CLINICAL STUDY PROTOCOL

A PHASE 1b/2, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, PARALLEL-ARM STUDY TO EXPLORE THE SAFETY, PHARMACOKINETICS, AND PROOF OF BIOLOGICAL ACTIVITY OF DS-7011a IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

PROTOCOL NUMBER: DS7011-107

IND NUMBER: 157883

VERSION 3.0, 12 Apr 2024

DAIICHI SANKYO, INC.

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DOCUMENT HISTORY

Version Number	Version Date
3.0	12 Apr 2024
2.0	17 Sep 2023
1.0	17 Oct 2022

INVESTIGATOR AGREEMENT

A Phase 1b/2, Double-Blind, Placebo-Controlled, Randomized, Parallel-Arm Study to Explore the Safety, Pharmacokinetics, and Proof of Biological Activity of DS-7011a in Patients with Systemic Lupus Erythematosus

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 2.0 (dated 17 Sep 2023) versus protocol Version 3.0 (dated 12 Apr 2024) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS7011-107 clinical study protocol (Version 3.0) by section.

Amendment Rationale:

This amendment has been made to clarify a few points, mainly the use of dextrose 5% in water or normal saline to administer DS-7011a or placebo.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this summary of changes.

Minor edits, such as update to language that does not alter the original meaning, update to version numbering, formatting changes, in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.

Section Number and Title	Description of Change	Brief Rationale
Protocol Synopsis: Primary endpoint Section 2.4 Benefit and Risk Assessment Table 3.1 Description of Objectives and Endpoints Section 8.8 Safety Assessments and Reporting	Identified COVID-19 as an adverse event of special interest (AESI)	In consideration of the possibility DS-7011a increases the specific risk of COVID-19 development in similarity to anifrolumab.
Protocol Synopsis: Key inclusion criteria Section 5.1 Inclusion Criteria	Eliminated the body weight limit	In consideration of the possibility, especially in Japan and China, that female systemic lupus erythematosus (SLE) patients are of light body weight and yet commensurate to short body height. Body mass index is better parameter in these cases to define study eligibility than body weight.
Protocol Synopsis: Key inclusion criteria Table 1.1 Schedule of Events Section 5.1 Inclusion Criteria Section 8.4 Demographics and Baseline Assessments Section 8.8.1.10 Pregnancy Testing	Added a clarification regarding the possible use of follicle-stimulating hormone (FSH) test for postmenopausal state based on investigator's discretion	To clarify the possible use of FSH testing.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES

Section Number and Title	Description of Change	Brief Rationale
Protocol Synopsis: Key exclusion criteria Table 1.1 Schedule of Events Section 5.2 Exclusion Criteria Section 8.4 Demographics and Baseline Assessments Table 10.1 Clinical Laboratory Tests	Antigenic testing added for detecting positive COVID-19	To admit the possibility to use COVID-19 antigenic testing as an alternative to molecular testing.
Section 5.3 Screening Failures, Rescreening, and Subject Replacement	Deleted text on unscheduled visit for rescreening	To avoid confusion and add clarity.
Protocol Synopsis: Investigational Medicinal Product, Dose, and Mode of Administration Section 6.1 Study Drug(s) Description	Added details for DS7011a and placebo dose preparation	For clarification of the use of dextrose 5% in water or normal saline to administer DS-7011a or placebo.
Section 6.7 Prohibited Therapies/Product	Modified wording to better describe prohibition of the therapies in the list	Changed the wording to improve clarity.
Section 8.8.1.3 Reporting Procedure for Investigators Section 8.8.1.4 Serious Adverse Events Reporting Section 8.8.1.7 Adverse Events of Special Interest	Clarified AESIs to include both serious and non-serious events and the process of capturing them; also clarified that COVID-19 is a respiratory tract infection that should be captured as an AESI	Changed the wording to improve clarity.
Section 8.8.3. Clinical Laboratory Evaluations	Clarified that swab for COVID-19 testing can be nasal, pharyngeal or oral	Changed the wording to improve clarity.
Table 10.2: Allowable Time Windows for Vital Signs, ECGs, and PK/PD Blood Draws	Clarified the allowable time window for PK/PD samples at the end of infusion	Clarified that PK sample must be taken within 5 minutes from the end of the infusion.

