8].

Corticosteroids remain a therapeutic mainstay for short- and long-term control of disease activity in SLE and LN, and are often administered in combination with chloroquine derivatives (i.e., antimalarials including hydroxychloroquine sulfate) and immunosuppressants (e.g., mycophenolate mofetil [MMF], methotrexate, azathioprine, cyclophosphamide, and cyclosporine). The chloroquine derivatives are of moderate effectiveness and may prevent flares, though breakthrough flares occur frequently [9], while the toxicity of the more aggressive drug regimens for SLE contributes significantly to morbidity and mortality.

Recently, more targeted therapies, i.e., monoclonal antibodies, have been utilized in the treatment of SLE. Inhibition of BLyS (B lymphocyte stimulator, also known as B-cell activating factor of the tumor necrosis factor [TNF] family [or BAFF]) with belimumab was shown to be safe and effective for SLE treatment [10, 11, 12]. Belimumab was approved by the US Food and Drug Administration (FDA) in 2011 and also in Canada and Europe for treatment of SLE.

Belimumab (Benlysta®) is the only targeted therapy approved. Patients treated with belimumab and standard of care (SoC) had increased rate of treatment response compared to those receiving placebo and SoC. In addition, results suggested that there was a reduced likelihood of severe flares and steroid doses. However, approximately 50% of the patients did not respond with a decrease in SLE activity when treated with belimumab [10, 11]. Therefore, there is a very high, unmet medical need for novel, targeted therapies with improved efficacy and benefit-risk ratio.

3.2 Scientific Background

Atacicept is a novel immunomodulator with B cell targeting properties. The lead disease indication for atacicept is SLE, a systemic autoimmune disease in which B cells play a major role in its etiopathogenesis. The molecule is a fusion protein comprising the fragment crystallizable (Fc) portion of human IgG1 and the extracellular domain of the TNF receptor superfamily member TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor). Two TNF homologs, BLyS and APRIL (a proliferation-inducing ligand), 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 (i.e., homotrimeric, heterotrimeric, multimeric, and soluble or membrane-expressed), deprives B cells of essential survival signals [13]. 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 [14, 15, 16, 17, 18].

3.3 Nonclinical Studies

The binding of BLyS and APRIL by atacicept and inhibition to their respective cognate receptors (i.e., TACI, B-cell maturation antigen, and BAFF-receptor) 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.

Mice and cynomolgus monkey studies demonstrate atacicept's intended pharmacodynamic (PD) effects, i.e., suppression of serum Igs, decreased circulating B cell numbers, and reduced splenic and lymph node B-cell areas. Atacicept's therapeutic benefit was also demonstrated in a collagen-induced arthritis model and SLE murine models.

In addition, due to reduced antigen-specific immune responses observed in atacicept mouse studies (Studies RES-10211, RES-10212, and RES-10213), additional 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-dose or repeat-dose experiments 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, which was the same route utilized in Phase II/III human clinical trials. Pharmacodynamic effects were long-lasting and consistent with atacicept's mechanism of action, including the dose-dependent, reversible decreases in B lymphocytes in circulation and in tissues (i.e., total and mature B cell subsets were affected), and in total serum Ig levels (e.g., IgG, IgM, and IgA).

Atacicept was 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 (e.g., 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 in both mice and rabbits. In a pre- and post-natal 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 and SC administration. 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 sub-acute and chronic toxicity studies, the no-observed-adverse-effect-level corresponded to the highest administered dose, i.e., 80 mg/kg administered every 2nd day in mice or every 3rd day in monkeys for 4 weeks, and

10 mg/kg administered every 2nd day for up to 26 weeks in mice or 10 mg/kg administered every 3rd day for up to 39 weeks in monkeys. Results obtained from animal studies support conduct of clinical trials in healthy volunteers and subjects with SLE and LN.

Please refer to the Investigator's Brochure (current edition) for details on the nonclinical and clinical program of atacicept.

3.4 Clinical Trials

Sixteen atacicept clinical trials have been conducted to date: a total of 8 Phase I, Ib, and I/II trials and 8 Phase II and II/III trials. Five trials have been conducted in the SLE and LN indications (Trials 25050 [Phase Ib], 25842 [Phase Ib], 27646 [Phase IIb], 28113 [Phase IIb], and 700461-014 [Phase Ib]), which are the current focus of the atacicept clinical program.

In addition to SLE and LN, atacicept was evaluated in a number of indications including B-cell malignancies, rheumatoid arthritis (RA), relapsing remitting multiple sclerosis (MS), and optic neuritis. B-cell malignancies and RA are no longer being pursued due to the lack of sufficient efficacy in these trials. As of 30 June 2013, a total of 1573 subjects (healthy volunteers and patients with RA, SLE, LN, MS, optic neuritis and B-cell malignancies) have been enrolled into the completed atacicept clinical trials, and 1088 subjects have been exposed to at least one dose of atacicept. Over 350 SLE subjects have been exposed to atacicept. Refer to the Investigator's Brochure (current edition) for additional details.

The 700461-014 study was a Phase Ib, open-label, multicenter, dose-escalation, repeat-dose trial to assess the safety, tolerability, PK, and PD of atacicept treatment in LN subjects on a stable MMF regimen, with or without CS. The primary objective was to characterize atacicept safety and tolerability in LN subjects taking a stable regimen of MMF. The trial also sought to establish the PK and PD profiles of atacicept in LN subjects taking a stable regimen of MMF. The first subject enrolled died suddenly from a possible myocardial infarction within 24 hours of the first and only dose of atacicept. Enrollment was suspended, and the sponsor terminated the trial. No other subjects were screened, enrolled, or treated. Because the subject died before postbaseline assessments, no efficacy, PK, PD, or pharmacogenetics (PGx) analyses were performed. The subject was a 33-year old woman with SLE and LN, who had a history of hypercholesterolemia and cigarette smoking (20 cigarettes/day). Cardiovascular disease is widespread among patients with SLE and LN, and is a major cause of death in this population. Indeed, this subject's autopsy revealed cardiac ischemic foci of at least several weeks duration and stenosis in the coronary arteries (including left anterior descending coronary artery, right coronary artery, left main, and left circumflex). The relationship to atacicept, though unlikely, could not be completely ruled out.

APRIL-LN (Trial 28113) was a phase II/III, randomized, double-blind, multicenter, placebo-controlled trial to evaluate the safety and efficacy of atacicept treatment in combination with MMF and high-dose CS in LN subjects. The primary objective was to evaluate the efficacy of atacicept treatment compared with placebo in LN subjects receiving or requiring MMF immunosuppressive therapy and high-dose CS. APRIL-LN was discontinued prematurely because of unexpectedly large decreases in IgG levels. The data from this trial revealed rapid

decreases in the levels of Ig following the initiation of MMF and CS in 4 of the 6 subjects enrolled. This Ig decrease was likely to have been due to the initiation of MMF and/or initiation of CS in the setting of significant proteinuria but the contribution of atacicept to these findings could not be excluded. The 4 subjects with Ig decreases were all randomized to receive atacicept and had higher levels of proteinuria at the outset than those patients who received placebo. The former continued to have rapid decreases in Ig levels after the start of atacicept. 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 SoC treatment, including antibiotics.

The APRIL-SLE 27646 trial 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 follow-up (FU) period. During the trial, 2 subjects who were receiving atacicept 150 mg experienced fatal infections due to suspected leptospirosis and *S. pneumoniae*, respectively, for which a contributing role of atacicept could not be excluded. One of the subjects was a 22-year-old, 40-kilogram (kg) male living in the Philippines who died from acute respiratory failure due to alveolar hemorrhage secondary to possible leptospirosis. In addition to SLE, the subject also had an overlap syndrome with features of scleroderma, complicated by a history of recurrent infected digital ulcers. The other patient was a 30-year-old, 40.8-kg female who, 10 months after starting treatment, was hospitalized due to pneumonia from *S. pneumoniae*. This led to life-threatening alveolar hemorrhage and then death. The subject did not have relevant medical history besides her lupus. Consistent with atacicept's mechanism of action, both subjects experienced decreases in their total IgG levels, but neither subject had an IgG level below 14.6 g/L (normal range approximately 6-18 g/L). Despite the risk factors related to the subjects' underlying disease and comorbidities, as well as reported possible delays in identifying and treating these infections, a possible role of atacicept could not be excluded (see current Investigator's Brochure for additional details).

Consequently, the atacicept 150 mg dose group was discontinued following a recommendation by the trial's Independent Data Monitoring Committee. 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 atacicept 75 mg-treated subjects showed no benefit compared to placebo-treated subjects in preventing new flares. However, a post-hoc analysis of the primary endpoint, where the subjects discontinuing treatment solely due to sponsor's termination of the 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.

The sponsor is continuing development of atacicept in SLE with this Phase IIb trial (ADDRESS II-**A**tacicept for a re**D**uction of active **D**isease **RE**sponse in **S**ystemic lupu**S** erythematosus II) to show induction of clinical response in subjects with moderate to severe

active SLE. Subjects who complete this trial will be offered participation in a long-term extension (LTE) trial (Phase II). Safety data from this extension trial will support the licensing and marketing applications with the relevant regulatory authorities.

3.5 Trial Rationale

Atacicept is a novel immunomodulator with B-cell targeting properties that is being developed by EMD Serono (US)/Merck KGaA[1] (Germany) for the treatment of SLE. It inhibits BLyS and APRIL. It ameliorates lupus disease progression animal models (BLyS $^{-/-}$ mice or by administration of soluble competitive receptors) by reducing B-cell numbers and consequently the level of anti-dsDNA antibodies [19]. In animal models where soluble TACI receptors were administered, decreases in disease manifestations were also observed [20]. In addition, inhibition of BLyS with belimumab (an anti-BLyS monoclonal antibody), approved by the FDA in 2011, was shown to be safe and effective for SLE treatment [10, 11, 12, 21].

This Phase IIb trial is being conducted to evaluate the efficacy and safety of atacicept compared to placebo in reducing the level of SLE disease activity in subjects with active SLE and to select a dose for further development in Phase III. This trial will recruit subjects with a similar level of disease activity as for the APRIL-SLE 27646 trial, i.e., those with moderate-severe SLE, but treatment will be initiated at the time of active disease (rather than low disease activity and evaluating prevention of flares as was studied in APRIL-SLE 27646). The APRIL-SLE trial suggested efficacy of atacicept in preventing flares of SLE. However, efficacy in reducing active disease is critical information for the medical community and patients. The time at which patients have active disease manifestations is often a treatment decision point. In addition, since the activity of SLE fluctuates over time, it is important to evaluate during clinical development whether atacicept has efficacy during both periods of low as well as moderate-severe disease activity.

3.6 Benefit-Risk Assessment

In the APRIL-SLE 27646 trial, both the atacicept 75 mg and 150 mg doses demonstrated significant PD effects (such as decrease in Ig, anti-dsDNA and B cell counts). In addition, the 150 mg dose was associated with a reduction in SLE flare incidence. In the proposed ADDRESS II trial, it is possible that both doses of atacicept will be associated with significant PD effects as well as clinical benefit in this reduction of active disease study design.

Atacicept's ability to block the effects of BLyS and APRIL and inhibit autoantibody production suggests that treatment with atacicept may reduce disease activity and thus limit the extent of tissue damage observed in SLE patients. Furthermore, increased levels of both BLyS and

[1] In the US, this is EMD Serono, which is a subsidiary of Merck KGaA, Germany. Merck KGaA is the global sponsor for this trial (including the US).

APRIL have been measured in serum samples from SLE subjects, extending the association of BLyS and APRIL with autoimmune disease from animal models to humans.

Inhibition of BLyS with belimumab was found to be effective and safe for the treatment of SLE, leading to its approval in 2011. In addition, in a Phase II study, the B-cell directed anti-CD22 therapy with epratuzumab was associated with clinical benefit in SLE patients. Atacicept is the only B cell modulator in clinical development that blocks the activity of both BLyS and APRIL, which may result in a more effective approach for autoimmune disease than other available therapies.

Atacicept exerts multiple affects the immune system which may lead to increased susceptibility to infection. An increased risk of serious infections (by absolute increase <2%) including 2 fatal respiratory infections, was observed after multiple dosing of 150 mg atacicept (see Section 3.4). The risk of infection associated with atacicept will be further evaluated in this and future clinical trials with atacicept.

For the reasons listed above, previous (such as ongoing DSMB, exclusion of subjects with an IgG<6 g/L [22], and exclusion of subjects with chronic recurrent infections) and additional risk mitigation measures will also be incorporated into these trials. These additional measures include subjects are to receive phone calls from the sites on those weeks when not coming in for an in-person visit in order to maintain vigilance in the evaluation of potential development of infections or other adverse events (AEs), exclusion of subjects with a cardiovascular event within 6 months prior to screening, review of eligibility criteria by the medical monitor for each subject, and vaccinations for *S. pneumoniae* and influenza virus.

The observation that atacicept exposure correlated with MS disease worsening led to premature discontinuation of the MS program. In response to the finding of increased MS disease activity in atacicept-treated subjects in the MS trial, subjects with a history of any demyelinating and active central nervous system disease are excluded from this trial.

As with other medications, subjects treated with atacicept may be at risk of developing allergic hypersensitivity reactions or anaphylaxis. For this reason, subjects will be monitored after their first 2 injections of atacicept in the clinic.

Trial 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 the trial. Based on the nonclinical and clinical data available to date, the conduct of the trial is considered justifiable using multiple doses of 75 and 150 mg of atacicept as specified in this clinical trial protocol (CTP). In this trial, a DSMB is planned for the ongoing unblinded assessment of the benefit-risk ratio. The trial shall be recommended to be discontinued in the event of new findings that would render continuation of the trial unjustifiable.

Subjects may experience side effects or be at risk for symptoms, illnesses or complications that could not be foreseen by the sponsor. This clinical trial will be conducted in compliance with the

CTP, Good Clinical Practice (GCP) (International Conference of Harmonisation [ICH] Topic E6, GCP) and the applicable regulatory requirements.

4 Trial Objectives

Primary

The primary objective of this trial is to evaluate the efficacy of atacicept compared to placebo in reducing SLE disease activity in subjects treated with SoC therapy and to investigate the dose-response relationship.

Secondary

Secondary objectives of the trial are to evaluate the:

1. Effect of atacicept in reducing corticosteroid (CS) usage.
2. Effect of atacicept on changes in disease activity over time.
3. Safety, tolerability and immunogenicity profiles of atacicept in SLE subjects.
4. Pharmacokinetics and PD profiles of atacicept in SLE subjects.
5. Effect of atacicept on patient-reported outcomes (PROs).

Other

Exploratory objectives

1. Identify potential associations of genetic variations and gene expression with atacicept response, efficacy and safety.
2. Identify potential associations of the profiles of circulating proteins with atacicept response, efficacy and safety.
3. Evaluate the effect of atacicept in reducing damage accrual from SLE (Systemic Lupus International Collaborating Clinics [SLICC]/American College of Rheumatology [ACR] Damage Index).

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a Phase IIb, multicenter, double-blind, placebo-controlled (DBPC) parallel-arm trial in which 279 subjects are planned to be randomized in a ratio of 1:1:1 to receive placebo, or atacicept 75 mg or 150 mg, given by SC injection once weekly for 24 weeks. This trial will be conducted at approximately 100 sites in about 25 countries.

The trial is composed of a screening period, a DBPC treatment period, and a safety FU period. The trial will be conducted on an outpatient basis for a treatment duration of 24 weeks. An LTE trial will be offered to completers of the 24-week treatment period as part of a separate protocol.

Screening Period: The first visit will be a screening visit and include review of the inclusion/exclusion criteria. The screening visit will be considered the baseline for disease activity (i.e., British Isles Lupus Assessment Group [BILAG] 2004 Disease Activity Index, SLE Disease Activity Index-2000 [SLEDAI-2K], and Physician's Global Assessment [PGA] and SLEDAI-2K Responder Index-50 [SRI-50]). For all other assessments, Day 1 will be considered the baseline. Duration of the screening period will be up to 4 weeks to determine the subject's eligibility; however, subjects should undergo the Day 1 visit as soon as possible after eligibility for the trial has been confirmed. Eligible subjects must have at least moderately active SLE, as defined by SLEDAI-2K score ≥6, at least 4 of the 11 ACR classification criteria for SLE, a disease duration of at least 6 months [23, 24], and positive anti-nuclear antibodies (ANA) and/or anti-dsDNA antibodies at screening. Corticosteroids may be initiated during this time, and the dose can be increased or decreased (see Section 6.5.1).

DBPC Treatment Period: Duration of the treatment period will be 24 weeks starting at randomization. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be reviewed again on Day 1 prior to randomization. Subjects will be monitored at trial visits at Weeks 1, 2 and 4, and every 4 weeks thereafter. Subjects will receive the last dose at Week 23. Week 24 is the end of treatment for the trial.

The Day 1 procedures (randomization) 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 Day 1.

LTE Trial: Subjects who complete the 24-week DBPC period will be offered participation in the LTE trial. The LTE trial will be conducted under a separate protocol. Subjects continuing in the LTE trial will receive the first dose of LTE trial at Week 24 following the completion of all Week 24 procedures. They will not attend the safety follow-up visits until treatment is stopped in the LTE, due to either a subject's premature withdrawal/early termination (ET) from the LTE, termination of the LTE by the sponsor, or completion of the LTE treatment period (see Figure 5-1). It is expected that the placebo arm of this ADDRESS II trial will be switched over to the 150 mg dose of atacicept while the subjects in the atacicept treatment arms will remain on their original respective doses of atacicept when enrolled in the LTE. Subjects are recommended to have signed the informed consent for the LTE at least 4 weeks prior to its start.

Safety FU Period: Duration will be 24 weeks. Subjects will enter this period directly from the DBPC period after the Week 24/ET visit. Safety visits are scheduled at 4, 12, and 24 weeks after the last IMP dose. This includes subjects who stop treatment prematurely and those who complete the DBPC period but do not enter the LTE (see Figure 5-2). FU Week 24 is the last scheduled visit for subjects not entering the LTE trial.

During the study, efficacy endpoints will be evaluated using several activity indices, including the BILAG 2004, SLEDAI-2K, SLEDAI-2K Responder Index-50 (SRI-50), and PGA. As part of the efficacy assessment, the effects of treatment on health-related QoL will be examined using the following PRO measures: Medical Outcomes Study 36-item Short Form Health Survey (SF-36), EuroQoL 5 Dimension (EQ-5D), LupusQoL, Patient Global Impression of Change (PGIC), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue.

Safety will be evaluated through the nature, incidence, severity and outcome of AEs, and assessment of changes over time in clinical laboratory parameters, vital signs, ECGs and physical examination findings.

Further Analysis: PK will be evaluated in all subjects through measurement of serum atacicept concentrations. PK sampling will also be performed at additional time points outside of the scheduled clinic visits; this will be done for a total of 40 subjects from all treatment groups (placebo=8, atacicept 75 mg=16, atacicept 150 mg=16) (see Section 7.5). The subjects who will be part of the subset will be registered by the trial's central randomization system. The time of collection of the PK samples in the PK subset may be adjusted based on the results of a Phase 1 trial in the atacicept program that is being initiated.

