A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ALPN-101 IN SYSTEMIC LUPUS ERYTHEMATOSUS

Sponsor Protocol Number:	AIS-A03	
Investigational Product:	ALPN-101 (acazicolcept)	
Investigational Phase:	2	
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Compliance:	The study will be conducted in accordance with the International Council for Harmonisation Guidelines for Good Clinical Practice and applicable local and federal regulations.	
Sponsor Approval:	[redacted]	

Protocol No. AIS-A03

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF ALPN-101 IN SYSTEMIC LUPUS ERYTHEMATOSUS

Version: 4.0 [07 NOV 2022]

I attest that I have read this protocol. I agree to conduct the trial in accordance with the provisions herein, the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice, and local and federal regulations.

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure(s), and other scientific data.

_____

Principal Investigator name

_____ _____

Principal Investigator signature **Date**

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1. STUDY SUMMARY

Protocol Title	A randomized, double-blind, placebo-controlled study of ALPN-101 in systemic lupus erythematosus
Protocol Number	AIS-A03
Investigational Phase	2
Investigational Product	ALPN-101 Injection
Study Sites	Approximately 75 international sites
Sample Size	At least 130 subjects
Study Duration	Each subject will participate for up to 34 weeks, including a Screening period of up to 6 weeks, a 24-week Treatment period, and a 4-week Follow-up period.
Study Population	Adults 18 to 70 years of age, inclusive, with active systemic lupus erythematosus (SLE)
Study Design	This is a Phase 2, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety, tolerability, efficacy, immunogenicity, pharmacokinetics (PK), [redacted] of ALPN-101 in adults with moderate to severe active SLE. After signing the Informed Consent Form (ICF), subjects will be evaluated during a Screening period of up to 42 days. Screening laboratory evaluations will be performed; assessment of disease activity will be performed by the Investigator and reviewed by the Sponsor or designee to confirm eligibility. Subjects will return to the clinic on Day 1 and undergo Baseline procedures, including assessment and confirmation of disease activity by the Investigator. Subjects who continue to meet eligibility criteria will be randomized 1:1 to receive blinded study drug once every 2 weeks (Q2W) for a total of 12 doses of: (1) 3 mg/kg ALPN-101 or (2) Placebo Baseline medications that are used for the treatment of SLE (i.e., hydroxychloroquine/hydroxychloroquine-like drugs, corticosteroids, immunosuppressants) must be maintained at stable doses through the Day 169 assessments, except for incidences of toxicity, for a protocol-permitted short-term increase (burst and taper) of corticosteroid dose in response to increased disease activity, or discretionary reduction in corticosteroids (taper) after Day 85 in the context of improvement in disease activity. Assessments of safety, efficacy, PK, anti-drug antibodies (ADA), and [redacted] will be performed throughout the study. Refer to the Schedule of Procedures and Assessments (Table 1). Cumulative safety data will be reviewed at intervals by the Data Monitoring Committee (DMC), which will provide recommendations regarding study conduct, if indicated.

Primary Objectives	• To evaluate the safety and tolerability of ALPN-101 compared to placebo in subjects with chronic, moderate to severe active SLE
Secondary Objectives	• To evaluate the efficacy of ALPN-101 in subjects with active SLE • To assess the PK of ALPN-101 in subjects with active SLE • To assess the incidence of ADA against ALPN-101 in subjects with active SLE
[redacted]	
Summary of Key Inclusion Criteria	• Males and females, age 18 through 70 years, inclusive, at Screening • Diagnosis of SLE for ≥ 6 months prior to Screening, as defined in §5.1 • Positive anti-nuclear antibodies (ANA) (≥ 1:80) and/or elevated anti-double-stranded DNA (dsDNA) and/or elevated anti-Smith antibody test • Active SLE as defined in §5.1 at Screening as confirmed by Sponsor or designee, and at Baseline (i.e., prior to randomization on Day 1) as confirmed by Investigator • Stable, appropriate standard of care for SLE, as described in §5.1
Summary of Key Exclusion Criteria	• Life-threatening or organ system-threatening SLE activity, that is sufficiently active that it is expected to require increase in treatment during the study • Proteinuria consistent with nephrotic syndrome: ≥ 3.5 g proteinuria/day, estimated based on urine protein-creatinine ratio (UPCR) ≥ 350 mg/mmol at Screening • Active lupus-related neuropsychiatric disease (with the exceptions of mild stable lupus headache, fatigue, mild stable organic brain syndrome) • Drug-induced lupus • Evidence of active infection or risk or history of serious infection with tuberculosis; hepatitis B, hepatitis C; HIV • Evidence of active infection with SARS-CoV-2
Study Drug Administration	ALPN-101 or matching placebo will be administered by intravenous (IV) infusion via an infusion pump over approximately 30 minutes; study drug will be given Q2W for 12 total doses.
Primary Endpoints and Assessments	Safety and tolerability will be assessed by evaluating the type, frequency, severity, and seriousness of adverse events, including clinically significant changes in symptoms, physical exam findings, vital signs, laboratory tests (hematology, serum chemistries and coagulation, urinalysis), and electrocardiograms. Additional laboratory assessments and/or documentation may be collected as needed for characterization of adverse events of interest (AEIs).
Efficacy Endpoints and Assessments	Efficacy endpoints will be assessed by evaluating disease activity relative to baseline and across treatment groups using the tools and assessments listed below, and derivatives calculated from them (e.g., SLE Responder Index [SRI] -4, -5, -6 response; time to and proportion with flare of SLE; others).

	Global Disease Activity Assessment Tools: • British Isles Lupus Assessment Group index (BILAG) 2004 • Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K); SLEDAI-2K 30-Day (SLEDAI-2K 30) • Physician's Global Assessment of SLE Disease Activity (PhGA) [redacted] Patient Reported Outcomes and Quality of Life Assessment tools: • Patient's Global Assessment of Disease Activity (PtGA) • Short Form-36 (SF-36) health survey • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (13-item) Clinical Biomarkers of SLE Activity: • High-sensitivity C-reactive protein (hsCRP) • Complement levels: C3, C4, CH50 • Anti-dsDNA antibodies Corticosteroids: • Dose of oral and parenteral corticosteroids
Pharmacokinetic Endpoints and Assessments	Serum concentrations of ALPN-101 will be measured. Pharmacokinetic endpoints include estimates of maximum concentration (C_{max}), area under the concentration-time curve (AUC), and trough concentration (C_{trough}) at the end of dosing intervals. A population PK approach may be used to characterize the PK of ALPN-101 in SLE subjects.
Immunogenicity Endpoints and Assessments	The presence and titer of ADA against ALPN-101 will be assessed at Baseline (prior to study drug administration on Day 1) and at intervals throughout the study. Samples confirmed positive for ADA may be explored for neutralizing capacity. The relationship between ADA and PK will be analyzed; relationship between ADA and clinical outcomes may be explored.
[redacted]	
Statistical Considerations	**Randomization**: Subjects will be randomized 1:1; randomization will be stratified by background immunosuppressive therapy and geographic region. Subjects who are randomized but do not receive study drug may be replaced.

	Sample Size: A sample size of approximately 130 (~65 subjects/arm) will provide approximately 83–88% power (chi square two-sided test, alpha 0.05) to detect an absolute increase of 25% compared to placebo in the proportion of responders (e.g., as assessed by SRI-4 at Day 169) in the active treatment group, assuming a placebo response rate of 20–40%. **Statistical Methods:** All safety data will be summarized descriptively by treatment group and analyzed based on the safety population. Categorical safety endpoints will be summarized using incidence rates. The mean change from baseline, standard deviation, minimum, and maximum will be used to summarize continuous safety endpoints. No statistical inference is planned for the analysis of safety endpoints. All efficacy endpoints will be summarized and analyzed for the modified Intent-to-Treat population. For categorical endpoints, the number and proportion of subjects in each category will be presented by treatment group. Proportions of subjects achieving response will be compared using a Cochran-Mantel-Haenszel test adjusted for randomization stratification factors. An estimate of the difference in proportions and corresponding 95% confidence interval. P-value will be presented for efficacy endpoints of primary interest. For continuous endpoints, the mean, standard deviation, median, minimum, and maximum will be presented by treatment group. For continuous endpoints with multiple post-Baseline visits, the treatment effect will be assessed through Mixed-effect Model Repeated Measures (MMRM) based on observed data. Difference in least-squares means will be derived using an analysis of covariance model controlling for stratification factors and baseline scores. For each treatment comparison, an estimate of the difference in least-squares means, and corresponding 95% confidence interval will be presented.

2. BACKGROUND

2.1. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disease that affects 0.01% to 0.2% of people worldwide, and is characterized by failures of immune self-tolerance, with the generation of pathogenic subsets of lymphocytes and autoantibodies that disrupt the function of cells and homeostatic systems and mediate tissue injury in multiple organs. Etiology remains incompletely defined; there is evidence that genetic, epigenetic, environmental, immunologic, and hormonal factors may contribute to disease susceptibility and severity (1-5).

Clinically, lupus is characterized by periods of remission and relapse of constitutional and organ-specific signs and symptoms that are highly variable across populations and can change over time in individual patients. The most common clinical features include fever, debilitating fatigue, joint inflammation, skin and mucosal lesions, serositis, hematologic disorders including anemia, leukopenia or thrombocytopenia, and lupus nephritis. The latter is the most common life- and organ-threatening manifestation of SLE, estimated to impact 40% to 70% of patients, with progression to renal failure in 10% to 20% (6, 7). Less common but serious SLE manifestations include neuropsychiatric, demyelinating and neurovascular disease, and antiphospholipid antibody syndrome with venous thrombosis, arterial occlusion and/or fetal loss. Most other organ systems can also be involved (8-17).

Therapeutic management is tailored to the severity of disease and organ systems involved. Practice guidelines and consensus statements have been developed for treatment of SLE, lupus nephritis, and other organ-specific manifestations, and are revised at regular intervals to incorporate emerging data (18-20). Current standard of care (SOC) includes antimalarial agents for treatment of skin disease to reduce risk of flare in all patients, nonsteroidal anti-inflammatory drugs (NSAIDs) for management of headache and musculoskeletal pain, and corticosteroids for rapid reduction of inflammation and management of fatigue. Oral immunosuppressive agents (e.g., methotrexate, azathioprine, mycophenolate and others) are used to reduce dependence on corticosteroids and to address more persistent manifestations. Belimumab, an inhibitor of B cell growth factors, has been approved for use in refractory SLE and B cell depletion with rituximab is indicated for immune thrombocytopenia, including that arising in SLE, with benefit reported in other manifestations. High dose corticosteroids and cytotoxic agents (e.g., cyclophosphamide) are used for serious manifestations refractory to other agents. Initial treatment for clinically significant lupus nephritis comprises corticosteroids together with cyclophosphamide, azathioprine or mycophenolate. For lupus nephritis refractory to initial therapy, selective inhibition of the T cell-mediated immune response through the addition of calcineurin inhibitors has demonstrated benefit (21).

Despite earlier diagnosis and improved treatment regimens, more than 60% of patients with access to current best standards of medical care develop clinically-detectable organ damage within 2 to 7 years (22). A recent meta-analysis involving over 27,000 patients with SLE reported a 3-fold increase in the risk of death compared with the general population, primarily due to cardiovascular disease (23). Toxicity associated with corticosteroids and immunosuppression contributes substantially to the burden of disease: corticosteroid use is associated with loss of bone integrity and development of metabolic syndrome, contributing to cardiovascular disease; broad spectrum immunosuppressants increase the risk of serious infection and neoplasm, and use of calcineurin inhibitors is limited by nephrotoxicity. There is a continuing need to develop pharmacologic interventions that more specifically target pathogenic pathways, with the goal of improving efficacy while limiting toxicity.

2.2. CD28 and ICOS Inflammatory Pathways in Murine and Human Lupus

Both the cluster of differentiation (CD) 28-B7 and inducible T cell co-stimulator (ICOS) ligand (ICOS-L) co-stimulatory pathways have been implicated in the pathogenesis of both murine and human lupus. Numerous studies demonstrated that therapeutic inhibition of CD28, CD80, and/or CD86 reduces disease activity in animal models of lupus (24-37). In humans, polymorphisms in CD28 may confer susceptibility to at least some subsets of SLE (38); circulating levels of CD28, CD80, and/or CD86 are associated with disease activity and/or severity (39-41); and in SLE, T cells may exhibit an exaggerated response to CD28 signaling (38). However, therapeutic intervention on the CD28-B7 pathway with abatacept (Cytotoxic T-Lymphocyte-Associated Antigen 4-immunoglobulin [Ig]) or antibodies against CD28 have shown promising, but not statistically significant, efficacy in human SLE or lupus nephritis (42-44), suggesting that additional pathogenic pathways compensate during CD28-B7 inhibition. Indeed, CD28-low or -negative T cells, which presumably function independently of CD28 co-stimulation, are observed in SLE, often correlating with disease activity and/or severity (45-50).

The ICOS/ICOS-L costimulatory system is a candidate for a pathway that may account for bypass of, or resistance to, CD28-B7 inhibition. ICOS is highly homologous to CD28, but in contrast to CD28 the expression of ICOS is rapidly increased during T cell activation. It may therefore provide complementary and/or compensatory costimulatory signals in activated and/or effector T cells, which may otherwise be less dependent on CD28 signaling (51). Similar to CD28-B7, numerous preclinical studies have demonstrated that therapeutic inhibition of and/or deficiency in ICOS or ICOS-L reduces disease activity in animal models of lupus (28, 49, 52-59). Polymorphisms in ICOS may also confer susceptibility to at least some subsets of SLE (60); and there is similarly a correlation between expression of ICOS or ICOS-L and disease activity and/or severity, especially in association with follicular helper T cells which characteristically express ICOS (30, 44, 61-68), and in association with a subset of T peripheral helper cells that is expanded in active lupus nephritis and expresses ICOS and PD-1 (69). However, also similar to CD28 pathway inhibition, blockade of the ICOS/ICOS-L pathway alone appears also to be insufficient for the treatment of SLE, at least as suggested by early studies with prezalumab (AMG-557), an anti-ICOS-L monoclonal antibody (61, 70).

