STATISTICAL ANALYSIS PLAN

Protocol Number	AIS-A03
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study of ALPN-101 In Systemic Lupus Erythematosus
Product:	ALPN-101 (acazicolcept)
Indication:	Systemic Lupus Erythematosus
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Protocol No. AIS-A03

Statistical Analysis Plan

Version: 2.0 (26 SEP 2024)

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LIST OF ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse event
AEI	Adverse event of interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under concentration-time curve
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BLOQ	Below limit of quantitation
BMI	Body Mass Index
CI	Confidence interval
CL	Clearance
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration
CV	Coefficient of variation
DMC	Data monitoring committee
dsDNA	Double stranded DNA
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	US Food and Drug Administration
ICH	International Counsel for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICOS-L	Inducible T cell co-stimulator ligand
IE	Intercurrent event
Ig	Immunoglobulin
Lambda z	Terminal elimination rate constant
LDA	Low Disease Activity by SLEDAI-2k
LLDAS	Lupus Low Disease Activity State

LOCF	Last observation carried forward
LS	Least squares
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	Minimum
mITT	Modified Intent-to-Treat
MMRM	Mixed effects models for repeated measures
NAb	Neutralizing antibody
[redacted]	[redacted]
PhGA	Physician's global assessment of disease activity
PK	Pharmacokinetics
PT	Preferred term
PtGA	Patient's global assessment of disease activity
Q2W	Every other week
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDI	SLICC/ACR Damage Index
SF-36	Short Form Health Survey-36
SLE	Systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLICC/ACR	Systemic Lupus International Collaborating Clinics/American College of Rheumatology
SOC	System organ class
SRI	SLE Responder Index
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to maximum concentration
ULN	Upper limit of normal
V_d	Volume of distribution

1. INTRODUCTION AND BACKGROUND

The purpose of this Statistical Analysis Plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report efficacy and safety results for Protocol AIS-A03, version 4.0 dated 7 November 2022, a randomized, double-blind, placebo-controlled study of ALPN-101 (acazicolcept) in systemic lupus erythematosus (SLE).

The structure and content of this plan provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

This plan is a supplement to the study protocol, which contains additional details on study design, study conduct, and other operational aspects of the study.

2. STUDY OBJECTIVES

2.1. Primary Study Objective

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

2.2. Secondary Study Objectives

The secondary objectives of this study are:

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

3. STUDY ENDPOINTS

3.1. Efficacy Endpoints

Definitions for efficacy endpoints are provided in Section 6.

3.1.1. Primary Efficacy Endpoints

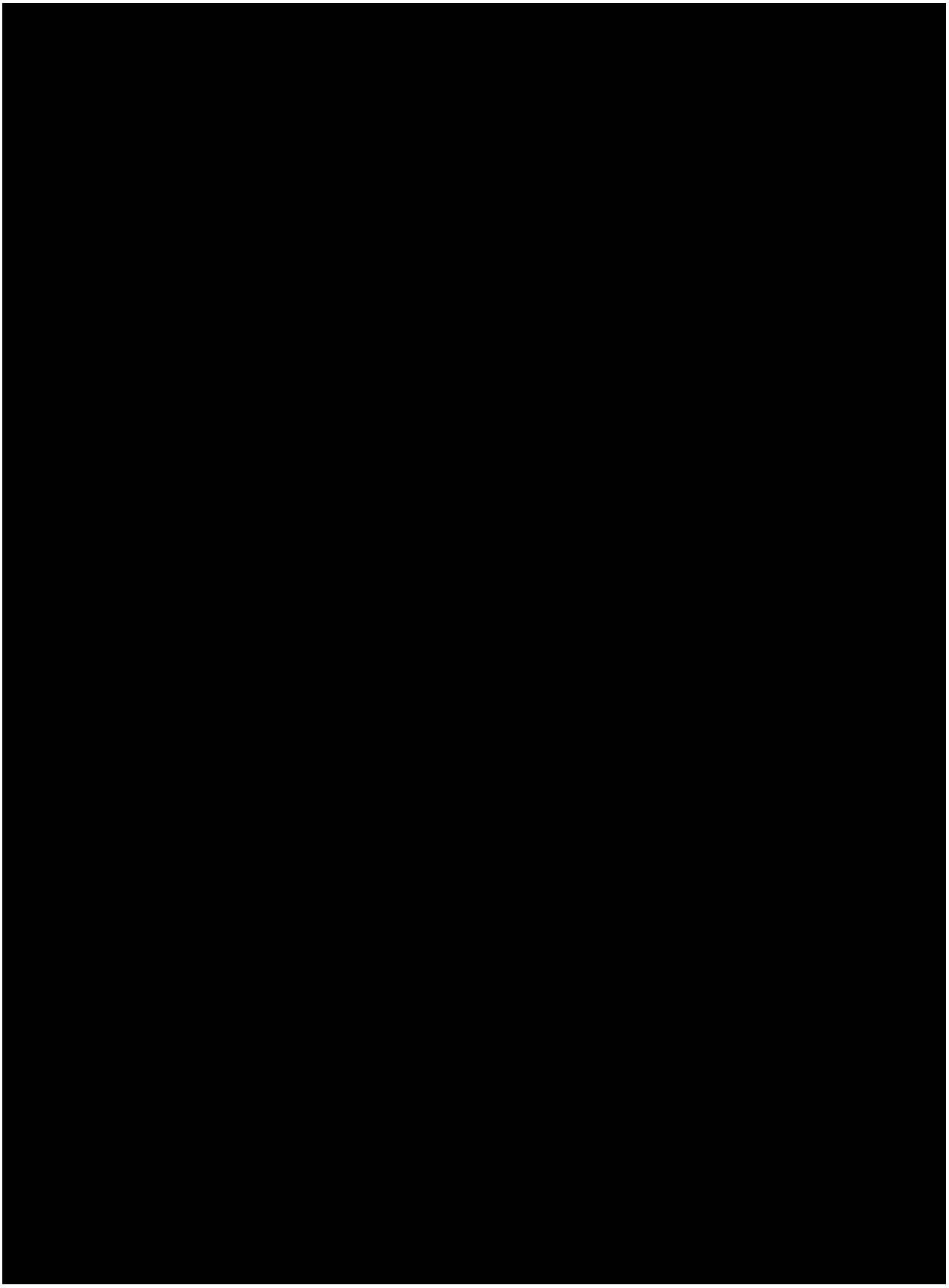
There are two primary efficacy endpoints being investigated for this study:

- Achievement of SLE responder index (SRI)-4 at Day 169, or
- Achievement of British Isles Lupus Assessment Group-based Composite Lupus Assessment (BICLA) response at Day 169

3.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints are provided below:

- Annualized flare rate by British Isles Lupus Assessment Group (BILAG)-2004 flare index through Day 169 – all flares
- Time-to-first flare by BILAG-2004 flare index
- Achievement of Lupus Low Disease Activity State (LLDAS) at Day 169
- Change from baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) total score at Day 169
- Cumulative prednisone-equivalent dose use (total area under the curve of daily prednisone-equivalent dose) through Day 169
- Achievement of ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score at Day 169 in the subgroup of subjects with baseline CLASI activity score ≥8



3.2. Safety Endpoints

The primary study objective of assessing safety and tolerability of ALPN-101 will be evaluated using the endpoints listed in below:

- Treatment-emergent adverse events (TEAEs), treatment-emergent adverse events of interest (AEIs; infusion-related reactions, oral mucocutaneous lesions, infections grade ≥3), and serious adverse events (SAEs)
- Abnormal laboratory test results and observed and change/shift from baseline in over time for:
  - Chemistry
  - Hematology
  - Coagulation
  - Urinalysis
- Abnormal vital signs results and observed and change/shift from baseline over time for:
  - Systolic and diastolic blood pressures (mmHg)
  - Heart rate (bpm)
  - Respiratory rate (bpm)
  - Body temperature (°C)
  - Weight (kg)
- Abnormal electrocardiogram (ECG) parameters and observed and change/shift from baseline over time for:
  - Heart rate (bpm)
  - QT interval (msec)

- PR interval (msec)
- QRS duration (msec)
- RR interval (msec)
- QTcB interval (msec)
- QTcF interval (msec)

3.3. Biomarker [redacted]

Key biomarker endpoints are specified below. Biomarker variables will also be analyzed over time, as applicable:

- Observed and change/percent change from baseline by visit for clinical biomarkers of SLE:
  - C-reactive protein
  - Complements - C3, C4, CH50
  - Immunoglobulins (Igs) – IgM, IgG, IgA, IgE
  - Anti-double stranded DNA (dsDNA) antibodies
- Proportion of subjects who converted from abnormal laboratory test values at baseline to normal laboratory test results at Day 169 in:
  - C-reactive protein
  - Complements - C3, C4, CH50
  - Immunoglobulins – IgM, IgG, IgA, IgE
  - Anti-dsDNA antibodies

[redacted]

3.4. Pharmacokinetic Endpoints

To examine the pharmacokinetics (PK) of ALPN-101 in subjects with active SLE the following variables will be analyzed:

- ALPN-101 concentrations for each timepoint
- Main PK parameters:
  - Area under the concentration-time curve (AUC)
  - Maximum concentration (Cmax)
  - Trough concentration (Ctrough)

  - Elimination half-life ($t_{1/2}$)
- Additional PK parameters:
  - Time to maximum concentration (Tmax)
  - Clearance (CL)
  - Volume of distribution (V_d)
  - Terminal elimination rate constant (Lambda z)
  - Accumulation ratios

3.5. Immunogenicity Endpoints

The following variables will be used to assess the immunogenicity of ALPN-101 over time:

- Incidence of ADA positive
- Minimum and maximum titer values
- Incidence of neutralizing antibodies (NAb) positive

4. STUDY DESIGN

4.1. General Description

This is a Phase 2, multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety, tolerability, efficacy, immunogenicity, PK [redacted] of ALPN-101 compared to placebo in adult subjects with chronic, moderate to severe active SLE. At least 130 subjects will be randomized in a 1:1 ratio to receive a weight-based dose of 3 mg/kg ALPN-101 administered by intravenous infusion via an infusion pump or matching placebo every other week (Q2W) for a total of 12 doses. An overview of the study design is provided in Appendix 15.1.