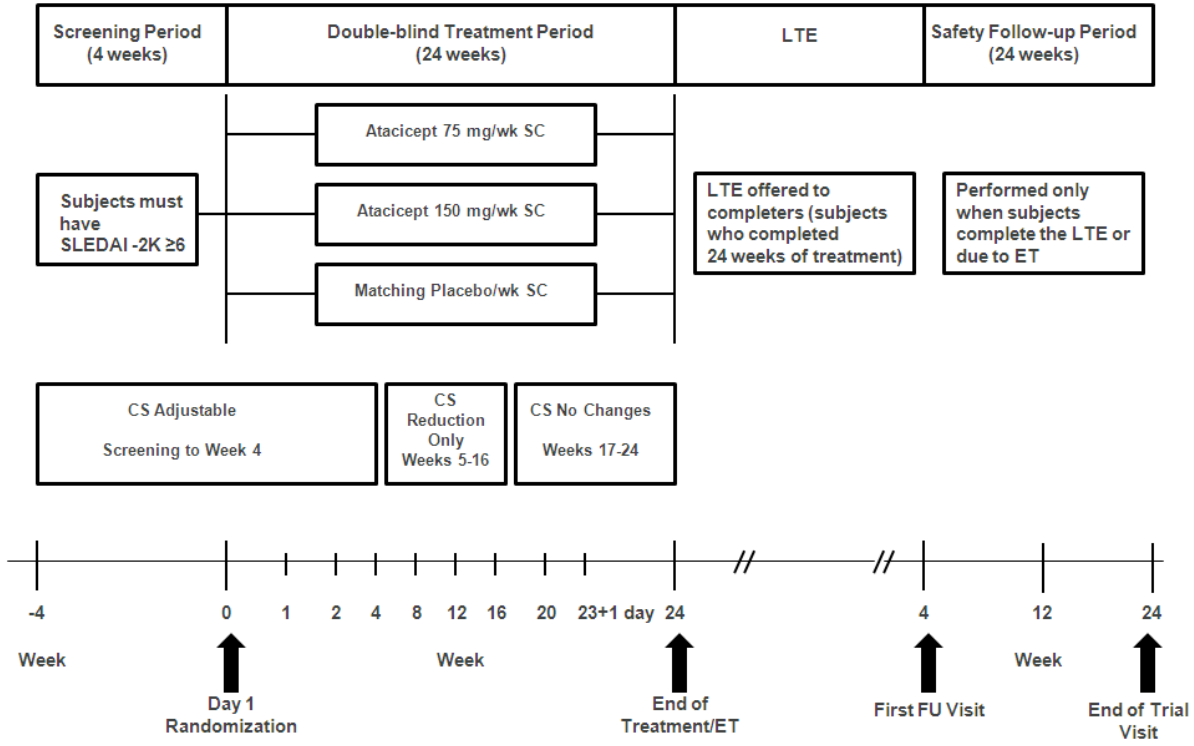
PD will be assessed through measurement of BLyS, APRIL, C-reactive protein (CRP), and Ig levels. Complement proteins C3, C4 and C4d levels, and levels of ANA and anti-dsDNA antibodies and other autoantibodies will also be assessed. Subjects will be tested for formation of antibodies to atacicept and for changes in antibody titers to pneumococcal antigens, tetanus toxoid and diphtheria toxoid.

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 free BLyS and free APRIL in the presence of atacicept. In a subset of subjects at selected sites, flow cytometry analyses of B cell subsets, T cell subsets and natural killer (NK) cells in peripheral blood will be performed to characterize atacicept's effects on these cell populations.

Exploratory Endpoints: Circulating proteins (e.g., cytokines, chemokines, and additional autoantibodies) and pharmacogenomic or ribonucleic acid (RNA) analyses will be performed to support further development of atacicept.

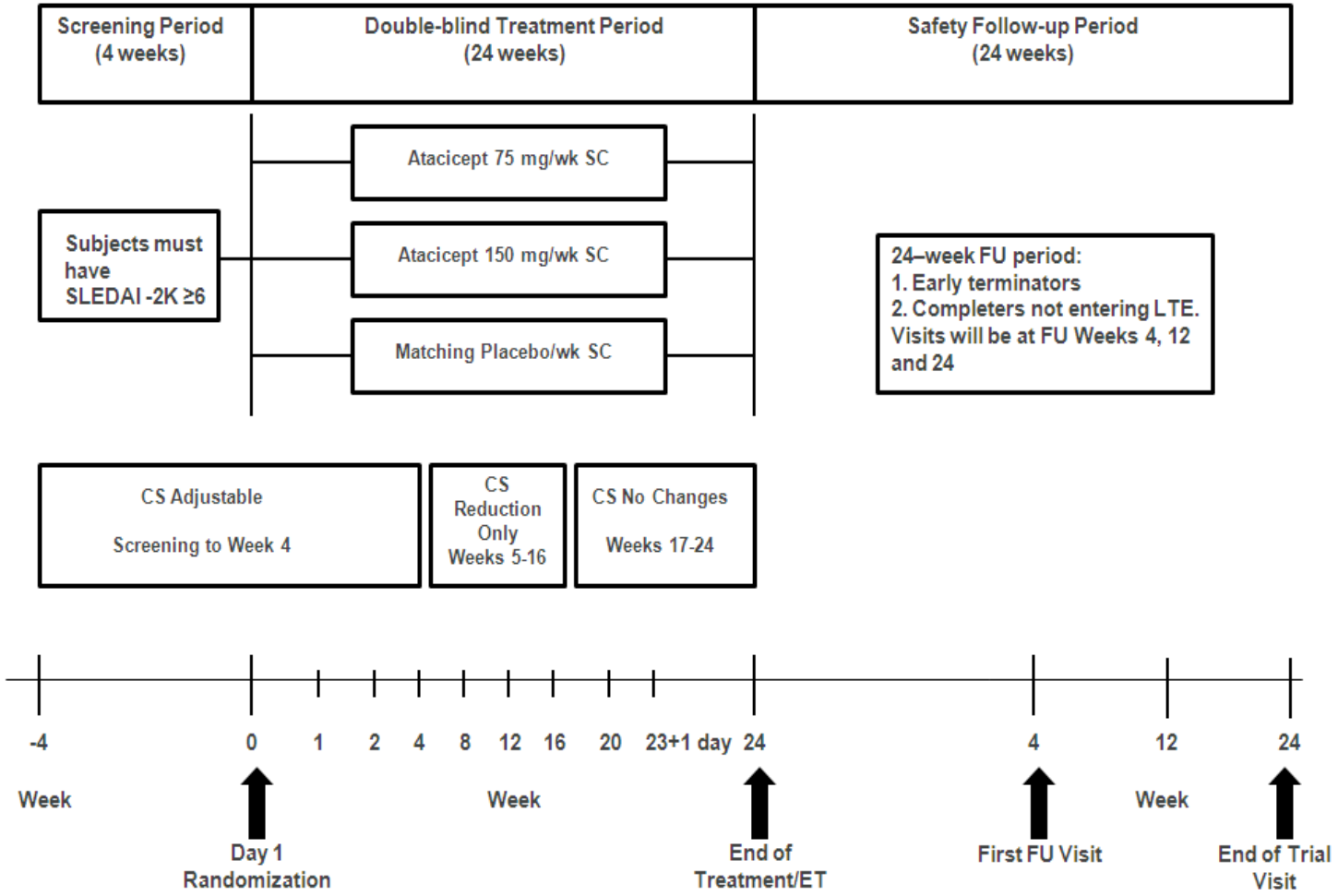
Pharmacogenetics or deoxyribonucleic acid (DNA) analysis (optional) will be performed in subjects who provide a separate informed consent (see Section 7.9.3).

Figure 5-1 Trial Design for Completers Continuing into LTE Trial



CS=corticosteroid; ET=early termination; FU=follow-up; LTE=long-term extension; SC=subcutaneous; wk=week.

Figure 5-2 Trial Design for Subjects Not Continuing into LTE Trial



CS=corticosteroid; ET=early termination; FU=follow-up; LTE=long-term extension; SC=subcutaneous; wk=week.

5.2 Discussion of Trial Design

The atacicept doses selected for this trial (75 mg and 150 mg) are based on the results from the APRIL-SLE 27646 clinical trial. Efficacy in preventing flares in patients with low disease activity at time of IMP initiation was observed at the 150 mg dose in the APRIL-SLE study, while at the 75 mg dose, significant PD effects (particularly for individuals with elevated baseline levels of BLyS and/or APRIL) were observed. Thus, in this ADDRESS II disease activity trial, 75 mg may be clinically effective in reducing disease activity in the target population of subjects with moderate to severely active SLE with disease duration of at least 6 months. At the 150 mg dose, safety is acceptable and manageable, with additional risk mitigation measures added to this trial design in comparison to the APRIL-SLE trial. These include requirement for vaccinations against pneumococcus and seasonal influenza, as well as weekly monitoring of subjects (remotely during weeks without a scheduled clinic visit).

A placebo control arm is needed to determine a treatment difference in the efficacy of atacicept added on to SoC compared to SoC alone (plus placebo). As the subjects enrolled will have active disease, it will be necessary to allow for the possibility of making some adjustments in background medication (e.g., CS) at the start of the trial.

The primary endpoint chosen is the one used for the Phase III studies of belimumab in SLE patients (BLISS-52 and BLISS-76), the SLE Responder Index (SRI), which demonstrated efficacy of this agent. The main reasons for including this endpoint into this ADDRESS II trial are that it differentiated active drug from placebo in large randomized trials and was accepted by regulators as valid. Efficacy will thus primarily be evaluated using a composite of several commonly used activity indices, including the SLEDAI-2K, BILAG, and PGA (visual analog scale [VAS]).

The secondary endpoints will analyze CS use, individual components of the SRI, key PD markers, and safety parameters. Use of CS is a central concern for health care providers and patients since there is high associated morbidity. Reduction of CS use is critical to measure in conjunction with disease activity. SLE-specific worsening will be assessed primarily using the disease activity indices which comprise the SRI. Although PD parameters were evaluated in the APRIL-SLE trial (as well as other non-lupus trials), they may provide different information with the same doses of atacicept when evaluated in a reduction of active disease trial. The safety assessments are standard for clinical trials.

The impact of SLE on subjects' lives is significant, and thus health-related QoL outcomes are meaningful to both patients and clinicians. This trial will evaluate the PRO measures SF-36, EQ-5D, LupusQoL, FACIT-Fatigue and PGIC.

Assessment of the primary endpoint after a treatment period of 24 weeks is considered sufficiently long to observe a decrease in disease activity. In trials performed with belimumab, the treatment arms reached near their near-maximal response rates based on the composite SRI endpoint at approximately 24 weeks. The result at 24 weeks is thus expected to be predictive of the responses that would be seen at 52 weeks with atacicept (the anticipated time of the primary endpoint analysis in Phase III).

The 24-week duration of the follow-up period was selected based on the expected duration of measurable atacicept effects after its discontinuation. Specifically, the Ig recovered by approximately 50% at the Week 12 follow-up in the APRIL-SLE study. Many other PD markers such as C3, C4 and anti-dsDNA had similar trends.

The exploration of biomarkers may allow the sponsor to: (a) monitor the treatment response, (b) identify markers predictive or prognostic of disease activity, (c) help refine dosing schemes, and (d) correlate baseline values of biomarkers to treatment response. The possibility exists that a broad spectrum of SLE patients will respond to atacicept, but that a biomarker may allow identification of a subgroup that has a particularly high benefit-risk ratio. To pursue these goals, the biomarker analysis might help evaluate both specific candidates in a hypothesis-driven manner as well as candidates chosen in a non-biased (hypothesis-free) way.

Collection of samples will allow analysis of circulating protein levels, genetic testing for gene polymorphisms and RNA analysis for gene expression variations.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

To be eligible for the trial, 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 and approved for randomization (see Section 5.4).

5.3.1 Inclusion Criteria

1. Male or female of ≥18 years of age, who provide written informed consent at the screening visit.
2. Diagnosis of SLE satisfying at least 4 out of the 11 ACR classification criteria for SLE during the course of their illness at the screening visit.
3. Disease duration of at least 6 months from the time of diagnosis (when the subject met at least 4 of the ACR criteria) at the screening visit.
4. SLEDAI-2K score ≥6 at screening visit.
5. Positive test results for ANA (human epithelial cell [Hep]-2 ANA ≥1:80) and/or anti-dsDNA antibody (≥30 IU/mL) at screening visit.
6. Women of childbearing potential (WOCBP) must use highly effective methods of contraception to prevent pregnancy for 4 weeks before randomization and must agree to continue to practice adequate contraception for 60 days after the last dose of IMP. For the purposes of this trial, WOCBP is defined as:

All female subjects after puberty unless they are postmenopausal (defined by continuous amenorrhea) for at least 2 years or are surgically sterile.

Highly effective contraception is defined as use of 2 barrier methods (e.g., female diaphragm and male condoms), 1 barrier method with spermicide, an intrauterine device or hormonal contraceptives (e.g., implant or oral). Note that because mycophenolate affects the metabolism of hormonal contraceptives and may reduce their effectiveness, women receiving mycophenolate who are using hormonal contraceptives for birth control should employ an additional contraceptive method (e.g., barrier method).

7. Women of childbearing potential must have a negative serum pregnancy test at screening visit and a negative urine pregnancy test at Day 1/randomization before dosing.
8. History of vaccinations against *S. pneumococcus* and influenza virus (as seasonally required), or vaccination against these pathogens at the screening visit. Subjects receiving one or more of these vaccinations at the screening visit must have at least 2 weeks between the vaccination and the date of randomization. (Live or live-attenuated vaccines are not permitted per Section 6.5.2).

5.3.2 Exclusion Criteria

Subjects are not eligible for this trial if they fulfill any of the following exclusion criteria.

Patients will be excluded if any of these conditions apply to previous or pre-existing therapies:

1. Within 2 weeks prior to screening visit:
   a. Use of corticosteroids (CS) exceeding 40 mg daily prednisone or equivalent.
   b. Increase in dosing of CS.
   c. Use of injectable CS.
2. During the screening period, use of oral CS exceeding 40 mg daily prednisone-equivalent (increases in oral CS doses are permitted).
3. Introduction of mycophenolate mofetil (MMF) or mycophenolate sodium (MPS) within 2 months prior to screening visit, increase in dosing within 1 month before screening visit or any change in dosing during the screening visit, or use of intravenous mycophenolic acid (MPA or mycophenolate) in the 2 months prior to the screening visit or during the screening visit.
4. Use of cyclophosphamide within 3 months before or during the screening visit.
5. Introduction of, increase in dosing, or use of a dose exceeding the maximum specified dose of any other medication considered to have immunosuppressant or immunomodulating properties within 1 month before the screening visit or introduction of or a change in dosing of any of these medications during the screening visit (see Section 6.5.2).

6. Use of more than 1 medication considered to have immunosuppressant or immunomodulatory properties as permitted by Section 6.5.1, not including antimalarials or CS, after the screening visit.

7. Initiation of antimalarial treatment after the screening visit.

8. Use of belimumab (or other anti-BLyS therapy) rituximab, ocrelizumab, or other B cell-directed biologic therapies within 1 year before the screening visit.

9. Use of abatacept or any TNF-inhibitor therapy within 2 months before the screening visit.

10. Immunization with live or live-attenuated vaccines within 1 month before or during the screening visit.

11. Use of Ig treatment within 2 months before the screening visit.

12. Initiation of or change in dosing of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker within 2 weeks before the screening visit.

13. 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.

14. Prior anaphylactic reaction to a biologic therapy.

15. Nonsteroidal anti-inflammatory drugs (NSAIDs) used above maximum prescribed dose per local label during the screening visit.

16. Subjects previously participating in any atacicept trial.

17. Presence of systemic rheumatic disease other than SLE (secondary Sjogren's syndrome due to SLE is permitted).

18. Weight is <41 kg (90.2 pounds) and body mass index is <17.5 at the screening visit.

19. Use of herbal supplements after the screening visit.

Medical Conditions:

20. Any condition, including any uncontrolled disease state other than SLE, that in the investigator's opinion or sponsor/designee opinion constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial objectives, conduct or evaluation.

21. Cardiovascular events including 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 before the screening visit.

22. Active cardiac arrhythmia or clinically significant abnormality on ECG at the screening visit or Day 1 (randomization) that in the investigator's or sponsor/designee's opinion constitutes an inappropriate risk or a contraindication for participation in the trial or that could interfere with the trial objectives, conduct or evaluation. These include, but are not limited to, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia (e.g., ventricular fibrillation or tachycardia) unless treated, as per central ECG reading at the screening visit and/or investigator ECG interpretation at the screening visit or Day 1.

23. Antiphospholipid antibody syndrome associated with a thromboembolic event in the 12 months prior to screening and/or associated with evidence of unstable or inadequate anticoagulation in the last 6 weeks prior to the screening visit.

24. Active, moderate to severe glomerulonephritis and/or severe renal impairment (spot urine protein:creatinine ratio [UPCr] ≥2 mg/mg and/or glomerular filtration rate [GFR] <40 mL/min/1.73 m^2 as calculated by the Modification of Diet in Renal Disease equation by the central laboratory):

    The Modification of Diet in Renal Disease equation:

    GFR = 170 x (serum creatinine in mg/dL) $^{-0.999}$ x (age in years) $^{-0.176}$ x 0.762 (if female) x 1.180 (if race is black) x (serum urea nitrogen in mg/dL) $^{-0.170}$ x (serum albumin g/dL) $^{+0.318}$

25. Active central nervous system SLE deemed to be severe or progressive including a history of recent uncontrolled seizures or change in seizure therapy in the 3 months prior to the screening visit, and/or associated with significant cognitive impairment leading to inability to provide informed consent and/or comply with the protocol.

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

27. 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).

28. History of or planned renal or other organ transplant.

29. 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 of or during the screening visit, or completion of oral anti-infectives within 2 weeks before or during the screening visit. Vaginal candidiasis, onychomycosis and genital or oral herpes simplex virus considered by the investigator to be sufficiently controlled would not be exclusionary.

30. History of splenectomy.

31. History of or positive human immunodeficiency virus (HIV), hepatitis C antibody and/or polymerase chain reaction, hepatitis B surface antigen (HBsAg) (+), and/or hepatitis B core IgG and/or IgM antibody (+) at the screening visit.

32. History of or current diagnosis of active tuberculosis (TB), or untreated latent TB infection (LTBI), determined by a TB skin test with purified protein derivative as evidenced by induration ≥5 mm or a positive Quantiferon or positive or borderline T-SPOT (Elispot) test performed locally, either at the screening visit or documented with results within 3 months of the screening visit. Subjects who have previously completed appropriate and documented LTBI treatment or who are undergoing current treatment for LTBI will not be required to be tested.

    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 (i.e., start of study treatment) 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.

    a) Subjects with current household contacts with active TB will also be excluded unless treated and evidence of household contacts being treated.

    b) Indeterminate Quantiferon or T-SPOT tests may be repeated once, and will be considered positive if retest results are positive or indeterminate.