Combined inhibition of both CD28 and ICOS pathways may therefore be required to achieve clinically meaningful outcomes in SLE. In preclinical studies, combined blockade is associated with superior inhibition of T and B cell activation, as well as reduced disease in multiple animal models of systemic autoimmunity including models with features of lupus, arthritis, and Sjögren's syndrome (71, 72) (Alpine Immune Sciences, data on file). Novel therapeutics that concomitantly antagonize both the CD28 and ICOS pathways may prove beneficial in SLE by addressing two dominant, non-overlapping T cell costimulatory pathways, and may be superior to existing therapeutics.

2.3. Investigational Agent

ALPN-101 (acazicolcept; ICOS-L vIgD-Fc) is an Fc fusion protein of a human ICOS-L variant Ig domain (vIgD™) designed to inhibit simultaneously the CD28 and ICOS inflammation pathways. It is currently being evaluated for the treatment of alloimmune, autoimmune and/or inflammatory conditions that may be dependent on CD28 and/or ICOS pathways.

This is the first study to evaluate ALPN-101 in subjects with active SLE. A previous first-in-human (FIH) study evaluated the safety, tolerability, pharmacokinetics (PK), [redacted] of single and repeat doses ALPN-101 in healthy volunteers (76). In this FIH study, ALPN-101 was generally well-tolerated with no evidence of cytokine release, clinically significant immunogenicity, or severe adverse events (AEs) following subcutaneous (SC) doses up to 3 mg/kg or single intravenous (IV) doses up to 10 mg/kg or up to 4 weekly IV doses of up to 1 mg/kg. An open label study of

ALPN-101 in subjects with steroid-resistant or steroid-refractory acute graft-versus-host disease (GVHD) (AIS-A02, NCT04227938) enrolled a single subject prior to discontinuation of the study due to a change in corporate strategy. As reported in a case study, the patient received ALPN-101 for treatment of severe (Grade 3) disease of the lower gastrointestinal tract. An IV infusion at 0.3 mg/kg was well-tolerated and sustained high level target saturation of circulating T cells for at least 7 days (77). Stool volume declined within 2 days, permitting steroid taper, and by study Day 8 acute GVHD had resolved to Grade 0. The course suggested that GVHD responded quickly to a single low dose of ALPN-101.

2.4. Nonclinical Data

ALPN-101 demonstrates high affinity binding to human and cynomolgus monkey CD28 and ICOS, with lower affinity binding to rodent orthologs. Nonclinical studies demonstrate potent inhibition of T cell activation and suppression of disease activity in mouse models of GVHD, inflammatory arthritis, sialadenitis (Sjögren's syndrome), SLE, and other models of autoimmune and inflammatory diseases.

Rats and cynomolgus monkeys were utilized for nonclinical safety assessment of ALPN-101. The program includes a 1-month SC and IV repeat dose toxicology study in rats and cynomolgus monkey, a 3-month SC and IV repeat dose study in cynomolgus monkey, and a 6-month IV repeat dose study in cynomolgus monkeys. ALPN-101 was well tolerated; the no-observed-adverse-effect level (NOAEL) in the 1-month toxicology studies for both rat and cynomolgus monkey was the highest dose evaluated in each species via SC and IV administration: 200 mg/kg/week in rats and 150 mg/kg/week in cynomolgus monkeys. The NOAEL for ALPN-101 in both the 3-month and 6-month toxicology studies in cynomolgus monkey was the highest dose evaluated via SC and/or IV administration: 150 mg/kg/week.

2.5. Clinical Studies

Results of clinical studies are summarized below; please refer to the Investigator's Brochure (IB) for detailed and updated information.

AIS-A01: An FIH study (Study AIS-A01, NCT03748836) was conducted to assess the safety, tolerability, PK, and PD of single and repeated doses of ALPN-101 (N=66) or placebo (N=30) in adult healthy volunteers. Overall, ALPN-101 was safe and well tolerated at single ascending IV (0.001–10.0-mg/kg) or SC (1.0 mg/kg or 3.0 mg/kg) doses, as well as at multiple IV doses either once weekly (0.3 mg/kg or 1 mg/kg weekly) or once every 2 weeks (Q2W) (1.0 mg/kg fortnightly) for 4 weeks.

There were no severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or greater) AEs, no treatment-related serious adverse events (SAEs), and no treatment-related trends in laboratory safety parameters. The proportions of subjects reporting AEs of infection, headache, and aphthous ulcers were higher among subjects randomized to ALPN-101 compared to placebo; most were mild (Grade 1), and all resolved without sequelae. There were no infusion-related reactions (IRRs), no treatment-related hypersensitivity reactions, and no significant changes from baseline in circulating cytokines.

Refer to the IB for details regarding PK [redacted] results from the study which are also reported by Yang et al (76).

AIS-A02: Study AIS-A02 (NCT 04227938) was intended to be a single ascending dose study to assess the safety, tolerability, and efficacy of ALPN-101 in adults with steroid-resistant or -refractory acute GVHD. Due to a change in sponsor strategy, the study was terminated after enrollment of the first subject (0.3 mg/kg dose cohort). The enrolled subject had 6th-line steroid-refractory gastrointestinal tract acute GVHD. ALPN-101 was administered on study Day 1. No serious or Grade ≥ 3 AEs

attributable to ALPN-101 were recorded after dosing. Disease activity in the gastrointestinal tract resolved from Grade 3 to Grade 0 (no clinical activity) by Study Day 8. The subject experienced critical thrombocytopenia, intracranial hemorrhage, aspiration pneumonia, and sepsis on Study Day 11 with fatal outcome, attributed to pre-existing thrombotic microangiopathy attributed to tacrolimus (77). There were no serious or Grade ≥ 3 AEs attributable to ALPN-101; AEs did not prompt early termination of the trial.

2.6. Trial Rationale

As outlined in §2.2 and §2.3, the results of preclinical and nonclinical data are consistent with the hypothesis that by inhibiting immune activation through CD28 and ICOS, ALPN-101 may attenuate the signs, symptoms, and clinical sequelae associated with autoimmune and inflammatory diseases such as active SLE. As summarized in §2.4 and §2.5, ALPN-101 has thus far shown a favorable safety profile at doses that achieve and maintain high level target saturation. The data to date support evaluation of ALPN-101 in patients with SLE.

2.7. Benefit-Risk Statement

There has been no prior clinical experience with ALPN-101 in SLE, so its risk (safety) and efficacy profile in SLE have not been determined. Participants in this study may gain benefit if ALPN-101 results in improved clinical outcomes (e.g., improvements in disease activity, quality of life).

In healthy volunteers, the most common AEs in subjects who received ALPN-101 included headache, upper respiratory tract infections, and aphthous ulcers. Subjects reporting these AEs should be monitored and treated when indicated in accordance with local practice.

ALPN-101 did not cause cytokine release, and no infusion reactions were observed in healthy volunteers. Nonetheless, as with any biologic therapeutic administered by IV infusion, all subjects should be monitored during and immediately after dosing and treated if indicated according to local standard practices and guidance provided in §8.1.1.

Based on its mechanism of action, ALPN-101 should be considered potentially immunosuppressive and therefore may potentially reduce immunosurveillance and increase infection risk; all subjects should be monitored for infections and treated as indicated. With respect to the coronavirus (COVID-19) pandemic, there has been no experience with ALPN-101 in patients or healthy volunteers who are known to have been exposed to SARS-CoV-2 or to have contracted COVID-19; therefore, it is not known whether subjects receiving ALPN-101 may be at an increased risk for COVID-19 infection or to experience serious illness if infected. Management of these AEs will be made on a case-by-case basis with consideration of benefit/risk.

ALPN-101 may attenuate immune responses to—and production of potentially protective antibodies following—immunizations, including vaccines for SARS-CoV-2. Therefore, prior to study participation, subjects should be up to date on all age-appropriate vaccinations, including COVID-19, per local and professional guidelines for immunocompromised individuals (e.g., Centers for Disease Control [CDC], local professional society guidelines). Live vaccines should not be administered while receiving ALPN-101. Refer also to §8.3.

Given the significant continued morbidity and mortality seen in patients with SLE despite treatment with current SOC therapies, evaluation of ALPN-101 in this population is appropriate.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of ALPN-101 compared to placebo in subjects with chronic, moderate to severe active SLE.

3.2. Secondary Objectives

The secondary objectives of this study are:

- To evaluate the efficacy of ALPN-101 in subjects with active SLE
- To assess the PK of ALPN-101 in subjects with active SLE
- To assess the incidence of anti-drug antibodies (ADA) against ALPN-101 in subjects with active SLE

4. TRIAL DESIGN

4.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the safety, tolerability, efficacy, immunogenicity, PK, [redacted] of ALPN-101 in adult subjects with chronic, moderate to severe active SLE. Approximately 75 international sites will participate in this study. A total of approximately 130 subjects will be randomized 1:1 to receive a weight-based dose of ALPN-101 or placebo Q2W for a total of 12 doses:

- ALPN-101 at 3 mg/kg (n≈65)
- Placebo (n≈65)

Randomization will be stratified based on SLE treatment at Baseline and geographic region (see §10.2). Subjects will be followed for 4 weeks from the End of Treatment (EoT) visit (i.e., 6 weeks after the last dose of study drug), from the end of Day 155 through Day 197. Assessments of AEs and disease activity, and collection of blood and urine for safety laboratory values, biomarkers of disease activity, PK, ADA, [redacted], will be performed throughout the study. Refer to the Schedule of Procedures and Assessments (Table 1).

Dense PK samples will be collected in subjects that agree to participate; subjects in this subset will stay in the clinic for 4 hours following administration of the first dose of study drug, and will return to the clinic 1, 3, and 7 days following the first study drug administration for collection of additional samples.

Medications that are used for treatment of SLE at baseline (i.e., hydroxychloroquine/ hydroxychloroquine-like drugs, corticosteroids, immunosuppressants) should be maintained at stable doses through the Day 169 assessments, except for incidences of toxicity or for a protocol-defined short-term increase (burst and taper) of corticosteroid dose in response to increased disease activity or reduction in corticosteroids (taper) to reduce toxicity in the context of improvement in disease activity are detailed in §8.2.

Randomization will be stratified by geographic region and will be stratified based on SLE treatment at Baseline (see §10.2).

4.2. Estimated Duration of Participation

Each subject will participate for up to 34 weeks, including a Screening period of up to 6 weeks, a 24-week Treatment period, and a 4-week Follow-up period.

4.3. Stopping and Discontinuation Criteria

4.3.1. Study Stopping Criteria

The Sponsor may choose to discontinue the study at any time for any reason.

If any event(s) occur that, in the opinion of the Medical Monitor(s) or the Data Monitoring Committee (DMC), may contraindicate further administration of ALPN-101, enrollment of additional subjects, as well as administration of study drug, may be suspended. Such events may include, but are not limited to:

- SAEs assessed as related to study drug
- Grade 3 or 4 AEs assessed as related to study drug

The DMC and Sponsor will conduct a prompt review of cumulative safety data and the circumstances of the event(s) in question to determine whether randomization and dosing should be resumed, whether the

dose should be modified, whether the protocol should be modified, or whether the study should be discontinued permanently. Where applicable, the regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any actions taken with the study.

In the event of unanticipated suspension of dosing, subjects will continue regularly scheduled visits until a decision is reached by the Sponsor. If the study is stopped, subjects who have received study drug will continue to be followed for assessment of safety and other outcomes for at least 8 weeks following the last dose of study drug.

4.3.2. Individual Subject Stopping Criteria

Discontinuation of Study Drug

Individual subjects must pause or discontinue treatment with study drug in the following settings:

- Development or worsening of lupus manifestations requiring introduction of certain prohibited medications or prohibited dosages of background drugs, when continuation of the study drug would place the subject at risk, as determined by the Investigator or Medical Monitor; see §8.2.2.
- Clinically significant abnormal laboratory results or AEs which rule out continuation of the study drug, as determined by the Investigator or the Medical Monitor.
- Infection with SARS-CoV-2 during the Treatment Period; the Medical Monitor must approve the resumption of study drug dosing for any subject with confirmed (viral test positive) or suspected COVID-19 infection.
- Grade ≥ 3 infection (e.g., pneumonia, sepsis) which cannot be sufficiently controlled within an adequate timeframe by anti-infective treatment or would put the subject at risk for continued participation in the trial, as determined by the Investigator or the Medical Monitor.
- Inclusion or exclusion criteria violation that was noted after the subject started study drug, AND the Investigator and/or Medical Monitor determine that continuation of the study drug would place the subject at risk.
- Development of an electrocardiogram (ECG) change considered clinically significant and with reasonable possibility of relationship to study drug; or a confirmed absolute QT interval corrected for heart rate using Fridericia's correction formula (QTcF) value > 500 msec or confirmed increase of ≥ 60 msec from Baseline (i.e., if a subject's QTcF increases from Baseline ≥ 60 msec, the Investigator will evaluate, confirm the value, and treatment should be stopped).
- Development of active or latent tuberculosis (TB) at any time during the study; a subject with active or latent TB must pause dosing with blinded study drug; dosing can only be resumed following initiation of appropriate treatment and with the approval of the Medical Monitor.
- Pregnancy while on study drug.
- Malignancy, except for localized non-melanoma skin cancer or carcinoma in situ of the cervix; if localized cancer is surgically excised with clear margins, dosing may resume following consultation with the Medical Monitor.
- Significant non-compliance with study procedures to a degree that would put the subject at risk for continued participation in the trial as determined by the Investigator or the Medical Monitor.