Randomization will be stratified based by SLE treatment at baseline and geographic region (Appendix 15.5). Subjects will be followed for 4 weeks after the End of Treatment (EOT) visit, 6 weeks after the last dose of study drug. Assessments of adverse events (AEs) and disease activity, and collection of blood and urine for safety laboratory values, biomarkers of disease activity, PK, ADA, and [redacted], will be performed throughout the study. The Schedule of Assessments is provided in Appendix 15.2.

Each subject will participate for up to 34 weeks, including:

- Screening Period: Up to 42 days prior to first dose date. All subjects must complete all screening assessments and make them available to the team for verification of disease activity. Subjects who appear to meet eligibility criteria must undergo central review and verification of SLE disease activity prior to randomization.
- Treatment Period: Up to 24 weeks from first dose date. Subjects will receive 12 doses of study treatments Q2W. Safety, biologic activity, PK, ADA, [redacted] will be conducted according to the Schedule of Assessments (Appendix 15.2).
- Follow-up Period: 4 weeks after EOT.

Dense PK will be collected in subjects who agree to participate. Additional PK samples will be collected from these subjects 4 hours following administration of the first dose of study drug, and on days 1, 3 and 7 following the first study drug administration.

Medications that are used for treatment of SLE at baseline 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.

Subjects who prematurely discontinue treatment with study drug should have all procedures outlined in the EOT visit and 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 from the study, should otherwise continue 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.

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.

It should be noted that while N=130 subjects were expected to be randomized in this study, enrollment was stopped at N=76 subjects.

4.2. Determination of Sample Size

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

Table 1 provides the estimated power to detect a range of potential differences in proportions. For these calculations, a sample size of 65 subjects per treatment group, a two-sided chi-square test statistic and a significance level (alpha) of 0.05 were used. Placebo response rates of 40% for SRI-4 and 20% for BICLA and effect sizes ranging from 15% to 35% were assumed.

No adjustments for multiplicity are planned for this early phase study.

Table 1: Estimated Power Based on N=65 Subjects per Treatment

SRI-4			BICLA		
Response Rate		Estimated Power*	Response Rate		Estimated Power*
Placebo	ALPN-101		Placebo	ALPN-101	
40%	55%	40%	20%	35%	48%
40%	60%	63%	20%	40%	71%
40%	65%	82%	20%	45%	87%
40%	70%	94%	20%	50%	96%
40%	75%	99%	20%	55%	99%

*Assuming a 2-sided significance level of 0.05 using SAS version 9.4

4.3. Methods of Assigning Subjects to Treatment

A centralized interactive web-based response system will be used to randomly assign subjects to receive either ALPN-101 or placebo in a 1:1 ratio. Randomization will be stratified by geographic region and by use of concomitant oral immunosuppressive therapy at enrollment. Levels of each stratification factor, which result in 6 unique strata, are defined as follows:

1. Background immunosuppressive therapy use:
    - Present: 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;

- Absent: No use of permitted immunosuppressants 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.

2. Geographic region:
   - Region 1: North America or Western Europe
   - Region 2: Eastern Europe
   - Region 3: Asia

Subjects, investigators, site staff, and individuals with direct contact with site staff (e.g., clinical research associates, project management, medical monitors, and data management) will remain blinded to treatment assignment until after final database lock. Select study team members may be unblinded to treatment assignment. A list of all individuals unblinded to treatment assignment prior to final database lock will be maintained.

5. ANALYSIS POPULATIONS AND SUBGROUPS

5.1. Analysis Populations

The following analysis populations will be used for the analysis of study data.

- **All Randomized Population:** The randomized population will include all subjects who are assigned to study treatment, regardless of whether study treatment is received. The randomized population will be analyzed according to the treatment group into which they were randomized, regardless of the actual treatment received.
- **Modified Intent-to-Treat Population:** The modified intent-to-treat (mITT) population includes 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 group into which they were randomized, regardless of the actual treatment received. Unless otherwise specified, this population will be used for the analysis of efficacy endpoints.
- **Safety Population:** The safety population includes all subjects who received any amount of study drug. The safety population will be analyzed by treatment actually received. Unless otherwise is specified, this population will be used for the analysis of safety endpoints.
- **Pharmacokinetics Population:** The PK population includes all subjects who received at least one dose of ALPN-101 and have at least one post-dose PK concentration reported. Unless otherwise is specified, this population will be used for the analysis of PK endpoints.

[redacted]

- **Anti-Drug Antibodies Population**: The ADA population includes all subjects who received at least one dose of study drug and have at least one post-baseline ADA value.

5.2. Subgroups of Interest

Analyses of subgroups of subjects may be used to better understand the biological activity of ALPN-101 in subjects with SLE. Subgroup analyses will be performed on a case-by-case basis as post-hoc analyses. Possible subgroups of interest, depending on available data, and may include, but are not limited to:

- Geographic region
- Age group: <50 years, ≥50 years
- Race
- Baseline SLEDAI-2K: <10, ≥10
- Baseline corticosteroid use: >7.5 mg/day, ≤7.5 mg/day
- Sex at birth: Male, Female

- Body Mass Index (BMI): <30 kg/m^2, ≥ 30 kg/m^2

6. ANALYTIC DEFINITIONS

6.1. Baseline and Change from Baseline

Baseline values are the last values recorded prior to the first administration of study drug, unless otherwise specified.

Change from baseline values for a subject are derived as the subject's post-baseline value minus the subject's baseline value of the same variable.

Percent change from baseline is calculated by dividing the change from baseline value by the baseline value as follows:

Percent change from baseline = ((post-baseline value – baseline value) / baseline value) x 100

6.2. Treatment Exposure Duration

Duration of treatment exposure is calculated as the number of days between the date of a subject's last dose of study drug and the date of the first dose of study drug. Intervals of dosing interruption between a subject's first and last doses will not be deducted from the overall treatment duration. That is:

Date of last dose of study drug – date of first dose of study drug + 1

6.3. Overall Treatment Compliance

Overall treatment compliance (%) with protocol-specified treatment for a subject will be calculated as:

100 x (number of doses received)/(weeks of study participation prior to the end of treatment/2)

6.4. Treatment-Emergent Adverse Events

TEAEs are defined as AEs that start or worsen in severity on or after the administration of the first dose of study drug through the end of study participation or at least 8 weeks after last study drug administration for subjects who discontinue treatment early.

6.5. Systemic Lupus Erythematosus Responder Index

SRI is a binary composite score defined by meeting all the following criteria:

- Reduction from baseline in SLEDAI-2K total score ≥x, where x=4 points for SRI-4, 5 points for SRI-5, 6 points for SRI-6, 7 points for SRI-7 and 8 points for SRI-8
- No new BILAG-2004 disease activity A scores (severe disease) and no more than 1 new activity score B (moderate disease)
- No worsening from baseline in subjects' lupus disease activity. Worsening is defined by an increase ≥10% (i.e., increase of ≥0.30 on a 3-point scale) in PhGA

6.6. British Isles Lupus Assessment Group-based Composite Lupus Assessment

BICLA response is a binary composite score defined by meeting all the following criteria:

- Reduction in all baseline BILAG-2004 A to B, C or D and baseline BILAG-2004 B to C or D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- No worsening from baseline in SLEDAI-2K. Worsening is defined as an increase from baseline of >0 points in SLEDAI-2K total score
- No worsening from baseline in subjects' lupus disease activity. Worsening is defined by an increase ≥10% in PhGA (i.e., increase of ≥0.30 on a 3-point scale)

Subjects with no BILAG-2004 A or B scores at baseline and no worsening in any organ systems (defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B), as well as subjects with a baseline PhGA score >2.7 on a 3-point scale will be considered as having met the criteria defined above for BILAG and PhGA, respectively.

6.7. Time-to-First Response

Time-to-first response of a specified efficacy endpoint, such as SRI-4 or BICLA, is defined as the number of days from the administration of the first dose of study drug to the date of the visit during which the first response of the specified endpoint is recorded. Time-to-first response is calculated as:

Date of first response – Date of first dose of study drug + 1

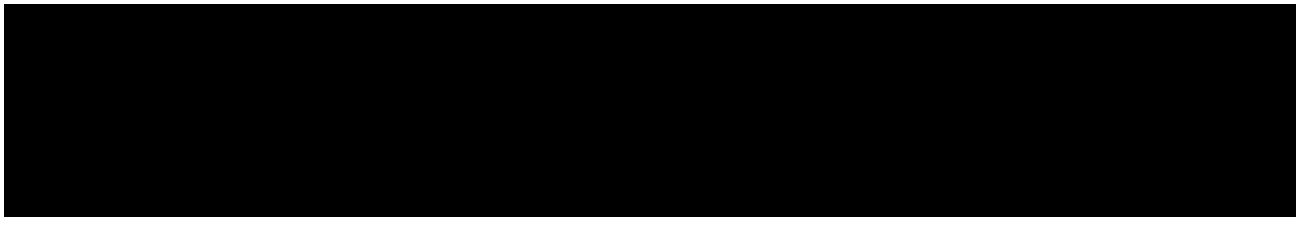
Subjects who do not achieve a response will be censored at their EOT date.

6.8. Systemic Lupus Erythematosus Flare

Three definitions will be used to examine the occurrence of SLE flares during the study.

BILAG Flare Index: BILAG-2004 responses will be used to identify SLE flares according to the following severity levels [Gordon, 2003].