33. Presence of uncontrolled or New York Heart Association (NYHA) Class 3 or 4 congestive heart failure.

    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 anginal pain.

    NYHA Class 4: Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased [25].

34. History of cancer, 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.

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

36. Major surgery within 6 weeks of the screening visit or planned or expected major surgery during the trial period (including trial FU).

37. History of alcohol or drug abuse in the 1 year prior to the screening visit as per investigator opinion or urine drug screen positive for non-prescribed drugs.

38. Breastfeeding/lactating or pregnant women.

39. Subjects who have evidence of serious suicide risk including any history of suicidal behavior in the last 3 months and/or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) in the last 1 month, or in the subject's lifetime as determined per the investigator's opinion.

Laboratory Abnormalities:

40. 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), or total bilirubin >1.5 x ULN, or hematologic test (hemoglobin <5.0 mmol/L [9 g/dL], white blood cells <2.5 x 10^9/L, platelets <75 x 10^9/L) unless attributable to active SLE (including serum chemistries) at the screening visit.

41. Clinically significant chest X-ray per investigator opinion or evidence of active TB on chest X-ray. Chest X-ray must have been performed in 3 months prior to the screening visit or during the screening period.

42. Serum IgG below 6 g/L at the screening visit.

43. Total B cell count <90% of the lower limit of normal at the screening visit.

Other:

44. Legal incapacity or limited legal capacity.

Subjects who do not meet the above inclusion/exclusion criteria within the specified time limits (i.e., 28 days) and screen fail may undergo rescreening once upon approval by the medical monitor. If the subject is re-screened, then the subject will receive a new subject identification number.

Excepting the TB testing as delineated above, subjects with other test results that do not meet the above inclusion/exclusion criteria may have testing repeated once 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 testing is repeated, all screening tests will need to be repeated except for the chest X-ray, ECG, TB test, HIV and hepatitis testing, which may be repeated in isolation of the other tests as necessary. If inclusion/exclusion criteria are not met based on the results of the repeated tests, the subject should be considered a screen failure and not be enrolled in the trial.

5.4 Criteria for Randomization/Initiation of Treatment with the Investigational Medicinal Product

Eligible subjects will be randomized to treatment with atacicept or placebo through a central randomization process by an Interactive Web Response System (IWRS). This trial will be double-blinded.

Randomization can only occur after confirmation that the medical monitor has reviewed the screening period data including SLE diagnostic criteria, inclusion/exclusion criteria,

SLEDAI-2K, medical history (including date of SLE diagnosis), concomitant medications, ECG and clinical laboratory assessments.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from the Trial

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

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

- Withdrawal of the subject's consent.
- Death of subject.
- Subject lost to follow up.

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

In case a subject has to be withdrawn from the trial, the responsible designee medical monitor will be informed immediately, who will then inform the sponsor's medically responsible individual (or Medical Responsible).

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 trial, to ensure the subject receives the appropriate follow-up and care.

If the subject is prematurely discontinuing due to withdrawal of consent, the investigator should clarify level of consent withdrawal with the subject and document this in the electronic case report form (eCRF) with regard to permission to utilize samples already collected but not analyzed and willingness to return for safety follow-up assessments.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for trial visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents all steps taken to contact the subject, e.g., dates of telephone calls and registered letters.

Subjects who are withdrawn from the trial for any reason after receipt of the trial's IMP on or after Day 1 will not be replaced.

If a subject is unblinded (see Section 6.11), the subject must be terminated early from the trial and complete all assessments and procedures specified for the ET visit and complete the safety follow-up period.

5.5.2 Withdrawal from the Investigational Medicinal Product

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 if discontinuation of trial drug is desired or considered necessary by the investigator and/or the subject.
- Participation in any other interventional trial during the duration of this trial for which the investigator considers discontinuation of the IMP necessary.
- Occurrence of pregnancy (for further details in case of pregnancy, refer to Section 7.4.2).
- If SLE disease activity is considered unacceptably high and treatment escalation beyond the allowable increases in CS is warranted in the view of the investigator.
- New onset MS or other demyelinating disease.
- Anaphylaxis, anaphylactoid, or other severe or life-threatening hypersensitivity reactions, based on investigator judgement.
- Use of a non-permitted concomitant drug, as defined in Section 6.5.2, where the predefined consequence is withdrawal from the IMP.
- Non-compliance, judged as significant by the investigator or sponsor including non-compliance to the required trial considerations, as defined in Section 6.5.3.
- Discontinuation of LTBI therapy before complete if present at the screening visit.
- Weight <41 kg and body mass index <17.5 upon at least 2 consecutive assessments over a period of at least 4 consecutive weeks.
- Serum IgG <3 g/L, confirmed by repeat testing.
- 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.

If subjects are withdrawn from IMP, they will be expected to complete all scheduled assessments through the end of the trial (i.e., including ET and through the safety FU period). All subjects who have received at least 1 dose of IMP and prematurely discontinue from the treatment (prior to Week 24), regardless of cause, must be seen as soon as possible and undergo the assessments specified for the ET visit (Section 7.1.3) (see Schedule of Assessments, Appendix A) and also complete the safety follow-up period. In any case, the appropriate eCRF section must be completed.

5.6 Premature Discontinuation of the Trial

The whole trial may be discontinued prematurely in the event of any of the following:

- New information leading to unfavorable risk-benefit judgement of the IMP, e.g., due to:

- Evidence of inefficacy of the IMP,
- Occurrence of or unexpectedly high intensity of known adverse reactions, or
- Other unfavorable safety findings.

  (Note: evidence of inefficacy may arise from this trial or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g., toxicology.)

- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of atacicept.

The health authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

The whole trial may be terminated or suspended upon request of the health authorities. The investigator will inform the subject's primary health care provider as applicable and if subject agrees to contact if the trial is terminated or suspended to ensure the subject receives the appropriate follow-up and care.

5.7 Definition of End of Trial

The end of trial is defined as when final database lock occurs.

6 Investigational Medicinal Product(s) and Other Drugs Used in the Trial

6.1 Description of Investigational Medicinal Products

The term IMP refers to the investigational drug (atacicept) undergoing evaluation or placebo.

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.

Atacicept is the active ingredient in the drug product. The dosage form will be supplied by the sponsor as a clear to slightly opalescent, slightly yellow to yellow sterilized solution, ready-to-use pre-filled type 1 glass syringe of atacicept prepared at a concentration of 75 mg/mL (75 mg dose group) or 150 mg/mL (150 mg dose group). The formulation contains trehalose as a

stabilizing agent and 10 mM sodium acetate buffer (pH 5). The 75 mg and 150 mg doses are supplied as single injections of 1 mL each.

Atacicept is manufactured by a suitable contract manufacturer; packaged, labeled and distributed for clinical trials by a suitable service provider and finally released by Merck KGaA under Good Manufacturing Practice (GMP) conditions.

Placebo will be supplied as a transparent, sterilized solution for injection in pre-filled syringes matching the atacicept pre-filled syringes, each containing 1 mL. The formulation contains trehalose and 10 mM sodium acetate buffer (pH 5). The placebo will be packaged, labeled, and distributed for this trial by a suitable service provider and finally released by Merck KGaA under GMP conditions.

6.2 Dosage and Administration

Participants of this Phase IIb trial will receive atacicept 75 mg or 150 mg or placebo as weekly SC injections of 1 mL.

Table 6-1 summarizes the administration of IMP in the trial.

Table 6-1 IMP Administration

Treatment	Number of Subjects	Administration	Duration	Dosing Instruction
Atacicept 75 mg	93	Weekly	24 weeks	1 mL of solution will be injected SC using pre-filled syringes
Atacicept 150 mg	93	Weekly	24 weeks	1 mL of solution will be injected SC using pre-filled syringes
Matching placebo	93	Weekly	24 weeks	1 mL of solution will be injected SC using pre-filled syringes

The IMP must be injected subcutaneously 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 as noted in the subject diary. All injection sites will be documented and evaluated in a standardized manner using the subject-recorded injection site diary and the injection site assessment worksheet. 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 when the first treatment kits are dispensed. The first dose (on Day 1) will be given at the trial 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. Training of subjects (or a caregiver) on self-injection will be provided on Day 1 and can be repeated at Week 1 or at

additional visits as required per investigator opinion (see Section 7.1.2.1). When dosing during the week of a scheduled visit, it is expected the patient 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 subset 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.

6.3 Assignment to Treatment Groups

Eligible subjects will be randomized through a central randomization process by the IWRS to receive atacicept 75 mg or 150 mg, or placebo in a 1:1:1 ratio prior to dosing on Day 1. Randomization to treatment arm will be stratified by the following baseline factors: SLEDAI-2K total score (<10 vs. ≥10), race (black vs. other), and mycophenolate use at screening (yes vs. no).

Treatment kits will contain enough medication for 4 administrations. At each visit when trial medication is dispensed, the trial staff will contact the IWRS to obtain appropriate kit numbers and the specified kits will then be dispensed.

All sponsor and CRO trial staff will be blinded to the trial group assignment. The DSMB and an independent third party statistician will be unblinded as described in the DSMB charter.

6.4 Other Drugs to be used in the Trial

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.

6.4.1 Rescue Medication During the Treatment Period

See Section 6.5.1 for permitted medications during the treatment period. The sponsor will not provide any rescue, permitted or concomitant medications during the trial.

Rescue medications to mitigate local effects of IMP which have occurred at the administration site (e.g., injection site reactions [ISRs]) are allowed as treatment. These may include topical or systemic antihistamines, topical corticosteroids, paracetamol, or NSAIDs. Subjects with concomitant severe hypogammaglobulinemia and infection can be considered for treatment with Ig supplementation. Treatment for severe SLE flares leading to discontinuation of IMP should be treated according to the local SoC. Any medications used should be recorded in the eCRF.

6.4.2 Rescue Medication During the Safety Follow-up Period

Subjects will be treated according to the appropriate SoC medications during the safety follow-up period per investigator opinion. If possible, it is preferable that the initiation of

immunosuppressives/immunomodulators and/or biologics be avoided during the first 12 weeks (approximately 5 half-lives of study drug) of the follow-up period (according to the discretion of the investigator).

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, i.e., up until the time at which they provide informed consent.

Concomitant medication is defined as any medication, other than the trial medication, which is taken during the trial from the time the subject enters the screening visit until the end of trial visit (FU Week 24) or Week 24 /ET, i.e., the last visit for the subject, including prescription and over-the-counter medicines. All concomitant medications taken while the subject is participating in the trial will be recorded on the eCRF.

6.5.1 Permitted Medicines

See Section 6.4 for rescue medications.

Permitted medications (including rescue medications) are any medications required per the medical history and not specifically prohibited by the protocol during the trial (i.e., from screening to the end of the 24-week treatment period) (see Section 6.5.2). Any such medications prescribed or used should be recorded in the eCRF.

Background SLE therapies

The SoC therapy that is allowed to be continued during the study for SLE includes use of one of the following single immunosuppressants or immunomodulators: azathioprine (up to 2.5 mg/kg/day), 6-mercaptopurine (up to 1.5 mg/kg/day), mycophenolate (either as MMF at up to 3 g/day or MPS up to 2160 mg/day), methotrexate (up to 25 mg/week), sulfasalazine (up to 3 g/day) or leflunomide (up to 20 mg/day). Other permitted SoC therapies include antimalarials such as hydroxycholoroquine, quinacrine and chloroquine as well as CS and NSAIDs. Although it is expected subjects will be on SoC medications, not all therapies are permitted, e.g., cyclophosphamide, thalidomide, and chlorambucil (see Section 6.5.2).

All background therapy for SLE given prior to screening must have been kept stable or discontinued according to the specifications in the exclusion criteria for a subject to be eligible for the study. These medications (i.e., single immunosuppressant/immunomodulator and/or antimalarials, if used) must remain stable during the screening period as well as the 24-week treatment period, with the exception of CS and NSAIDs which can be adjusted as long as doses are consistent with allowed levels as indicated below. Background therapy may only be changed for documented safety issues. Initiation of any new immunosuppressant or immunomodulator therapy would be considered a treatment failure and should result in withdrawal of the subject from the IMP (see Section 5.5.2). The SoC medications are part of the subject's previous SLE treatment and thus will not be provided by the sponsor.

Additional treatments commonly given to subjects with SLE are permitted during the trial as follows:

- Vitamin D (≥400 IU/day) and calcium supplementation (≥800 mg/day) is encouraged per local SoC guidelines. Subjects not already taking these medications at screening should, according to the investigator's judgement, initiate treatment as soon as possible after screening. These medications will not be supplied by the sponsor.
- Subjects taking an NSAID (including COX-2 inhibitors) for SLE symptoms at randomization can continue to do so throughout the trial. Subjects may have the dose adjusted during the trial. These changes should be recorded in the diary cards. The NSAIDs should not be used above the maximum allowable doses and site should perform regular AE monitoring of these concomitant medications. NSAIDs may not be initiated during the 24-week treatment period.
- Low-dose aspirin (≤350 mg/day) for cardiovascular prophylaxis.
- Paracetamol (acetaminophen) up to 3 g/day may be initiated or continued for pain control of SLE symptoms during the study. This should be titrated off as tolerated.
- Opioids are permitted for stable use for SLE if initiated by Day 1. Initiation of opioids and/or prn (as needed) dosing of opioids after Day 1 for SLE is not permitted. These may be titrated off as tolerated during the study.
- Analgesics, including opiates, may be used at stable doses or prn for temporary relief of symptoms not due to SLE, but then are strongly recommended to be avoided 24 hours prior to each trial visit.
- It is recommended that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers if used at screening be maintained at a stable dose during the trial as subjects with certain degrees of LN (up to 2 g daily proteinuria) will be permitted into the study and the proteinuria will be followed, unless dose change or initiation is required for safety reasons.
- Medications for the treatment of ISRs (see Section 6.4.1).

Any medications (other than those excluded by the CTP) that are considered necessary for the subjects' welfare and will not interfere with the trial medication may be given at the investigator's discretion.

Corticosteroids

Corticosteroid dose above 40 mg/day prednisone-equivalent is excluded.

Investigators are encouraged to decrease the oral CS dose as much as tolerated by the subject up until Week 16 of the treatment period, within the rules for dose changes outlined below. There is no minimum CS dose required during the trial.

Rules regarding the use of oral CS during the study are provided below. Doses given are for a total daily dose of prednisone or prednisolone; CS other than prednisone/prednisolone may be used instead orally at the equivalent doses (Table 6-2):

Table 6-2 Prednisone Equivalence Calculation

Medication	Equivalent (mg) to 1 mg of Prednisone
Betamethasone	0.15
Cortisone	5
Dexamethasone	0.15
Hydrocortisone	4
Prednisolone	1
Methylprednisone	0.8
Triamcinolone	0.8

1. **Oral corticosteroid changes:**

   Screening visit to Week 4 (Visit 6):
   Corticosteroids may be initiated during this time, increased or decreased. The initiated or increased dose should not be higher than 40 mg/day.

   At Week 4, the dose has to be ≤30 mg/day. The dose must also be ≤screening visit dose; however, subjects taking <7.5 mg/day at Day 1 (Week 0) can have a dose of up to 7.5 mg/day at Week 4.

   Weeks 5-16:
   The CS dose must always be ≤Week 4 dose. However, subjects may have the CS dose increased 1 time for SLE activity. The dose can go up to 30 mg/day, but must be returned to ≤Week 4 dose within 7 days. A dose increase is strongly recommended not to be initiated within 1 week of a planned trial visit.

   Decreases in the CS dose from the Week 4 dose level should be performed as tolerated.

   Weeks 17-24:
   The CS dose must be maintained at the Week 16 dose. No increases or decreases are allowed.

2. **Non-systemic corticosteroids** (defined as optic, otic, topical, intranasal, inhaled, and ophthalmic):

   Screening to Week 24/ET
   There are no restrictions in dosing.

The investigator will record all concomitant medications taken by the subject during the trial, from the date of signature of informed consent, in the appropriate section of the eCRF, after recording them in the source documents.

Any additional concomitant therapy that becomes necessary during the trial 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 had pneumococcal vaccination and seasonal flu vaccine no later than the screening visit to be eligible to participate in the study as per Section 5.3. In addition, it is strongly recommended that investigators review the subject's vaccine status, and ensure they are up to date with vaccinations as per local guidelines. Live vaccinations will not be permitted as per Section 5.3 and Section 6.5.2.

6.5.2 Non-permitted Medicines

The following treatments and therapies are not permitted during the trial:

- Treatment with preparations from herbal plants.
- Use of cyclophosphamide, thalidomide, or chlorambucil (alkylating agents), tacrolimus, cyclosporine or other immunosuppressant or immunomodulator therapies not listed in Section 6.5.1.
- Use of more than one immunosuppressant therapy at any time (see Section 6.5.1).
- Biologic therapies other than IMP.
- Ig therapy, plasmapheresis, or Prosorba.
- Bone marrow transplant.
- Vaccines: Live and live-attenuated vaccines are prohibited within 1 month before screening or during the trial period. The effect of atacicept on the ability of the immune system to clear an infection has not been fully evaluated in humans.
- Use of medications not permitted as mentioned in Section 6.5.1.

Any additional concomitant therapy that becomes necessary during the trial 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.

Refer to the inclusion and exclusion criteria (Section 5.3) for prohibited medications before and during the trial. See also Section 5.5.2.

6.5.3 Other Trial Considerations

Subjects within this trial must follow the following restrictions:

- Women of childbearing potential must be willing to use a form of highly effective contraception, during the trial, and for 2 months (60 days) after the last dose of IMP.

Other therapies

Use of potentially excluded procedures such as acupuncture or joint replacement therapy is to be discussed with the sponsor or designee on a case-by-case basis. Use of acupuncture is allowed to continue if it is started before the screening visit. Major planned surgeries such as abdominal, thoracic or joint replacement surgeries are exclusionary. Unplanned joint replacement surgery should be discussed in advance with the medical monitor regarding continuation of the subject in the study.

6.5.4 Special Precautions

Subjects with SLE are more susceptible to infections (bacterial, viral, fungal). In addition, the use of corticosteroids and immunosuppressives further increase the risk of infection in subjects with SLE. Atacicept, a biologic therapy, has an increase in trend of infection when administered to SLE subjects. Therefore, certain precautions should be taken by subjects participating in the trial. As described in Section 3.5 and Section 3.6, given the safety outcomes of previous SLE and LN studies, risk mitigation strategies must be employed in order to improve subject safety.

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 laboratory findings raise concern, in the opinion of the investigator, that there may be ongoing subclinical or chronic infection, this constitutes an exclusion criterion for participation as per Section 5.3.2. 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 due to the combination of atacicept and immunosuppressives, safety visits including IgG assessments at Weeks 1 and 2 are planned. This will allow early detection of such a potential drop.

In addition, subjects should be consistently reminded of the importance of good hygiene practices such as hand washing for their care providers and/or social contacts, especially if they are suffering from upper respiratory illness symptoms. They should be advised to avoid contact with infectious persons. It is recommended they be vaccinated according to local recommendations for individuals with a chronic disease and/or immunosuppression. They should be advised to promptly report to the investigator any signs or symptoms suggestive of an infection.