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title		
A Phase 1b/2, Double-Blind, Placebo-Controlled, Randomized, Parallel-Arm Study to Explore the Safety, Pharmacokinetics, and Proof of Biological Activity of DS-7011a in Patients with Systemic Lupus Erythematosus		
Protocol Short Title		
Phase 1b/2 Study of DS-7011a in Patients with Systemic Lupus Erythematous (SLE)		
Protocol Number		
DS7011-107		
Sponsor/Collaborators		
Daiichi Sankyo, Inc.		
Registry Identification(s)		
Not applicable		
IND Number		
157883		
Study Phase		
Phase 1b/2		
Planned Geographical Coverage, Study Sites and Location		
Study to be conducted at approximately 20 to 30 study sites in the US (mostly) and 2 to 4 other countries.		
Study Population		
Adult subjects with SLE including cutaneous lupus erythematosus (CLE).		
Study Objectives and Endpoints		
The table below lists primary, secondary, and exploratory study objectives and endpoints.		
Objectives	**Endpoints**	**Category**
Primary		
To explore the safety and tolerability of 3 doses of DS-7011a given intravenously (IV) every 4 weeks (q4w) in subjects with SLE.	Key safety parameters including, but not limited to: Adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESIs), such as herpes zoster and respiratory tract infections, including COVID-19, physical examination findings, vital sign recordings (body temperature, blood pressure, heart rate, respiratory rate), results of safety laboratory analyses of blood and urine, electrocardiogram (ECG) findings, and immunoglobulin	Safety

	(Ig)M, IgG, IgA values, vaccine (diphtheria, tetanus, and pneumococcus) titers, and lymphocyte subset (cluster of differentiation [CD]3-, CD4-, CD8-, CD20-, CD16-, and CD56-positive) values.	
Secondary		
To explore the pharmacokinetic (PK) properties of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Key PK parameters including, but not limited to: area under the plasma concentration-time curve from time zero to time t (AUC_t), maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), elimination half-life ($t_{1/2}$), apparent total body clearance of the drug from plasma (CL), apparent volume of distribution at steady state (V_{ss}).	PK
To explore the clinical efficacy of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Several endpoints indicative of clinical efficacy including: Cutaneous Lupus Area and Severity Index Activity (CLASI-A), Cutaneous Lupus Activity Investigator Global Assessment (CLA-IGA), SLE Disease Activity Index 2000 (SLEDAI-2K), Physician's Global Assessment Systemic Lupus Erythematosus (PGA-SLE), Clinician's Global Impression of Change (CGI-C), Patient Reported Outcomes (PROs) such as quality of life assessments obtained using the Skindex-29+3 and the Short Form 36 (SF-36) Questionnaires, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Itch Numeric Rating Scale (NRS), and Patient Global Impression of Change (PGI-C), and laboratory parameters, such as autoantibodies (including antinuclear, anti-dsDNA, anti-Smith [Sm], and anti-ribonucleoprotein [RNP] antibodies), complement factors (C3, C4), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).	Efficacy
To explore the immunogenicity of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Anti-drug antibodies (ADAs) against DS-7011a as the immunogenicity endpoint.	Immunogenicity

Exploratory		
To explore the mechanistic efficacy of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Several endpoints indicative of mechanistic efficacy, including, but not limited to: circulating anti-Toll-like receptor 7 (TLR7) and interferon (IFN)-Type I gene signatures (GS); skin messenger ribonucleic acid (mRNA) coding for proteins under IFN-Type I regulation, such as myxovirus resistance protein (MxA), and for markers of inflammatory cells, such as CD45; and cytokines, including interleukin (IL)-6.	Pharmacodynamics (PD)

Study Design

This Phase 1b/2 study will be double-blind, placebo-controlled, and randomized. It will be the second study in humans with DS-7011a, following a first-in-human (FIH) study in healthy subjects. It will enroll up to 24 subjects with SLE in 2 parallel arms randomized to receive 2:1 DS-7011a or placebo. Tentatively, 9 of these 24 subjects will be of African descent. Since SLE appears to be particularly prevalent and difficult to treat in subjects of African descent, it will be interesting to see if DS-7011a may show initial evidence of efficacy in this population. Also, tentatively, 9 of these 24 subjects will be positive for anti-Sm and/or anti-RNP autoantibodies, since TLR7 may play a prominent role especially in SLE with anti-Sm and/or anti-RNP autoantibodies. This will be a multicenter study conducted at approximately 20 to 30 study sites in the US (mostly) and 2 to 4 other countries.