- Mild BILAG Flare: One new BILAG-2004 B grade in an organ system with grade C, D or E at the previous visit, or 3 or more new BILAG-2004 C grades in organ systems with grade D or E at the previous visit
- Moderate BILAG Flare: Two or more new BILAG-2004 B item in organ systems with grades of C, D or E at the previous visit
- Severe BILAG Flare: One or more new BILAG-2004 A item compared to the previous visit



[redacted]

6.9. Time-to-First Systemic Lupus Erythematosus Flare

Time-to-first SLE flare is defined as the number of days from the administration of first dose to the first occurrence of flare. That is:

Date of first occurrence of SLE flare – date of first dose of study drug + 1

Subjects who do not experience any SLE flares will be censored at their EOT date.

Time-to-first SLE flare will be summarized for each definition of SLE flare.

6.10. Annualized Flare Rate

The annualized flare rate for each subject is defined as the number of flares observed during the treatment period divided by the flare exposure time in days multiplied by 365.25. Flare exposure time of a subject is defined as the difference in days between the last BILAG-2004 assessment date and the date of first dose + 1. For subjects who do not experience any flares for each of the SLE flare definitions, then the number of flares for that subject will be set to zero for each definition.

Annualized flare rate will be calculated for each definition of SLE flare.

6.11. BILAG-2004 System Organ-Specific Response

For each system organ with A or B scores at baseline, treatment response is achieved if all of the following criteria are satisfied:

- Reduction from A at baseline to B, C or D or reduction from B at baseline to C or D
- No early discontinuation of study drug
- No use of restricted medications beyond the protocol-allowed threshold before assessment (see Section 6.21)

Response will not be calculated for system organ with no baseline score of A or B.

[redacted]

[redacted]

6.14. Lupus Low Disease Activity State

Lupus Low Disease Activity State [Franklyn, 2016] is binary state achieved if all the following criteria are satisfied:

- SLEDAI-2K total score ≤4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity
- No new features of lupus disease activity compared with the previous assessment,
- PhGA ≤1 on a 3-point scale
- Current prednisolone-equivalent dosage ≤7.5 mg/day
- Well-tolerated standard maintenance dosages of immunosuppressive drugs and approved biologics

6.15. SLEDAI-2K Total Score

Total score is defined as the sum of the weighted scores of each individual item within each organ system class.

[redacted]

6.17. Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity Score

The CLASI activity score is calculated by adding the numeric values of the responses to items in the erythema, scale/hypertrophy categories, the mucous membrane involvement question, questions about acute hair loss and non-scarring alopecia. The scores for affected body parts are weighted equally regardless of surface area and number of lesions present. More severe manifestation within an area is scored higher then less severe manifestation.

6.18. 50% Improvement in CLASI Activity Score

A 50% reduction in CLASI activity score compared to baseline defined by meeting all of the following criteria:

- Achieve ≥50% reduction from baseline in CLASI activity score at Day 169

6.21. Restricted/Rescue Medications

During the Treatment Period, subjects treated with new concomitant medications or increased dose of the existing treatment will be considered non-responders (treatment failures) for assessments of SRI-X, BICLA, SLEDAI-2K Improvement, and 50% Improvement in CLASI activity score efficacy endpoints for visits after taking the restricted medication. Criteria for restricted/rescue medications include the following:

- Oral corticosteroids (prednisone, methylprednisolone, prednisolone, fludrocortisone acetate) can be taken during the study per the protocol criteria however the following would qualify the subject as a treatment failure:
  - Increase in dose from baseline of oral corticosteroids (burst) from Day 1 through Day 141 lasting more than 14 days (i.e., subject must taper back down to baseline dose level by Day 14 of the increase; for subjects not previously taking oral corticosteroids, taper must be down to 0 mg/day within 14 days); such a course also cannot be initiated more frequently than every 28 days
  - Dose greater than 40 mg prednisone/day (or equivalent)
  - Initiation of new oral corticosteroids or an increase in dose after Day 141
- Intramuscular corticosteroids can be taken during the study however, the following would qualify the subject as a treatment failure:
  - Intramuscular methylprednisolone dose greater than 160 mg administered at a single timepoint from Day 1 through Day 169
  - Intramuscular corticosteroids given at a frequency greater than 28 days
  - Initiation of new intramuscular corticosteroids or an increase in dose after Day 141

- Topical corticosteroids can be taken during the study however, the following would qualify the subject as a treatment failure
  - Increase in dose from baseline of topical corticosteroids (burst) from Day 1 through Day 141 lasting more than 14 days (i.e., subject must taper back down to baseline dose level by Day 14 of the increase; for subjects not previously taking topical corticosteroids, taper must be down to 0 mg/day within 14 days); such a course also cannot be initiated more frequently than every 28 days
  - Initiation of new topical corticosteroids or an increase in dose after Day 141
- Intravenous corticosteroids
- Increase in dose or addition of hydroxychloroquine or hydroxychloroquine-like drugs (hydroxychloroquine, hydroxychloroquine sulfate, chloroquine phosphate)
- Any new medication started during the study for SLE. The following exceptions are allowable:
  - Corticosteroid burst as specified above
  - Medication may be reduced or temporarily discontinued for safety reasons and then started again. This would not be considered a new medication
- Other restricted medications taken any time during the study:
  - Biologics (e.g., abatacept, anifrolumab, atacicept, belatacept, belimumab, obinutuzumab, ocrelizumab, rituximab, telitacicept)
  - Investigational agents

7. STATISTICAL METHODS AND ANALYSIS

Summaries of study data will be presented by treatment group (ALPN-101 or placebo) and for all subjects combined, as applicable.

Summaries of continuous data will present the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). Min and max values will be reported using the same number of decimal places as the raw data values; mean and medians will be reported to one more decimal place than the raw data values; and SD will be reported to two more decimal places than the respective raw data. If the raw data have three decimal places or more, three decimal places will be presented for all statistics.

For categorical data, the frequency in each category and the percentage of the relevant population will be presented. In general, percentages will be presented to one decimal place. Percentages equal to 100 will be presented as 100% and percentages equal to 0 will be presented as 0%.

Analyses will be conducted using SAS®, version 9.4 or higher.

7.1. Subject Accountability and Disposition

Subject disposition will be summarized by treatment group and for all subjects combined. The summary of subject disposition will include the numbers of subjects screened and randomized, the number of randomized subjects in each randomization stratification category, the number of subjects treated, and the numbers of subjects in each analysis population. The number and percentage of subjects in the randomized population who completed study treatment and who discontinued study treatment prematurely will be summarized with the primary reasons for treatment discontinuation. Similarly, the number percentage of subjects in the randomized population who completed the study and who permanently discontinued from study participation prematurely will be summarized with the primary reasons for study discontinuation.

A summary of the number and percentage of subjects screened, randomized, and completing study participation will be presented by geographic region and country within geographic region.

A listing of disposition for all randomized subjects including date of the subject's completion or discontinuation and reasons for treatment or study discontinuation will be presented. A separate listing of analysis populations and randomization stratification will also be provided.

Protocol deviations will be tracked throughout the study. Deviations may be related to inclusion/exclusion criteria, trial conduct, subject management or subject assessment. Prior to database lock all deviations will be reviewed and designated as important or not important. A summary of the number and percentage of subjects in the randomized population with important protocol deviations reported will be presented by treatment group and type of deviation. A by-subject listing of important protocol deviations will be provided.

7.2. Demographics and Baseline Characteristics and Medications

Descriptive summaries of demographics and baseline characteristics will be presented by treatment group for all randomized subjects. No formal statistical comparisons between the treatment arms will be performed. A by-subject listing of demographic and key baseline data will be provided.

History of significant non-SLE conditions and current medical conditions reported at screening and/or baseline will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). The number and percentage of subjects in each treatment group of the safety population who reported each SOC and PT will be reported.

The number and percentage of unique subjects in the safety population who report use of prior and concomitant medications will be summarized separately by treatment group and for all subjects combined. Prior medications are medications with start and end dates prior to the date of the first dose of study drug. A medication that was started prior to the first dose of study drug and continued after first dose of study or that has a first dose date after the first dose of study drug will be summarized as a concomitant medication. An additional table summarizing all concomitant medications which are initiated on or after the date of the first administration of study drug will be provided. Concomitant medications for treatment of SLE, including concomitant corticosteroids, will be summarized separately. A single subject will be counted once, regardless of the number of times a specific medication was used.

Oral corticosteroid use during the study will be summarized for the mITT population using the following variables:

- Incidence of subjects oral corticosteroid use
- Incidence of subjects with changes in oral corticosteroid use
- Total exposure to oral corticosteroid use (area under the oral corticosteroid exposure curve while on study treatment) using prednisone-equivalent doses as described in Appendix 15.6
- Duration (days) of oral corticosteroid use while on study treatment

Rescue medications will be summarized for the mITT population for each treatment group and for all subjects combined.

A listing of all reported medications will be presented that includes the verbatim medication name reported, the Anatomical Therapeutic Chemical (ATC) coded terms, dosage, and frequency. Additionally, a listing of restricted medications taken during the study will be presented.

7.3. Treatment Exposure and Compliance

The extent of exposure to study drug will be summarized for the safety population by treatment group. Exposure duration in days will be calculated as defined in Section 6.2. Descriptive summaries of exposure days and the number and percentage of subjects in each exposure duration category, defined as ≥4 weeks, ≥12 weeks and ≥24 weeks will be presented.

To assess compliance with protocol-specified administration of study treatment, subjects in the safety population who missed a study drug infusion at any scheduled dosing visit prior to treatment completion or discontinuation or who do not receive the targeted amount of study drug are considered non-compliant. The number and percentage of non-compliant subjects will be summarized by treatment group and visit.

Overall compliance will be summarized descriptively. A by-subject listing of study drug administration will be provided.

7.4. Analysis of Efficacy Endpoints

7.4.1. General Considerations

Unless otherwise stated, all efficacy analyses will be conducted on the mITT population according to the randomized treatment. For efficacy endpoints, point estimates of treatment differences and 95% confidence intervals (CI) will be provided. Two-sided p-values will also be provided for efficacy endpoints, as applicable. Where possible, study outcomes will be presented graphically also. Due to small sample sizes of subjects randomized to the Asia geographic region, this region will be pooled with the Eastern Europe region in the statistical analysis models.