During the trial, investigators must routinely inquire by weekly monitoring telephone calls about possible infectious symptoms and should examine subjects for possible infections at scheduled visits, and unscheduled visits as appropriate. Any subject who experiences a serious and/or severe, or chronic or recurrent significant infections should be re-evaluated as to whether or not continued treatment with atacicept is appropriate.

Hypersensitivity

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 as per Section 6.4.1.

Cardiac

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 paroxysmal atrial tachycardial, atrial fibrillation, conduction disturbance, long QT syndrome, Wolff-Parkinson-White syndrome or a malignant ventricular arrhythmia, e.g., ventricular fibrillation or tachycardia) 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.

Other withdrawal criteria

Any subject who develops new onset of neurological symptoms or signs that are suggestive of a demyelinating process (such as but not limited to MS, optic neuritis or transverse myelitis) should stop dosing of IMP.

6.6 Packaging and Labeling

Atacicept and placebo will be supplied to the investigational site in pre-filled 1 mL glass syringes with 29 gauge needles.

Atacicept and placebo will be packed in boxes containing 4 pre-filled 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.

Atacicept and placebo will be shipped in cool transport containers that are monitored with temperature control devices.

All subjects will be issued subject cards at the time of randomization. The cards will include at least the following information:

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

Packaging and labeling will be in accordance with applicable local regulatory requirements and applicable GMP guidelines, and to protect the blinded nature of the trial. The labeling will not indicate whether the medication is atacicept or placebo.

6.7 Preparation, Handling and Storage

All IMP (atacicept and matching placebo) is provided in pre-filled syringes to the site via cooled transport. No additional preparation will be required at the site.

All IMP supplied to each site must be stored carefully, safely, and separately from other drugs in their original containers. The storage facility at the trial site should be locked and temperature-controlled. The IMP **has to 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.

Subjects or family members/caregivers who receive appropriate training will be permitted to administer medication in this trial. To ensure compliance with recommended storage conditions, all subjects will be provided with cooler bags to transport the IMP back home. Subjects will be provided instructions on proper storage, including instructions to store their study treatment 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, e.g., inside a car. Subjects should have access to refrigeration to store the IMP.

Atacicept and placebo should NOT be frozen.

In case there has been a temperature deviation at the clinical site, the site must contact the clinical research associate without delay for further evaluation and assessment by the designated quality assurance (QA) personnel at Merck KGaA. The medication 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”.

The IMP syringes should be removed from the refrigerator and it is suggested to keep it 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 described in the drug administration instructions and provided to subjects as required for home injection.

Atacicept should not be administered after the date of expiration indicated on the product packaging.

6.8 Investigational Medicinal Product Accountability

The investigator is responsible for ensuring accountability for IMP, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of IMP, the investigator (or designee) will check for accurate delivery and acknowledge receipt either by signing (or initialing) and dating the documentation provided

by the sponsor/designee and returning it to the sponsor/designee or by using an appropriate IWRS module. A copy will be retained for the investigator file.

- The dispensing of the IMP will be carefully recorded on the appropriate drug accountability forms provided and an accurate accounting will be available for verification by the responsible monitor at each monitoring visit.
- IMP accountability records will include:
  - Confirmation of IMP delivery to the trial site.
  - The inventory at the site of IMP provided by the sponsor.
  - The use of each dose by each subject.
  - Disposal of unused IMP (unused product will not be returned to the sponsor).
  - Dates, quantities, batch numbers, expiry dates and formulation, as well as the subjects' trial numbers.
- The investigator should maintain records that adequately document:
  - Subjects were provided the doses specified by the CTP/amendment(s).
  - All IMP provided by the sponsor was fully reconciled.
  - Any discrepancies with a written explanation.

Unused IMP and its boxes must not be used for any purpose other than the present trial. Any IMP that has been dispensed to a subject must not be re-dispensed 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.

The responsible monitor or designee will periodically review the IMP accountability forms and will check all unused syringes and used syringe boxes and sharps containers before authorizing their destruction by the trial site. Sites should destroy syringes used for in-clinic dosing per institutional procedure after approval by the responsible monitor.

6.9 Assessment of Investigational Medicinal Product Compliance

The IMP will be administered at the site on visits defined in Appendix A. All other dosing will be done by the subject or subject's caregiver at home throughout the rest of the trial. Prior to discharge from each scheduled site visit, subjects will be given sufficient IMP for at-home dosing until the next scheduled visit. Information on the time and date of each dose will be recorded by the subject in the subject-recorded injection site diary for at-home dosing and by the trial staff in the injection site assessment worksheets for on-site dosing and on the eCRF pages. Subjects will be instructed to return all unused IMP including the boxes and their subject-recorded injection site diaries at each clinic visit, in order to allow the assessment of compliance with trial treatment.

6.10 Method of Blinding

This trial will be double-blinded.

Packaging and labeling will be prepared to protect the blinded nature of the trial. Trial 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 prevent subjects and trial personnel from noticing any differences in the colors of the solutions of atacicept vs. placebo. 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 as described in Section 6.3.

If at any time during this trial, any specified personnel will be unblinded to the treatment code for any reason, the circumstances and reason must be documented. All sponsor and CRO trial staff will be blinded to the trial group assignment. The DSMB and an independent third party statistician will be unblinded as described in the DSMB charter.

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: total Ig (IgA, IgM, and IgG), autoantibodies (anti-dsDNA, ANA, Anti-Sm, anti-RNP, anti La, anti-Ro, RF, anticardiolipin, lupus anticoagulant panels, and vaccine immunization), and flow cytometry (B-cell levels). If the investigator considers it necessary to have any of the above results for acute medical management of the subject after Day 1, then this should be discussed with the medical monitor. It should be noted that in the presence of atacicept, the clinical utility of monitoring anti-dsDNA levels can be greatly diminished due to the significant drop in levels as a consequence of the its PD effects. Lymphocyte counts as assessed by routine complete blood counts will not be blinded; these results are not anticipated to reveal PD effects, since B lymphocytes represent a small proportion of total lymphocytes (5%-20%).

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 Ig can be considered in situations of severe hypogammaglobulinemia (e.g., serum IgG <3 g/L) associated with infection.

The trial blind 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 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 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). 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. 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 trial and go into safety follow up. These subjects will also complete all assessments and procedures specified for the ET visit before entering the safety follow-up period.

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

If a serious adverse event (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 DSMB will have access to unblinded trial 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 trial 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 trial.

6.12 Treatment of Overdose

An overdose is defined as receiving more than one dose equivalent within ≤4 days. Any overdose must be recorded in the trial medication section of the eCRF.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the sponsor's Global Drug Safety department or designee in an expedited manner using the appropriate reporting form (see Section 7.4.1.4).

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 Trial

After a subject has completed the trial through the safety follow-up period or has withdrawn early, standard treatment should be administered, if required, in accordance with the trial site's SoC and generally accepted medical practice and depending on the subject's individual medical needs.

Subjects who complete the 24-week treatment period will be offered participation in the LTE trial (see Section 5.1). This LTE trial will be conducted under a separate CTP. It is expected that the placebo arm of the ADDRESS II trial will be switched over to the 150 mg dose of atacicept while the subjects in the treatment arms will remain on their original respective doses of atacicept when enrolled in the LTE.

7 Trial Procedures and Assessments

Prior to performing any trial 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 subject's enrollment in the trial.

The following procedures should be done in the following order: health-related QoL assessments or PROs (subject self-assessments), vital signs, ECG (if scheduled), PK sampling (if scheduled), collection of laboratory samples, and other trial assessments.

Subjects should complete subject self-assessments (e.g., subject-reported disease activity assessments in diary cards, SF-36, EQ-5D, LupusQoL, PGIC and FACIT-Fatigue) before other trial assessments and administration of trial medication.

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

On days when PK assessments are scheduled to occur on the same day as trial medication, the trial medication must be administered AFTER collection of samples for PK analysis. All PK samples, except at Day 2 and Week 23 Day 2 (Day 163) (see Appendix A), must be taken within 25 hours prior to dosing, i.e., 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 Week 23 Day 2 are collected 24 hours following atacicept administration (i.e., 24 hours post-first dose on Day 1 and 24 hours post-dose on Week 23 Day 1). In exceptional cases, on Day 2, Week 1 and Week 23 Day 2, the visits and blood sampling can be omitted if there are major logistical hurdles for the subject to attend this visit.

For each IMP dose, the date and time of administration and whether the full dose was administered will be entered on the subject diary card.

Unscheduled visits may occur at any time during the trial in case of suspected flares or AEs (assessments to be performed according to the investigator's judgement).

7.1 Schedule of Assessments

7.1.1 Screening Visit

The subjects' eligibility will be assessed at a screening visit that will occur up to at most 4 weeks (28 days) of the randomization visit (Day 1). Demographic data such as date of birth, ethnic origin, gender, weight, height, and body mass index (calculated by the eCRF) will be collected at screening.

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

- Obtain written informed consent prior to screening procedures.
- Obtain additional written informed consent if participating in the optional PGx sampling and/or PK substudy as necessary.
- Review inclusion and exclusion criteria.
- 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, tuberculosis, 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).
- Documentation of the criteria for SLE diagnosis according to the ACR Classification Criteria (at least 4 of the ACR criteria must have been present during the course of their illness) for eligibility and also the SLICC Classification Criteria.
- History and status of medications, surgeries and other procedures, with particular attention to current and previous treatments for SLE.
- Vital signs: seated systolic and diastolic blood pressure (BP), pulse rate, oral temperature, height and weight measurements (see Section 7.4.4.1 for details).
- Standard, single, 12-lead ECG (see Section 7.4.4.3).
- Complete physical examination.
- 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.
- Assessment of TB (performed locally).
- Disease activity assessments:
  - BILAG 2004.
  - SLEDAI-2K score.

- PGA.

- Perform and review C-SSRS questionnaire to assess the subject's suicide risk.
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis), serum virology, and PD analyses (see Table 7-1). The laboratory tests will include:
  - Urinalysis: urine protein, urine creatinine, GFR and urine sediments.
  - Serum pregnancy test (β-hCG) required only for WOCBP. Any woman with a positive pregnancy test will be ineligible for the trial. [**NOTE**: It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 2 years or who are surgically sterile.]

  PD analyses (see Section 7.8.2)
  - C3, C4, C4d, ANA and anti-dsDNA antibodies.
  - Total IgG.
  - Free BLyS and free APRIL levels.

  Other exploratory endpoints
  - Circulating proteins (see Section 7.9.1).
- AEs will be recorded after the informed consent form (ICF) has been signed.
- Review/record prior and concomitant medications, vaccinations, and therapies. Administer pneumococcal and seasonal injectable influenza virus vaccine, if needed.

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 will be reminded to fast (no food or drink other than water for 8 hours) before they return to the site for Day 1.

Diary cards will be dispensed to subjects at the screening visit. The information to be recorded on these cards will include AEs, concomitant medications or changes in medications and procedures. Diary cards will be collected at the visits specified in Appendix A.

Subjects who do not meet the screening criteria can be re-screened one additional time upon approval of the medical monitor (see Section 5.3.2).

7.1.2 Treatment Period

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

Subjects will remain on site for at least 2 hours after the first and second injection of atacicept (Day 1 and Week 1) to monitor for any hypersensitivity reactions. Subjects in the PK subgroup will remain on the site for at least 4 hours after the first injection of atacicept (Day 1) for the 4 hours postdose PK sampling.

Fasting and non-fasting blood samples will be collected for all subjects. Fasting blood samples will only be collected (to assess lipids) at Day 1, Week 12, and Week 24/ET. Subjects must have fasted (no food or drink other than water for 8 hours) before these 3 visits.

In subjects taking MMF or MPS, blood samples will be collected to measure MPA levels at Day 1, Week 12, and Week 24/ET. Subjects should have taken their last MMF or MPS dose at least 10 or more hours prior to the visit.

Scheduled site visits after Day 1 may take place within ±3 days of the protocol-specified day. PK samples taken as part of the PK substudy must be taken on the scheduled day and time.

Diary cards will be provided to the subjects on Day 1. The information to be recorded on these cards will include dosing, AEs, concomitant medications or changes in medications and procedures. Diary information should be collected in the same way for subjects who do and do not self-administer trial medication. Diary cards will be collected at the visits specified in Appendix A.

7.1.2.1 Randomization/First Administration of IMP (Day 1)

The following assessments will be conducted on Day 1. All subjects will report 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.

Fasting blood samples will be collected on Day 1. Subjects must have fasted (no food or drink other than water for 8 hours) prior to this visit. Subjects taking MMF/MPS must not have taken any within the last 10 hours.

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):

- Health-related QoL assessments by SF-36 (see Section 7.10.1.1), EQ-5D (see Section 7.10.1.5), LupusQoL (see Section 7.10.1.2) and FACIT-Fatigue (see Section 7.10.1.4) evaluations. These should be completed before any other procedures are performed.
- Vital signs (BP, pulse rate, oral temperature), and weight measurements (see Section 7.4.4.1 for details).
- Standard, single, 12-lead ECG (see Section 7.4.4.3).
- Review inclusion and exclusion criteria.
- Complete physical examination.
- Review prior and concomitant medications and therapies.

- Record AEs.
- Disease activity assessments:
  - BILAG 2004.
  - SLEDAI-2K.
  - PGA.
  - SRI-50.
- Assessment of SLICC/ACR Damage Index score.
- Collect blood and urine samples for routine laboratory tests (clinical chemistry, hematology, and urinalysis) and PD analyses (see Table 7-1). The laboratory tests will include:
  - Urinalysis: urine protein, urine creatinine, GFR, urine sediments and urine protein electrophoresis (UPEP).
  - 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.
  - Coombs test.
  - Anti-atacicept antibodies (binding and neutralizing) (see Section 7.7).
  - Lipid levels: Fasting blood samples will be collected after an 8-hour fast (water will be allowed). This visit should take place in the morning (see Section 7.4.4.5).
  - MPA levels (for subjects taking MMF/MPS only) (see Section 7.4.4.6). Subjects should have taken their last MMF dose at least 10 or more hours prior to the visit.

  PK (see Section 7.6.1)
  - 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.

  PD analyses (see Section 7.8.2)
  - Blood samples will be collected to assess free BLyS and free APRIL **prior to the first dose** of IMP (predose).
  - Vaccine immunization status: antibody titers to tetanus toxoid, diphtheria toxoid, and selected pneumococcal antigens (see Section 7.8.1).
  - CRP.
  - C3, C4, C4d, ANA and anti-dsDNA antibodies.
  - Total Ig, IgG, IgA, and IgM.
  - Anti-Sm, anti-RNP, anti-La and anti-Ro antibodies, and rheumatoid factor (RF).
  - Anticardiolipin and lupus anticoagulant panels.
  - Flow cytometry analyses in peripheral blood (see Section 7.8.2) (at selected sites only).

Exploratory endpoints

- Circulating proteins (see Section 7.9.1).
- Gene expression/pharmacogenomics profiling (RNA) (see Section 7.9.2).
- PGx sampling for genotyping (optional): At Day 1, a 4-mL sample of blood will be collected from the subject. However, the blood sample may be collected anytime after a subject has provided PGx consent to participate, and the subject is found to be eligible for the trial.

- Instruct/review with subject (or caregiver) the trial requirements and how to self-administer SC injection.

Randomization

Eligible subjects will be randomized to 1 of 3 treatment groups by the IWRS. Subjects will receive 24 weeks of IMP treatment from Days 1 to 169 and be treated as outpatients during the trial.

Treatment with IMP (first dose)

Qualified site personnel will provide the appropriate training in injection technique, and will verify that the subject's or caregiver's administration technique is satisfactory. Thereafter, subjects or caregivers will be permitted to administer the IMP at home. Training of subjects (or a caregiver) on self-injection will be provided on Day 1 and can be repeated at Week 1 or at additional visits as required per investigator 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 health care personnel as the site staff deems appropriate).

- The trial staff will instruct the subject (or caregiver) in proper technique of SC administration and demonstrate it by administering the allocated IMP to the subject via SC injection.
- The trial staff will record the exact time and location of dosing and monitor the following:
  - The trial staff will monitor and record ISRs (local tolerability) (see Section 7.4.4.4).
  - The trial staff will monitor and record 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 Sections 6.4.1 and 7.4.4.7).

PK sampling (post-first dose)

- If participating in the PK sampling subset (see Section 7.5), blood samples will be collected only for PK analysis at the following time points after dosing: 4 hours post-first dose and 24 hours post-first dose. The subject can be registered to this subset 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 subject may leave the site once the following procedures have been completed:

- Collect and review daily dairy cards.
- Provide subjects with daily diary cards for up until the next visit and instruct subjects (or caregivers) to record the date, time, location of administration of each subsequent dose of IMP and whether the full dose was administered, and any ISRs.
- Provide subjects with emergency contact numbers.

7.1.2.2 Weeks 0 (Day 2) to 24 (Day 169)

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

- Week 0 (Day 2) (only for subjects in the PK subset).
- Week 1 (Day 8±3).
- Week 2 (Day 15±3).
- Week 4 (Day 29±3).
- Week 8 (Day 57±3). Subjects will be reminded to fast (no food or drink other than water for 8 hours) before their next site visit at Week 12.
- Week 12 (Day 85±3). Subjects must have fasted (no food or drink other than water for 8 hours) before the Week 12 visit.
- Week 16 (Day 113±3).
- Week 20 (Day 141±3). Subjects will be reminded to fast (no food or drink other than water for 8 hours) before their next site visit at Week 24.
- Week 23 Day 2 (Day 163).
- Week 24 (Day 169±3) or ET visit. Subjects must have fasted (no food or drink other than water for 8 hours) before the Week 24/ET visit.

All visits should occur within the timeframe as stated above.

Unless otherwise indicated, the subject will return to the site at Day 2 (only for subjects in the PK subset) and Weeks 1, 2, 4, 8, 12, 16, 20, Week 23 Day 2, and Week 24, and the following procedures will be performed:

Predose Assessments

- Health related QoL assessments (these should be completed before any other procedures are performed at the relevant visits):

  - SF-36, PGIC, EQ-5D, LupusQoL and FACIT-Fatigue (**Weeks 4, 8, 12, 16, 20 and 24 only**).
- Vital signs (BP, pulse rate, and oral temperature) and weight measurements (see Section 7.4.4.1 for details) (**except at Day 2 and Week 23 Day 2**).
- Complete physical examination (**Week 24 only**).
- Complaint-driven physical examination (see Section 7.4.4.2 for details) (**Weeks 1, 2, 4, 8, 12, 16 and 20 only**).
- Review prior and concomitant medications and therapies.
- AEs will be recorded throughout the study.
- Standard, single, 12-lead ECG (central reader; see Section 7.4.4.3) (**Weeks 4 and 24 only**).
- Disease activity assessments:
  - BILAG 2004 (see Section 7.3.1), SLEDAI-2K (see Section 7.3.2), SRI-50 (see Section 7.3.3) and PGA (see Section 7.3.4) (**Weeks 4, 8, 12, 16, 20 and 24 only**).
- Assessment of SLICC/ACR Damage Index score (**Week 24 only**).
- Blood and urine samples will be collected for routine laboratory tests (clinical chemistry, hematology, and urinalysis) (see Table 7-1) (**except at Day 2, Week 1 and Week 23 Day 2**). The laboratory tests will include:
  - Urinalysis: urine protein, urine creatinine, GFR, and urine sediments.
  - UPEP (**Day 1 and Week 24 only**).
  - Coombs test (**Weeks 4, 8, 12, 16, 20 and 24 only**).
  - Anti-atacicept antibodies (binding and neutralizing) (**Weeks 12 and 24 only**) (see Section 7.7).
  - Urine pregnancy test for all WOCBP (**except at Day 2, Week 2 and Week 23 Day 2**). A serum pregnancy will be done if the urine test is positive.
  - Lipid levels: Fasting blood samples will be collected after an 8-hour fast (water will be allowed). This visit should take place in the morning (see Section 7.4.4.5) **(Weeks 12 and 24 only)**. Subjects should be reminded to come fasting for these visits.
  - MPA levels (for subjects taking MMF/MPS only) (see Section 7.4.4.6) **(Weeks 12 and 24 only)**. Subjects should be reminded that they should have taken their last MMF dose at least 10 or more hours prior to these visits.