Randomization will follow a randomization schedule generated by an independent biostatistician. Subjects, investigators, and site staff will be blinded, except for the unblinded site pharmacist or designee who will be responsible for preparing the study drugs. Sponsor's staff or representative (eg, contract research organization) will also be blinded. If an unblinded clinical function representative is needed for any reason, firewall procedures will be followed to ensure blinding for the study remains intact.

The study will be divided into 3 periods: Screening, Treatment, and Follow-up. The Screening Period will be a maximum of 28 days. Rescreening is permitted during this phase after consultation with the Sponsor if the subject fails initial screening. Subjects will be randomized once considered eligible and will then enter the Treatment Period. Subjects will receive a single dose of DS-7011a or placebo q4w 3 times (Weeks 0, 4, and 8). Dosing will be subordinate to a negative coronavirus disease 2019 (COVID-19) antigenic test, which will be performed on each study day of drug administration. Subjects will be followed until a final visit on Day 113 after the first study drug administration, when DS-7011a exposure and activity are expected to have declined. However, additional extended follow-up will be conducted until Day 169 to monitor SAEs, AEs, and AESIs by telephone, unless there is the need to collect blood samples for ADA.

Study Duration

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed. Overall study duration for a subject is expected to be approximately 28 weeks, which includes the 28-day Screening Period, Treatment, and Follow-up. A subject is expected to receive study drug for approximately 3 months, administered as single doses 3 times q4w (Weeks 0, 4, and 8). Anticipated total duration of the study is approximately 15 months.

Key Inclusion Criteria

Subjects eligible for inclusion in this study will meet all the inclusion criteria for this study and none of the exclusion criteria. Below is a list of the inclusion criteria:

- Male and female subjects must be of 18 years or more with definite SLE for at least 6 months prior to Screening, defined according to the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria for SLE, including documented history of positivity for antinuclear antibody (titer ≥1:80).
- Body mass index (BMI) ≥18 kg/m^2.
- Presence of active CLE (acute, subacute, and chronic cutaneous lupus) with active skin involvement and a CLASI-A score of 4 or higher at the time of Screening and randomization, as recognized by 2 adjudicators, ie, the investigator in the periphery at the site and a centrally located arbiter contracted ad hoc (in case of disagreement between these 2 adjudicators, a third adjudicator, also centrally located and contracted ad hoc, will solve the disagreement and provide a final decision), despite adequate use of conventional therapies (either topical corticosteroids or antimalarial agents used for at least 12 weeks prior to Screening) or because of the requirement to discontinue these therapies due to side effects or poor tolerability.
- Subjects must be willing to have skin tape harvests collected from the affected skin area (skin tape stripping done on the target lesion).
- If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at randomization, and she must be willing to use one method of highly effective birth control, and one barrier method, such as condom, diaphragm, or cervical cap with spermicide, upon enrollment, during the Treatment Period, and for 3 months following the last dose of study drug. A female is considered of childbearing potential following menarche and until reaching postmenopausal state, which is defined as no menstrual periods for a minimum of 12 months (a follicle-stimulating hormone [FSH] test may be conducted to confirm postmenopausal state according to investigator's discretion), unless made permanently sterile by surgery (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 1 month before the first dose).
- If male, the subject must be surgically sterile or willing to practice birth control upon enrollment, during the Treatment Period, and for 3 months following the last dose of study drug.
- Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 3 months after the final study drug administration.
- Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study Treatment Period, and for at least 3 months after the final study drug administration.
- Subjects must agree not to participate in any other investigational study during the study Treatment Period and for 3 months after the last dose of study drug.
- Subjects must give written informed consent to participation in the study prior to Screening.
- Subjects must be vaccinated against COVID-19.