7.4.2. Handling of Missing Data and Intercurrent Events (IE)

Intercurrent events in this study include the following:

- IE1: Premature discontinuation of study treatment
- IE2: Restricted/rescue medication use (criteria for restricted/rescue medication use is provided in Section 6.21)

The strategies to be used in the handling of intercurrent events and missing data for efficacy endpoints, when applicable, are provided below:

- Binary endpoints (primary and secondary efficacy endpoints):
  - IE1 and IE2: subject is considered a non-responder (composite strategy)
  - Missing data for Day 169: subject is considered a non-responder
- Continuous endpoints measured through time (SLEDAI-2K total score):
  - IE1 and IE2: data after IE1 and IE2 occurs will not be included in the analysis (hypothetical strategy)
  - Missing data caused by applying the intercurrent event handling described above and other missing data will be handled by the mixed effects models for repeated measures (MMRM) analysis
- Other efficacy endpoints:
  - Treatment policy strategy will be applied and all observed data during the treatment period will be used regardless of IE1 or IE2
  - Missing data for Day 169 for binary endpoints: subject is considered a non-responder for applicable endpoints

7.5. Analysis of Primary Efficacy Endpoints

7.5.1. Main Analysis

Response rates for subjects in the ALPN-101 group and in the placebo group will be calculated and the corresponding 95% CI will be reported for each treatment group. These response endpoints will be analyzed through Day 169 for subjects who complete treatment and through

the last assessment recorded ≤28 days after treatment discontinuation date for subjects who discontinue treatment early.

For the main analyses of SRI-4 response rate and BICLA response rate, non-responder imputation will be used for IE and missing data as described in Section 7.4.2.

Response rates will be compared using Cochran-Mantel-Haenszel (CMH) test statistic stratified by the factors used at randomization. Estimated treatment effect will be reported as the difference between the response rate in the ALPN-101 treatment group and the response rate in the placebo group. Corresponding 95% CI for the difference in proportions and the two-sided p-value for the difference will be reported.

[redacted]

7.6. Analysis of Secondary [redacted] Efficacy Endpoints

Unless otherwise stated, the mITT population will be the basis for analyses of all efficacy endpoints. These data will be analyzed through Week 24 (Day 169) for subjects who complete treatment and through the last assessment recorded ≤28 days after treatment discontinuation for subjects who discontinue treatment early.

7.6.1. Analysis of Categorical Endpoints

Analyses of other categorical efficacy endpoints will be conducted using the stratified CMH approach described for the efficacy endpoints of primary interest. Response will be summarized for each treatment group by visit as the proportion of subjects in the category of interest at the specified visit, and across the 24-week treatment period as the proportion of subjects in the

category of interest at any time during treatment. The difference in proportions between the ALPN-101 treatment group and the placebo group and the associated 95% CI for this difference will be reported.

7.6.2. Analysis of Continuous Endpoints

MMRM will be used for the analysis of continuous longitudinal data. Terms in the model will include treatment group, baseline value of the analysis variable, stratification factors (concomitant oral immunosuppressive therapy use at enrollment and geographic region), analysis visit, and the interactions of treatment-by-visit and baseline value-by-visit as fixed effects. An unstructured covariance matrix will be used to model within-subject error. If the model fails to converge with an unstructured covariance matrix, a heterogeneous compound symmetric structure will be used. Kenward-Roger degrees of freedom, Type III sums of squares, and least squares (LS) mean values will be reported for each treatment group and for the difference between treatments. Standard errors and 95% CI for the estimated mean difference at each visit will be presented. Plots of LS mean values and 95% CIs by visit with separate lines for each treatment group will be provided for continuous secondary efficacy endpoints.

Annualized flare rates and cumulative prednisone-equivalent dose use will be analyzed using an analysis of variance model. Terms in the model include treatment group and stratification factors (concomitant oral immunosuppressive therapy use at enrollment and geographic region). Type III sums of squares, and least squares (LS) mean values will be reported for each treatment group and for the difference between treatments. Standard errors and 95% CI for the estimated mean difference will be presented.

7.6.3. Analysis of Time-to-Event Endpoints

Time-to-event analyses, such as time-to-first SLE flare and time-to-first BICLA response, will be analyzed using a Cox proportional hazards models adjusted for stratification factors (concomitant oral immunosuppressive therapy use at enrollment and geographic region). Subjects who do not experience the specified event will be censored on the date at which the last non-missing response data were collected. For example, in the time-to-first SLE flare, subjects who do not experience flares will be censored on the date of the last available BILAG value. In the analysis of time to first BICLA response, subjects who do not achieve a positive BICLA response will be censored on the date of their last non-missing BICLA response value. Estimated hazard ratios and corresponding 95% CI will be reported. If estimable, median, 25^{th} and 75^{th} percentiles of the time to specified event and corresponding 95% CI will be reported. Time to event secondary efficacy endpoints will be displayed in Kaplan-Meier curves.

7.7. Estimands for the Primary and Secondary Endpoints

Estimand definitions for the primary and secondary efficacy endpoints are provided below:

Table 2: Estimand Attributes Corresponding to the Primary and Secondary Efficacy Endpoints

Attributes of the Estimand					
Estimand	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Primary	ALPN-101 vs. Placebo	Achievement of SRI-4 response at Day 169	Subjects with moderate to severe SLE	IE1 and IE2: subject is considered a non-responder (composite strategy) Missing data: subject is considered a non-responder	Difference in the proportion of subjects achieving SRI-4 response
Primary	ALPN-101 vs. Placebo	Achievement of BICLA response at Day 169	Subjects with moderate to severe SLE	IE1 and IE2: subject is considered a non-responder (composite strategy) Missing data: subject is considered a non-responder	Difference in the proportion of subjects achieving BICLA response
Secondary	ALPN-101 vs. Placebo	Annualized flare rate by BILAG-2004 flare index through Day 169 for all flares	Subjects with moderate to severe SLE	All observed data used (treatment policy strategy)	Difference in the LS means for annualized flare rate by BILAG-2004 flare index for all flares
Secondary	ALPN-101 vs. Placebo	Time-to-first flare by BILAG-2004 flare index	Subjects with moderate to severe SLE	All observed data used (treatment policy strategy)	Hazard ratio for time-to-first flare by BILAG-2004 flare index
Secondary	ALPN-101 vs. Placebo	Achievement of LLDAS response at Day 169	Subjects with moderate to severe SLE	IE1 and IE2: subject is considered a non-responder (composite strategy) Missing data: subject is considered a non-responder	Difference in the proportion of subjects achieving LLDAS response

Attributes of the Estimand					
Estimand	**Treatment**	**Endpoint**	**Population**	**Handling of Intercurrent Events**	**Statistical Summary**
Secondary	ALPN-101 vs. Placebo	Change from baseline in SLEDAI-2K total score at Day 169	Subjects with moderate to severe SLE	All observed data used (hypothetical strategy)	Difference in the LS means for change from baseline in SLEDAI-2K total score
Secondary	ALPN-101 vs. Placebo	Cumulative prednisone-equivalent dose use through Day 169	Subjects with moderate to severe SLE	All observed data used (treatment policy strategy)	Difference in the LS means for cumulative prednisone-equivalent dose use
Secondary	ALPN-101 vs. Placebo	Achievement of ≥50% reduction in CLASI activity score at Day 169 in the subgroup of subjects with baseline CLASI activity score ≥8	Subjects with moderate to severe SLE	IE1 and IE2: subject is considered a non-responder (composite strategy) Missing data: subject is considered a non-responder	Difference in the proportion of subjects achieving ≥50% reduction in CLASI activity score

7.8. Analysis of Safety Endpoints

The primary study objective of assessing safety and tolerability of ALPN-101 in subjects with active SLE will be assessed using TEAEs, AEIs, SAEs, physical exam findings, vital signs, ECG measurements, and laboratory tests. All safety data will be descriptively summarized by treatment group. No formal inference is planned. Analyses will be based on subjects in the safety population. Individual subjects will only be counted once when calculating the incidence of AEs.

7.8.1. Treatment-Emergent Adverse Events

AEs will be recorded at all scheduled and unscheduled visits during the study. Summaries will be presented for TEAEs. In this study, signs and symptoms of SLE activity are captured in the disease activity assessments and will not be reported as AEs. Clinically significant changes in physical exam findings, laboratory test results, and ECG results will be recorded and analyzed as AEs. The incidence, seriousness, and severity of TEAEs and the relationship of the events to study drug will be used to assess safety.

All AEs terms will be classified using MedDRA and reported based on system organ classes and preferred terms. Adverse event severity will be graded using Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. AEIs will be reviewed by the medical monitor lead.

In general, the incidence of AEs will be summarized by the number and the percentage of unique subjects in the safety population who experiencing an event. As such, subjects who report the

same event on multiple occasions will only be counted once. A by-subject listing of all AEs reported will be provided. Rules for the imputation of missing and partial AE dates and missing designations of AE severity, relatedness and seriousness are defined in Section 13.

7.8.2. Laboratory Tests

Safety laboratory tests collected in this study include hematology, serum chemistry, coagulation and urinalysis as specified Appendix 15.5. Numeric laboratory results that are reported using non-numeric qualifiers, such as less than (<) a certain value or greater than (>) a certain value, will be analyzed using the numeric portion of laboratory values minus one or plus one, respectively.

Descriptive summaries of continuous laboratory values and changes in these values from baseline will include the number of non-missing observations, mean, SD, median, min and max value at each scheduled visit, at the last on-treatment visit and at the end of study visit. Data will be summarized in standardized units.

The severity of laboratory result abnormalities will be graded using the CTCAE grading scale. Laboratory values that are within the limits of normal and are not graded as 1-4 will be summarized as a normal result with grade equal to 0. Treatment-emergent abnormal laboratory values are defined as those reported normal (i.e., grade=0) at baseline and abnormal (grade 1-4) after starting study medication. The numbers and percentages of subjects reporting a max (worst) treatment-emergent post-baseline grade observed through the end of the study will be summarized for each laboratory parameter. Percentages will be based on the number of subjects in the safety population with at least one post-baseline value of the respective laboratory parameter.