  PD analyses

  - Vaccine immunization status: antibody titers to tetanus toxoid, diphtheria toxoid, and pneumococcal antigens (see Section 7.8.1) (**Week 24 only**).
  - CRP (**Weeks 2, 4, 8, 12 and 24 only**).
  - IgG (**Weeks 1, 2, 4, 8, 12, 16, 20 and 24 only**)

- Total Ig, IgA, IgM, C3, C4 and C4d (**Weeks 2, 4, 8, 12, 16, 20 and 24 only**).
- ANA and anti-dsDNA antibodies (**Weeks 4, 8, 12, 16, 20 and 24 only**).
- Anti-Sm, anti-RNP, anti-La and anti-Ro antibodies, and RF **(Weeks 12 and 24 only)**.
- Anticardiolipin and lupus anticoagulant **(Weeks 12 and 24 only)**.
- Flow cytometry analysis (see Section 7.8.2) **(Weeks 2 [for subjects who are in the PK substudy only], 4, 12 and 24 only)**.
- Blood samples will be collected **within 25 hours before the next scheduled dose of IMP** to assess free BLyS and free APRIL (**Weeks 4 and 12 only**). At Week 24, where analysis of BLyS and APRIL is planned, blood samples will be collected (exact time and date to be recorded). The IMP will not be administered at this visit.

Exploratory endpoints

- Circulating proteins (see Section 7.9.1) (**Weeks 4, 12 and 24 only**).
- Gene expression/pharmacogenomics profiling (**Weeks 4, 12 and 24 only**) (see Section 7.9.2).

PK blood sampling (see Section 7.5)

- Blood sample will be collected **within 25 hours before the next scheduled dose of IMP** to assess trough levels of serum atacicept (**Weeks 2, 4, 8, 12, 16 and 20)**. An additional blood sample to assess PK will be collected at **Week 24**. The exact time and date of blood sampling should be recorded.
- If participating in the PK sampling subset, a blood sample will be collected only for PK analysis at the following visits: **Day 2 (24 hours post-first dose), Week 1 (within 25 hours before the next scheduled dose) and Week 23 Day 2 (24 hours post-last dose**). The subject can be registered to this subset analysis through the IWRS (this will be done during the randomization process).

  At Day 2 and Week 23 Day 2 only: Samples will be collected near peak levels 24 hours after the first (Day 1) and last (Week 23 Day 1) administration of atacicept.

Treatment with IMP **(Weeks 1, 2, 4, 8, 12, 16 and 20 only)**

- 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 trial staff.
- The trial staff will record the exact time and location of dosing and monitor the following:
  - The trial staff will monitor and record ISRs (local tolerability) (see Section 7.4.4.4). This will be monitored continuously throughout the treatment period (**Weeks 0 to 24**).
  - If hypersensitivity reaction occurs at any time, treat subject symptomatically (see Section 7.4.4.7).

During the trial, regular monitoring for early symptoms of infection or cardiac ischemia will be conducted weekly and will be continuous throughout the trial (Weeks 0 to 24 of the safety FU visit). This will be done by telephone during the weeks the subject is not scheduled to return for a site visit.

Completion of All Site Visits

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 (**Weeks 4, 8, 12, 16, 20 and 24 only)**.
- Dispense IMP (**Weeks 2, 4, 8, 12, 16 and 20 only)** 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.
- Collect and review subject daily diary card (**Weeks 1, 2, 4, 8, 12, 16, 20 and 24 only)**. Return diary card to subject at Weeks 1 and 2.
- Dispense subject daily diary card and instruct subjects (or caregivers) to record the date, time, and location of each subsequent dose of IMP (**Weeks 4, 8, 12, 16, 20 and 24 only)**.

At each trial visit, the 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.

7.1.3 Early Termination (Week 24)

Criteria for discontinuation are provided in Section 5.5.

Subjects who discontinue early from the trial prior to completing 24 weeks of treatment will complete the end of treatment assessments planned for Week 24 within 5 days after discontinuation (see Section 7.1.2.2). Safety follow-up visits will be scheduled for these subjects after the last dose of IMP (see Section 7.1.4).

7.1.4 Safety Follow-up Visits (FU Weeks 4, 12 and 24)

Subjects who stop treatment prematurely and those who complete the 24-week treatment period (but do not enter the LTE trial) will have 3 safety follow-up visits, which are scheduled to take place approximately 4 weeks (FU Week 4), 12 weeks (FU Week 12) and 24 weeks (FU Week 24) (±5 days) after the last dose of IMP.

At the follow-up visits, the following assessments will be performed (see Appendix A), except where indicated otherwise. Where possible, the investigator should schedule these visits to take place in the morning.

- Vital signs (BP, pulse rate, oral temperature) (see Section 7.4.4 for details).
- Complaint-driven physical examination, including weight (see Section 7.4.4.2 for details).
- Disease activity assessments: BILAG 2004, SLEDAI-2K, SRI-50 and PGA.
- Blood and urine samples will be collected for routine laboratory tests (clinical chemistry, hematology, and urinalysis) as detailed in Table 7-1. The laboratory tests will include:
  - Urinalysis: urine protein, urine creatinine, GFR and urine sediments.
  - Urine pregnancy test for all WOCBP.
  - Coombs test.
  - Anti-atacicept antibodies (binding and neutralizing) (**FU Weeks 12 and 24 only**) (see Section 7.7).
  - Lipid levels (see Section 7.4.4.5) (**FU Week 12 only**): Fasting blood samples will be collected after an 8-hour fast (water will be allowed). This visit should take place in the morning.
- Blood samples will be collected for PK analysis of serum atacicept levels.
- Blood samples will be collected for the following PD analyses:
  - Measurement of free BLyS and free APRIL.
  - Vaccine immunization status: antibody titers to tetanus toxoid, diphtheria toxoid, and pneumococcal antigens (see Section 7.8.1) (**FU Week 24 only**).
  - CRP.
  - Total Ig, IgG, IgA, IgM, C3, C4 and C4d.
  - ANA and anti-dsDNA antibodies (**FU Week 12 only**).
  - Anti-Sm, anti-RNP, anti-La and anti-Ro antibodies, and RF (**FU Week 12 only**).
  - Anticardiolipin and lupus anticoagulant panels (**FU Week 12 only**).
  - Flow cytometry analysis (see Section 7.8.2) (**FU Week 24 only**).

Exploratory analyses

- Circulating proteins (see Section 7.9.1) (**FU Week 24 only**).
- Gene expression/pharmacogenomics profiling (RNA) (see Section 7.9.2) (**FU Week 24 only**).
- Dispense subject daily diary card (**FU Weeks 4 and 12 only**).
- Collect and review subject daily diary card.

Regular monitoring for early symptoms of infection or cardiac ischemia will be conducted weekly and will be continuous throughout the safety follow-up period (Week 24 through FU Week 24). This will be done by telephone during the weeks the subject is not scheduled to return for a site visit.

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 including neurological assessment and serology will be performed.

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

7.3 Assessment of Efficacy

Efficacy will be evaluated using the instruments and outcomes described below and at the visits specified in Appendix A in accordance with recommendations for outcome measures in SLE trials which suggest assessment of current disease activity, permanent damage and health-related QoL, ideally using an instrument sensitive to fatigue.

All data collection and all query handling will be done via an eCRF system. An electronic device (ePRO system) will be used to collect the following PRO questionnaires: LupusQoL, SF-36, EQ-5D, PGIC, and FACIT-Fatigue.

7.3.1 BILAG 2004

The BILAG 2004 Disease Activity Index evaluates SLE activity in a number of organ systems, based on the principle of "physician's intention to treat" (see Manual of Procedures). The primary purpose of the BILAG in this trial is to assess possible worsening in specific organ systems. Additional analyses of improvements in disease activity as assessed by the BILAG 2004 will also be done.

A separate alphabetic score is assigned to each organ system, corresponding in general to the following definitions:

BILAG A: Severe disease activity requiring any of the following treatments (e.g., systemic high dose oral CS, intravenous pulse CS, systemic immunosuppressants, or therapeutic high dose anticoagulation in the presence of high dose CS or ≥20 mg prednisone). Note that in the context of a clinical trial protocol with medication restrictions and blinded study drug, the term "requiring" is not taken literally, but indicates that if all else were equal this would be the degree of treatment indicated. It is also understood that some patients respond to different levels of medication than others, so that in assessing patients with the BILAG "intent to treat" really

means that most patients with this degree of symptom would require this level of treatment, not necessarily the patient in question.

BILAG B: Moderate disease activity requiring treatment with systemic low dose oral glucocorticoids, intramuscular or intra-articular or soft tissue CS injection, topical CS or immunosuppressants, or symptomatic therapy such as antimalarials or NSAIDs.

BILAG C: Mild disease.

BILAG D: System previously affected but now inactive.

BILAG E: System never involved.

The BILAG 2004 is evaluated by scoring each of a list of signs and symptoms as: improving (1); same (2); worse (3); new (4); not present (0); not done (ND). For some items, appropriate responses may be: Y/N or numerical values where indicated or Y/N Confirm this is due to SLE activity.

All signs and symptoms scored must be due to SLE. Use of a glossary provided with the BILAG 2004 instrument and training of assessors in use of the instrument are essential to obtaining reliable and consistent results.

Use of the BILAG 2004 index for evaluating flares has been identified as a robust way of evaluating the efficacy of drugs; this judgement has been corroborated by external advisors and regulatory authorities.

BILAG assessments should be conducted by a trained evaluator.

A copy of the BILAG 2004 and glossary is provided in the Manual of Procedures.

7.3.2 SLEDAI-2K

The SLEDAI-2K is a reliable, valid, simple, 1-page activity index that measures disease activity and records features of active lupus as present or not present [24]. It is a modification of the SLEDAI to reflect persistent, active disease in those descriptors that had previously only considered new or recurrent occurrences. The SLEDAI-2K has been validated against the SLEDAI which has been shown to be reliable at different levels of disease activity [26, 27].

The SLEDAI-2K uses a weighted checklist to assign a numerical score based on the presence or absence of 24 symptoms at the time of assessment or during the previous 10 days. Each symptom present is assigned between 1 and 8 points based on its usual clinical importance, yielding a total score that ranges from 0 points (no symptoms) to 105 points (presence of all defined symptoms). However, if scored correctly, it is rare for even the sickest patients to score more than 20 points. The assessor is also requested to assess the subject's symptoms using the VAS for the PGA (see Section 7.3.4).

The SELENA SLEDAI Flare Index (SFI) can be used with any version of the SLEDAI and will be used with the SLEDAI-2K in this trial.

A mild/moderate flare is defined as any of the following:

- Increase in SLEDAI instrument score of 3 points or more (but total score not to more than 12).
- New or worse discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus; or nasopharyngeal ulcers; or pleuritis; or pericarditis; or arthritis; or fever due to SLE.
- Increase in prednisone, but not to >0.5 mg/kg/day.
- Added NSAID or hydroxychloroquine (or chloroquine) for SLE activity.
- ≥1.0 increase in PGA score, but score not to more than 2.5.

A severe flare is defined as any of the following:

- Increase in SLEDAI instrument score leading to total score greater than 12.
- New or worse central nervous system SLE; or vasculitis; or nephritis; or myositis; or platelets <60,000/mm^3; or hemolytic anemia with hemoglobin <70 g/L or decrease in hemoglobin >30 g/L AND requiring: doubling prednisone, or prednisone increase to >0.5 mg/kg/day, or hospitalization due to SLE.
- Increase in prednisone to >0.5 mg/kg/day.
- New cyclophosphamide, azathioprine, methotrexate, or mycophenolate for SLE activity.
- Hospitalization for SLE activity.
- Increase in PGA score leading to total score >2.5.

The SLEDAI and SFI assessments should be conducted by a trained evaluator.

A copy of the SLEDAI-2K form is provided in the Manual of Procedures.

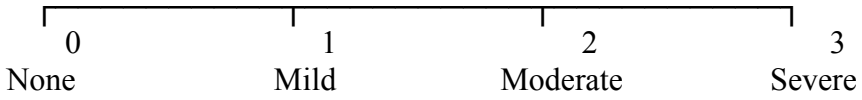
7.3.3 SLEDAI-2K Responder Index-50 (SRI-50)

The sensitivity of the SLEDAI-2K to clinical improvement can be limited because it cannot detect partial improvement in a disease manifestation. The SRI-50 index was derived from the SLEDAI-2K and can capture 50% or better improvement in each descriptor between any 2 visits in SLE patients when there is incomplete resolution. An extended definition for each of the original descriptors of SLEDAI-2K was created to set landmarks for 50% improvement. The new assigned scores for the descriptors of SRI-50 were derived by dividing the score of each SLEDAI-2K descriptor by 2 [28, 29].

A copy of the SRI-50 form is provided in the Manual of Procedures.

7.3.4 Physician Global Assessment (PGA)

The PGA is used to quantify disease activity and is measured using an anchored VAS. The PGA will be determined on a continuous VAS that asks the investigator to assess the subject's current disease activity from a score of 0 (none) to 3 (severe), with the assessment made relative not to the subject's most severe state but the most severe state of SLE per the investigator's assessment.



7.3.5 SLICC/ACR Damage Index

The SLICC/ACR Damage Index evaluates cumulative damage in SLE [30]. These changes may or may not be related to SLE. In order to ensure that features are not reversible components of active inflammation, most items are scored only if they have been present for at least 6 months. Scores range from 0 to 47 points, with higher scores indicating greater cumulative damage. However it would be exceedingly rare to see a damage index score of greater than 5 and most patients in clinical trials have scores ranging from 0-2.

Further information on the SLICC/ACR Damage Index is provided in the Manual of Procedures.

7.3.6 Complement Proteins and Antibodies

Changes in C3, C4, C4d, ANA and anti-dsDNA antibodies may be predictive of disease development and reflective of disease activity and response to therapy in SLE [31, 32]. These will be assessed at the visits specified in Appendix A.

7.4 Assessment of Safety

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), cardiac, local tolerability (ISRs) and hypersensitivity reactions.

Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any AE, whether observed by the investigator or reported by the subject (see Section 7.4.1.2).

The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 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/intensity 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 trial procedures.

Not related: 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 (e.g., 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 (e.g., 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.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgement, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., 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 trial visit that do not worsen in severity or frequency during the trial 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.

Exacerbation of SLE

SLE flares would not usually be reported as AEs unless they are unexpected in the context of the subject's medical history. SAEs due to SLE are always reported whether or not consistent with the subject's prior medical history.

Pre-defined AEs of Special Interest for Safety Monitoring

AEs of special interest will include infections, cardiac events and ISRs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be asked about changes in his/her condition. During the reporting period of the trial any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator, unless it is a lupus flare that is not unexpected based on the patient's medical history. Any increase in usual flares attributable to study agent would be found by analysis of the efficacy data. Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be reported using an AE Safety Report Form (Clinical Trial) as described in Section 7.4.1.4.

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 trial 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.

7.4.1.3 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 trial's post treatment follow-up period, defined as the safety FU period (FU Week 4 through FU Week 24). 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 safety follow-up (until FU Week 24, Day 330±5 days), 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.

7.4.1.4 Procedure for Reporting Serious Adverse Events

1. The investigator is responsible for reporting potential initial SAEs and pregnancies to Merck Serono Pharmacovigilance within 24 hours of being aware of the SAE/pregnancy.

2. SAEs and follow-ups to SAEs are reported by completing and/or updating the SAE form (Microsoft Word document). This Word document is printed by site, signed and scanned – hereby converting the SAE form to a PDF document.

3. The scanned SAE form is named using the following naming convention:

   Subject Number_Date(DDMMMYYYY)_Initial/FU1, 2, 3 etc.

   Example: 9990999_01JAN2013_FUP3

   The SAE form should be sent to Merck Serono Global Drug Safety by fax or email to:

   Fax: +49 6151 72 6914 or
   Email: GlobalDrugSafety@merckgroup.com

When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail.

Reporting procedures and timelines are the same for any new information on a previously reported SAE (i.e., SAE follow-up).

For names, addresses, telephone and fax numbers for SAE reporting, see information included in the AE Safety Report Form (Clinical Trials).

All written reports should be transmitted using the AE Safety Report Form (Clinical Trials), which must be completed by the investigator following specific completion instructions.

Relevant pages from the eCRF may be provided in parallel (e.g., medical history, concomitant drugs). In all cases, the information provided in the AE Safety Report Form (Clinical Trials) must be consistent with the data on the event that are recorded in the corresponding sections of the eCRF.

The investigator/reporter must respond to any request for follow-up information (e.g., additional information, outcome and final evaluation, specific records where needed) or to any question the sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the sponsor and (as applicable) to allow the company to meet strict regulatory timelines associated with expedited safety reporting obligations.

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

The sponsor or designee will send safety notifications to health authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP guidelines, the sponsor will inform the investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." This includes AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The investigator should place copies of safety reports in the Investigator Site File. National regulations with regard to safety report notifications to investigators will be taken into account.

When specifically required by regulations and guidelines, the sponsor will provide safety reports directly to an IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for notifying the applicable IEC/IRB of safety reports provided by the sponsor in accordance with applicable timelines and will be required to file copies of all reports and related correspondence in the Investigator Site File.

For trials 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.

7.4.1.6 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical trial and is considered to be possibly related to the IMP 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 appropriate additional therapeutic measures and follow-up procedures are performed if possible. The sponsor or designee will actively follow-up and collect information on any AE that occurs during the course of a clinical trial; however while this activity will continue for any SAEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must

be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and in female partners of male subjects. The investigator must notify the sponsor 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 7.4.1.4.

If possible, investigators must actively follow up, document and report on the outcome of pregnancies, even if the subject is withdrawn from the trial (see Section 5.5.1 and Section 5.5.2). The Pregnancy Report Form will be used to report outcomes and in case of adverse outcomes, the AE Safety Report Form (Clinical Trials) will be used for events occurring to the subject and the Parent-Child/Fetus AE Report Form will be used when the child/fetus has an AE.