- Development of active neuropsychiatric SLE (excluding lupus headache) sufficiently severe to interfere with ability of the subject to provide ongoing informed consent.
- Investigator decision: Investigator believes it is in the best interest of the subject to discontinue treatment with study drug.

Subjects who prematurely discontinue treatment with study drug should have all procedures outlined in the EoT visit, as well as an unscheduled ECG, performed as soon as possible, and not later than the next scheduled visit.

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue treatment, and who do not withdraw consent, should otherwise continue with their regular study visit schedule without receiving study drug. In subjects who are unable to continue their regularly scheduled visits, a follow-up phone call should occur approximately 8 weeks (corresponding to 5X half-life) after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

Discontinuation from the Study (Early Termination)

In addition to the criteria for discontinuing study drug summarized above, individual subjects may be discontinued from the study prematurely (i.e., prior to Day 197) for any of the following reasons:

- Subject decision / withdrawal of consent; subjects can request to be discontinued from participation in the study at any time for any reason
- Investigator decision: Investigator believes it is in the best interest of the subject to be withdrawn from the study

For subjects who withdraw from the study prematurely (i.e., prior to Day 197), the End of Study (EoS) evaluations should be completed if possible, preferably within 2 weeks of study drug discontinuation. In addition, a follow-up phone call should occur approximately 8 weeks (corresponding to 5X half-life) after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

4.4. Rationale for Study Design, Dose Regimen, and Population

4.4.1. Choice of Study Population

The study population will comprise adults with at least 6 months history of SLE, who have moderate to severe active disease on stable SOC, but who do not require immediate aggressive therapy to prevent organ system damage. Subjects are required to have activity in the musculoskeletal system, and/or mucocutaneous system, and/or renal system and/or have pleuritis or pericarditis at Screening and Baseline. This population will allow assessment of the safety of ALPN-101 in the context of active inflammatory disease, and on a background of treatments commonly used for SLE. Assessment in subjects with this level of activity and involvement of relatively assessable organ systems at baseline may allow changes to be detected through use of general and/or organ-specific assessment tools.

A central verification system will be used to confirm that the level of disease activity at Screening is consistent with inclusion/exclusion criteria, thereby reducing the impact of variability in Investigator assessment of disease activity and use of assessment tools.

4.4.2. Justification of Study Design

The study will be randomized, placebo-controlled, and blinded to minimize bias in reporting of safety events, partially-subjective disease activity measures, and patient-reported outcomes.

Randomization will be stratified by use of concomitant oral immunosuppressive therapy; stratification will reduce the risk that the safety assessment of ALPN-101 may be confounded by imbalance in SOC agents that carry their own risks of AEs.

Randomization also will be stratified by geographic region.

4.4.3. Justification of Dose

The dosing regimen for this study is 3 mg/kg IV administration Q2W for 12 total doses. This regimen was selected to provide sufficient drug exposure to achieve and sustain high target saturation (≥ 90%) on peripheral T cells and to be within appropriate safety margins of the NOAEL in Good Laboratory Practice (GLP) toxicology studies in cynomolgus monkeys.

Specifically, the geometric mean and lower limit of 95% confidence interval of the serum concentration of ALPN-101 at 3 mg/kg Q2W are predicted to maintain target saturation greater than 90% for at least 24 weeks. The projected steady state exposures at 3 mg/kg are 47-fold (maximum concentration [C_{max}]) and 31-fold (area under the concentration-time curve [AUC]) lower relative to exposures at NOAEL (150 mg/kg/week) in the 13-week and 6-month GLP toxicology studies in cynomolgus monkeys.

4.4.4. Justification of Endpoints

This is the first clinical investigation to evaluate ALPN-101 in patients with active SLE, and the first clinical investigation of dosing over a duration of greater than 4 weeks. Therefore, the primary objective is safety and tolerability which will be assessed by the type, frequency, severity, and seriousness of AEs, including clinically significant changes in symptoms, physical exam findings, vital signs, laboratory tests (hematology, serum chemistries, coagulation and urinalysis), and ECGs, and will be evaluated by comparison to placebo. Additional assessments and/or documentation will be collected for SAEs and may be collected for adverse events of interest (AEIs) related to mechanism of action (i.e., infections), mode of administration (e.g., infusion reactions), or observations in completed and ongoing trials (e.g., aphthous ulcers).

A secondary objective is to evaluate the efficacy of ALPN-101 based on change in disease activity compared to placebo. The measurement of disease activity in SLE involves an assessment of characteristic signs and symptoms across multiple organ systems, along with the results of laboratory parameters. Multiple tools for assessment of global disease activity have been developed. The present study employs the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and SLEDAI-2K 30-Day (SLEDAI-2K 30), British Isles Lupus Assessment Group index (BILAG) 2004, the Patient's Global Assessment of Disease Activity (PtGA), and a Physician's Global Assessment of SLE Disease Activity (PhGA). The data from these tools can be used alone or combined as responder indices to measure efficacy.

To gain a broad understanding of the potential impact of the novel mechanisms of ALPN-101 on SLE activity, change from baseline over time and comparison to placebo in results of several other assessments will be explored. These include assessments that may be more sensitive to change in selected organ systems (Cutaneous Lupus Erythematosus Disease Area and Severity Index [CLASI] for mucocutaneous disease; [redacted]); proteinuria and renal function for nephritis); combined responder indices (e.g., SLE Responder Index [SRI]-4, -5, -6, -7, BILAG-based responder indices, others); prevention of increases in disease activity (e.g., proportion with, and time to new BILAG A or new or worsening BILAG B score; requirement for increased or new treatment); changes in laboratory parameters associated with SLE activity (e.g., C3, C4, CH50, high-sensitivity C-reactive protein (hsCRP), level of antibodies to double-stranded DNA [dsDNA]); and/or changes in [redacted] potentially

associated with SLE disease activity. Detailed description of assessment tools is provided in the Procedures Manual.

Corticosteroids are associated with significant morbidity but are often highly effective and are often used to quickly control disease flares or when other therapeutic measures are inadequate. Within defined limits, the present study permits short term use (burst and taper) for increased activity during the study and provides guidelines for taper from baseline dose if disease activity improves (see §8.2.2). Dose and indication for change in dose of corticosteroids will be captured as concomitant medications. Change from baseline, number of bursts, and total corticosteroid use will be explored as a potential indication of efficacy.

Patient-reported outcomes provide information that expand upon, and may differ from, information derived from disease activity assessments, in that they incorporate important subjective experience, including fatigue and quality of life, and integrate potential negative impact of therapeutic interventions. Therefore, the PtGA, Short Form-36 (SF-36) health survey version 2, and the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (13-item) will be assessed at intervals, [redacted] of change from baseline and across treatment groups will be performed.

Pharmacokinetic parameters, the impact of ADA, and the relationships between exposure and target saturation that were defined in healthy volunteers may not be fully applicable in SLE patients, due to potential effects of SLE-related immune dysregulation, ongoing inflammation, proteinuria, and background medication. Serum levels of ALPN-101, target saturation by ALPN-101 on circulating T cells, and ADA will be assessed throughout the study. The impact of exposure, target saturation, and ADA on clinical outcomes may be explored.

5. SELECTION OF SUBJECTS

Prospective approval of protocol deviations to recruitment and enrollment criteria is not permitted.

5.1. Inclusion Criteria

Subjects who provide informed consent are eligible to be included in the study only if all the following criteria apply:

1. Males and females, age 18 through 70 years, inclusive, at Screening.
2. SLE onset ≥ 6 months prior to Screening based on Investigator judgement with approval by Sponsor.

   Subject must have met the 2019 European League Against Rheumatism (EULAR) / American College of Rheumatology (ACR) Classification Criteria for SLE (73), including at least one clinical criterion and an additive criterion score of ≥ 10 at any time in the past up to and including the day of Screening.
3. Subjects must have a positive anti-nuclear antibodies (ANA) (titer ≥ 1:80) and/or elevated anti-dsDNA and/or elevated anti-Smith antibody test (if the screening test(s) are negative [based on central or local testing], then an historic positive serology for ANA, elevated anti-dsDNA, and/or elevated anti-Smith antibody test, with unequivocal documentation, may be accepted).
4. Subjects must demonstrate active SLE at Screening, as indicated by a SLEDAI-2K 30 score of ≥ 6 (excluding lupus headache and/or organic brain syndrome), and must have a clinical score at Baseline (i.e., Day 1 prior to randomization) of ≥ 4 (excluding lupus headache and/or organic brain syndrome).
5. Subjects must have SLEDAI-2K 30 clinical points in at least one of the following at Screening and Baseline: arthritis; myositis; urinary casts; hematuria; proteinuria; pyuria; rash; alopecia; mucosal ulcers; pleurisy; pericarditis. In addition:
   a. If all 4 of the required entry points are for arthritis, there must be a minimum of **3** joints that are painful and show signs of inflammation (i.e., tenderness, swelling, or effusion).
   b. If entry is based on renal parameters, at least <u>one</u> of the following must be true:
      - Active urinary sediment, assessed after excluding infection or contamination.

        OR
      - Urine protein-creatinine ratio (UPCR) at Screening of least 50 mg/mmol (or 24-hour urine protein at least 0.5 g) that has not improved by at least 25% over the prior month; if records are not available, this assessment should be made by the Investigator based on history and best judgement.

        OR
      - Histologic evidence of active nephritis within the last 3 months.
6. The Investigator's preliminary determination of organ system activity at Screening must be verified by the Sponsor or their designee to confirm eligibility. The Investigator will determine and confirm eligibility at Baseline (i.e., Day 1 prior to randomization).
7. Subjects must be on appropriate SOC (i.e., at least one anti-malarial or an immunosuppressant) for SLE, based on the Investigator's judgement. If taking the following medications, the subject must be on a stable dose prior to Baseline (i.e., Day 1 prior to randomization) for the period of

time specified below, and must intend to continue at stable doses throughout the 24-week Treatment Period, unless otherwise specified by this protocol:

- Corticosteroids: stable between Screening and Baseline (NOTE: dose must not be greater than 20 mg/day prednisone or equivalent).
- Hydroxychloroquine/hydroxychloroquine-like drugs: stable between Screening and Baseline (NOTE: dose must not be greater than 400 mg daily hydroxychloroquine or equivalent).
- NSAIDs or cyclooxygenase-2 (COX-2) inhibitors that are used continuously (at or below the maximum approved dose, and with approval by the Sponsor or designee): stable for 14 days prior to Baseline; the requirement for stable and continuous use does not apply to NSAIDS that are used intermittently for management of pain.

  Subjects who are using NSAIDs infrequently or "as needed" should make every attempt to withhold dosing on study visit days until SLE assessments have been completed.

For the following drugs, subjects must be on stable doses for 4 weeks prior to Screening until Baseline and for the remainder of the study:

- Methotrexate (7.5–25 mg weekly)
- Azathioprine (50–150 mg daily)
- Leflunomide (10–20 mg daily)
- 6-Mercaptopurine (50–200 mg daily)
- Mycophenolate mofetil (500–2000 mg daily)
- Mycophenolic acid (360–1440 mg daily)
- Permitted dose and stability period for agents not listed here, but not specifically excluded by this protocol, require discussion with, and agreement by, the Medical Monitor

8. Willing to provide consent for serial photographic documentation of any cutaneous manifestations of SLE, and/or oral mucocutaneous lesions (including aphthous ulcers) not attributed to SLE, from Screening through the EoS.
9. Women of child-bearing potential (WOCBP; defined in APPENDIX 1) or male patients with a WOBCP partner must agree to use highly effective methods of contraception as defined in APPENDIX 1 during study treatment and for 3 months following the last dose of study drug.
10. Able to provide written, informed consent.
11. Should be up-to-date on all age-appropriate vaccinations, including COVID-19, per local and professional guidelines for immunocompromised individuals (e.g., CDC, local professional society guidelines).
12. Peripheral venous access anticipated to be adequate to tolerate planned dosing regimen of IV infusions and blood draws Q2W per Table 1.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. Life-threatening or organ system-threatening SLE activity that is sufficiently active that it is expected to require increase in treatment during the study.
2. Proteinuria consistent with nephrotic syndrome (i.e., ≥ 3.5 grams proteinuria/day, estimated based on UPCR ≥ 350 mg/mmol) at Screening.
3. Active lupus-related neuropsychiatric disease at Screening or Baseline (i.e., Day 1 prior to randomization), as defined by the central nervous system portion of SLEDAI-2K 30 or BILAG 2004 (with the exceptions of mild stable lupus headache, fatigue, mild stable organic brain syndrome).
4. Drug-induced lupus.
5. Any serious health condition, which, in the opinion of the Investigator or Sponsor, would place the subject at undue risk from the study or would confound interpretation of safety or efficacy outcomes, including, but not limited to:
    a. Uncompensated congestive heart failure as defined by New York Heart Association Class III or IV.
    b. Clinically significant active cardiac disease (e.g., unstable angina or acute myocardial infarction ≤ 3 months prior to first dose of study drug).
    c. Clinically relevant or significant ECG abnormalities at Screening, including ECG with QTcF; in subjects with ventricular conduction delay (QRS > 120 msec), cardiologist consultation and discussion with, and agreement of, Medical Monitor is required for participation.
    d. Active cerebrovascular disease (e.g., stroke or transient ischemic attack) ≤ 3 months prior to first dose of study drug, unless attributed to SLE disease and stable on treatment.
    e. Uncontrolled hypertension, defined by a persistent systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg.
    f. Uncontrolled diabetes.
    g. Known clinically significant immunodeficiency.
    h. Current or recent (within the past 12 months) history of alcoholism or significant drug abuse (recreational use of cannabis is not an exclusion criterion).
    i. Elective major surgery anticipated to take place during the study period.
6. Recent serious or ongoing infection; risk or history of serious infection, including:
    a. Active or latent TB (refer to §6.7 for specific requirements for TB screening).