Key Exclusion Criteria

Subjects for whom any of the following key exclusion conditions apply will not be enrolled in the study:

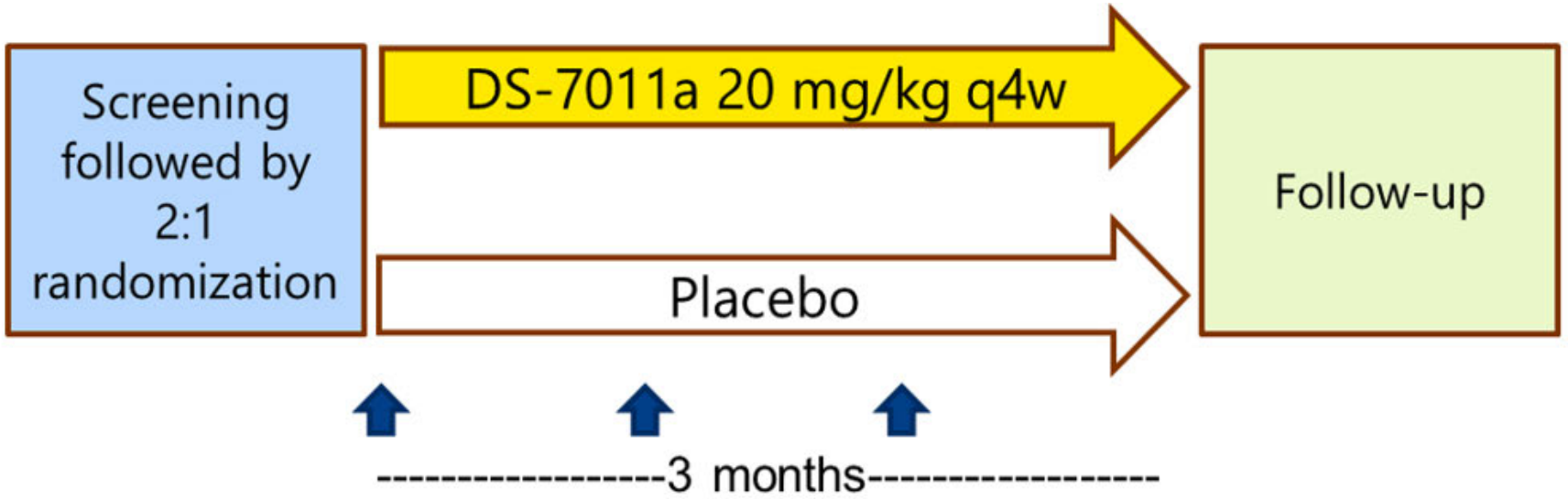
- Active lupus nephritis (LN) on induction therapy, or induction therapy completed within 12 weeks prior to Screening (stable maintenance therapy with mycophenolate or azathioprine allowed).
- Active neuropsychiatric SLE, including, but not limited to, the following: seizure, new or worsening impaired level of consciousness, psychosis, delirium or confusional state, aseptic meningitis, ascending or transverse myelitis, chorea, cerebellar ataxia, mononeuritis multiplex, or demyelinating syndromes.
- Primary diagnosis of autoimmune or rheumatic disease other than SLE (secondary Sjögren's syndrome or autoimmune thyroiditis are not exclusionary) or drug-induced lupus.
- History of chronic, recurrent (3 or more of the same type of infection in 1 year) or recent serious infection (eg, pneumonia, septicemia), including viral infections, as determined by the investigator, or requiring anti-infective treatment within 12 weeks prior to Screening.