Adverse outcomes must be reported in an expedited manner as described in Section 7.4.1.4, while non-adverse outcomes must be reported within 45 days from delivery. In the event of pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The sponsor must be notified without delay and the subject should be followed as described above.

7.4.3 Laboratory Assessments

The list of laboratory normal ranges will be supplied to Merck KGaA/EMD Serono by the central laboratory prior to shipment of trial IMP. Any change in laboratory normal ranges during the trial will additionally be forwarded to Merck KGaA/EMD Serono. Both fasting and non-fasting blood samples will be collected. Fasting blood samples will be collected (only for lipids) at Day 1, Week 12, and Week 24/ET. Laboratory data will be reported as Système International (SI) units.

Samples for the following laboratory tests (Table 7-1) will be collected at the visits specified in Appendix A. Sample collection, preparation and handling/shipment procedures are described in the Manual of Procedures.

Urine samples will be collected using a clean catch method. 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 2 years, serum pregnancy tests will be performed at initial screening and urine pregnancy tests will be performed at the visits specified in Appendix A. It is not mandatory to perform pregnancy tests for women who are postmenopausal for at least 2 years or who are surgically sterile. Urine pregnancy tests will be performed locally.

Free BLyS and free APRIL, anti-atacicept antibody titers (binding and neutralizing), and serum atacicept levels will be analyzed by the sponsor's bioanalytical laboratory. Post-baseline (or postdose) samples for free BLyS and free APRIL will be analyzed only if the appropriate assays are available.

All other parameters will be analyzed at the central laboratory.

Table 7-1 Clinical Laboratory Evaluations

Chemistry Panel	Hematology (CBC)	Complete Urinalysis[1]	Other Tests
Albumin	Hematocrit	pH	Direct Coombs test
Alkaline phosphatase	Hemoglobin	Leukocytes	**PK parameters**
Alanine aminotransferase	Mean corpuscular hemoglobin	Nitrite	Serum atacicept levels
Aspartate aminotransferase	Mean corpuscular hemoglobin concentration	Glucose	**PD parameters**
Total bilirubin	Mean corpuscular volume	Ketones	Anti-atacicept antibody titers (binding and neutralizing)
Bilirubin-direct (only if total bilirubin is outside the normal range)	Platelet count	Protein	Vaccine immunization status (antibody titers to tetanus toxoid, diphtheria, and pneumococcal antigens)
Calcium	Red blood cells	Blood	Free APRIL and free BLyS
Serum creatinine (GFR will be calculated from serum creatinine using the Modification of Diet in Renal Disease equation)	White blood cells and differential	**Urine sediment analysis (reflex testing only for abnormal urinalysis)**	CRP
Glucose		Red blood cells and white blood cells/high powered field	Serum total Ig, IgG, IgA, IgM
Potassium		Casts	Serum C3, C4 and C4d
Sodium		Organisms	ANA and anti-dsDNA antibodies
Total protein		Crystals	Anticardiolipin and lupus anticoagulant panels
Uric acid		**Additional urinalysis**	Anti-Sm, anti- RNP, anti-La, and anti-Ro antibodies, and RF
Fasting lipid profile		Urine protein, urine creatinine (UPCr)	Flow cytometry analysis of total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and plasma cells, plasmablasts, and NK cells (at selected sites only)
			UPEP
			Other Tests:
			HBsAg, anti-HBc [IgG and IgM] (hepatitis B)
			anti-HCV (hepatitis C), anti-HIV 1 and 2
			Pregnancy test (females only): serum qualitative and urine [performed locally])

ANA=antinuclear antibodies; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; anti-HCV =antibodies to hepatitis C virus; anti-HIV 1 and 2=antibodies to human immunodeficiency virus 1 and 2; anti-RNP=anti-ribonucleoprotein; anti-Sm=anti-Smith; APRIL=a proliferation-inducing ligand; BLyS=B lymphocyte stimulator; CRP=C-reactive protein; 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; RF=rheumatoid factor; UPCr=urine protein:creatinine ratio; UPEP=urine protein electrophoresis.

[1] Urine samples will be collected using a clean catch method. 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.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

7.4.4.1 Vital Signs

Vital sign measurements (BP, pulse rate, oral temperature), weight and height will be measured prior to any other trial-related procedures, except PROs (see Section 7), at the visits specified in Appendix A. Height will be measured at the screening visit only.

- BP (systolic and diastolic) and pulse rate must be measured with the subject in a seated position, after at least 3 minutes resting.
- Body temperature will be measured by the site's standard procedure.
- 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.

7.4.4.2 Physical Examination

A complete physical examination will be performed at the visits specified in Appendix A.

Physical examinations driven by the subject's complaints upon questioning will be performed during the trial as deemed necessary for routine medical care at the visits specified in Appendix A.

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.

At other visits, physical examination should always include assessment of HEENT, lungs, heart, abdomen, and extremities. Additional assessments should be performed as needed to fully obtain information needed for the BILAG 2004 and/or SLEDAI assessments if scheduled, as well as to fully evaluate any subject complaints or AEs.

7.4.4.3 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, Day 1, Day 2 (in those subjects providing additional PK sample on this day), Week 4, Week 23 Day 2 (in those subjects providing additional PK sample on this day) and Week 24 (see Appendix A).

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 trial IMP due to AEs or are SAEs.

7.4.4.4 Local Tolerability (Injection Site Assessment)

Any local ISRs will be recorded as AEs, starting after first IMP administration and continuing through the treatment period (Weeks 0 to 24 [Days 1 to 169]).

The definition of ISR is the following:

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 (e.g., injection site necrosis, injection site abscess, injection site cellulitis), these should be reported separately, using specific descriptions (e.g., injection site necrosis, injection site abscess, injection site cellulitis) rather than the term “injection site reaction”.

Subjects will be provided with a subject diary at each site visit and be instructed on how to complete it. The diary will be collected at each site visit and reviewed for completeness and dosing compliance before the subject leaves the site. Subject verbatim terms used to describe an injection site event will be reviewed by the investigator or trial nurse for consideration in their clinical evaluation of each injection site. The completed diaries will be filed with the subject source documents. The diary will be provided as part of the trial supplies.

Subjects will also record the use of lupus-related medications in the diary (see Section 6.5.1).

Subjects who complete Week 24 with persistent ISRs will be contacted regularly via telephone until resolution. Medical care for ISRs should be provided as required (see Section 6.4.1). 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).

7.4.4.5 Lipid Levels

Fasting lipid levels will be checked to evaluate if there is an effect of atacicept in modifying the lipid profile leading to a potential decrease in cardiovascular risk. Cardiovascular disease is one of the most common causes of morbidity and mortality among SLE patients, along with infection and renal disease [33]. The cardiovascular disease may be due to contributions from SLE disease activity as well as SLE medications such as CS [34, 35, 36, 37].

7.4.4.6 Mycophenolic Acid Levels

The MPA levels will be measured in subjects taking MMF/MPS only. The last MMF/MPS dose should have been taken at least 10 or more hours prior to plasma MPA sampling and the subject should receive the next MMF/MPS dose only after MPA sampling has been performed. The MPA levels will be measured to see if there is an association between the levels and possible outcomes during the trial, e.g., whether there is any interference on any PK/PD parameters.

7.4.4.7 Suspected Hypersensitivity Reaction

In the event of a suspected hypersensitivity reaction to the IMP, the subject should be treated symptomatically (see Section 6.4.1).

7.4.4.8 Review of Concomitant Medications and Procedures

Data concerning concomitant medications and procedures will be collected throughout the trial. These data will be obtained at scheduled or unscheduled trial visits, based on information spontaneously provided by the subject and through questioning of the subject.

Data concerning concomitant medications and procedures may also be obtained from subject diary cards, but information thus collected must be reviewed and assessed medically before it is transcribed to the eCRF.

7.4.4.9 Columbia- Suicide Severity Rating Scale (C-SSRS)

SLE patients, especially those with neuropsychiatric manifestations, are at higher risk for suicide than expected. In a review of the medical records of 300 SLE patients over a 20-year period, 2% had a documented history of attempted suicide; one of them was fatal [38]. All patients had a history of depression at the time of the suicide attempt.

The C-SSRS [39] assesses the suicidal behavior and suicidal ideation in subjects. Occurrence of suicidal behavior after randomization is defined as having answered “yes” to a least 1 of the 4 suicidal behavior subcategories (actual attempt, interrupted attempt, aborted attempt, and

preparatory acts or behavior). Occurrence of suicidal ideation after randomization is defined as having answered "yes" to at least one of the suicidal ideation sub-categories (wish to be dead, non-specific active suicidal thoughts, active suicidal ideation with any methods [not plan] without intent to act, active suicidal ideation with some intent to act [without specific plan], and active suicidal ideation with specific plan and intent).

Rationale

The C-SSRS is a low burden, clinician-administered tool designed to track suicidal AEs throughout any treatment trial and is considered to be the "gold standard" for assessment [39]. The measure succinctly covers the full spectrum of suicidality addressing both behavior and ideation and is now strongly recommended by the US FDA in clinical trials. It is the prospective version of the Columbia suicide classification system commissioned by the FDA, which provided the data for their safety analyses, and is used across numerous industry and National Institutes of Mental Health-sponsored studies.

Assessments

The C-SSRS is a unique and simple method of assessing both behavior and ideation that tracks all suicidal events, and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation and deterrents), all of which are significantly predictive of completed suicide.

The C-SSRS will be performed at the visits specified in Appendix A. The trained rater will record the clinical observation on the scale which will be used as the source document. If at all possible, the same individual should perform the assessment at each visit to reduce scoring variability. In the event the primary rater is not available, a designated back-up rater who meets the same qualifications may perform the C-SSRS.

Subjects who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care and the medical monitor notified.

7.4.4.10 Unscheduled Visits

Unscheduled visits may occur at any time during the trial in case of suspected flares or AEs (assessments to be performed according to the investigator's judgement).

7.5 Pharmacokinetics

Blood samples for PK analysis will be collected from all subjects. Instructions for preparation and shipping these samples will be provided in the "Special Laboratory Analysis" manual.

Serum atacicept levels will be assessed at trough (within 25 hours before dosing) at the following visits: Day 1 (predose) and at Weeks 2, 4, 8, 12, 16, 20, 24 or ET, and at the follow-up visits (FU Weeks 4, 12 and 24).

In a subset (PK subset) of subjects, 4 additional blood samples for PK will be collected at the following time points: Day 1 (4 hours post-first dose), Day 2 (24 hours post-first dose), Week 1 (8 days post-first dose and prior to next dose) and Week 23 Day 2 (Day 163, 24 hours post-last dose). Participation will be selected by IWRS. It is planned to include 40 subjects from all dose groups (placebo=8, atacicept 75 mg=16, atacicept 150 mg=16).

The sampling time points of the PK subgroup may be adjusted during the trial based on the outcome of upcoming Phase 1 trial result.

Subjects will be registered to the subset through the IWRS during randomization to the trial. Pre-selected/qualified sites will participate and a separate "Special Laboratory Analysis" manual will be provided.

7.6 Body Fluid(s)

The approximate total volume of blood that will be drawn from each subject in this trial during the 24-week treatment period, including the follow-up visits, is as follows (see Table 7-2).

Table 7-2 Volume of Blood to be Drawn From Each Subject

Visit	Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Screening	Clinical chemistry (including β-hCG), serology (HBsAg, Anti-HCV, HIV + confirmation), IgA, IgG, IgM, complement C3, C4, C4d, ANA, dsDNA	12	1	**12**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	Coombs test	2	1	**2**
Day 1 (Week 0)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, ANA, dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP, trough MPA levels, tetanus IgG, diphtheria IgG, pneumococcal IgG	15	1	**15**
	Hematology	2	1	**2**
	Lupus anticoagulant	2.7	1	**2.7**
	Serum atacicept	3.5	1	**3.5**
	Anti-atacicept antibodies	5	1	**5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	PGx (optional)	4	1	**4**
	Gene expression	2.5	1	**2.5**
	Coombs test	2	1	**2**

Visit	Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Day 2 (Week 0), Week 1 (Day 8)	Serum atacicept	3.5	2	**7**
Week 2 (Day 15)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, trough MPA levels, tetanus IgG, diphtheria IgG, pneumococcal IgG	7	1	**7**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
Week 4 (Day 29)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, ANA, dsDNA	8.5	1	**8.5**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	Gene expression	2.5	1	**2.5**
	Coombs test	2	1	**2**
Week 8 (Day 57)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, ANA, dsDNA	8.5	1	**8.5**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
	Coombs test	2	1	**2**
Week 12 (Day 85)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, ANA, dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP, trough MPA levels	13.5	1	**13.5**
	Hematology	2	1	**2**
	Lupus anticoagulant	2.7	1	**2.7**
	Serum atacicept	3.5	1	**3.5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	Gene expression	2.5	1	**2.5**
	Coombs test	2	1	**2**
Week 16 (Day 113), Week 20 (Day141)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, ANA, dsDNA	8.5	2	**17**
	Hematology	2	2	**4**
	Serum atacicept	3.5	2	**7**

Visit	Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
	Coombs test	2	2	**4**
Week 23 (Day 163)	Serum atacicept	3.5	1	**3.5**
Week 24/ET (Day 169)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, ANA, dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP, trough MPA levels, tetanus IgG, diphtheria IgG, pneumococcal IgG	15	1	**15**
	Hematology	2	1	**2**
	Lupus anticoagulant	2.7	1	**2.7**
	Serum atacicept	3.5	1	**3.5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	Gene expression	2.5	1	**2.5**
	Coombs test	2	1	**2**
FU Week 4 (4 weeks post-last dose; Day 190)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, trough MPA levels, tetanus IgG, diphtheria IgG, pneumococcal IgG	7	1	**7**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Coombs test	2	1	**2**
FU Week 12 (12 weeks post-last dose; Day 246)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, complement C3, C4, C4d, anticardiolipin IgG, IgM, ANA, dsDNA, anti-Sm, anti-Ro, anti-La, anti-RNP	12	1	**12**
	Hematology	2	1	**2**
	Lupus anticoagulant	2.7	1	**2.7**
	Serum atacicept	3.5	1	**3.5**
	Anti-atacicept antibodies	5	1	**5**
	Free BLyS/APRIL	3.5	1	**3.5**
	Coombs test	2	1	**2**
FU Week 24 (24 weeks post-last dose; Day 330)	Clinical chemistry (including β-hCG), IgA, IgG, IgM, Complement C3, C4, C4d, tetanus IgG, diphtheria IgG, pneumococcal IgG	8.5	1	**8.5**
	Hematology	2	1	**2**
	Serum atacicept	3.5	1	**3.5**
	Anti-atacicept antibodies	5	1	**5**

Visit	Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
	Free BLyS/APRIL	3.5	1	**3.5**
	Circulating proteins	17	1	**17**
	Gene expression	2.5	1	**2.5**
	Coombs test	2	1	**2**
Day 1 (Week 0), Week 2 (Day 15), Week 4 (Day 29), Week 12 (Day 85), Week 24/ET (Day 169), FU Week 24 (24 weeks post-last dose; Day 330)	Flow cytometry	4.6	6	**27.6**
Total blood volume to be drawn for subject during the 24-week trial period (including PGx, PK sampling and flow cytometry subsets)		**-**	**-**	**422.4**

ANA=antinuclear antibodies; dsDNA=anti-double-stranded deoxyribonucleic acid; anti-HCV =antibodies to hepatitis C virus; anti-RNP=anti-ribonucleoprotein; anti-Sm=anti-Smith; APRIL=a proliferation-inducing ligand; BLyS=B lymphocyte stimulator; β-hCG=beta-human chorionic gonadotropin; ET=early termination; FU=follow-up; HBsAg= Hepatitis B surface antigen; HIV= human immunodeficiency virus; Ig (A, G, M)=immunoglobulin (A, G, M); MPA=mycophenolic acid; PGx=pharmacogenetics.

7.6.1 Pharmacokinetics Calculations

The PK analysis will be performed by the sponsor according to the sponsor's standard operating procedures. Atacicept serum concentrations will be summarized at the time points shown in Appendix A. The blood volume to be drawn will range from 376.8-422.4 mL depending on whether the subjects will be part of the PGx, PK and/or flow cytometry subset. In addition, the blood volume will not exceed 450 mL in each individual subject. Details of the analysis will be provided in the statistical analysis plan (SAP). For PK sampling time points, see Section 7.5.

7.7 Anti-Drug Antibodies

Blood samples for assessment of anti-drug antibodies, both binding and neutralizing antibodies, to atacicept will be collected at the visits specified in Appendix A. Samples when evaluated will be tested first for binding activity, and those found to be positive will be tested for neutralizing activity. Instructions for the collection, preparation and handling/shipment of blood samples are provided in the Manual of Procedures. The samples will be analyzed under the responsibility of the sponsor`s bioanalytical laboratory.

7.8 Biomarkers

7.8.1 Vaccine Immunization Status

In order to examine the impact of atacicept treatment on vaccine immunization status, antibody titers to selected pneumococcal antigens, tetanus toxoid and diphtheria toxoid will be measured via blood samples at the visits specified in Appendix A.

Instructions for the preparation and handling/shipment of blood samples are provided in the Manual of Procedures. The samples will be analyzed by the central laboratory.

7.8.2 Pharmacodynamic Assessments

Blood samples will be collected at the time points specified in Appendix A.

The following markers will be evaluated: free BLyS, free APRIL, CRP, serum total Ig, IgG, IgA, and IgM, serum C3, C4, and C4d, ANA; anti-dsDNA, anticardiolipin, anti-Sm, anti-RNP, anti-La, and anti-Ro antibodies; RF and lupus anticoagulant. Changes in C3, C4, C4d, ANA, and anti-dsDNA antibody levels may be predictive of disease development and severity and reflective of response to therapy in SLE.

Instructions for the collection, preparation and handling/shipment of blood samples are provided in the Manual of Procedures. All samples will be analyzed by the central laboratory. Predose free BLyS and free APRIL will be analyzed by the sponsor`s bioanalytical laboratory.

After screening, free BLyS and free APRIL will be analyzed if an accurate assay can be established in the presence of atacicept.

Flow Cytometry Analysis

Blood samples will be collected at the time points specified in Appendix A.

Total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and plasma cells, plasmablasts, and NK cells will be measured.

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

7.9 Exploratory Endpoints

7.9.1 Circulating Proteins

Blood samples will be collected at the time points specified in Appendix A. The final list of markers will be based on the available technologies and on the results of other atacicept trials.

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

Sampling and storage will be in accordance with local ethical and regulatory requirements. Samples will be stored for 5 years after trial completion under the sponsor's responsibility. During this time, it is possible that the samples will be re-analyzed. This may include analyses for newly identified markers and/or a repeat of the original analysis with newer improved technologies. After this period of 5 years, samples will either be destroyed or new IEC/IRB approval to keep samples for an additional period will be requested.

Instructions for the preparation and handling/shipment of blood samples for assessment of circulating proteins are provided in the Manual of Procedures.

7.9.2 Gene Expression

Blood samples will be collected at the time points specified in Appendix A.