       Subjects with a history of latent TB are allowed with documentation of completed treatment with a regimen recommended by an appropriate local or national health authority (e.g., CDC).
    b. Hepatitis B virus: serologic evidence of hepatitis B infection based on the results of testing for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B surface antibody (HBsAb) as follows:
        i. Subjects positive for HBsAg are excluded.

ii. Subjects negative for HBsAg but positive for HBcAb, regardless of HBsAb status will be excluded.

c. Hepatitis C virus (HCV): HCV RNA detectable in any subject with positive HCV antibody.

d. Seropositivity for HIV at Screening.

e. Positive reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at Screening.

Patients who test positive for SARS-CoV-2 may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:

- Symptomatic patients: At least 2 negative RT-PCR viral tests in a row, ≥ 24 hours apart, after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath).
- Asymptomatic patients: At least 2 negative RT-PCR viral tests in a row, ≥ 24 hours apart, after at least 10 days have passed since prior positive result.

f. History of progressive multifocal leukoencephalopathy.

g. Receipt of oral or parenteral anti-infectives (antibacterials, antivirals, antifungals, or antiparasitic agents) for infection, ≤ 2 weeks prior to Day 1 (NOTE: chronic oral antibiotics used for prophylaxis may be permitted, dependent on discussion with, and agreement of, the Medical Monitor).

7. Receipt of live vaccination ≤ 8 weeks prior to Baseline (i.e., Day 1 prior to randomization), or expected to require live vaccines during the study (see also §8.3).

8. Screening laboratory abnormalities of any of the following:

a. Hemoglobin < 8.0 g/dL.

b. Absolute neutrophil count < 1000/μL (< 1.0×10^9/L).

c. Platelet count < 50,000/μL.

d. B cell count < 50 cells/μL.

e. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN) unless associated with elevated creatine phosphokinase (CPK) in the context of active myositis.

f. Serum total bilirubin > 1.5 x ULN, or > 3x ULN for patients with Gilbert's syndrome.

g. Estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73m^2 as assessed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-equation.

9. History of new, ongoing, or recurrent malignancy ≤ 5 years prior to first dose of study drug except basal cell carcinoma of the skin, squamous cell skin cancer, or in situ carcinoma that has been adequately treated with no evidence of recurrent disease for ≥ 12 months.

10. Pregnant or breastfeeding at the time of screening, or plans to become pregnant ≤ 3 months following the last dose of study drug.

11. Fulfills diagnostic criteria for another rheumatic disease that overlaps with SLE (e.g., mixed connective tissue disease, overlap connective tissue disease) that may confound clinical

assessments in the study. However secondary sicca or Sjögren's syndrome or antiphospholipid antibody syndrome that is stable on appropriate therapy is allowed.

12. Prior diagnosis of, or fulfills diagnostic criteria for, another autoimmune or inflammatory disease that may confound clinical assessments or increase subject risk in the study, including Behçet's disease, periodic fever syndrome, spondyloarthritis (including psoriatic arthritis, ankylosing spondylitis, reactive arthritis, enteropathic arthritis), inflammatory bowel disease including celiac sprue, or multiple sclerosis. Autoimmune thyroid disease and history of type 1 diabetes are allowed. Other disorders not specifically named are subject to discuss with, and agreement by, the Sponsor or designee.
13. Diagnosis of fibromyalgia or fulfills ACR Diagnostic Criteria for Fibromyalgia (e.g., 2010 Preliminary Diagnostic Criteria).
14. Functional class IV as defined by the ACR 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis.
15. Medications not intended to be continued during the study period in compliance with Inclusion Criterion 7 must meet the following washout requirements prior to Baseline (i.e., Day 1 prior to randomization):
    a. Oral or parenteral glucocorticoids: 2 weeks if highest administered dose was 20 mg or less; 4 weeks if highest administered dose was > 20 mg (NOTE: this applies only if corticosteroids are not planned to be continued. See Inclusion Criterion 7 if corticosteroids are planned to be used during the study).
    b. Cyclophosphamide: 12 weeks.
    c. Plasmapheresis: 24 weeks.
    d. Cyclosporine, tacrolimus, methotrexate, leflunomide, azathioprine, 6-mercaptopurine, mycophenolate, tofacitinib, or other Janus kinase inhibitors: 4 weeks.
    e. Biologic therapies, including but not limited to: atacicept, telitacicept, belimumab, abatacept, belatacept, anifrolumab, inhibitors of interleukin (IL) pathways IL-6, IL-12/23, IL-17, IL-1, tumor necrosis factor α, or interferon α: 12 weeks (exception: the use of prophylactic COVID-19 monoclonal antibodies in immunocompromised subjects is encouraged as per Principal Investigator's discretion and local guidelines).
    f. Rituximab, ocrelizumab, obinutuzumab or other B cell-modulating therapies: 48 weeks, or at least 24 weeks if B cells have returned to 50 cells/μL).
    g. Vaccinations targeting immune pathways (e.g., interferon kinoid vaccination) (Note: this does not apply to vaccinations against infectious organisms): 104 weeks.
    h. Other biologics, including investigational products: 12 weeks or 5 half-lives, whichever is longer.
    i. Other drugs, including investigational products: 4 weeks or 5 half-lives, whichever is longer.
    j. Combination therapy with ≥ 2 immunosuppressants for the treatment of SLE: A discussion with, and agreement by, the Medical Monitor and Sponsor will be required.
16. Serious SLE disease activity, which, in the opinion of the Investigator, warrants immediate immunosuppressive therapy not appropriate for the study (e.g., severely active neuropsychiatric SLE, rapidly progressive glomerulonephritis or vasculitis warranting immediate pulse corticosteroids and/or immunosuppressants such as cyclophosphamide) or which makes the possibility of receiving placebo or investigational agent an inappropriate risk.

Note: Independent of the Investigator's opinion regarding therapy, subjects with histologic evidence of diffuse proliferative glomerulonephritis within 12 weeks of the start of Screening are not eligible.

17. Ongoing participation in another therapeutic clinical trial.
18. Known hypersensitivity to ALPN-101, components thereof, or excipients contained in the drug formulation.
19. Any condition or circumstances which in the opinion of the Investigator or Sponsor may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.

6. CLINICAL TRIAL PROCESSES AND PROCEDURES

The schedule of study visits, procedures, and assessments is provided in Table 1. All visit windows are noted and should be calculated from randomization (Day 1). Unscheduled evaluations may be performed at any time at the discretion of the Investigator as needed to assess subject's clinical status; in the event of increased disease activity requiring a change in treatment, subjects should return to clinic as soon as possible to facilitate detailed documentation of disease flare.

All per-protocol clinical laboratory disease-related and safety assessments should be performed by the central laboratory. Planned time-sensitive laboratory evaluations may be duplicated at the site. A Laboratory Manual will provide specifics regarding procedures for the collection, processing, storage, and shipment of samples.

A Procedures Manual will provide details regarding processes for subject screening, data collection, skin photography, oral mucocutaneous lesion photography, ECG requirements, eligibility verification, randomization, follow-up, and other study-related activities. The Procedures Manual will also include information regarding training, conduct, and reporting for efficacy assessments and quality of life measures.

6.1. Screening (Day -42 to -1)

All screening procedures must be performed within 42 days of Baseline (Day 1 prior to randomization). The screening evaluations may be carried out over more than one visit; however, all assessments should be completed and documented as soon as possible—and no later than 14 days prior to planned randomization—to ensure that verification of disease activity can be completed within the screening window. Screening laboratory assessments that are out-of-range may be repeated once.

Subjects must undergo the following screening assessments and evaluations:

- Obtain written informed consent inclusive of appropriate privacy authorization prior to undergoing any study-specific interventions.
- Obtain Medical History, including complete EULAR/ACR SLE disease history and diagnosis form (refer to Procedures Manual).
- Obtain demographic information.
- Complete Review of Systems.
- Perform complete physical exam including height measurement; obtain vital signs and weight.
- Perform Investigator disease activity assessments (refer to Procedures Manual):
  - BILAG 2004
  - SLEDAI-2K 30
  - PhGA

  - In subjects with cutaneous involvement considered to be attributable to SLE, skin photography should be performed

- Perform TB screening, including chest x-ray (if applicable), as described in §6.7.
- Obtain ECG.
- Using the provided kits, collect blood, urine, and saliva or nasal swab for safety laboratory evaluations, thyroid stimulating hormone, infectious disease screen, diagnosis and characterization of SLE, and clinical biomarkers of SLE disease activity (see APPENDIX 2).
- Perform urine pregnancy test for WOCBP (see APPENDIX 1) using the provided kits.

Results from all Screening evaluations must be promptly entered, and no later than 14 days prior to planned randomization. Subjects who appear to meet eligibility criteria must undergo central review and verification of SLE disease activity by the Sponsor and/or designee prior to randomization (see Inclusion Criterion 2 and 6). Refer to the study Procedures Manual for details.

Note: At screening, a local laboratory can be used with permission from the Sponsor.

6.2. Day 1: Baseline, Randomization and Initiation of Treatment

Baseline (Pre-randomization, Pre-dose)

Ensure that Screening eligibility has been reviewed and verified.

Perform the baseline assessments noted below:

- Update medical history with any changes from the Screening visit as indicated
- Update concomitant medications as indicated
- Perform complete physical examination; obtain vital signs and weight

  Note: the baseline weight should be used to calculate all doses of study drug
- Obtain ECG
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE

  Note: all lab samples should be submitted to the central lab; local (duplicate) results may be used to confirm Baseline eligibility
- Perform urine pregnancy test for WOCBP using the provided kits
- Complete the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI) (73)

  NOTE: Documentation to support damage will be collected when available (e.g., radiographic evidence to support diagnosis of avascular necrosis); refer to Procedures Manual
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]

NOTE: Additional procedures may be required to support activity in some organ systems (e.g., radiographic confirmation of pleural or pericardial effusion); refer to Procedures Manual.

- Obtain skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)
- Confirm subject's eligibility based on Baseline assessments (see Inclusion Criterion 4)

- Using the provided kit, collect blood samples for PK[redacted]
- Using the provided kit, collect DNA sample for subjects who have provided appropriate informed consent

Randomization, Dosing, and Follow-up

- Randomize eligible subjects according to the study Procedures Manual
- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- Subjects should be observed for at least 2 hours following their first infusion of study drug
- At 10 minutes (± 10 min) after dosing, obtain the following in the order listed:
  - Blood for PK[redacted] using the provided kit, vital signs, and ECG
  - Record AEs and concomitant medications
- **Dense PK Subset only**: at 4 hours (± 30 min) after dosing, obtain blood for PK using the provided kit

6.3. Days 2, 4, and 8 (Dense PK Subset Only)

The following assessments and procedures will be performed for subjects in the Dense PK subset only:

- Record AEs and concomitant medications
- Using the provided kit, collect blood sample for PK

6.4. Treatment Period

6.4.1. Day 15

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform physical examination and obtain vital signs
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Perform limited Investigator disease activity assessments
  - SLEDAI-2K: For this date, SLEDAI is assessed based on presentation without reference to the previous 30 days
  - PhGA
- Skin photography, if applicable

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs

- Subjects should be observed for 30 minutes following infusion of study drug

6.4.2. Day 29

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform physical examination; obtain vital signs and weight
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collected blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]
- Skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.3. Day 43

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination and obtain vital signs
- Perform urine pregnancy test for WOCBP using the provided kits

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.4. Day 57

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable

- Perform physical examination; obtain vital signs and weight
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]
- Skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.5. Day 71

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination and obtain vital signs
- Perform urine pregnancy test for WOCBP using the provided kits

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.6. Day 85

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform physical examination; obtain vital signs and weight
- Obtain ECG
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]

- Perform urine pregnancy test for WOCBP using the provided kits
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]
- Skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain the following in the order listed: blood for PK/PD using the provided kit, vital signs, and ECG
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.7. Day 99

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination and obtain vital signs
- Perform urine pregnancy test for WOCBP using the provided kits

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.8. Day 113

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination; obtain vital signs and weight
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]

- Skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.9. Day 127

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination and obtain vital signs
- Perform urine pregnancy test for WOCBP using the provided kits

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.10. Day 141

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform physical examination; obtain vital signs and weight
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]
- Skin photography, if applicable
- Obtain subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain vital signs

- Subjects should be observed for 30 minutes following infusion of study drug

6.4.11. Day 155

Predose

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination and obtain vital signs
- Obtain ECG
- Using the provided kit, collected blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits

Dosing and Follow-up

- Prepare and administer study drug in accordance with instructions in the Pharmacy Binder
- At 10 minutes (± 10 min) after dosing, obtain the following in the order listed: blood for PK using the provided kit, vital signs, and ECG
- Subjects should be observed for 30 minutes following infusion of study drug

6.4.12. Day 169 (End of Treatment)

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform problem-oriented physical examination; obtain vital signs and weight
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]
- Perform urine pregnancy test for WOCBP using the provided kits
- Complete the SDI

  NOTE: Additional procedures and/or documentation to support diagnosis of new damage, compared to Baseline, may be required (e.g., radiographic evidence to support diagnosis of avascular necrosis; photography to support new diagnosis of skin damage; other); refer to Procedures Manual.
- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI, [redacted]
- Skin photography, if applicable
- Obtain Subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)

6.5. Day 197 (End of Study)

The EoS visit should be scheduled 4 weeks after the EoT visit (Day 169) and should include the following:

- Record AEs and concomitant medications
  - Photography of any oral mucocutaneous lesions reported as AEIs, if applicable
- Perform complete physical examination; obtain vital signs and weight
- Obtain ECG
- Using the provided kit, collect blood and urine samples for safety laboratory evaluations and clinical biomarkers of SLE
- Using the provided kit, collect blood samples for PK[redacted]/ADA
- Perform urine pregnancy test for WOCBP using the provided kits
- Complete the SDI

NOTE: Additional procedures and/or documentation to support diagnosis of new damage, compared to Baseline, may be required (e.g., radiographic evidence to support diagnosis of avascular necrosis; photography to support new diagnosis of skin damage; other); refer to Procedures Manual

- Perform Investigator disease activity assessments: BILAG 2004, SLEDAI-2K 30, PhGA, CLASI,[redacted].