To examine hepatic laboratory parameters, additional summaries of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and alkaline phosphatase (ALP) will be presented. The number and percentage of subjects in the safety population who meet the following criteria at any time during treatment or follow-up will be summarized:

- Peak ALT value falling within ranges of central laboratory upper limit of normal (ULN) of:
  - >3x ULN and ≤5x ULN
  - >5x ULN and ≤10x ULN
  - >10x ULN and ≤20x ULN
  - >20x ULN
- Peak AST value falling within ranges of central laboratory ULN of:
  - >3x ULN and ≤5x ULN
  - >5x ULN and ≤10x ULN
  - >10x ULN and ≤20x ULN
  - >20x ULN
- Peak total bilirubin within ranges of central laboratory ULN of:

  - <ULN
  - ≥ULN and <2x ULN
  - ≥2x ULN
- Peak ALP of >1.5 x ULN
- Simultaneous ALT or AST >3x ULN and total bilirubin >1.5x ULN
- Simultaneous ALT or AST >3x ULN and total bilirubin >2x ULN

For qualitative laboratory values such as urinalysis data, shift tables comparing baseline results (for example, negative, trace, positive) to the worst post-baseline results will be presented.

Listings of laboratory results for each subject will be presented by type of laboratory test and parameter. Values outside of the corresponding reference range will be flagged in the listings. Laboratory values assessed as part of screening (i.e., infectious disease assessments and screening biomarker values) and pregnancy test results will be presented in by-subject listings but will not be summarized.

7.8.3. Vital Signs

Vital signs data will be summarized descriptively for the safety population by study visit and by measurement time, if applicable. Reported values and changes from baseline in weight, BMI, temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate will be summarized. The number and percentage of subjects with markedly abnormal vital signs, as defined below, will be summarized. Abnormalities of interest include:

- American Heart Association categories for hypertension:
  - Elevated: systolic blood pressure of ≥120 to ≤129 mmHg with diastolic blood pressure <80 mmHg
  - Stage 1 Hypertension: systolic blood pressure of ≥130 to ≤139 mmHg or diastolic blood pressure of ≥80 to ≤89 mmHg
  - Stage 2 Hypertension: systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg
  - Hypertensive Crisis: systolic blood pressure of >180 mmHg and/or diastolic blood pressure of >120 mmHg
- Heart rate (beats per minute, bpm):
  - Abnormally low: a decrease from baseline of ≥15 to a value ≤50 bpm
  - Abnormally high: an increase from baseline of ≥15 to a value ≥120 bpm
- Temperature (°C):
  - Abnormally high: value ≥38.3°C and ≥0.8°C increase from baseline.
- Respiratory rate (bpm):
  - Abnormally low: <12 breaths/min

- Abnormally high: >25 breaths/min

All vital signs including the reported values for each parameters and overall interpretations will be listed by subject.

7.8.4. Electrocardiogram

ECG measurements and change from baseline in ECG measurements, including heart rate (bpm), QT interval (msec), PR interval (msec), QRS interval (msec), RR interval (msec), QTcB interval (msec), and QTcF interval (msec), will be summarized descriptively in the safety population.

To identify potential clinically significant QTcF results, the numbers and percentages of subjects in the safety population who experience confirmed post-baseline absolute QTcF values >450 msec, >480 msec, and >500 msec will be summarized, as will the numbers and percentages of subjects who experience confirmed increases from baseline in QTcF ≥30 msec and ≥60 msec. In addition, a shift table comparing the baseline overall ECG interpretations, based on investigator interpretation, of normal, abnormal – not clinically significant, and abnormal – clinically significant to the investigator interpretation at each post-baseline visit will be presented.

A listing of ECG measurements and investigator-reported ECG interpretations will be presented.

7.8.5. Physical Examinations

Complete physical examinations will be performed at intervals designated in the scheduled of assessments (Appendix 15.2) and will include examination of head, eyes, ears, nose and throat, lungs, abdomen, joints, muscle and soft tissues, neurologic system, skin, and lymph nodes.

Clinically relevant findings identified during a physical examination will be reported and summarized as AEs.

7.9. Analysis of Biomarkers [redacted]

Descriptive summaries of the absolute, change from baseline, and percent change from baseline [redacted]. Additionally, the incidence of subjects with shifts from abnormal baseline values to normal values at EOT in clinical biomarkers will be presented for each treatment group.

7.10. Analysis of Pharmacokinetic Endpoints

ALPN-101 concentration data will be summarized by visit for the PK population. Mean concentration data will also be presented graphically. In summaries of concentration data, concentrations that are reported below the lower limit of quantitation (BLOQ) will be treated as missing.

The PK data obtained in dense PK subset subjects will be analyzed using non-compartmental analysis. The PK parameters including C_{max}, AUC, $t_{1/2}$, and C_{trough} will be determined based on the available data. Descriptive statistics (n, arithmetic mean, standard deviation, % coefficient of variation (CV), min, median, max, geometric mean, and geometric %CV) will be calculated for the PK parameters. For individual PK parameter estimation, BLOQ will be treated as missing if

the value occurs after T_{max}. Investigational population PK modeling and exposure-response analysis is outside the scope of this SAP.

7.11. Analysis of Immunogenicity Endpoints

The incidence of ADA positive to study drug will be summarized by visit and overall for each treatment group for the ADA population. The min and max of the ADA titer value will also be presented. For subjects who are ADA positive, the incidence of NAb positive will be summarized by visit and overall for each treatment group.

8. CHANGES IN ANALYSIS FROM PROTOCOL

Analyses described in this plan are consistent with the protocol-specified analyses. Changes made to the planned analyses described in this SAP will be documented in an SAP amendment or described in the Clinical Study Report.

9. INTERIM ANALYSIS

An administrative interim analysis may be performed when approximately 50% of subjects have completed assessments through Week 24 (Day 169).

10. DATA REVIEW COMMITTEE

Cumulative safety data will be reviewed by a Data Monitoring Committee (DMC), which will provide recommendations regarding study conduct, if indicated. Roles and responsibilities of the DMC are defined in the DMC charter. The specifications for the presentation of study data in the DMC report is defined in a separate analysis plan.

11. MULTIPLICITY ADJUSTMENT

No adjustments for multiplicity will be applied in the analyses of data from this first clinical study of APN-101 in subjects with active SLE.

12. VISIT WINDOWS

All scheduled study visits and corresponding time windows for data analysis are listed in Table 3. Similarly, scheduled study visits and analysis windows for data collected at a subset of study visits are presented in Table 4 and Table 5. Visit windows for data collection are calculated from date of first dose of study drug (Day 1). Unscheduled visits occurring within a defined analysis window will be included in an analysis of specified endpoints. Analysis visit windows are defined to capture data collected at all scheduled and unscheduled visits on or after the first day of the analysis visit window until the day prior to the start of the next window in visit-based analyses.

For analyses of clinical data based on specific visits, if multiple values are recorded within a single analysis window, the following rules will be applied for analysis, unless otherwise specified for the analysis.

- If two or more values are recorded within the same analysis window, the non-missing value collected closest to the scheduled visit will be used in the analysis.
- If two values are collected on dates equidistant from the scheduled visit, the non-missing observation with the earlier collection date will be used in the analysis.
- If more than one value is collected on the same day, the non-missing value with the earlier collection time will be used in the analysis.

Unless otherwise noted, PK data will be summarized using nominal visit labels.

Table 3: Visit Windows for Data Collected at All Visits

Visit Number	Visit Label	Study Day	Protocol Defined Visit Window		Analysis Defined Window	
			From	To	From	To
1	Baseline	1	1	1	≤1	
2	Day 15	15	14	16	2	≤21
3	Day 29	29	27	31	22	≤36
4	Day 43	43	41	45	37	≤49
5	Day 57	57	54	60	50	≤64
6	Day 71	71	68	74	65	≤78
7	Day 85	85	82	88	79	≤92
8	Day 99	99	96	102	93	≤106
9	Day 113	113	110	116	107	≤120
10	Day 127	127	124	130	121	≤134
11	Day 141	141	138	144	135	≤148
12	Day 155	155	152	158	149	≤162
13	Day 169/EOT	169	166	172	163	≤183
EOS	Day 197/EOS	197	194	200	184	EOS visit date

Notes: EOS=End of study; EOT=End of treatment.

Table 4: Visit Windows for Efficacy Date Collected in a Subset of All Visits

Visit Number	Visit Label	Study Day	Protocol Defined Visit Window		Analysis Defined Window	
			From	To	From	To
1	Baseline	1	1	1	≤1	
2	Day 15	15	14	16	2	≤21
3[1]	Day 29	29	27	31	22	≤43
3[2]	Day 29	29	27	31	2	≤43
5	Day 57	57	54	60	44	≤71
7	Day 85	85	82	88	72	≤99
9	Day 113	113	110	116	100	≤128
11	Day 141	141	138	144	129	≤159
13	Day 169/EOT	169	166	172	160	≤183
EOS	Day 197/EOS	197	194	200	184	EOS visit date

1 Indicates Day 29 visit window definition applicable to efficacy assessments scheduled for Day 15
2 Indicates Day 29 visit window definition applicable to efficacy assessments NOT scheduled for Day 15
Notes: EOS=End of study; EOT=End of treatment.

There will be no windowing for the SDI endpoint as this endpoint is only collected at Day 1, end of treatment, and end of study.

Table 5: Visit Windows for ECG Data

Visit Number	Visit Label	Study Day	Protocol Defined Visit Window		Analysis Defined Window	
			From	To	From	To
1	Baseline	1	1	1	≤1	
7	Day 85	85	82	88	2	≤120
12	Day 155	155	152	158	121	≤176
EOS	Day 197/EOS	197	194	200	177	EOS visit date

13. DATA HANDLING

Data handling rules for specific missing efficacy and safety data and missing and partial dates is provided below.