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

Samples will be stored for 5 years after trial completion under the sponsor's responsibility. During this time, it is possible that the samples will be re-analyzed. This may include analyses for newly identified markers and/or a repeat of the original analysis with newer improved technologies. After this period of 5 years, samples will either be destroyed or new IEC/IRB approval to keep samples for an additional period will be requested.

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

7.9.3 Pharmacogenetics (Genotyping)

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 trial 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 trial 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 trial, only the sponsor's authorized personnel and agents will have access to the confidential genetic data. The results of the PGx part of the trial 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 trial number and subject number only. The subject will not be identifiable in reports or publications resulting from this trial.

Blood samples will be collected preferably at Day 1 and prior to administration of the IMP. Samples will be stored for 5 years after trial completion under the sponsor's responsibility. During this time, it is possible that the samples will be re-analyzed. This may include analyses for newly identified markers and/or a repeat of the original analysis with newer improved

technologies. After this period of 5 years, samples will either be destroyed or new IEC/IRB approval to keep samples for an additional period will be requested.

Instructions for the preparation and handling of blood samples for PGx analysis are provided in the Manual of Procedures.

7.10 Other Assessments

7.10.1 Health-related QoL

The impact of SLE on patients' lives is significant, and thus health-related QoL outcomes are meaningful to both patients and clinicians. As part of the trial's examination of efficacy, the effects of treatment on health-related QoL will be assessed through changes in the SF-36, EQ-5D, LupusQoL, PGIC, and FACIT-Fatigue scores.

7.10.1.1 Medical Outcomes Study 36-item Short Form Health Survey (SF-36 version 2®)

The SF-36 is a 36-item scale constructed to survey health-related QoL on 8 domains: limitations in physical activities due to health problems; limitations in social activities due to physical or emotional problems; limitations in usual role activities due to physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities due to emotional problems; vitality (energy and fatigue); and general health perceptions [40].

The SF-36 form asks for subjects to reply to questions (items) according to how they have felt over a specifically defined period of time. The items use Likert-type scales, some with 5 or 6 points and others with 2 or 3 points and yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the Physical Component Summary (PCS) and Mental Component Summary (MCS). The interval level scoring for all 8 scales ranges from 0 (for worse health) to 100 (best possible health as measured by the questionnaire) with standardized summary scores for the PCS and MCS (mean=50, standard deviation [SD]=10).

Higher scores represent a better quality of life. Low scores on the PCS indicate significant limitations in performing physical activities, high degree of bodily pain and poor general health, while high scores reflect little or no such limitations. Low scores on the MCS indicate frequent psychological distress, social and role disability due to emotional problems and poor general health, while higher scores reflect little or no psychological distress or limitations. At each assessment visit, the SF-36 will be completed by the subject prior to the initiation of any other study activities or treatments.

This questionnaire will be used in the countries for which validated translations are available. A copy of the SF-36 questionnaire is provided in the Manual of Procedures.

7.10.1.2 LupusQoL

The LupusQoL is a lupus-specific health related QoL questionnaire consisting of 34 items grouped in 8 domains: physical health, pain, planning, intimate relationships, burden to others, emotional health, body image and fatigue [41]. Subjects indicate their responses on a 5-point Likert response format, where 4=never, 3=occasionally, 2= a good bit of the time, 1=most of the time, and 0=all of the time. Summary scores can be calculated for all 8 domains. The LupusQoL showed good internal reliability, test-retest reliability, and concurrent validity with the SF-36 and discriminant validity for different levels of disease activity and damage in SLE patients.

The questionnaire will be used in the countries for which validated translations are available. A copy of the LupusQoL questionnaire is provided in the Manual of Procedures.

7.10.1.3 PGIC

The PGIC is self-rated scale that asks the subject to describe the change in activity limitations, symptoms, emotions, and overall QoL related to the subject's painful condition on the following scale: 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse) and 7 (very much worse). The subject will select the number that matches the subject's degree of change since beginning the treatment with atacicept.

A copy of the PGIC is provided in the Manual of Procedures.

7.10.1.4 FACIT-Fatigue

The FACIT-Fatigue [42] is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function. It uses a 5-point Likert-type scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0–4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best. To obtain the 0-52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score. Fatigue is among the most prevalent symptoms of SLE, and can have profound effects on subjects' health-related QoL [43, 44]. The FACIT-Fatigue has been validated in subjects with SLE being a valid and responsive measure of fatigue in patients with SLE [45, 46].

This questionnaire will be used in the countries for which validated translations are available. A copy of the FACIT-Fatigue scale is provided in the Manual of Procedures.

7.10.1.5 EQ-5D

The EQ-5D questionnaire comprises 5 questions (items) relating to current problems in the dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [47]. Responses in each dimension are divided into 3 ordinal levels coded (1) no problems, (2) moderate problems, (3) extreme problems. This part, called the EQ-5D descriptive system,

provides a 5-dimensional description of health status. Theoretically, different health states can be defined. The EQ-5D descriptive system is followed by a VAS (EQ VAS), similar to a thermometer, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The EQ VAS records the respondent's self-rated valuation of health state, i.e., a value which is based on the respondent's preferences (EQ VAS score). With respect to psychometric properties, the EQ VAS showed acceptable validity and reliability in patient with SLE [48].

Based on the EQ-5D, the EQ-5D index can be derived. The EQ-5D index is frequently used in economic evaluations: it represents societal preference values for the full set of 243 EQ-5D health states with the best state (perfect health) and "death" being assigned values of 1 and 0, respectively. This questionnaire will be used in the countries for which validated translations are available.

A copy of the EQ-5D questionnaire is provided in the Manual of Procedures.

8 Statistics

8.1 Sample Size

This Phase IIb trial is designed to evaluate the efficacy of atacicept compared to placebo in reducing SLE disease activity in subjects treated with SoC therapy and to investigate the dose-response relationship. To achieve this goal, SoC plus 2 atacicept doses (75 mg and 150 mg) or placebo will be evaluated. Thus, 3 treatment groups with equal numbers of randomized subjects will be enrolled.

In order to have 80% power to detect 20% absolute difference in proportion of subjects achieving a response defined by SRI-50, 93 subjects per arm are required, assuming a placebo response rate of 30% and a 2-sided α=0.05. The total sample size is thus planned to be 279 subjects with a randomization ratio of 1:1:1.

8.2 Randomization

Eligible subjects will be randomly assigned in a ratio of 1:1:1 to atacicept doses of 75 mg or 150 mg or placebo, stratified by baseline factors: SLEDAI-2K total score (<10 vs. ≥10), race (blacks vs. others), and mycophenolate use at screening (yes vs. no).

Subjects will be randomized by the IWRS. 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 Primary Endpoint

The primary endpoint is the proportion of subjects with SRI response at Week 24 compared to the screening visit. The SRI response, a measure of reduced SLE disease activity, is defined by meeting all of the following conditions:

1. ≥4 point reduction in SLEDAI-2K score.
2. No significant worsening in PGA score (<10% increase).
3. No new BILAG A organ domain scores and ≤1 new BILAG B organ domain score.
4. No protocol-prohibited medication/treatment.

8.3.2 Secondary Endpoints

Key Secondary Endpoints:

1. Proportion of subjects at Week 24 whose prednisone-equivalent CS dose has been reduced from screening visit by ≥25% and to a dose of ≤7.5mg/day, and have no BILAG A or 2B flare in disease activity during Weeks 16 through 24. A BILAG A or 2B flare is defined by ≥1 new BILAG A organ domain score and/or ≥2 new BILAG B organ domain scores compared to screening visit.
2. Proportion of subjects in the PGIC categories of 1 or 2, 3 or 4 or 5, 6 or 7 at Week 24.

Corticosteroid dosing:

3. Proportion of subjects at each visit whose prednisone-equivalent CS dose has been reduced from screening visit by ≥25% and to a dose of ≤7.5mg/day, and have no BILAG A or 2B flare in disease activity (at that visit).
4. Change from screening visit to Week 24 in prednisone-equivalent CS daily dose.
5. Proportion of subjects at Week 24 with a decrease from screening visit in prednisone-equivalent CS daily dose of 0-<25%, 25%-50%, >50%, or an increase.
6. Cumulative prednisone-equivalent CS dose from the screening visit until completion of the treatment period.

Disease activity (induction of response):

7. Proportion of subjects with a SRI response at each trial visit.
8. Time to first SRI response during the treatment period.
9. Proportion of subjects with a confirmed SRI response at each trial visit. A confirmed response is defined as having at least 2 consecutive assessments (4 weeks apart) meeting the SRI response criteria at each time point of interest.
10. Time to first confirmed SRI response during the treatment period.
11. Proportion of subjects with ≥4 point reduction from screening visit in SLEDAI-2K score at each trial visit.
12. Proportion of subjects with no significant worsening of the PGA, defined as <10% increase from screening visit at each time point.

13. Proportion of subjects with no new BILAG A organ domain scores and ≤1 new BILAG B organ domain score at each time point compared to screening visit.

14. Proportion of subjects responding to treatment according to the BILAG-based Combined Lupus Assessment (BICLA), at each trial visit. The BICLA response is defined as meeting all of the following conditions compared to screening visit:

    a) BILAG-2004 improvement (all screening visit BILAG A improving to B/C/D, all screening visit BILAG B to C/D, and ≤1 new BILAG B and no new BILAG A),

    b) no deterioration in SLEDAI total score,

    c) PGA increase by <10%, and

    d) no protocol-prohibited medication/treatment.

15. Change from screening visit in total and in organ specific SLEDAI-2K scores at each time point.

16. Change from screening visit in PGA score at each time point.

17. Change from screening visit in total and in organ specific BILAG score (using validated numerical score A=12, B=8, C=1, D/E=0) at each time point.

18. Change from screening visit in modified total SLEDAI-2K scores at each time point. A modified (clinical) SLEDAI-2K total score is a sum of the numerical scores for the 22 descriptors that exclude the complement and autoantibody levels.

19. Proportion of subjects with a modified SRI response at each time point. A modified SRI response is defined by using the modified SLEDAI-2K scores and meeting all of the following conditions compared to screening (in those subjects with a modified SLEDAI-2K total score of at least 4 at screening):

    a) ≥4 point reduction in modified SLEDAI-2K score,

    b) no significant worsening in PGA score (<10% increase),

    c) no new BILAG A organ domain scores and ≤1 new BILAG B organ domain score, and

    d) no protocol-prohibited medication/treatment.

20. Absolute values and change from screening visit in UPCr, at each time point (in subjects with UPCr >0.5 mg/mg at screening visit).

21. SRI-50 scores at each time point.

22. Change from Day 1 in SF-36 PCS, MCS and total score at each time point.

23. Change from Day 1 in FACIT-Fatigue and EQ-5D at each time point.

24. Proportion of subjects in the PGIC categories of 1 or 2, 3 or 4 or 5, 6 or 7 at each time point.

Disease activity (analysis of worsening/flares):

25. Proportion of subjects with at least one BILAG A flare at each time point. A BILAG A flare is defined by ≥1 new BILAG A organ domain score compared to screening visit.

26. Time from screening visit to first BILAG A flare.

27. Proportion of subjects with at least one BILAG A or 2B flare at each time point. A BILAG A or 2B flare is defined by ≥1 new BILAG A organ domain score and/or ≥2 new BILAG B organ domain scores compared to screening visit.

28. Time to first BILAG A or 2B flare.

29. Proportion of subjects with any flare per the SFI at each time point.

30. Time to first SFI severe flare (as defined in Section 7.3.2).

PK endpoint

Atacicept concentrations.

PD endpoints

1. Absolute values and change from screening visit in serum complement C3, C4, and C4d levels at each time point, in subjects with low levels of C3 or C4 and/or elevated levels of C4d at screening visit, respectively.

2. Change from screening visit in anti-dsDNA antibodies (in subjects with anti-dsDNA antibodies ≥30 IU/mL at baseline) and proportion of subjects with positive ANA levels (in subjects with Hep-2 ANA ≥1:80 at baseline) at each time point.

3. Absolute values and change from screening visit in levels of total Ig classes (IgG, IgA, and IgM) at each time point.

4. Absolute values and change from Day 1 in titers of antibodies to pneumococcal antigens, tetanus toxoid and diphtheria toxoid.

5. Absolute values and change from Day 1 in total T, helper T, cytotoxic T, total B, mature naïve B, memory B, and plasma cells, plasmablasts, and NK cells by flow cytometry analysis at each time point.

6. Absolute values and change from screening in free BLyS and free APRIL if an appropriate assay is available.

8.3.3 Safety Endpoints

To evaluate the safety of atacicept 75 mg or 150 mg, administered as weekly SC injections vs. placebo after 24 weeks of treatment, as assessed by:

- The nature, incidence, severity, and outcome of AEs.

- C-SSRS outcome.
- Changes in standard laboratory parameters and vital signs.
- Antibodies to atacicept, both binding and neutralizing.

Additionally, safety and tolerability will also be evaluated in terms of the AEs, AEs of special interest, SAEs, deaths and associated causes; changes in clinical laboratory test results, ECGs, and vital signs will be analyzed for each subject according to treatment group and/or visit. In addition, the incidence of immunogenicity developed in the treatment groups will be summarized.

8.3.4 Further Endpoints of Interest

Exploratory endpoints

In addition to the primary and secondary endpoints, the following additional exploratory analyses are planned:

1. Change in LupusQoL domain scores at each time point.
2. Health resource utilization: (a) number of emergency room visits and (b) number of inpatient admissions.
3. Genetic variants, and gene expression variations associated with subjects' responses to atacicept therapy.
4. Change in levels of circulating proteins (e.g., cytokines, chemokines, and additional autoantibodies).
5. Change from Day 1 in SLICC/ACR Damage Index score at Week 24.
6. Absolute values and change from Day 1 in anticardiolipin, anti-Sm, anti-RNP, anti-La and anti-Ro antibodies, RF and lupus anticoagulant (recorded as absent or present) at each time point, in subjects with abnormal values at Day 1.

8.4 Analysis Sets

The statistical analyses described in this protocol will be based on the analysis populations defined below:

Intent-to-treat (ITT)

The ITT population consists of all randomized subjects.

Modified intent-to-treat (mITT)

The mITT population is defined as all randomized subjects who have received at least 1 dose of the IMP.

Per protocol (PP)

The PP population consists of all randomized subjects who do not have any major protocol deviations. Details of the criteria for exclusion from the PP population will be provided in the SAP.

Safety

The safety population consists of all randomized subjects who receive at least 1 dose of IMP.

Subjects in the ITT, mITT and PP populations will be analyzed according to their randomized treatment and subjects in the safety population will be analyzed according to the actual treatment received during the trial.

8.4.1 Subgroups

Descriptive analyses of efficacy will be performed for the following subgroups:

- Race (black, white, Native American, Asian, other).
- Ethnicity (for US sites: Hispanic and subsets of Asian [Japanese, Chinese, Korean, Indian subcontinent])
- Severity of disease at screening (severe, mild/moderate). Severe is defined as at least one BILAG A; mild/moderate is defined as at least one BILAG B and no BILAG A.
- Age (<65, ≥65).
- Gender (male, female).
- Region (North America, Latin America, Europe, Asia & Pacific).
- Mycophenolate use at screening (yes, no).
- Free APRIL at baseline (below median, median and above).
- Free BLyS at baseline (below median, median and above).

8.5 Description of Statistical Analyses

8.5.1 General Considerations

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Prior to locking the database, a detailed SAP will be developed.

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 (e.g., 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. Treatment comparisons for categorical data will be analyzed using Chi-square tests or appropriate statistical models specified in each section. The statistical methods for assessing treatment comparisons for continuous data will be an analysis of covariance model that includes terms for treatment and the baseline value as a covariate. Time to event data will be analyzed by the Kaplan-Meier survival method and/or the Cox proportional hazards model to adjust for the baseline factors. Alternative or additional statistical methods may be used as appropriate as outlined in the SAP.

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 CTR. Additional exploratory analyses will be conducted as deemed appropriate.

8.5.2 Analysis of Primary Endpoint

The primary efficacy endpoint, the proportion of subjects with reduced SLE disease activity at Week 24, will be analyzed using a logistic regression model as the primary analysis for the comparison of each atacicept arm versus placebo. The 3 stratification factors (race, screening SLEDAI-2K total score [<10 and ≥10] and mycophenolate use [yes/no]) will be included in the model, and the interaction with treatment will be tested. If interactions are significant, additional analyses will be performed to further examine the interactions and to better interpret the treatment effect, including subgroup analyses.

A step-down sequential testing procedure will be used to control for multiplicity in atacicept doses. The atacicept 150 mg arm will first be compared with the placebo arm (2-sided α=0.05) and if statistically significant, the atacicept 75 mg arm will be compared with the placebo arm (2-sided α=0.05).

The primary efficacy analysis will be performed using the mITT population. If a subject did not have a result for the primary endpoint, the subject will be included as a non-responder. The imputation of missing data for the primary endpoint and its components will be described in the SAP. The comparison of atacicept 150 mg and 75 mg will be performed as an exploratory analysis only.

Robustness of the statistical analyses results pertaining to the primary efficacy variable will be assessed by conducting sensitivity analyses. The purpose of sensitivity analyses is to demonstrate the consistency of the primary analyses under conditions which are conservative with respect to the efficacy of atacicept and that statistical significance is not necessarily anticipated for all sensitivity analyses. Sensitivity analysis will include repeating the analysis of the primary endpoint using the PP population and checking the impact of missing data.

8.5.3 Analysis of Secondary Endpoints

Key secondary endpoints:

1. Proportion of subjects at Week 24 whose prednisone-equivalent CS dose has been reduced from screening visit by ≥25% and to a dose of ≤7.5mg/day, and have no BILAG A or 2B flare in disease activity during Weeks 16 through 24. A logistic regression model will be used to compare the treatment arms, adjusted for the stratification variables used for the randomization.

2. Proportion of subjects at Week 24 in the categories of PGIC (1 or 2, 3 or 4 or 5, 6 or 7). A proportional odds model for ordinal responses will be used to compare the treatment arms, adjusted for the stratification factors used for the randomization.

If the primary endpoint is met for both atacicept doses, to control the overall type I error rate (2-sided α=0.05), the evaluation of statistical significance for the hypothesis testing of the key secondary endpoints in both atacicept doses will be performed in the following hierarchical order:

- Key secondary endpoint 1: atacicept 150 mg vs. placebo.
- Key secondary endpoint 2: atacicept 150 mg vs. placebo.
- Key secondary endpoint 1: atacicept 75 mg vs. placebo.
- Key secondary endpoint 2: atacicept 75 mg vs. placebo.

If the primary endpoint is not met in either atacicept dose, the analysis of the key secondary endpoints will become exploratory.

All the other secondary endpoints will be analyzed including descriptive summary and statistics as described in Section 8.5.1. Missing data for subjects who prematurely discontinued the study will be imputed via the last-observation-carried-forward method. Alternative approaches for handling drop-outs or missing data if used to support the robustness of the study results will be described in the SAP.

All other secondary endpoints and exploratory endpoints as described in Section 8.3.2 and Section 8.3.4 will be analyzed descriptively using appropriate summary statistics as described in Section 8.5.1, and will be detailed in the SAP.