NOTE: Additional procedures are required to support activity in some organ systems (e.g., confirmation of pleural or pericardial effusion). Refer to Procedures Manual

- Obtain Subject's disease assessments: PtGA, SF-36, FACIT-F (13-item)
- Skin photography, if applicable

6.6. Unscheduled Visits

6.6.1. Early Termination

If a subject withdraws consent for study participation prior to Day 197, the EoS evaluations should be completed if possible, preferably within 2 weeks of study drug discontinuation. In addition, a follow-up phone call should occur 8 weeks after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

As noted in §4.3, subjects who prematurely discontinue treatment with study drug (i.e., due to subject choice, Investigator decision, an AE or other contraindication for ongoing receipt of study drug, etc.), and who do not withdraw consent, should have all procedures outlined in the EoT visit as well as an unscheduled ECG, as soon as possible, preferably within 2 weeks. Afterwards, subjects should resume following the regular visit schedule as outlined in Table 1, and adhere to all study procedures except for study drug dosing. As the subject has discontinued study drug, all concomitant medication restrictions as outlined in §8.2.2 no longer apply. If at any point subsequently a subject no longer wants to provide assessments (withdrawal of consent) following discontinuation of study drug and completion of the EoT assessments, an EoS visit is not required.

6.6.2. Unscheduled Visits for Increased SLE Activity

Subjects requiring an unscheduled visit due to an increase in their SLE activity should have all safety assessments completed, SLEDAI-2K (assessed based on presentation without reference to the previous 30 days), the PhGA, and the clinical biomarkers of SLE. BILAG will not be performed at an unscheduled visit for increased SLE activity; increased activity should be captured at the next scheduled BILAG assessment, if applicable. See Procedures Manual.

6.6.3. Other Unscheduled Visits

At any other unscheduled visits, the full set of safety assessments should be completed.

6.7. Description of Study Procedures

Medical and Disease History, Demographics

Includes medical, surgical, and disease histories. Disease history includes date of diagnosis, prior treatment and responses, and remarkable toxicities. Demographic information includes sex, age, and self-reported race/ethnicity. Ongoing medical conditions will be documented, together with medications and therapeutic procedures that are expected to continue during the study. At Screening, a detailed history of prior SLE activity will be obtained.

Physical Examination

Complete physical examination will be performed at intervals designated in the schedule of assessments, and will include examination of head, eyes, ears, nose and throat, lungs, heart, abdomen, joints, muscle and soft tissues, neurologic system, skin and lymph nodes.

Physical examination that is adequate to assess SLE disease activity by BILAG and SLEDAI-2K 30 will be performed at each visit at which those assessment tools are employed, as designated in the schedule of assessments and detailed in the Procedures Manual.

Physical examination directed based on the review of system and/or AEs will be performed at planned and unplanned visits as indicated.

Vital Signs

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be obtained with the subject at the times indicated in the summary of assessments. Unless otherwise specified, all vital signs should be measured after the subject has been resting, preferably for at least 5 minutes, and prior to invasive procedures such as drawing blood.

Weight

Body weight (kilograms) will be obtained with the patient's shoes and jacket or coat removed. Total dose of blinded study drug administered will be based on the weight at Baseline (Day 1) unless weight has changed from baseline by more than 10%. In that case, total dose of blinded study drug administered will be based on the most current weight.

Electrocardiogram

All ECGs should be obtained in accordance with the central ECG instructions in the Procedures Manual. Subjects are to be resting, preferably in the supine position for approximately 5 minutes before each ECG.

TB Screening

The imaging and diagnostic tests for TB screening should be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the Investigator to determine if a subject has previous, active, or latent TB.

At Screening, a chest x-ray will be performed for all subjects to rule out the presence of TB; however, the chest x-ray will not be required if a subject had a previously normal imaging result (chest x-ray or computed tomography) within 3 months of screening, provided all source documentation is available at the site and provided nothing has changed in the subject's medical history to warrant a repeat test.

All subjects will be tested for TB infection by QuantiFERON-TB Gold test at Screening. However, if a subject had a negative QuantiFERON-TB Gold (or interferon-gamma release assay equivalent test, such as T-SPOT TB test) or negative purified protein derivative (PPD) test within 3 months of screening, and source documentation is available, the test does not need to be repeated, provided nothing has changed in the subject's medical history to warrant a repeat test.

Note: If the QuantiFERON-TB Gold test is indeterminate, the site should repeat the test. If the second QuantiFERON-TB Gold test is indeterminate, then a PPD test should be administered and interpreted per local guidance. If either the second QuantiFERON-TB Gold test or PPD test is negative, then the subject is considered negative for TB.

Laboratory Evaluations

Laboratory evaluations will include infectious disease, hematology, clinical chemistry, coagulation, urinalysis, and pregnancy tests. Tests to evaluate and characterize disease activity of SLE will also be performed, as will PK and PD. All per-protocol laboratory samples should be collected and sent to the central lab using the kits provided, as described in the Laboratory Manual. At Screening, a local laboratory can be used with permission from the Sponsor. Variables to be tested and reported are summarized in APPENDIX 2. If time-sensitive laboratory results are needed (e.g., in the context of an AE or increase in SLE activity), every attempt should be made to send duplicate samples for analysis at the central laboratory.

Physicians Characterization of SLE and Assessment of Disease Activity

Detailed descriptions of the assessment tools, including information on how they should be administered and recorded, are provided in the Procedures Manual. These include SDI, BILAG-2004, SLEDAI-2K (SLEDAI-2K and SLEDAI-2K 30 versions), PhGA, CLASI, [redacted] and photography of skin lesions (photography when lesions are present and imaging is appropriate).

Prior to initiation of the study, all assessors must be trained and certified on the assessment tools (e.g., SLEDAI-2K 30, BILAG-2004, SDI, CLASI, and others as per the Procedures Manual) unless certification within the past 2 years is documented. Whenever possible, all SLE activity assessments should be performed by the same assessor.

Photography of Oral Mucocutaneous Lesions Reported as AEIs

Oral mucocutaneous lesions reported as AEIs should be documented photographically at presentation and in the event of significant change (see §9.8.2 and the Procedures Manual for more information).

Patient Reported Outcomes

Detailed description of the patient reported outcomes' tools, including information on how they should be administered and recorded, are provided in the Procedures Manual. These include SF-36, PtGA, and FACIT-F (13-item). Patient's assessments should be completed before the physician's assessments.

Table 1 Schedule of Procedures and Assessments

Study Period:	Screen	Treatment[1]															EoT	EoS[2]
Visit:		1	1b[3]	1c[3]	1d[3]	2	3	4	5	6	7	8	9	10	11	12	13	
Day:	-42 to -1	1	2	4	8	15	29	43	57	71	85	99	113	127	141	155	169	197
Visit Window:	NA	NA	NA	± 1	± 1	± 1	± 2	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3
Demographics	X																	
Medical History	X	X[5]																
Eligibility Review	X[4]	X[5]																
Chest X-ray	X[6]																	
Physical Exam[7]	X	X[5]				X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X
Electrocardiogram	X	2X[9]									2X[9]					2X[9]		X
Weight	X	X[5]					X		X		X		X		X		X	X
Vital Signs	X	2X[9]				2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	2X[9]	X	X
SLE Damage Assessment (SDI)		X[5]															X	X
Physician SLE Assessment[10]	X[11]	X[5]				X[12]	X		X		X		X		X		X	X
Skin Photography[13]	X	X				X	X		X		X		X		X		X	X
Patient SLE Assessment[14]		X[5]					X		X		X		X		X		X	X
Safety Lab Evaluations[15]	X[16]	X[5]				X	X		X		X		X		X		X	X
Infectious Disease Screen[17]	X																	
Urine Pregnancy Test[18]	X	X[5]				X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Biomarkers of SLE[19]	X	X[5]				X	X		X		X		X		X		X	X
PK/ADA/[redacted]		2X[9]				X	X		X		2X[9]		X		X	2X[9]	X	X
(Dense PK Subset)[21]		(3X[22])	(X)	(X)	(X)	(X)	(X)		(X)		(2X[9])		(X)		(X)	(2X[9])	(X)	(X)
(DNA)[21]		X																
Randomization		X																
Study Drug Administration[23]		X				X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications		X	(X)	(X)	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[24]		X	(X)	(X)	(X)	X	X	X	X	X	X	X	X	X	X	X	X	X

ADA, Anti-drug antibodies; AEI, Adverse event of interest: BILAG, British Isles Lupus Assessment Group index; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; EoS, End of study; EoT, End of treatment; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; [redacted] PhGA, Physician's Global Assessment of SLE Disease Activity; PK, Pharmacokinetics; PtGA, Patient's Global Assessment of Disease Activity; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; [redacted]; SF-36, Short Form-36; SLE, Systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; [redacted]; TSH, Thyroid stimulating hormone.

Notes:

1 On the days of study drug administration, all assessments and procedures must be performed prior to dosing except where otherwise specified.
2 Assessments should also be performed in the event of early discontinuation.
3 Visit held only for subjects in the Dense PK [redacted] subset.
4 Investigator's screening eligibility assessment must be reviewed and confirmed by Sponsor or designee. Refer to Inclusion Criterion 4.
5 Perform prior to randomization and study-drug dosing.
6 This requirement may be met with documentation of a previous chest x-ray performed within 3 months of Screening.
7 Complete physical examination required at Screening, Baseline, and EoS or early discontinuation.
8 A problem-oriented exam may be performed at the physician's discretion; however, at applicable visits, physical examination required for SLEDAI and BILAG assessment must be performed.
9 Obtain pre-dose, and then at 10 minutes (± 10 min) following completion of infusion.
10 BILAG, SLEDAI-2K 30 (or SLEDAI-2K on Day 15 per footnote 12), PhGA, CLASI, [redacted] NOTE: only a subset of these will be conducted at Screening (see footnote 11) and Day 15 (see footnote 12).
11 SLEDAI-2K 30, BILAG, [redacted] and PhGA; lupus history should be recorded at Screening.
12 SLEDAI-2K, PhGA.
13 Skin photography should be performed as indicated if any abnormalities are recorded on CLASI.
14 PtGA, SF-36, FACIT-F (13-item). Note: Patient's assessments should be completed before physician's assessment.
15 Collect blood and urine samples using kit provided by the central laboratory; refer to APPENDIX 2.
16 In addition to standard safety lab evaluations, includes TSH.
17 Collect samples using kit provided by the central laboratory; refer to APPENDIX 2.
18 Perform at the clinical site using provided kit; negative results must be confirmed prior to study drug dosing.
19 Collect blood samples using kit provided by the central laboratory; refer to APPENDIX 2.
20 Pharmacokinetics, anti-drug antibodies, [redacted] biomarkers. Please reference Procedures Manual for more detailed timepoints and instructions.
21 In subjects who provide supplemental consent.
22 Obtain pre-dose, and then at 10 minutes (± 10 min) and 4 hours (± 30 min) following completion of infusion.
23 Subjects should be observed for at least 2 hours following their first infusion of study drug and for 30 minutes following each subsequent infusion.
24 For oral mucocutaneous lesions reported as AEIs (see §9.8.2), photographic documentation should be collected at presentation and in the event of significant change (as detailed in the Procedures Manual).

7. STUDY DRUG

7.1. Packaging, Labeling and Storage

Blinded study drug is a sterile, clear to slightly opalescent, colorless to yellow preservative-free liquid solution contained in clear glass, single-dose vials. Each 3 mL vial has 2 mL extractable volume containing either:

- ALPN-101 Injection [redacted] or
- Placebo

Blinded study drug should be stored at 2°C to 8°C, protected from light.

The Pharmacy Binder contains additional information regarding the receipt, storage, and preparation of study drug.

Table 2 Investigational Product Description

	ALPN-101	Placebo
Components	ALPN-101 (active ingredient), 20 mM L-histidine, 250 mM sucrose, pH 6.7	20 mM L-histidine, 250 mM sucrose, pH 6.7
Dosage Form:	Liquid solution for IV infusion	Liquid solution for IV infusion
Unit Dose	[redacted]	Each 3 mL vial contains an extractable volume of 2 mL
Route of Administration	IV	IV
Physical Description	Clear to slightly opalescent, colorless to yellow liquid solution	Clear to slightly opalescent, colorless to yellow liquid solution

IV, Intravenous.

7.2. Preparation and Dosing

Subject eligibility must be independently confirmed prior to randomization and administration of study drug.