Missing Lab Data for BILAG Renal and Hematological Organ System Scoring:

In the event there is missing lab data for the renal or hematological BILAG organ systems at a particular visit, the preceding visits lab data will be used in the derivation of the renal and hematological BILAG grading. If the preceding visits lab data is also missing, then the lab data will be missing and a BILAG grade for that organ system will not be derived.

Missing BILAG D or E Grades After a Missed Visit:

Due to constraints within the electronic clinical outcome assessment vendor system, BILAG grades of D and E cannot be scored after a subject has a missed visit. Organ system grades for these non-missing visit cases will be derived by carrying forward the previous non-missing D or E grade for these organ systems. This does not apply to grades of A, B, or C.

Table 6: Dummy Coding for Multiple Imputation Modeling

Region	Strata2d	Strata3d
North America/Western Europe	0	0
Eastern Europe	1	0
Asia	0	1

Region	Strata2d	Strata3d
North America/Western Europe is the reference region		

- Step 2: A CMH test will be conducted for each imputed dataset on the Day 169 endpoint. The Wilson-Hilferty transformation will be applied to the CMH general association test statistic to create a normally distributed statistic with a mean=0 and standard deviation=1. Generic SAS code is provided below:

```
proc freq data=d_log;
  tables strata1n*strata2n*treatment*resp_D169 / CMH;
  ods output CMH=cmh;
  by Imputation;
run;
```

Where strata1n and strata2n are the stratification factors for concomitant oral immunosuppressive therapy use at enrollment and geographic region from the Interactive Response Technology system for randomization.

```
data cmh_wh; set cmh (where=(AltHypothesis="General Association"));
  cmh_value_wh=((VALUE/DF)**(1/3) – (1-2/(9*DF)))/SQRT(2/(9*DF));
  cmh_sterr_wh = 1.0;
run;
```

- Step 3: Combine the transformed values from the 100 imputed datasets using PROC MIANALYZE. The combined p-value for the CMH test will be obtained as the upper-tailed p-value from the test produced by PROC MIANALYZE.

```
proc mianalyze data=cmh_wh;
  ods output parameterestimates = est1;
  modeleffects cmh_value_wh;
  stderr cmh_sterr_wh;
run;

data fin_cmh; set est1;
   if tValue > 0 then Probt_upper = Probt/2;
  else Probt_upper = 1-probt/2;
run;
```

Missing Safety Information:

For analyses of AE data, events with missing severity grade will be imputed as Grade 3 for analysis. Similarly, AEs with missing relationship to study drug will be imputed as drug-related. If no designation of event seriousness is available, the AE will be considered serious.

Missing and Partial Dates:

Algorithms applied for imputing partial and missing date values are described below:

Table 7: Imputation of Partial and Missing Date Values

Partial/Missing Start or Stop Date	Imputed Start Date	Imputed Stop Date
Missing year, month, and day	Date of randomization visit	
Missing month and day, and the year is present	Date of randomization visit if the year is the same as the year of randomization date, else January 1 of the start year.	December 31 of that year
Missing day, but year and month are present	Date of randomization visit if the year and month are the same as the year and month of randomization date, else the 1st of the start month.	Last day of that month
Missing month, but year and day are present	Assume day is also missing and impute as above	Missing month imputed as December

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15. APPENDICES

15.1. Study Overview

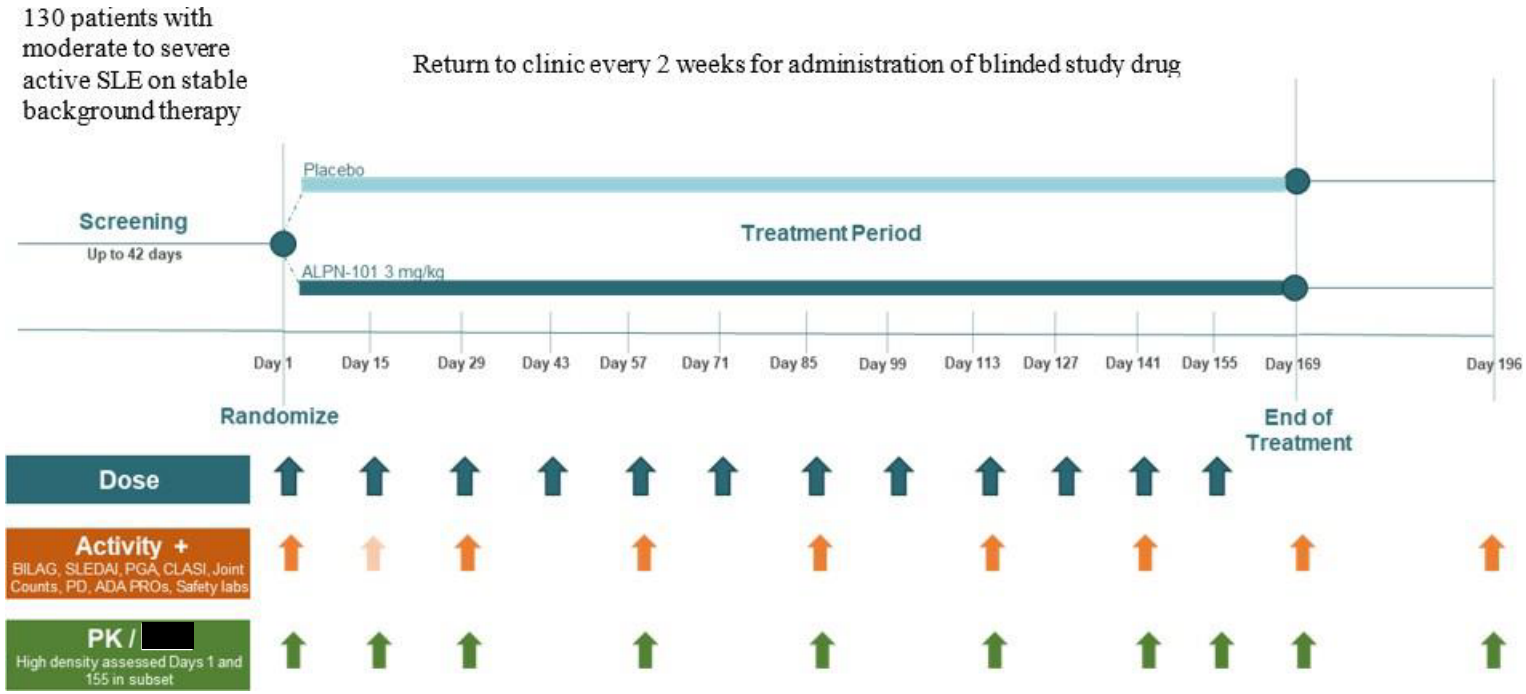

Figure 1: Study Overview

Notes: ADA=Anti-drug antibodies; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; BILAG=British Isles Lupus Assessment Group; [redacted] PGA= Physician's Global Assessment; PROs=Patient - Reported Outcomes; PK=Pharmacokinetics; SLE=Systemic lupus erythematosus; SLEDAI=SLE Disease Activity Index.

15.2. Schedule of Assessments

Table 8: 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 Subject 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

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] ubset.
4 Investigator's screening eligibility assessment must be reviewed and confirmed by Sponsor or designee.
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.
16 In addition to standard safety lab evaluations, includes TSH.
17 Collect samples using kit provided by the central laboratory.
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.
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, photographic documentation should be collected at presentation and in the event of significant change (as detailed in the Procedures Manual).

Abbreviations: 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.

15.3. Disease Assessment Tools

15.3.1. SLEDAI-2K

The SLEDAI-2K is a global measure of disease activity. The raw data set contains responses for 24 items, each of which are assigned weighted scores of 1 to 8 points. The total score is the sum of the weights of the items which are present at the time of assessment. The range of the SLEDAI total score is 0 to 105.

Weighted SLEDAI-2K scores for the presence of each of the 24 items on the data collection tool are shown in below.

Table 9: SLEDAI Weighted Score by Item

Organ System	Item Name	Description	Score
Neuropsychiatric	Seizure	Recent onset, exclude metabolic, infectious or drug causes	8
	Psychosis	Altered ability to function in normal activity due to severe disturbance in perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uraemia and drug causes	8
	Organic Brain Syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes	8
	Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves	8
	Lupus Headache	Severe, persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia	8
	CVA	New onset cerebrovascular accident(s). Exclude arteriosclerosis.	8
Ophthalmic	Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes	8
Mucocutaneous	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis	8
	Rash	Inflammatory type rash	2
	Alopecia	Abnormal, patchy or diffuse loss of hair	2
	Mucosal ulcers	Oral or nasal ulcerations	2

Organ System	Item Name	Description	Score
Musculoskeletal	Arthritis	≥2 joints with pain and signs of inflammation	4
	Myositis	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase/aldolase, or EMG changes or a biopsy showing myositis	4
Renal	Urinary Casts	Heme-granular or RBC casts	4
	Hematuria	>5 RBC/high power field. Exclude stone, infection or other cause	4
	Proteinuria	>0.5 gram/24 hours	4
	Pyuria	>5 WBC/high power field. Exclude infection	4
Cardiorespiratory	Pleurisy	Pleuritic chest pain or pleural rub with effusion, or pleural thickening (requires objective component)	2
	Pericarditis	Classic pericardial pain and/or rub, effusion with ECG or echocardiogram confirmation	2
Hematological	Low complement	Decrease in CH50, C3 or C4 below lower limit of normal for testing laboratory	2
	Increased DNA Binding	Increased DNA binding above normal range for testing lab	2
	Thrombocytopenia	<100 x 10^9 platelets/L, exclude drug causes	1
	Leukopenia	<3 x 10^9 WBC/L, exclude drug causes	1
Constitutional	Fever	>38°C Exclude infectious cause	1

Source: Gladman, 2000.