8.5.4 Exploratory Endpoints

The exploratory biomarker endpoints will be described in a separate exploratory biomarker SAP.

8.5.5 Safety Analyses

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 percents.

8.5.5.1 Adverse Events

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, and all summary tables for AEs will be organized by these categories. Frequency counts and percentages will be presented for subjects with at least 1 treatment-emergent AE within each system organ class and preferred term, separated by treatment group. Treatment-emergent AEs will also be summarized by relationship to treatment and by severity within each treatment group.

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

By-patient 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 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.

8.5.5.3 C-SSRS

The C-SSRS outcome is a numerical score derived from the 10 C-SSRS categories. The score is created at each assessment for each subject and is used for determining treatment-emergence. Descriptive statistics will be summarized by treatment group for the Suicidal Ideation Score and the 10 individual categories.

8.5.5.4 Other Safety Variables

All other safety variables (injection site assessments, physical examinations) will be summarized, as appropriate, with listings and descriptive statistics by dose cohort, treatment group, and assessment 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. Additionally, the number and percentage of subjects with ISRs will be summarized by erythema, edema, pruritis, and pain in the treatment group.

8.5.5.5 Pharmacodynamics

Results of PD endpoints will be summarized by treatment group and by dose. The frequency and percentage of subjects with reactive antibodies will be summarized by means of tabulated descriptive statistics for all subjects overall and by time point (if applicable).

8.5.6 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 Analysis

No interim analysis is planned.

8.7 Data Safety Monitoring Board

An independent DSMB will be formed to monitor interim safety and disease activity data on a regular basis to ensure the safety of the subjects in this trial, assess the evidence of benefit or adverse effects of atacicept, and to monitor the conduct of the trial, including recommendations about additional monitoring measures that may be deemed necessary. After consideration, the sponsor will inform the DSMB of any action that will be taken in response to the DSMB recommendations. No α-spending boundary or formal statistical stopping rule will be used for this DSMB. Details regarding DSMB roles, responsibilities, activities, and possible recommendations will be provided in a separate DSMB charter.

The DSMB will consist of a minimum of at least 4 expert members who are independent of the sponsor. The members will be appointed by the sponsor based on their expertise in biostatistics, SLE, cardiology and/or infectious disease. All DSMB members will have experience in the conduct of clinical trials. Members will not be investigators in the trial, nor will they have any conflict of interest with the sponsor. Members will not have a bias with regard to the use of atacicept for the treatment of SLE. Sponsor representatives are not eligible for membership on the DSMB.

The DSMB will review unblinded interim data. The recommendations of the DSMB will not contain unblinded data or other information that could lead to investigators or sponsor representatives becoming unblinded. An independent statistician, who is not involved with study conduct and not a member of DSMB, is responsible for producing the unblinded interim data for DSMB review.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the CTP and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the investigator must ensure that only subjects who have given their informed consent are included into the trial.

In 1998, the US FDA introduced a regulation (21 Code of Federal Regulations, Part 54) entitled "Financial Disclosure by Clinical Investigators". For trials conducted in any country that could result in a product submission to the FDA for marketing approval and could contribute significantly to the demonstration of efficacy and safety of the IMP (named "covered trials" 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 trial and for 12 months following completion of the trial. This trial is being conducted under a US Investigational New Drug (IND), therefore all investigational sites must complete an FDA Form 1572.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. The ICF must be approved by the IEC/IRB and regulatory authorities (in some countries) before it is provided to the subject.

Adequate information must therefore be given to the subject by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (ICH Topic E6, 1996) will be provided by the sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial, including potential PGx testing (see Section 9.3). The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on national regulations, a person other than the investigator may inform the subject and sign the ICF, as above.

Where the information is provided by the investigator, the ICF must be signed and personally dated by the subject and the investigator.

The signed and dated declaration of informed consent will remain at the investigator's site, and must be safely archived by the investigator 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 the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The investigator will explain the changes to the previous version.

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

9.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the investigator will be able to link the subject's trial data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the monitor, audits and health authority inspections will be kept strictly confidential.

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.

Confidentiality of information relating to the PGx sample testing will be protected to the extent permitted by law. To protect against the risk of loss of confidentiality, all DNA samples will be marked with a code number only and will not be identified by subject name. Upon receipt at the analytical laboratory, the samples are recoded with a specific code (PGtID) that is different from the subject code number. The data generated with these samples will also be tracked with the PGtID. Only authorized personnel will have access to this code and to the key linking both codes. The key will be maintained in a restricted location. The results obtained from the PGx samples in this trial are for research purposes only. The results of the tests conducted with the PGx samples will not be made available to the subject, members of their family, their personal physician, or other third parties, except as specified as follows.

Unless required by law or regulatory authorities for the purpose of verifying information obtained from this trial, only the sponsor's authorized personnel and agents will have access to the confidential genetic data. The results and other information from the PGx tests trial 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 subject and trial number only. The subject will not be identified in any reports or publications resulting from this trial.

By default, results from genotyping will only be accessible to the sponsor's authorized personnel and agents and be handled without disclosure of subject identification. However, upon written request by the subject, the results from genotyping will be made available to the subject, if permitted by local law and regulations. If required by law or regulatory authorities for the purpose of verifying information obtained from this trial, only the sponsor's authorized personnel and agents will have access to the confidential genetic data. The subject will not be identified in any reports or publications resulting from this trial.

9.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be furnished by the sponsor. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying

themselves as participating in a clinical trial, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical trial; and this may include the possibility of emergency unblinding if needed, in case of blinded trials.

Clinical trial 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, she or he will answer any questions. Any subsequent action (e.g., unblinding) will follow the standard processes established for the investigators.

In cases where the investigator is not available, Merck Serono/EMD Serono provides the appropriate means to contact a CRO/sponsor physician. This includes the provision of a 24-hour contact number at a call centre, whereby the health care providers will be given access to the appropriate CRO/Sponsor physician. The CRO/sponsor physician will assist the health care provider in medical emergencies by providing information, advice and assistance relating to the study and IMP. The CRO/sponsor physician is not responsible or required for potential emergency unblinding, but may provide advice or assistance if requested.

9.5 Clinical Trial Insurance and Compensation to Subjects

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

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, the CTP will be submitted together with its associated documents to the responsible IEC/IRB for its favorable opinion/approval. The written favorable opinion/approval of the IEC/IRB will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File.

The trial must not start at a site before the sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC/IRB. The IEC/IRB will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the CTP version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

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

9.7 Health Authorities

The CTP and any applicable documentation (e.g., IMP dossier, subject information and ICF) will be submitted or notified to the health authorities in accordance with the regulations of the countries involved in the trial.

10 Trial Management

10.1 Case Report Form Handling

The investigator or designee will be responsible for entering trial data in a timely manner in the eCRF provided by the CRO's Data Management Group and follow the data standards of the sponsor. It is the investigator's responsibility to ensure the accuracy of the data entered in the eCRFs.

The data will be entered in to a validated database (InForm version 5.5). The CRO's Data Management Group will be responsible for data processing, in accordance with data management procedures agreed upon between the sponsor and CRO. Database lock will occur once quality control procedure, and QA procedures (if applicable) have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the trial.

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 trial. This file will contain the available demographic and medical information for the subject, and should be as complete as possible. 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.
- Date of subject's inclusion into the trial (i.e., date of giving informed consent).

- Subject number in the trial.
- Dates of the subject's visits to the site.
- Any medical examinations and clinical findings predefined in the CTP.
- All AEs observed in the subject.
- Date of subject's end of trial, and
- Date of and reason for early withdrawal of the subject from the trial or from IMP, if applicable.

It must be possible to identify each subject by using this subject file.

Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, ECG recordings, and laboratory value listings. Such documents must bear at least the subject number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the investigator.

10.3 Investigator Site File and Archiving

The investigator will be provided with an Investigator Site File and a Study Reference Manual upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the monitor, and must be ready for sponsor audit as well as for inspection by health authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the sponsor) after the end of the trial. The documents to be thus 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.

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 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 trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The site monitor will perform visits to the trial site at regular intervals.

Representatives of the sponsor's QA unit or a designated organization, as well as health authorities, must be permitted to inspect all trial-related documents and other materials at the

site, including the Investigator Site File, the completed eCRFs, the IMP(s), and the subjects' original medical records/files.

The CTP, each step of the data capture procedure, and the handling of the data, including the final CTR, will be subject to independent QA activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

10.5 Changes to the Clinical Trial Protocol

Changes to the CTP will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the health authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) 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 have an impact on the subject's agreement to participate in the trial requires the subject's informed consent prior to implementation (see Section 9.2).

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a CTR according to ICH Topic E3 will be written by the sponsor in consultation with the CRO.

All exploratory biomarker analyses will be reported in a separate exploratory biomarker report.

10.6.2 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint that will include data from all trial sites.

The investigator will inform the sponsor in advance about any plans to publish or present data from the trial. 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 pre-submission review by the sponsor.

The sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

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12 Appendices

Appendix A Schedule of Assessments

Trial Period	**Screening**	**Visit Weeks During Treatment Period**											**FU Visit # weeks post-last dose[1]**		
Week		0	0	1	2	4	8	12	16	20	23+1 day	24/ET	4	12	24
Trial Day	-28 to -1	1	2	8	15	29	57	85	113	141	163	169	190	246	330
Visit		Wk0 Day1	Wk0 Day2	Wk1 Day1	Wk2 Day1	Wk4 Day1	Wk8 Day1	Wk12 Day1	Wk16 Day1	Wk20 Day1	Wk23 Day2	Wk24/ ET	FU Wk4	FU Wk12	FU Wk 24
Visit window (±day)	-	-	-	±3	±3	±3	±3	±3	±3	±3	-	±3	±5	±5	±5
Informed consent	X														
Inclusion/exclusion criteria	X	X [2]													
PGx informed consent	X														
Demographic data	X														
SLE & other medical history, medications, surgery/procedures	X														
Documentation of SLE classification criteria	X														
Chest X-ray [3]	X														
12-lead ECG	X	X	X[9]			X					X[9]	X			
Tuberculosis assessment[4]	X														
Serum virology (HIV, HCV, HBV)	X														
Serum pregnancy test [5]	X														
Urine pregnancy test [4, 5]		X		X		X	X	X	X	X		X	X	X	X
Complete physical examination	X	X		X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]		X	X[6]	X[6]	X[6]
Vital signs, weight, height [7]	X	X		X	X	X	X	X	X	X		X	X	X	X

Trial Period	**Screening**	**Visit Weeks During Treatment Period**											**FU Visit # weeks post-last dose[1]**		
Week		0	0	1	2	4	8	12	16	20	23+1 day	24/ET	4	12	24
Trial Day	-28 to -1	1	2	8	15	29	57	85	113	141	163	169	190	246	330
Visit		Wk0 Day1	Wk0 Day2	Wk1 Day1	Wk2 Day1	Wk4 Day1	Wk8 Day1	Wk12 Day1	Wk16 Day1	Wk20 Day1	Wk23 Day2	Wk24/ ET	FU Wk4	FU Wk12	FU Wk 24
Visit window (±day)	-	-	-	±3	±3	±3	±3	±3	±3	±3	-	±3	±5	±5	±5
C-SSRS	X	X				X	X	X	X	X		X			
SLICC/ACR Damage Index		X										X			
SLEDAI-2K, PGA	X	X				X	X	X	X	X		X	X	X	X
SRI-50		X				X	X	X	X	X		X	X	X	X
BILAG 2004	X	X				X	X	X	X	X		X	X	X	X
Randomization		X													
IMP injection [18]		Once weekly throughout the treatment period (Weeks 0 to 23)													
Laboratory Assessments															
Routine hematology, chemistry, urinalysis [8]	X	X			X	X	X	X	X	X		X	X	X	X
UPCr	X	X			X	X	X	X	X	X		X	X	X	X
Coombs test	X	X				X	X	X	X	X		X	X	X	X
UPEP		X										X			
Antibodies to atacicept		X						X				X		X	X
Lipids[10]		X						X				X		X	
MPA levels[11]		X						X				X			
Vaccine immunization status[12]		X										X			X
Pharmacokinetics[13a]															
Serum atacicept		X[13d]	X[13b;c]	X[13a,b]	X[13a]	X[13a]	X[13a]	X[13a]	X[13a]	X[13a]	X[13b, c]	X	X	X	X

Trial Period	**Screening**	**Visit Weeks During Treatment Period**											**FU Visit # weeks post-last dose[1]**		
Week		0	0	1	2	4	8	12	16	20	23+1 day	24/ET	4	12	24
Trial Day	-28 to -1	1	2	8	15	29	57	85	113	141	163	169	190	246	330
Visit		Wk0 Day1	Wk0 Day2	Wk1 Day1	Wk2 Day1	Wk4 Day1	Wk8 Day1	Wk12 Day1	Wk16 Day1	Wk20 Day1	Wk23 Day2	Wk24/ ET	FU Wk4	FU Wk12	FU Wk 24
Visit window (±day)	-	-	-	±3	±3	±3	±3	±3	±3	±3	-	±3	±5	±5	±5
Pharmacodynamics															
Free BLyS, Free APRIL [14]	X	X				X		X				X	X	X	X
CRP		X			X	X	X	X				X	X	X	X
IgG	X	X		X	X	X	X	X	X	X		X	X	X	X
Total Ig, IgA, IgM		X			X	X	X	X	X	X		X	X	X	X
C3, C4, C4d	X	X			X	X	X	X	X	X		X	X	X	X
ANA and anti-dsDNA antibodies	X	X				X	X	X	X	X		X		X	
Anti-Sm, anti-RNP, anti-La, anti-Ro, RF		X						X				X		X	
Anticardiolipin and lupus anticoagulant panels		X						X				X		X	
Sample for flow cytometry analysis (at select sites only)		X			X	X		X				X			X
Sample for circulating proteins	X	X				X		X				X			X
Sample for gene expression profiling		X				X		X				X			X
Sample for PGx (genotyping)[15]		X[16]													
Questionnaires[17]															
SF-36		X				X	X	X	X	X		X			

Trial Period	**Screening**	**Visit Weeks During Treatment Period**											**FU Visit # weeks post-last dose[1]**		
Week		0	0	1	2	4	8	12	16	20	23+1 day	24/ET	4	12	24
Trial Day	-28 to -1	1	2	8	15	29	57	85	113	141	163	169	190	246	330
Visit		Wk0 Day1	Wk0 Day2	Wk1 Day1	Wk2 Day1	Wk4 Day1	Wk8 Day1	Wk12 Day1	Wk16 Day1	Wk20 Day1	Wk23 Day2	Wk24/ ET	FU Wk4	FU Wk12	FU Wk 24
Visit window (±day)	-	-	-	±3	±3	±3	±3	±3	±3	±3	-	±3	±5	±5	±5
EQ-5D		X				X	X	X	X	X		X			
LupusQoL		X				X	X	X	X	X		X			
PGIC						X	X	X	X	X		X			
FACIT-Fatigue		X				X	X	X	X	X		X			
Safety															
IMP accountability						X	X	X	X	X		X			
IMP distribution					X	X	X	X	X	X					
Dispense subject diary	X	X				X	X	X	X	X		X	X	X	
Collect and review subject diary		X	X	X	X	X	X	X	X	X		X	X	X	X
Concomitant medications/ procedures	Continuous throughout trial														
Adverse events	Continuous throughout trial														
Weekly monitoring		Continuous throughout treatment and follow-up periods													
Local injection tolerability		Continuous throughout treatment period (Weeks 0 to 24)													

ACR=American College of Rheumatology; APRIL=a proliferation-Inducing ligand; ANA=antinuclear antibody; anti-Sm=anti-Smith; BILAG=British Isles Lupus Assessment Group; BLyS=B-lymphocyte stimulator; C=complement; CRP=C-reactive protein; C-SSRS=Columbia-Suicide Severity Rating Scale; dsDNA=double-stranded DNA; ECG=electrocardiogram; EQ-5D=EuroQoL 5 Dimension; ET=early termination; FACIT=Functional Assessment of Chronic Illness Therapy; FU=follow-up; HBV=hepatitis B virus serologies; HCV=hepatitis C virus; HIV=human immunodeficiency virus; Ig=immunoglobulin; IMP=investigational medicinal product; LupusQoL=Lupus Specific Quality of Life; MPA=mycophenolic acid; PGA=Physician's Global Assessment; PGIC=Patient Global Impression of Change; PGx=pharmacogenetics; RF=rheumatoid factor; RNP=ribonucleoprotein; SF-36=Medical Outcomes Study 36-item Short Form Health Survey; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC=Systemic Lupus International Collaborating Clinics; SRI-50=SLEDAI-2K Response Index-50; UPCr=urine protein:creatinine ratio; VAS=visual analog scale; wk=week.

1. Safety follow-up visits will be conducted at 4, 12 and 24 weeks after the last dose of IMP for subjects who have been discontinued from IMP or have completed the 24-week treatment period.
2. Subject eligibility (based on screening assessments of the inclusion and exclusion criteria) must be checked again on Day 1 prior to randomization.
3. 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.
4. Performed locally.
5. For women of childbearing potential or who are postmenopausal for less than 2 years. At Day 1, if the urine test is negative, the subject can be randomized and receive the first dose of IMP before the results of the serum pregnancy test are available.
6. Complaint-driven physical examination at these visits. Complaint-driven physical examination should always include assessment of HEENT, lungs, heart, abdomen, and extremities. Additional assessments should be performed as needed to fully obtain information needed for the BILAG and/or SLEDAI assessments if scheduled, as well as to fully evaluate any subject complaints or AEs.
7. Vital signs include seated arterial BP, heart rate and body temperature. Height will be measured at Day 1 only. Weight will be measured at each trial visit. Body weight will be measured with a balance beam scale, if possible.
8. See Table 7-1 for list of routine laboratory assessments.
9. For subjects in the PK subset only.
10. After an 8-hour fast (water allowed). Visit preferably takes place in the morning.
11. In subjects taking MMF/MPS only. The last MMF/MPS dose should have been taken at least 10 or more hours prior to plasma mycophenolate sampling and the subject should receive the next MMF dose after mycophenolate sampling has been performed.
12. Assessment of antibodies to tetanus toxoid, diphtheria toxoid and pneumococcal antigens.
13. a) Samples will be collected within 25 hours before the next scheduled dose of IMP.
    b) Samples will be taken from subjects in the PK sampling subset.
    c) At Day 2 and Week 23 Day 2 (Day 163), samples will be collected 24 hours following atacicept administration at Day 1 and Week 23 Day 2 (Day 163).
    d) At Day 1, 1 PK sample will collected pre-first dose. Another PK sample will be taken 4 h post-first dose from the PK-subset only.
14. Post-baseline samples will be analyzed only if appropriate assays are available.
15. For consenting subjects only.
16. If blood sample is not obtained at Day 1, this sample can be taken at another visit when possible.
17. Questionnaires should be completed before any other procedures are performed.
18. Training of subjects on self injection (or a caregiver) will be provided at the baseline visit and can be repeated at Week 1 as required per Investigator opinion.

NOTE: There is no visit window for the PK subset.