The planned dosing regimen for this study is 3 mg/kg ALPN-101 or placebo IV administered Q2W for 12 total doses. If a dose of study drug is missed, consult with the Medical Monitor. Dose or dose intensity may be decreased based on DMC recommendation and Sponsor decision; refer to §4.3.

Doses of study drug are calculated and prepared based on each subject's body weight at Baseline, rounded to the nearest kilogram, unless weight changes by more than 10%; in that case doses of study drug will be calculated and prepared based on the subject's most current body weight. Study drug will be prepared in accordance with instructions in the Pharmacy Binder and will be infused over approximately 30 minutes (±15 minutes) using a volumetric pump with a 0.2 micron in-line filter. Study drug is NOT to be administered as an IV push or bolus injection.

Subjects should be observed for at least 2 hours following their first infusion of study drug and for 30 minutes following each subsequent infusion.

The Investigator is responsible for the education of study staff in the correct administration of study drug.

7.3. Accountability

A record will be maintained by the investigational site which will account for all dispensing, destruction, or return of any used and unused study drug.

8. CLINICAL MANAGEMENT GUIDELINES AND REQUIREMENTS

8.1. Clinical Management of Adverse Events of Interest

8.1.1. Infusion-Related Reactions

Guidelines for assessing, grading, and reporting IRRs are provided in §9.8 and §9.8.1.

No infusion reactions were observed following single or repeated IV infusions of ALPN-101 in a previous study in healthy volunteers. The incidence and nature of ALPN-101-related IRRs, if any, remain uncharacterized. Based on experience with other immunomodulatory compounds, including approved CD28 pathway inhibitors, IRRs may include hypersensitivity reactions (e.g., anaphylaxis) and/or cytokine release syndromes. IRRs typically present with dizziness, headache, circulatory (hypo- or hypertension), respiratory (cough, wheezing, dyspnea), mucocutaneous (flushing, urticaria, pruritis, rash), and abdominal (nausea, vomiting, cramps, diarrhea) symptoms. Symptoms typically begin during or within 24 hours of drug administration.

If any subject experiences an infusion reaction, including anaphylaxis or cytokine release syndrome:

- Monitoring frequency and duration will be increased, and will continue until episode is resolved.
- Supportive care will be initiated per institutional guidelines. This may include, but is not limited to, slowing and/or interruption of the current infusion; administration of antihistamines such as diphenhydramine or loratadine; administration of antipyretics such as acetaminophen or paracetamol; administration of corticosteroids; IV fluid support such as normal saline; vasopressors; anti-rigor medication such as meperidine.
- Using the kits provided by the central laboratory, blood will be collected for assessment of serum levels of mast cell tryptase and quantitative IgE; blood should be collected as soon as possible after initiation of the event, and repeated at 60 minutes and following resolution or discharge from care for the event. In addition, a serum sample for exploratory analysis of chemokines and cytokines should be collected.

In the event that an IRR occurs when the subject is not in the clinic, all subjects should undergo an unscheduled visit as soon as possible (< 24 hr).

Table 3 Guidelines for Management of IRRs

AE Grade	ALPN-101 Dose Modification	Toxicity Management
Any		Manage per institutional standards at the discretion of Investigator. Monitor subjects for signs and symptoms of IRR (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., acute onset of generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
1	The infusion rate may be decreased by 50% or temporarily interrupted until resolution of the event.	Acetaminophen, antihistamines, meperidine, etc. may be administered per institutional standards Consider premedication, such as with antihistamines, acetaminophen, NSAIDs, or meperidine per institutional standard prior to subsequent doses Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions
2	The infusion rate may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions, if applicable, may be given at 50% of the initial infusion rate	
3	Consult with Medical Monitor or Sponsor	Stop infusion. Manage per institutional standards (e.g., oral or parenteral corticosteroids, antihistamines, antipyretics, meperidine) Premedication per institutional standard prior to subsequent doses Consider hospitalization.
4	Permanently discontinue	Stop infusion. Hospitalize. Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

AE, Adverse event; IM, Intramuscular; IRR, Infusion-related reaction; IV, Intravenous; NSAIDs, Nonsteroidal anti-inflammatory drugs.

8.1.2. Oral Mucocutaneous Lesions

Aphthous ulcers were observed in 5 of 66 (7.5%) of healthy volunteers randomized to ALPN-101 in the previous study in healthy volunteers. All events were mild or moderate and were self-limited or resolved with topical therapy (i.e., lidocaine; corticosteroids).

Oral mucocutaneous lesions (including aphthous ulcers) not attributed to SLE are considered AEIs for assessment in the present study; any oral mucocutaneous lesions attributed to underlying SLE should be reported in the appropriate disease index and not as AEs. Guidelines for reporting oral mucocutaneous lesions are provided in §9.8 and §9.8.2.

The differential diagnosis of new or worsening oral mucocutaneous lesions that may occur during this study includes, but is not limited to: new or worsening SLE activity; infections (e.g., coxsackie A, herpes simplex, herpes zoster, cytomegalovirus, Epstein-Barr, HIV, TB; other bacterial or fungal infections); trauma (e.g., dental appliances); drug reactions (e.g., methotrexate-related mucositis, others); other autoimmune or inflammatory diseases (e.g., inflammatory bowel disease; Behcet's; others). If new oral mucocutaneous lesions are observed during this study, efforts should be made to definitively determine cause, to the extent possible.

Evaluation should include:

- Culture to assess for infection, if indicated

- Consider specialist evaluation by ear, nose and throat or oral medicine if diagnosis is not clear; biopsy may be indicated in severe or refractory cases
- For lesions reported as AEIs: photographic documentation of lesions at presentation and in the event of significant change

Therapy should be guided by diagnosis, severity, and response to initial therapy. Options may include:

- Oral and/or topical analgesics, if indicated for discomfort
- Topical corticosteroids, if indicated for control of inflammation
- Treatment of underlying condition

8.1.3. Infections Grade ≥ 3

In general, study drug administration should be withheld in the event of any infection that the Investigator judges to be clinically significant. If the infection resolves, study drug may be restarted at the next scheduled dose, with approval of the Medical Monitor. For this study, infections of Grade ≥ 3 are considered AEIs (see §9.8.3). Reporting requirements for AEIs are described in §9.8.

8.2. Allowed Medications or Treatments

8.2.1. Non-SLE Concomitant Medications

Use of non-SLE concomitant medications (including prescription and over-the-counter medications, herbal supplements/teas and vitamins, analgesics, non-prescription NSAIDs and other agents for treatment of AEs or supportive care that are not specifically prohibited) is permitted when deemed necessary by the Investigator or subject's care provider; subjects who are using NSAIDs infrequently or "as needed" should make every attempt to withhold dosing on study visit days until SLE assessments have been completed.

For all non-SLE concomitant medications used at baseline, or that are used intermittently and expected to be used during the study (e.g., NSAIDs for menstrual discomfort; rescue inhalers for asthma), name and indication should be recorded in the medical history.

For all non-SLE medications initiated during the study, date of initiation, dose, date of change in dose or discontinuation, and indication should be recorded. The associated AE should be documented.

8.2.2. Concomitant Medications for SLE

From the signing of informed consent through completion of all assessments though the EoS visit, subject should receive stable doses of medications used as SOC for SLE (including oral corticosteroids, hydroxychloroquine/hydroxychloroquine-like drugs and permitted immunosuppressants, as listed in Inclusion Criterion 7), except in circumstances summarized below:

- Reduction in dose or discontinuation due to toxicity (§8.2.2.1)
- Changes to control increased disease activity or flare/ significant worsening of disease (§8.2.2.3)

8.2.2.1. Reduction in SLE Medication Dose Due to Toxicity

Standard of care medications for SLE may be reduced or temporarily discontinued if indicated for management of immediate safety concerns; the event leading to reduction or discontinuation should be documented as an AE, and the relationship to SOC should be recorded (e.g., mucosal ulcers secondary to methotrexate; poor diabetic control secondary to corticosteroids; nausea and vomiting secondary to mycophenolate; others).

8.2.2.2. Discretionary Reduction in Corticosteroid Dose Due Decreased SLE Disease Activity After Day 85

Corticosteroids may not be reduced due to decreased disease activity until after all assessments have been completed through Study Day 85 (End of Week 12). Thereafter, corticosteroids may be tapered if all of the following are true (note that taper is permitted, but is NOT required):

- In the Investigator's judgement, it is in the subject's best interest to taper corticosteroids.
- If there has been an increase in disease activity during the Treatment Period that required a burst and taper of corticosteroids to control increased SLE disease activity (§8.2.2.3), the corticosteroids have been tapered back to the dose at Baseline or the dose prior to initiation of the burst, and must have remained stable for at least 4 weeks.
- The SLEDAI-2K 30 score must have improved (be reduced) by at least 4 points from the score recorded at the Baseline Visit.
- The taper must be anticipated to be completed by Day 141 (end of Week 20); corticosteroid dose should be planned to remain stable from Day 141 (end of Week 20) through Day 169 (EoT).

General guidelines for tapering corticosteroids:

- If the current dose is ≥ 15 mg/day prednisone equivalent, taper by not more than 5 mg over the following 28 days.
- If the current dose is 7. 5 to < 15 mg/day prednisone equivalent, taper by no more than 2.5 mg prednisone equivalent over the following 28 days.
- If the current dose is > 0 to < 7.5 mg/day, taper by not more than1 mg over the following 28 days.

8.2.2.3. Treating Increases in SLE Activity

The decision to treat increased SLE disease activity is based on the judgement of the Investigator. Increased disease activity should not be recorded as an AE; however, information regarding the organ system involved and the severity of disease activity leading to treatment should be captured in the disease assessments tools (e.g., BILAG 2004, SLEDAI-2K 30, PhGA) and also recorded as the indication for treatment with the concomitant medication. Increase in corticosteroids is treated separately from increase in, or addition of, other agents, as detailed below.

Burst and Taper of Corticosteroids

Prior to initiation of a burst of corticosteroids, all assessments should be completed that pertain to the visit at which the increased disease was recognized, if possible. If the increased disease was recognized between scheduled visits, then the subject should return to the clinic and all assessments listed for an unscheduled visit due to increased SLE activity (see §6.6.2) should be performed.

From Day 1 through Day 141, subjects with increased disease activity that require a temporary increase from the baseline oral corticosteroid dose may initiate either of the following:

- Oral corticosteroids administered up to a maximum dose of 40 mg prednisone/day (or equivalent) and tapered to the Day 1 dose by the end of the 14th day after initiation at the latest, or
- Intramuscular methylprednisolone up to a maximum of 160 mg administered at a single timepoint

The following additional guidelines apply:

- A course of oral or intramuscular corticosteroids cannot be initiated more frequently than every 28 days

If a subject requires initiation of a burst of corticosteroids after Day 141, or at a higher dose, or more frequently, or for longer than permitted, the subject should remain in the study for evaluation of safety and outcomes. Blinded study drug may be continued if not contraindicated in the judgement of the Investigator following discussion with, and agreement by, the Medical Monitor.

Increase or Addition of Hydroxychloroquine/Hydroxychloroquine-like Drugs and/or Immunosuppressants for Increased SLE Activity

If during the Treatment period (Day 1 to 169) the SOC medications used at Baseline, together with the permitted bursts and taper of corticosteroids, are considered to not be adequate for the treatment of increased disease activity, a subject may receive medications deemed necessary by the Investigator or treating physician. In that case, all of the following should be done:

- Blinded study drug will be discontinued
- The subject should remain in the study for assessment of outcomes, including safety
- The Investigator should consult the Medical Monitor AND the updated IB to discuss any additional safety assessments to be performed in addition to those included in the protocol

8.3. Prohibited Medications or Treatments

The inclusion criteria list medications that are permitted for SOC treatment of SLE in the present study. For each permitted medication, the dose and duration over which it must be stable prior to Screening or Baseline is provided.

No new medication for treatment of SLE can be started during the study, and no SOC treatment can be increased or decreased, excepted as detailed in §8.2.

Subjects should not receive live vaccines during the study; **all** vaccinations (live, killed, or conjugated) must be approved by the Medical Monitor prior to administration.

Medications that are specifically excluded are listed in the exclusion criteria (§5.2). These agents must have been discontinued prior to Screening or Baseline. The length of time that must have passed following the last dose of each agent is provided in (§5.2).

Other medications not listed, but with significant immunosuppressive or immunomodulatory activity, should be reviewed and approved by the Medical Monitor prior to initiation.

9. ADVERSE EVENT REPORTING

The following sections describe the minimum requirements for assessing and reporting AEs, including SAEs and serious, unexpected, suspected adverse reactions for subjects participating in trial AIS-A03.

9.1. Adverse Event Definition

An AE is any untoward medical occurrence associated with the use of a drug in a patient or clinical trial participant, whether or not considered drug-related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a drug, whether or not considered related to the drug (i.e., does not imply any judgment about causality).

In the context of a clinical trial, AEs include exacerbation of a pre-existing illness or symptom, an increase in frequency or intensity of a pre-existing episodic event or condition, or a condition detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study.

Events that do not meet the definition of an AE include:

- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure should be reported as an AE if applicable;
- Situations where an untoward medical occurrence did not occur (e.g., social and/or observational and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Abnormal laboratory values or test results constitute AEs if they are clinically significant and/or induce clinical signs or symptoms, or if they require intervention or therapy. Wherever possible, the clinical rather than laboratory term should be reported (e.g., “anemia” rather than “low hemoglobin”).

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication should also be reported as AEs (overdose per se will not be reported as an AE/SAE).