Notes: C3=Complement component 3; C4=Complement component 4; CH50=Total complement; CVA=Cerebrovascular accident; ECG=Electrocardiogram; EMG=Electromyogram; RBC=Red blood cell; SLE=Systemic lupus erythematosus; WBC=White blood cell.

15.3.2. BILAG 2004

The BILAG 2004 index is an 86-item assessment of nine organ domains. The first seven organ systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, and ophthalmic) contain clinical parameters which are assessed by the investigator and given scores of 0=not present, 1=improving, 2=same, 3=worse, or 4=new. Renal and haematologic scores are based on laboratory values reported at the time of assessment. The numeric parameter scores within each organ system are used to assign a letter grade indicating disease activity. Table 10 displays each level of organ system grading.

Table 10: BILAG Organ System Grades

BILAG Grade	Description
BILAG A	Requires disease-modifying treatment such as prednisone >20 mg/day or immunosuppressant
BILAG B	Mild, reversible problems requiring symptomatic therapy such as anti-malarials, NSAIDS, or prednisone ≤20 mg/day
BILAG C	Stable, mild disease
BILAG D	System previously involved but not currently active
BILAG E	System never involved

Notes: BILAG=British Isles lupus assessment group; NSAIDS=Non-steroidal anti-inflammatory drugs

Table 11 lists the grading algorithms for each body system.

Table 11: BILAG Grading Algorithms

	BILAG Grade				
Organ System	**A**	**B**	**C**	**D**	**E**
Constitutional	Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND** Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new): • Weight loss • Lymphadenopathy/ splenomegaly • Anorexia	Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR** Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new): • Weight loss • Lymphadenopathy/ splenomegaly • Anorexia BUT do not fulfill criteria for Category A	Pyrexia recorded as 1 (improving) **OR** One or more of the following recorded as >0: • Weight loss • Lymphadenopathy/ splenomegaly • Anorexia BUT does not fulfill criteria for category A or B	Previous involvement, currently inactive	No previous involvement
Mucocutaneous	Any of the following recorded as 2 (Same), 3 (Worse), or 4 (New): • Skin eruption – severe • Angio-oedema – severe • Mucosal ulceration – severe • Panniculitis/ Bullous lupus – severe • Major cutaneous vasculitis/thrombosis	Any Category A features recorded as 1(Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Skin eruption – mild • Panniculitis/Bullous lupus – mild • Digital infarcts or nodular vasculitis • Alopecia-severe	Any Category B features recorded as 1(Improving) **OR** Any of the following recorded as 1(Improving), 2 (Same), 3 (Worse) or 4 (New): • Angio-oedema – mild • Mucosal ulceration – mild • Alopecia – mild • Periungual erythema/chilblains • Splinter haemorrhages	Previous involvement, currently inactive	No previous involvement

	BILAG Grade				
Organ System	**A**	**B**	**C**	**D**	**E**
Neuropsychiatric	Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Aseptic meningitis • Cerebral vasculitis • Demyelinating syndrome • Myelopathy • Acute confusional state • Psychosis • Acute inflammatory demyelinating polyradiculoneuropathy • Mononeuropathy (single/multiplex) • Cranial neuropathy • Plexopathy • Polyneuropathy • Status epilepticus • Cerebellar ataxia	Any Category A features recorded as 1 (Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Seizure disorder • Cerebrovascular disease (not due to vasculitis) • Cognitive dysfunction • Movement disorder • Autonomic disorder • Headache severe unremitting • Headache due to raised intracranial hypertension	Any Category B features recorded as 1 (improving)	Previous involvement, currently inactive	No previous involvement
Musculoskeletal	Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Myositis-severe • Arthritis (severe)	Any Category A features recorded as 1 (Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Myositis-mild • Arthritis (moderate)/ Tendonitis/Tenosynovitis	Any Category B features recorded as 1 (Improving) **OR** The following recorded as 1 (Improving), 2 (Same), 3 (Worse) or 4 (New): • Arthritis (mild)/ Arthralgia/ Myalgia	Previous involvement, currently inactive	No previous involvement

	BILAG Grade				
Organ System	**A**	**B**	**C**	**D**	**E**
Cardiorespiratory	Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Myocarditis/Endocarditis + Cardiac failure • Arrhythmia • New valvular dysfunction • Cardiac tamponade • Pleural effusion with dyspnoea • Pulmonary haemorrhage/vasculitis • Interstitial alveolitis/ pneumonitis • Shrinking lung syndrome • Aortitis • Coronary vasculitis	Any Category A features recorded as 1 (Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Pleurisy/Pericarditis • Myocarditis – mild	Any Category B features recorded as 1 (improving)	Previous involvement, currently inactive	No previous involvement
Gastrointestinal	Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Peritonitis • Lupus enteritis/colitis • Intestinal pseudo-obstruction • Acute lupus cholecystitis • Acute lupus pancreatitis	Any Category A feature recorded as 1 (Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Abdominal serositis or ascites • Malabsorption • Protein-losing enteropathy • Lupus hepatitis	Any Category B features recorded as 1 (improving)	Previous involvement, currently inactive	No previous involvement

	BILAG Grade				
Organ System	**A**	**B**	**C**	**D**	**E**
Ophthalmic	Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Orbital inflammation/myositis/proptosis • Keratitis – severe • Posterior uveitis/retinal vasculitis – severe • Scleritis – severe • Retinal/choroidal vaso-occlusive disease • Optic neuritis • Anterior ischaemic optic neuropathy	Any Category A features recorded as 1 (Improving) **OR** Any of the following recorded as 2 (Same), 3 (Worse) or 4 (New): • Keratitis – mild • Anterior uveitis • Posterior uveitis/retinal vasculitis – mild • Scleritis-mild	Any Category B features recorded as 1 (Improving) **OR** Any of the following recorded as 1 (Improving), 2 (Same), 3 (Worse) or 4 (New): • Episcleritis • Isolated cotton-wool spots (cytoid bodies)	Previous involvement, currently inactive	No previous involvement
Renal	Two or more of the following providing 1, 4 or 5 is included: 1. Deteriorating proteinuria (severe): a. urine dipstick increased by ≥2 levels (only if other methods of urine protein estimation not available); or b. 24-hour urine protein >1 g that has not decreased by ≥25%; or c. urine protein-creatinine ratio >100 mg/mmol that has not decreased by ≥25%; or d. urine albumin-creatinine ratio >100 mg/mmol that has not decreased by ≥25% 2. Accelerated hypertension 3. Deteriorating renal function (severe): a. plasma creatinine >130 µmol/L and having risen to >130% of previous value; or b. GFR having fallen to <67% of previous value; or	One of the following: 1. One of the Category A features 2. Proteinuria (not fulfilling Category A criteria): a. urine dipstick which has risen by 1 level to at least 2+ (only if other methods of urine protein estimation not available); or b. 24-hour urine protein ≥0.5 g that has not decreased by ≥25%; or c. urine protein-creatinine ratio ≥50 mg/mmol that has not decreased by ≥25%; or d. urine albumin-creatinine ratio ≥50 mg/mmol that has not decreased by ≥25% 3. Plasma creatinine >130 µmol/L and having risen to ≥115% but ≤130% of previous value	One of the following: 1. Mild/Stable proteinuria: a. urine dipstick ≥1+ but not fulfilling Category A & B criteria (only if other methods of urine protein estimation not available); or b. 24-hour urine protein >0.25 g but not fulfilling Category A & B criteria; or c. urine protein-creatinine ratio >25 mg/mmol but not fulfilling Category A & B criteria; or d. urine albumin-creatinine ratio >25 mg/mmol but not fulfilling Category A & B criteria 2. Rising blood pressure (providing the recorded values are >140/90 mm Hg) not fulfilling Category A & B criteria, defined as: a. systolic rise of ≥30 mmHg; and b. diastolic rise of ≥15mmHg	Previous involvement, currently inactive	No previous involvement

	BILAG Grade				
Organ System	**A**	**B**	**C**	**D**	**E**
	c. GFR <50 ml/min per 1.73 m², and last time was >50 ml/min per 1.73 m² or was not measured. 4. Active urinary sediment 5. Histological evidence of active nephritis within last 3 months 6. Nephrotic syndrome				
Haematological	TTP recorded as 2 (Same), 3 (Worse) or 4 (New) **OR** Any of the following: • Evidence of haemolysis and Haemoglobin <8 g/dl • Platelet count <25 x 10^9/l	TTP recorded as 1 (Improving) **OR** Any of the following: • Evidence of haemolysis and Haemoglobin 8-9.9 g/dl • Haemoglobin <8 g/dL (without haemolysis) • White cell count <1.0 x 10^9/L • Neutrophil count <0.5 x 10^9/L • Platelet count 25-49 x 10^9/L	Any of the following: • Evidence of haemolysis and Haemoglobin ≥10g/dl • Haemoglobin 8-10.9 g/dl • White cell count 1-3.9 x 10^9/L • Neutrophil count 0.5-1.9 x 10^9/L • Lymphocyte count <1.0 x 109/L • Platelet count 50-149 x 10^9/l • Isolated Coombs' test positive	Previous involvement, currently inactive	No previous involvement

Notes: BILAG=British Isles Lupus Assessment Group; GFR=Glomerular filtration rate.

15.3.3. CLASI

The CLASI assesses activity of disease and damage done by the disease in 13 anatomical locations [Klein, 2011]. These locations are:

- Scalp
- Ears
- Nose
- Rest of face
- V-area of neck (frontal)
- Posterior neck and/or shoulders
- Chest
- Abdomen
- Back, buttocks
- Arms
- Hands
- Legs
- Feet

To calculate the CLASI activity score, the numeric scores of each anatomical location for degree of erythema (0=absent, 1=pink; faint erythema, 2=red, or 3=dark red; purple/violaceous/hypertonic) are added to the responses for mucous membrane lesions (0=absent, 1=lesion or ulceration), recent hair loss (0=no, 1=yes), and non-scarring alopecia (0=absent, 1=diffuse; non-inflammatory, 2=focal or patchy in one quadrant, 3=focal or patchy in more than one quadrant). The CLASI activity score ranges from 0 to 70.