- History of severe herpes infection (eg, herpetic encephalitis, ophthalmic herpes, or disseminated herpes) or signs of herpes or varicella zoster viral infection (chicken pox, shingles, or herpes zoster) within 12 weeks prior to Screening.
- Positive COVID-19 test (either molecular, based on polymerase chain reaction [PCR], or antigenic) at Screening or symptoms suggestive of SARS-CoV-2 infection (such as fever, chills, cough, shortness of breath, fatigue, myalgia, headache, new loss of taste or smell, sore throat, nasal congestion, rhinitis, nausea, vomiting, or diarrhea) or close contact with an individual with SARS-CoV-2 infection within 2 weeks prior to randomization.
- History of malignant disease within the 2 years before Screening or ongoing at the time of Screening, except basal cell carcinomas and squamous cell carcinomas of the skin, or completely excised carcinoma in situ of the cervix.
- Chronic kidney disease with significant proteinuria (ie, >2 g/24 h or urine protein to creatinine ratio >200 mg/g) or decreased renal function (estimated glomerular filtration rate [eGFR] <30 mL/min).
- New York Heart Association class III or IV congestive heart failure.
- Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
- Treatment with SLE standard-of-care medications, except for the following, which are allowed: oral prednisone (or equivalent at a maximum of 20 mg/d); antimalarials at standard-of-care dose (maximum: hydroxychloroquine 400 mg/d, chloroquine 250 mg/d, quinacrine 100 mg/d); methotrexate (maximum 25 mg/wk); leflunomide (maximum 20 mg/d); mycophenolate (mycophenolate mofetil [MMF] maximum 3000 mg/d or mycophenolic acid sodium [MPS] maximum 2160 mg/d); azathioprine (maximum 200 mg/d); and tacrolimus (maximum 3 mg/d). These medications are allowed as long as they were initiated at least 12 weeks prior to randomization, have been stable for at least 4 weeks prior to randomization, and will remain stable for the duration of the study. Subjects who are not planning to continue these medications during the study must have discontinued them at least 4 weeks prior to randomization.
- These medications are prohibited as follows:
    - Topical corticosteroids and other topical immunosuppressive agents, including topical calcineurin inhibitors, within 2 weeks prior to randomization (Day 1)
    - Intralesional corticosteroids, IV, intramuscular (IM), and intra-articular corticosteroids within 4 weeks prior to randomization (Day 1)
    - Cyclosporine, voclosporin, pimecrolimus, and sirolimus within 4 weeks prior to randomization (Day 1)
    - Cyclophosphamide within 24 weeks prior to randomization (Day 1)
    - IV Ig or plasmapheresis within 12 weeks prior to randomization (Day 1)
    - All biologic agents, including anti-B-cell antibodies (eg, rituximab, ocrelizumab, and belimumab), other antibodies (eg, anifrolumab, adalimumab, and tocilizumab), Fc constructs (eg, abatacept and etanercept), cytokines, and live vaccines within 12 weeks prior to randomization (Day 1)
- History of suicide attempt or suicidal ideation within 1 year prior to Screening.
- History of substance abuse within 6 months prior to Screening or a urine drug test at Screening resulting positive for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiate. Medical marijuana may be used per discretion of the investigator.
- History or positive test result for human immunodeficiency virus (HIV) at Screening.
- Active hepatitis B virus (HBV) infection determined at Screening as positive test result for hepatitis B surface antigen.
- Active hepatitis C virus (HCV) infection determined at Screening as HCV ribonucleic acid (RNA) above the limit of detection in subjects with positive HCV antibody titer.

• History of, or ongoing, active tuberculosis (TB) or untreated latent TB infection (LTBI), determined by a positive QuantiFERON-TB Gold or positive or borderline T-SPOT (Elispot) test performed locally at Screening. Subjects with documented previously completed appropriate LTBI treatment and without evidence of re-exposure will not be required to be tested. Indeterminate QuantiFERON-TB Gold or T-SPOT tests may be repeated once; it will be considered positive if retest results are positive or indeterminate. • Any other significant condition (eg, medical, psychiatric, or social) that according to the investigator's judgment would prevent compliance with study protocol and full study participation. • Subjects must not be participating in another investigational study or have participated in an investigational study within the past 30 days prior to randomization (Day 1). • History of or current inflammatory skin disease other than SLE that in the opinion of the investigator could interfere with the inflammatory skin assessments and confound the disease activity assessments. • History of any non-SLE disease that had required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to randomization.
Investigational Medicinal Product, Dose, and Mode of Administration
DS-7011a will be provided as a sterile solution in vials of 2 mL at a concentration of 100 mg/mL and will be infused diluted in dextrose 5% in water (D5W). Placebo will be prepared using D5W or normal saline as a possible alternative. DS-7011a and placebo will be administered by IV infusion. DS-7011a will be given at the dose of 20 mg/kg q4w. This dose has been selected based on the safety, tolerability, PK, and PD results of the DS-7011a FIH Phase 1a study, in which it proved to be safe, well tolerated, and maximally active pharmacodynamically. Namely, in this study, it resulted after a single IV administration in extensive ex vivo inhibition of IL-6 production, which was of early onset and lasting duration. In fact, after 4 weeks from the administration, this inhibition was still 86% on average, more than 65% in each subject, and more than 95% in 40% of subjects.
Active Ingredient
DS-7011a
Planned Sample Size
Up to 24 subjects with SLE in 2 parallel arms randomized to receive 2:1 DS-7011a or placebo.