For this study, **signs and symptoms of SLE activity are not to be reported as AEs,** but should be captured in activity assessment tools. However, if SLE symptoms meet SAE criteria (see §9.3), expedited reporting requirements apply as per §9.4.

9.2. Adverse Event Reporting and Follow-up

Any medical condition with an onset or diagnosis before the first administration of study drug, but after signing the informed consent form (ICF), will be noted as part of the subject’s baseline medical conditions. **Signs and symptoms of SLE activity should not be reported as AEs, but should be documented in the relevant activity assessments.**

Information regarding all AEs will be collected from the time of first dose of study drug until the EoS visit, or for at least 8 weeks following the last infusion of study drug if the subject discontinues early. Adverse events that are thought to be related to the study drug and continue beyond this collection period will be followed until resolution or until stabilized. Adverse events that begin after the defined collection period, but that the Investigator considers to be related to study drug, may be reported at any time.

Adverse event severity will be graded using CTCAE, version 5.0. When CTCAE criteria cannot be used, the AE should be graded as follows:

- Grade 1 (Mild): Mild transient (< 48 hr) or mild discomfort not requiring medical intervention or therapy.
- Grade 2 (Moderate): Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required.
- Grade 3 (Severe): Marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalizations possible.
- Grade 4 (Life-threatening): Extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization or hospice care probable.
- Grade 5 (Fatal): Results in death

In general, the use of a unifying diagnosis as the AE term is preferred to the listing of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical practice. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE.

9.3. Serious Adverse Event Definition

An SAE is any AE that, in the view of either the Investigator or the Sponsor, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions.

The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. CTCAE Grade 4 events are not automatically defined as life threatening for SAE determination. For example, a Grade 4 increase in ALT may or may not be deemed as life threatening by the Investigator and/or Sponsor.

For hospitalizations and surgical procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the therapeutic action taken in response to the illness.

Additionally, hospitalization itself is not an AE but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an SAE. The following are examples of hospitalization that may not be considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission

- Protocol-specified admission (e.g., for procedure required by study protocol)
- Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
- Administrative admission (e.g., for annual physical)
- Social admission (e.g., placement for lack of place to sleep)
- Elective admission (e.g., for elective surgery)
- Admission to a palliative unit or hospice facility

9.4. Emergency Unblinding

This study is blinded; neither subjects nor investigators or site staff will be aware of subjects' treatment assignments. However, in the event of a medical emergency when knowledge of the treatment received is needed for medical management of an SAE, the investigator may unblind an individual subject's treatment allocation. When possible, prior to unblinding, the investigator should attempt discuss the reason for wanting to unblind with the Medical Monitor. Instructions for emergency unblinding are contained in the Procedures Manual (IRT/Suvoda, Site Safety Reporting Instructions).

9.5. Serious Adverse Event Reporting and Follow Up

SAEs will be collected from the time of the first dose of study drug until the EoS visit, or for at least 8 weeks following the infusion of study drug if the subject discontinues early. SAEs that are related to the investigational product and continue beyond the normal collection period will be followed until resolution or until stabilized. SAEs that begin after the defined collection period, but that the Investigator considers to be related to study drug, may be reported at any time.

All SAEs must be reported to the Sponsor or designee within 24 hours of clinical site personnel becoming aware of the event. Refer to the study Procedures Manual for SAE reporting requirements and details.

9.6. Suspected Adverse Reaction Definition

A suspected adverse reaction is any AE for which there is a reasonable possibility that the investigational product caused the AE. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. The following criteria may be used as a guide for assessing causality:

- Yes/Related

  There is evidence exists to suggest a causal relationship between the drug and the AE, such as:

  – An event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)

  – An event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)

- No/Unrelated

  Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible.

9.7. Adverse Event Expectedness

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the ALPN-101 IB. The Sponsor or Medical Monitor is responsible for determining the expectedness of all reported SAEs, including serious suspected adverse reactions.

9.8. Adverse Events of Interest

The occurrence of an AEI whether serious or nonserious, must be immediately reported to AIS within ≤ 24 hours of site awareness by entering the information into the electronic data capture (EDC) system, then completing an AEI narrative form and sending it to the following email address:

- safety@alpineimmunesciences.com

The AEI reporting period will begin at the time of first dose of study drug and continues until the final study day (i.e., EoS visit, or end of follow-up for subjects prematurely withdrawn).

Recommendations regarding the medical management of AEIs can be found in §8.1.

AEIs are listed below:

- IRRs (see §9.8.1)
- Oral mucocutaneous lesions (including aphthous ulcers) not attributed to SLE (see §9.8.2)
- Infections Grade ≥3 (see §9.8.3)

9.8.1. Infusion-related Reactions

Terminology and Grading of IRRs

The term "IRR" should generally be used and the severity assessed per CTCAE v5.0. More specific terms should only be used when the mechanism and/or diagnosis can be definitively determined. For instance, "anaphylaxis" should only be used for events fitting the criteria in Table 4, while "cytokine release syndrome" should be used for fitting the description in Table 5 and determined to be in association with the release of cytokines.

An allergic reaction which occurs in relationship to study drug administration should be reported as an IRR. Each sign or symptom of the reaction should be recorded as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Table 4 NIAID/FAAN Clinical Criteria for Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the three following criteria are fulfilled:	
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) **and at least one of the following:**	
	• Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	• Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):	
	• Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
	• Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
	• Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
	• Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):	
	• Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
	• Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
BP, Blood pressure; NIAID/FAAN, National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network; PEF, Peak expiratory flow. *Low systolic BP for children is defined as < 70 mm Hg from 1 month to 1 year, < (70 mm Hg + [2 x age]) from 1 to 10 years, and < 90 mm Hg from 11 to 17 years.	
From (75)	

Table 5 AE Terms and Grades for Reporting IRRs

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion Related Reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					

Table 5 AE Terms and Grades for Reporting IRRs (Continued)

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O_2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O_2	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

IRRs, Infusion-related reactions; NSAIDs, Nonsteroidal anti-inflammatory drugs; IV, Intravenous; O_2, Oxygen.
From NCI-CTCAE v5.0.

9.8.2. Oral Mucocutaneous Lesions

Efforts should be made to determine the cause of oral mucocutaneous lesions (including aphthous ulcers) observed during the study (see §8.1.2).

Any oral mucocutaneous lesions attributed to underlying SLE (including new or worsening lesions) should not be reported as AEs, but should be recorded in SLEDAI-2K 30 (mucosal ulcers) and/or BILAG 2004 (mucosal ulceration–mild, or mucosal ulceration–severe, as appropriate consistent with glossary definitions) and/or CLASI (mucosal lesions). Treatment should be recorded as concomitant medications, listing SLE activity as the indication for treatment.

Any oral mucocutaneous lesions not attributed to SLE should be reported as AEIs and graded according to CTCAE (see §9.2). Whenever possible, the specific cause or type (e.g., thrush) should be reported. Aphthous ulceration, if not assessed as related to SLE, may be reported as "aphthous ulcer," "aphthous stomatitis" or other similar verbatim term as considered appropriate by the Investigator. However, in such cases when no specific term exists in CTCAE, the AE should be graded according to "mucositis oral" or "pharyngeal mucositis," as appropriate to the anatomical location of the lesion(s). Table 6 provides terms and for grading for some oral mucocutaneous lesions per CTCAE.

Note: For lesions reported as AEIs, photographic documentation should be collected at presentation and in the event of significant change (as detailed in the Procedures Manual).

Table 6 AE Terms and Grades for Reporting Oral Mucocutaneous Lesions

AE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis, oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by ulceration or inflammation of the oral mucosa.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the pharynx.					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	
Definition: A disorder characterized by an infectious process involving a mucosal surface.					
Pharyngitis		Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Fatal
Definition: A disorder characterized by inflammation of the throat.					
Thrush	Asymptomatic; local symptomatic management	Oral intervention indicated (e.g., antifungal)	IV antifungal intervention indicated		
Definition: A disorder characterized by a suspected candidal infection involving an oral mucosal surface.					
ADL, Activities of daily living; AE, Adverse event; IV, Intravenous. From NCI-CTCAE v5.0.					

9.8.3. Infections Grade ≥ 3

For this clinical study, severe (Grade ≥ 3) infections have been defined as AEIs (see §9.2 for details regarding severity grading).

9.9. Pregnancy

Pregnancies that occur from the time of first study drug dose until the EoS visit, including any pregnancies that occur in the female partner of a male study subject, must be reported to the Sponsor or designee within 48 hours of the Investigator becoming aware of the pregnancy. Pregnancy outcomes of elective or spontaneous abortion, stillbirth, or congenital anomaly, as well as any pregnancy-related events that meet the criteria for an SAE (see §9.3) must be reported as per §9.5.

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Refer to the Procedures Manual for complete instructions.

10. STATISTICAL AND DATA ANALYSIS METHODS

10.1. Overview of Statistical Methods

Detailed methodology and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized prior to unblinding the study database. A general overview of the planned methodology is provided below. Any deviation from the planned analysis will be detailed in the SAP. In all cases, analyses defined in the SAP take precedence over descriptions in the Protocol. All post-hoc analyses will be detailed in the final clinical study report.

10.2. Sample Size

The primary purpose of this phase 2 study is to access the safety of ALPN-101 in subjects with moderate to severe SLE. As such, the anticipated sample size of approximately 130 subjects randomized 1:1 to receive ALPN-101 or placebo was not derived to support formal hypothesis testing of efficacy endpoints.

To estimate the power to detect potential differences in efficacy endpoints of primary interest, placebo response rates of 40% for SRI-4 and 20% for BILAG were assumed. A sample size of 65 subjects per treatment arm will provide 82% and 87% power to detect a difference of at least 25% between the ALPN-101 arm and the placebo arm at Day 169 in SRI-4 and BILAG response, respectively, based on a chi-square test with a two-sided significance level of 0.05 and no adjustments for multiple testing.

10.3. Method of Assignment to Treatment

Randomization will be stratified by geographical region and by use of concomitant oral immunosuppressive therapy at enrollment in two groups:

- Concomitant use of at least one of the permitted immunosuppressants (e.g., methotrexate, leflunomide, azathioprine, 6-mercaptopurine, mycophenolate mofetil, mycophenolic acid), and/or corticosteroids at doses > 5 mg prednisone or equivalent daily with or without hydroxychloroquine/ hydroxychloroquine-like drugs ; vs
- No use of permitted immunosuppressant and/or corticosteroids at doses > 5 mg prednisone or equivalent daily; with or without use of lower doses of corticosteroids and/or hydroxychloroquine/ hydroxychloroquine-like drugs

10.4. Analysis Populations

- **Modified Intent-To-Treat (mITT) Population:** all randomized subjects who received any amount of study drug and completed at least one post-baseline disease assessment. mITT subjects will be analyzed according to the treatment arm into which they were randomized regardless of the actual treatment received. The mITT is the analysis population for the primary efficacy analysis.
- **Safety Population:** all randomized subjects, classified according to the actual treatment received, who received any amount of study drug and have at least one post-baseline safety evaluation. This is the primary analysis population for the safety analysis.
- **PK Population:** all subjects who received ≥ 1 dose of ALPN-101 and have ≥ 1 post-dose PK concentration reported.

Other analysis populations may be defined in the SAP.

10.5. Planned Analyses

10.5.1. Disposition of the Study Subjects

The disposition of the randomized subjects will be described by treatment group of the number of subjects randomized, the number of subjects treated, the number of subjects in each analysis set, and the number of subjects permanently discontinued (from the study along with the primary reasons for discontinuation).

10.5.2. Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized and compared by treatment group.

Medical history will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term, according to treatment group. Prior medications will be categorized using the Anatomical Therapeutic Chemical (ATC) codes in the World Health Organization Drug (WHODRUG) dictionary and summarized according to treatment group.

10.5.3. Investigational Product and Concomitant Therapies

Exposure to investigational product will be calculated for each subject and summarized. The total amount of investigational product given will be calculated for each subject and will be compared to the amount expected to be given for each subject. Treatment compliance will be calculated for each subject and summarized using descriptive statistics.

Concomitant therapies will be classified according to the ATC codes in the WHODRUG dictionary. Corticosteroid usage will be standardized to equivalent prednisone doses. The incidence rate of each coded concomitant medication will be tabulated by treatment group. The table will be sorted by the incidence use of the entire sample.

10.5.4. Efficacy Analyses

In all cases, analyses defined in the SAP take precedence over descriptions in the Protocol.

To address the secondary study objective of assessing evidence of efficacy, the efficacy endpoints of primary interest include the proportion of subjects achieving SRI-4 response at Day 169 and the proportion of subjects achieving BILAG-based Composite Lupus Assessment (BICLA) response at Day 169.

All efficacy measures will be summarized and analyzed for the mITT population.

For categorical endpoints, the number and proportion of subjects in each at each visit will be presented by treatment group. Proportions will be compared using a Cochran-Mantel-Haenszel test adjusted for randomization stratification factors. An estimate of the difference in proportions and corresponding 95% confidence interval will be presented. P-values may be presented for the efficacy endpoints of primary interest.

For continuous endpoints, the mean, standard deviation, median, minimum, and maximum at each visit. For continuous endpoints with multiple post-Baseline visits, the treatment effect will be assessed through Mixed-effect Model Repeated Measures (MMRM) based on observed data.

10.5.5. Safety Analyses

All safety data will be summarized descriptively by treatment group and analyzed based on the safety population. The safety endpoints include the incidence of treatment-emergent AEs, SAEs, AEIs, and the incidence of clinically significant abnormalities in laboratory analytes, ECG parameters, and vital signs.