To calculate the CLASI damage score the total numeric scores for dyspigmentation (0=absent, 1=dyspigmentation) for the 13 anatomical locations is calculated. If the response to the dyspigmentation duration question indicates that dyspigmentation usually lasts for at least 12 months, the total dyspigmentation score is multiplied by two. The resulting dyspigmentation score is added to the sum of the scarring scores (0=absent, 1=scarring, 2=severe) for all locations except for the scalp. Scalp scarring, scored as part of the alopecia assessment with possible values of 0=absent, 3=one quadrant, 4=two quadrants, 5=3 quadrants, or 6=whole skull, is then added to compute the total damage score. The CLASI damage score ranges from 0 to 56.

15.3.4. SLICC/ACR Damage Index

The SLICC/ACR Damage Index (SDI) measures non-reversible change occurring since the onset of SLE and present for at least six months in 12 different organ systems. A total of 39 items within 12 organ systems are scored as 0, indicating no damage, or ≥1, indicating damage, for a max total score of 47. The SDI organ systems, items and their possible scores are shown in Table 12.

Table 12: SLICC/ACR Organ Systems and Items

Organ System	Item Name	Score
Ocular	Any cataract ever	0, 1
	Renal change or optic atrophy	0, 1
Neuropsychiatric	Cognitive impairment	0, 1
	Seizures requiring therapy ≥6 months	0, 1
	CVA ever (score 2 if >1)	0, 1, 2
	Cranial or peripheral neuropathy	0, 1
	Transverse myelitis	0, 1
Renal	eGFR <50%	0, 1
	Proteinuria ≥3.5 gm/24 hr	0, 1
	End-stage renal disease	3
Pulmonary	Pulmonary hypertension	0, 1
	Pulmonary fibrosis	0, 1
	Shrinking lung	0, 1
	Pleural fibrosis	0, 1
	Pulmonary infarction	0, 1
Cardiovascular	Angina or coronary artery bypass	0, 1
	Myocardial infarction ever (score 2 if >1)	0, 1, 2
	Cardiomyopathy	0, 1
	Valvular disease	0, 1
	Pericarditis or pericardiectomy	0, 1
Peripheral Vascular	Claudication ≥6 months	0, 1
	Minor tissue loss	0, 1
	Significant tissue loss (score 2 if >1 site)	0, 1, 2
	Venous thrombosis or venous stasis	0, 1
Gastrointestinal	Infarction or resection of bowel (score 2 if >1 site)	0, 1, 2
	Mesenteric insufficiency	0, 1
	Chronic peritonitis	0, 1
	Stricture or upper GI surgery ever	0, 1

Organ System	Item Name	Score
Musculoskeletal	Atrophy or weakness	0, 1
	Deforming or erosive arthritis	0, 1
	Osteoporosis with fracture or vertebral collapse	0, 1
	Avascular necrosis (score 2 if >1 site)	0, 1, 2
	Osteomyelitis	0, 1
Skin	Scarring chronic alopecia	0, 1
	Extensive scarring or panniculum	0, 1
	Skin ulceration	0, 1
Premature gonadal failure		0, 1
Diabetes		0, 1
Malignancy (score 2 if >1 site)		0, 1, 2

Source: Gladman, 1996.
Notes: CVA=Cerebrovascular accident; eGFR=Estimated glomerular filtration rate; GI=Gastrointestinal

15.3.5. FACIT – Fatigue

The scoring of the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is based on guidelines published by the FACIT group [FACIT, 2003]. The following steps are required to score the FACIT-F.

1. The 13 questions constituting the FACIT – fatigue assessment are identified by unique item code numbers. Possible responses for each item are 0="not at all", 1="a little bit", 2="somewhat", 3="quite a bit", or 4='very much".
2. The reported item responses for each question are converted to a final score by subtracting the reported response from the reversal factor for the specified item listed in Table 13. For example, if a subject's response to item HI7, "I feel fatigued", is 4 (very much), the item score is equal to 0 (4 – 4).
3. The resulting item scores are added to derive a total score.
4. The total score is multiplied by the number of items in the subscale (n=13 for FACIT-F).
5. Finally, the result of step 4 is divided by the number of items answered to obtain the final FACIT-F score.

The resulting FACIT – F scores range from 0 to 52 with a higher score indicating a better quality of life. The final score will be used for all analyses of FACIT – F data.

Table 13: FACIT – Fatigue Item Scoring

FACIT Item Code	Item Reversal Factor	Valid Resulting Item Scores
HI7	4	4, 3, 2, 1, 0
HI12	4	4, 3, 2, 1, 0
An1	4	4, 3, 2, 1, 0
An2	4	4, 3, 2, 1, 0
An3	4	4, 3, 2, 1, 0
An4	4	4, 3, 2, 1, 0
An5	0	0, 1, 2, 3, 4
An7	0	0, 1, 2, 3, 4
An8	4	4, 3, 2, 1, 0
An12	4	4, 3, 2, 1, 0
An15	4	4, 3, 2, 1, 0
An16	4	4, 3, 2, 1, 0

Source: FACIT, 2003.
Notes: FACIT=Functional Assessment of Chronic Illness Therapy.

15.3.6. Tender and Swollen Joint Count

For each of 14 anatomical regions, i.e., locations, the presence of tender, swollen or tender and swollen joints is recorded. These values are collected separately for the left and right sides of the body, i.e., laterality, yielding 28 values.

Three separate joint count scores (Tender, Swollen and Tender/Swollen) will be derived as follows for each visit:

- If the status variable in the record states “Intentionally left blank”, all joint counts are set to missing for that visit.
- For each location and laterality, if the result contains “Tender”, add 1 to the tender joint count.
- For each location and laterality, if the result contains “Swollen”, add 1 to the swollen joint count.
- For each location and laterality, if the results contains “Tender|Swollen”, add 1 to the tender/swollen joint count.

Results reported as “NA” will not be counted in the total joint count. Responses of “NA” will be displayed in the data listing with the reason given for this response.

15.3.7. SF-36

The Short Form Health Survey – 36 (SF-36) is a general health patient-reported outcome survey containing 36 items. Individual items on the SF-36 have different numbers of valid responses. Scores are calculated for the eight subscales and two component scales by transforming responses to a 0 to 100 scale. Higher scores indicate better health. Scoring will be performed using the vendor software.

15.4. Randomization Algorithm

Subjects enrolled in this study were randomly assigned to receive either ALPN-101 or placebo in a 1:1 ratio. Randomization was stratified by geographic region and by use of concomitant oral immunosuppressant therapy at enrollment using a centralized interactive web-based response system.

Geographic regions include the following:

- Geographic region 1: Sites located in North America or Western Europe
- Geographic region 2: Sites located in Eastern Europe
- Geographic region 3: Sites in Asia

15.5. Laboratory Assessments

All per-protocol laboratory assessments will be performed by the central lab per the assessment schedule shown in Table 14. Investigators must document their review of each laboratory safety report.

Table 14: Clinical Laboratory Assessments

Assessment	Parameters
Safety: Hematology	Platelet count
	RBC count and indices: MCV, MCH, percent reticulocytes
	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
	CPK
	LDH
	Renal function: creatinine, eGFR
	Liver Function Tests: ALT, albumin, alkaline phosphatase, AST, total and direct bilirubin, total protein
Safety: Coagulation	PT (i.e., INR) , aPTT
Safety: Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, microscopic examination if blood or protein is abnormal, UPCR
Infectious Disease	Hepatitis B and C viruses, Human Immunodeficiency Virus, tuberculosis, SARS-CoV-2
Other Tests	TSH, FSH and estradiol (female subjects only, if needed to confirm menopausal status)
Clinical Biomarkers of SLE	**Screening only**: ANA, anti-Smith antibodies, anti- SSA antibodies, anti-SSB antibodies, anti- RNP antibodies, Scl 70 (topoisomerase 1) antibodies, centromere antibodies, anticardiolipin antibodies (IgG and IgM), LAC, anti-beta-2-glycoprotein I antibodies **All applicable visits**: hsCRP, complements (C3, C4, CH50), quantitative IgM, IgG, IgA, IgE, dsDNA antibodies

Notes: ALT=Alanine aminotransferase; ANA=Anti-nuclear antibodies; aPTT=Activated partial thromboplastin time; AST=Aspartate aminotransferase; C3=Complement component 3; C4=Complement component 4; CD=Cluster of differentiation; CH50=Total complement; CPK=Creatinine phosphokinase; dsDNA=Double stranded DNA eGFR=Estimated glomerular filtration rate; FSH=Follicle stimulating hormone; hsCRP=High-sensitivity C-reactive protein; INR=International normalized ratio; LAC=Lupus anticoagulant; LDH=Lactate dehydrogenase; MCH=Mean corpuscular hemoglobin; WBC=White blood cell; MCV=Mean corpuscular volume; PT=Prothrombin time; RBC=Red blood cell;

RNP=Ribonucleoprotein; Ig=Immunoglobulin; SSA=Sjögren's syndrome type A; SSB=Sjögren's syndrome type B; TSH=Thyroid stimulating hormone; UPCR=Urine protein-creatinine ratio.

15.6. Prednisone-Equivalent Conversion Table

Table 15: Prednisone-Equivalent Conversion

Glucocorticoid	Approximate equivalent dose (mg)	Conversion Factor
Cortisone	25	0.20
Hydrocortisone	20	0.25
Methylprednisolone, Methylprednisolone Sodium Succinate, Methylprednisolone Acetate	4	1.25
Prednisolone	5	1.00
Prednisone	5	1.00
Triamcinolone, Triamcinolone Acetonide	4	1.25
Betamethasone, DIPROSPAN /00582101/	0.70	7.15
Dexamethasone	0.75	6.67
Deflazacort	6	0.83
Fludrocortisone acetate	2	2.5

Sources: Dixon, 1991, Meikle, 1977, Nayak, 2008.