1.2. Study Schema

Figure 1.1: Study Design



q4w = every 4 weeks
Note: Arrows indicate study drug dosing times on Day 1 (Baseline), Day 29, and Day 57.

1.3. Schedule of Events

Table 1.1: Schedule of Events

	Screening Period	Treatment Period						Follow-up Period[a]	
								EOT Visit	EOS Visit
Study Assessments and Tests	**Within 4 weeks (28 days) prior to randomization**	**Week 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
		Day 1	**Day 2**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 169**
				±1 day	**±2 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Informed Consent	X								
Inclusion/Exclusion Criteria	X	X							
Demographic Data	X								
Medical History (SLE, CLE, medications, and other medical history)	X								
Documentation of SLE by EULAR/ACR Criteria	X								
AEs (including SAEs and AESIs)	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Physical Examination	X	X			X	X	X	X	
Weight	X	X			X	X			
Height	X								
Vital Signs	X	X	X	X	X	X	X	X	
Serum Pregnancy Test (local laboratory)	X								
Urine Pregnancy Test (local laboratory)		X			X	X	X	X	
FSH Test (postmenopausal females) (local laboratory)	X[f]								
Serum Virology (HIV, HBV, and HCV) (local laboratory)	X								
TB Test (local laboratory)	X								
Urine Drug Screen (local laboratory)	X								

	Screening Period	Treatment Period						Follow-up Period[a]	
								EOT Visit	EOS Visit
Study Assessments and Tests	**Within 4 weeks (28 days) prior to randomization**	**Week 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
		Day 1	**Day 2**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 169**
				±1 day	**±2 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
COVID-19 Molecular (PCR) or Antigenic Test (local laboratory)	X								
COVID-19 Antigenic Test (local laboratory)		X			X	X			
Chest X-Ray	X								
12-lead ECG	X						X	X	
Efficacy Assessments (ClinROs)									
CLASI-A	X	X			X	X	X	X	
Skin Photography	X[b]	X			X	X	X	X	
CLA-IGA	X	X			X	X	X	X	
SLEDAI-2K	X	X			X	X	X	X	
PGA-SLE	X	X			X	X	X	X	
CGI-C		X			X	X	X	X	
Safety Laboratory Assessments									
Blood Chemistry (central laboratory)	X	X			X	X	X	X	
Hematology (central laboratory)	X	X			X	X	X	X	
Coagulation (central laboratory)	X	X			X	X	X	X	
Urinalysis (central laboratory)	X	X			X	X	X	X	
Urine Protein/Creatinine Ratio (central laboratory)	X	X			X	X	X	X	
Immunoglobulin (IgG, IgA, IgM) (central laboratory)		X[c]					X	X	
Vaccine (diphtheria, tetanus, and pneumococcus) Titers (central laboratory)		X					X	X	