All AEs will be coded using MedDRA and will be assessed for severity, relationship to investigational product, and seriousness. Incidence will be presented by System Organ Class and Preferred Term. The mean change from baseline in the continuous safety measures including vital signs and laboratory values will be summarized by treatment arm and visits.

Continuous endpoints will be summarized using descriptive statistics, including number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using frequency distributions and corresponding percentages.

10.5.6. Pharmacokinetic [redacted] Analyses

In all cases, analyses defined in the SAP take precedence over descriptions in the Protocol.

Data from the PK population will be used in the analysis of PK endpoints. The PK data obtained in dense PK subset subjects will be analyzed using non-compartmental analysis (NCA). The PK parameters including C_{max}, AUC, and trough concentration (C_{trough}) will be determined based on the available data. Descriptive statistics (n, arithmetic mean, standard deviation, minimum, median, and maximum) will be calculated for the PK parameters. The PK data may be analyzed using a population approach via nonlinear mixed effect modeling. Estimated PK parameters and population PK parameters, if available, may be examined for relationship with patient factors such as age, weight, sex, disease characteristics, safety, efficacy, [redacted]

The incidence, timing, and titer of ADA to study drug will be summarized using descriptive statistics by treatment groups. Samples confirmed positive for ADA may be explored for neutralizing capacity. The possible effects of ADA on PK, efficacy and safety may be explored.

[redacted]

10.6. Interim Analysis

An administrative interim analysis may be performed when approximately 50% of subjects have completed assessments through Week 24. Details regarding interim analysis will be included in the SAP.

11. REGULATORY AND ADMINISTRATIVE REQUIREMENTS

11.1. Trial Conduct

The study will be conducted in accordance with the International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and applicable local and federal regulations. No deviation from the protocol will be implemented without the prior approval from the study's Sponsor, as well as review and approval from the IRB/IEC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB/IEC as soon as possible in accordance with IRB/IEC policies.

11.2. Informed Consent

Patients meeting the criteria set forth in the protocol may be offered the opportunity to participate in this study. Candidate subjects will receive an explanation of the study, including the investigational status of ALPN-101, a summary of known or observed adverse reactions, alternative therapies available, and other factors which are part of obtaining appropriately informed consent. Subjects will be given the opportunity to ask questions of qualified personnel who are knowledgeable about the study and provided adequate time to consider whether to participate.

Informed consent will be documented with an ICF that has been approved by the IRB/IEC. The ICF is to be signed and dated by the subject, by the person who conducts the consent process, and any additional signatures required by the IRB/IEC.

Any changes to the ICF must be reviewed and approved by the IRB/IEC. The revised ICF must be used to re-consent any subject currently enrolled in the study who is affected by the change.

If a subject's partner becomes pregnant during the subject's participation in the study, their partner will be asked to sign the pregnant partner ICF to allow the collection of safety data regarding the pregnancy and its outcome. The pregnant partner ICF should be obtained at the time the Investigator becomes aware of the pregnancy.

11.3. Institutional Review Board/Independent Ethics Committee Approval

The protocol, ICF, and all relevant supporting materials must be reviewed and approved by the IRB/IEC or equivalent. A copy of the IRB's/IEC's written approval must be provided to the study's Sponsor or its representatives prior to commencement of subject enrollment. The IRB/IEC should be informed by the Investigator of the study's progress and provide written documentation of periodic review and ongoing approval according to IRB/IEC policies.

Any changes in the study protocol, revisions to the ICF, and all unanticipated problems involving risks to human subjects must be submitted promptly to the IRB/IEC in accordance with their policies. Written approval from the IRB/IEC must be obtained prior to implementation of any change(s), if applicable.

11.4. Subject Privacy

The Investigator, Contract Research Organization (CRO), and Alpine Immune Sciences shall comply with applicable local and federal privacy laws. The medical records of participating subjects are considered confidential and disclosure to third parties other than those noted below is prohibited.

The medical records of participating study subjects and all data generated as a result of participation in this study are to be available for review upon request by the Alpine Immune Sciences or its representatives or partners, the IRB/IEC, and applicable regulatory authorities. The IRB/IEC-approved

ICF must clearly indicate that the subject's medical records will be inspected by said parties, and permission for such review and use of personal information is a requirement for study participation.

11.5. Investigator Responsibilities and Requirements

By agreeing to participate in this clinical trial, the Principal Investigator and all sub-Investigators agree to perform the study in accordance with all stipulations of the protocol, ICH Guidelines for GCP, and local and federal regulations.

The Principal Investigator must provide the CRO or Alpine Immune Sciences with the following documentation prior to initiation of the study at his/her clinical site:

- Signed clinical study agreement
- Signed Investigator Protocol Agreement
- Signed FDA form 1572 or Statement of Investigator
- Curriculum vitae of all Investigators
- Current medical licenses for all Investigators
- Copy of IRB/IEC approval for the study and informed consent form
- IRB/IEC Membership List or Assurance Number/Letter as applicable

11.6. Data Identification, Handling, and Record Keeping

11.7. Source Documentation

Adequate and accurate case histories, including all data and observations relevant to the clinical investigation, should be maintained for each subject screened or enrolled in the study. Such case histories include all medical records or original documents regarding the subject's participation in the study, including medical history, progress notes, laboratory reports, imaging studies, ECG tracings, hospital records, and details regarding administration of investigational drug.

11.7.1. Case Report Forms and Electronic Data Capture

The Investigator will be provided with access to a secure, web-based system for capturing and reporting all study-related data (EDC). Such data will be entered into the EDC system by the Investigator or site personnel in a timely and accurate manner. The Investigator must review all submitted data and attest to its accuracy and consistency with the protocol.

11.7.2. Essential Documents

The Principal Investigator and clinical site personnel are responsible for maintaining a file of all essential documents required to demonstrate compliance with applicable regulatory authority requirements. Such documents include, but are not limited to:

- Protocol with all amendments, signed Investigator Protocol Agreements, and ICFs
- IB, including all updates
- Copy of the signed FDA form 1572 or Statement of Investigator
- CVs and medical licenses for the Principal Investigator and sub-Investigators

- IRB/IEC approval of the protocol and amendment(s), ICF(s), and any other study-related materials
- IRB/IEC membership list or Assurance Letter/Number as applicable
- Subject Screening and Enrollment Log, denoting the subjects' names and assigned study subject identifier
- IRB/IEC submissions of relevant safety information as required by IRB/IEC policies
- Laboratory certifications and reference ranges
- Significant correspondence from the CRO or Sponsor

These files must be available for inspection by the CRO or Alpine Immune Sciences, their representatives, the IRB/IEC, or applicable regulatory authorities at any time.

11.7.3. Record Retention

The Investigator will retain all study records for a period of 2 years after marketing approval is received for ALPN-101, or for 2 years after all clinical and product development of ALPN-101 is discontinued. The Investigator must notify Alpine Immune Sciences prior to the destruction of any records relating to this study.

11.8. Quality Control and Quality Assurance

11.8.1. Site Training and Monitoring Procedures

Prior to the initiation of the study, personnel from the Sponsor or its representatives will meet with the Investigator and clinical staff to review and discuss the protocol, all procedural and administrative requirements, the investigational drug, GCP guidelines, and monitoring requirements. During the course of the study, representatives from the Sponsor will provide additional study-specific training to site staff upon request by the Investigator, in response to a change in key clinical site staff, or if issues with study conduct or GCP compliance are observed.

A representative from Alpine Immune Sciences will monitor adherence to the protocol and review study-related data. The frequency of monitoring visits depends on the rate of enrollment at the site, and the Investigator will permit the Sponsor's representatives to monitor the study as frequently as the Sponsor deems necessary to determine that protocol adherence and data entry are acceptable. The monitor will be permitted full access to subjects' complete medical records. Other study records, such as essential regulatory documents, subject screening log, and study drug disposition logs will also be inspected.

11.8.2. Deviation Reporting

Important protocol deviations will be presented in a listing.

11.8.3. Auditing Procedures

Alpine Immune Sciences maintains the right to conduct audits at the clinical site.

11.9. Publication Plan

The publication policy is addressed separately from this clinical study protocol.

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APPENDIX 1 GUIDANCE ON CHILDBEARING POTENTIAL AND HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Contraceptive Guidance

Investigators shall counsel WOCBP and fertile male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise these participants on the use of highly effective methods of contraception for WOCBP and will check for adherence during study visits.

Guidance for WOCBP Participants

WOCBP must use a highly effective method of contraception consistently and correctly during the study and for at least 3 months after the last dose of investigational product.

Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

The following methods of contraception are considered highly effective:

- Combined hormonal (estrogen + progestin) contraception (oral, intravaginal, transdermal) associated with inhibition of ovulation.
- Progestogen- or progestin-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence: defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments (i.e., during the study and for at least 3 months after the last dose of investigational product). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

Guidance for Male Participants with WOCBP Partners

Male participants with a pregnant or non-pregnant WOCBP partner must use a condom during the study and for at least 3 months after the last dose of investigational product. In addition, non-pregnant WOCBP partners of fertile male participants must use a highly effective method of contraception as defined above for WOCBP participants.

Woman of Childbearing Potential

A woman is considered a WOCBP, i.e., fertile, following menarche and until becoming postmenopausal unless permanently sterile.

- Permanent sterilization methods include the following: hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.
- Postmenopausal is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormone

replacement therapy. However, in the absences of 12 months of amenorrhea, a single follicle stimulating hormone (FSH) measurement is insufficient.

Fertile Man

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

APPENDIX 2 CLINICAL LABORATORY ASSESSMENTS

All per-protocol laboratory assessments will be performed by the central lab as scheduled in Table 1. At Screening, a local laboratory can be used with permission from the Sponsor. Screening laboratory assessments that are out-of-range may be repeated once. Investigators must document their review of each laboratory safety report. **NOTE: the Investigator is responsible for performing urine pregnancy testing using the provided kits as noted in Table 1.**

Assessment	Parameters
Safety: Hematology	Platelet count
	Red blood cell (RBC) count and indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), percent reticulocytes
	White blood cell (WBC) count with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils
	Absolute neutrophil count and lymphocyte count; CD4 and CD8 lymphocytes
	Hemoglobin
	Hematocrit
Safety: Clinical Chemistry	Electrolytes: sodium, potassium, chloride, bicarbonate
	Other cations: calcium, magnesium, phosphorus
	Amylase
	Lipase
	Glucose
	Creatine phosphokinase (CPK)
	Lactate dehydrogenase (LDH)
	Renal Function: creatinine, estimated glomerular filtration rate (eGFR)
	Liver Function Tests: alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase (AST), total and direct bilirubin, total protein
Safety: Coagulation	Prothrombin time (PT) (i.e., international normalized ratio [INR]), activated partial thromboplastin time (aPTT),
Safety: Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase; microscopic examination if blood or protein is abnormal; urine protein-creatinine ratio (UPCR)
Infectious Disease	Hepatitis B and C viruses, Human Immunodeficiency Virus (HIV), tuberculosis (TB), and SARS-CoV-2
Other Tests	Thyroid stimulating hormone Follicle-stimulating hormone (FSH) and estradiol (female subjects only, if needed to confirm menopausal status [see Appendix 1])
Clinical Biomarkers of SLE	**Screening only:** anti-nuclear antibodies (ANA), anti-Smith antibodies, anti-Sjögren's syndrome type A (SSA) antibodies, anti-Sjögren's syndrome type B (SSB) antibodies, anti-ribonucleoprotein (RNP) antibodies, Scl 70 (topoisomerase 1) antibodies, anti-centromere antibodies, anti-cardiolipin antibodies (IgG and IgM), lupus anticoagulant (LAC), anti-beta-2-glycoprotein I antibodies

Assessment	Parameters
	All applicable visits: high-sensitivity C-reactive protein (hsCRP); complement (C3, C4, CH50); quantitative IgM, IgG, IgA, IgE; anti-double-stranded DNA (dsDNA) antibodies

APPENDIX 3 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
AE	Adverse event
AEI	Adverse event of interest
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANA	Anti-nuclear antibodies
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
ATC	Anatomical therapeutic chemical
AUC	Area under the concentration-time curve
BILAG	British Isles Lupus Assessment Group index
C3	Complement component 3
C4	Complement component 4
CD	Cluster of differentiation
CDC	Centers for Disease Control
CH50	Total complement
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	Maximum concentration
COVID-19	Coronavirus Disease of 2019
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
dsDNA	Double-stranded DNA
ECG	Electrocardiogram
EDC	Electronic data capture
EoS	End of Study
EoT	End of Treatment
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GVHD	Graft-versus-host disease
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus

Abbreviation or Term	Definition/Explanation
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICOS	Inducible T cell co-stimulator
ICOS-L	Inducible T cell co-stimulator ligand
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No-observed-adverse-effect level
NSAID	Nonsteroidal anti-inflammatory drug
[redacted]	
pH	Hydrogen ion concentration
PK	Pharmacokinetics
PPD	Purified protein derivative
PhGA	Physician's Global Assessment of SLE Disease Activity
PtGA	Patient's Global Assessment of Disease Activity
Q2W	Once every 2 weeks
QTcF	QT interval corrected for heart rate using Fridericia's correction formula
RNA	Ribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SDI	SLICC/ACR Damage Index
SF-36	Short Form-36
[redacted]	
SLE	Systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLEDAI-2K 30	Systemic Lupus Erythematosus Disease Activity Index 2000 30-Day
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology
SOC	Standard of care

Abbreviation or Term	Definition/Explanation
SRI	SLE Responder Index
TB	Tuberculosis
[redacted]	
ULN	Upper limit of normal
UPCR	Urine protein-creatinine ratio
WHODRUG	World Health Organization Drug
WOCBP	Woman of Childbearing Potential