	Screening Period	Treatment Period						Follow-up Period[a]	
								EOT Visit	EOS Visit
Study Assessments and Tests	**Within 4 weeks (28 days) prior to randomization**	**Week 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
		Day 1	**Day 2**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 169**
				±1 day	**±2 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Lymphocyte Subsets (CD3-, CD4-, CD8-, CD20-, CD16-, CD56-positive) (central laboratory)	X	X[c]			X[c]	X[c]	X	X	
Randomization and Study Drug Administration									
Randomization		X							
Study Drug Administration		X			X	X			
Pharmacokinetics									
Plasma DS-7011a (central laboratory)[d]		X	X	X	X	X	X	X	
Pharmacodynamic and Other Biomarkers									
ESR and CRP (local laboratory)	X	X[c]			X[c]	X[c]	X	X	
Complement Factors (C3 and C4) (local laboratory at Screening and central laboratory thereafter)	X	X[c]			X[c]	X[c]	X	X	
SLE-related Autoantibodies (anti-nuclear, anti-dsDNA, anti-Sm, anti-RNP) (local laboratory at Screening and central laboratory thereafter)	X	X[c]			X[c]	X[c]	X	X	
TLR7 and IFN-Type I GS		X[c]	X	X	X[c]	X[c]	X	X	
Cytokines (central laboratory)		X[c]			X[c]	X[c]	X	X	
Skin Tape Harvesting for mRNA (central laboratory)		X					X	X	
Immunogenicity									
Anti-drug Antibodies (central laboratory)		X[c]			X[c]	X[c]	X	X	X[e]
Pharmacogenetics									
Blood sample for genotyping (central laboratory)		X[c]							

	Screening Period	Treatment Period						Follow-up Period[a]	
								EOT Visit	EOS Visit
Study Assessments and Tests	**Within 4 weeks (28 days) prior to randomization**	**Week 0**	**Week 0**	**Week 1**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 24**
		Day 1	**Day 2**	**Day 8**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 169**
				±1 day	**±2 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**
Patient Reported Outcome Questionnaires									
Quality of life questionnaires (Skindex-29+3 and SF-36)		X			X	X	X	X	
FACIT-Fatigue		X			X	X	X	X	
Itch NRS		X			X	X	X	X	
Patient's Global Impression of Change		X			X	X	X	X	

ACR = American College of Rheumatology; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; CD = cluster of differentiation; CGI-C = Clinician's Global Impression of Change; CLA-IGA = Cutaneous Lupus Activity Investigator Global Assessment; CLASI-A = Cutaneous Lupus Area and Severity Index Activity; CLE = cutaneous lupus erythematosus; ClinROs = Clinician Reported Outcomes; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ESR = erythrocyte sedimentation rate; EULAR = European League Against Rheumatism; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; GS = gene signature; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IFN = interferon; Ig = immunoglobulin; mRNA = messenger ribonucleic acid; NRS = Numeric Rating Scale; PCR = polymerase chain reaction; PGA-SLE = Physician's Global Assessment of Systemic Lupus Erythematosus; RNP = ribonucleoprotein; SAE = serious adverse event; SF-36 = Short Form 36; SLE = systemic lupus erythematosus; SLEDAI-2K = SLE Disease Activity Index 2000; Sm = Smith; TB = tuberculosis; TLR7 = Toll-like receptor 7.

[a] The subject's End of Study (EOS) Visit is the date of their last study visit/contact. Scheduled EOS Visit on Day 169 will be by telephone, unless there is the need to collect blood (see Note [e] below).

[b] Subjects will be assessed at Screening for active skin involvement. Only subjects with the active presence of CLE will be enrolled. Skin photographs of the scalp, ears, nose/malar area, rest of face, V-area neck (frontal), posterior neck and shoulders, chest, abdomen, back/buttocks, arms, hands, legs, and feet will be taken every 4 weeks.

[c] Blood sample collected predose at this visit.

[d] Blood sample will be collected and analyzed for DS-7011a in plasma on Day 1 (at predose and at end of infusion), Day 2 (24 hours after administration), Day 8 (1 week after administration), Days 29 and 57 (at predose and at end of infusion), and Days 85 and 113.

[e] Plasma samples will be collected only from subjects positive for anti-drug antibodies (ADA) on Day 113. For subjects positive for ADA on Day 169, additional plasma ADA samples will be collected every 3 months (±1 month) up to 1 year from Day 1, or until the subject becomes negative (or, applicable to when preexisting ADA is observed, ADA titer becomes less than baseline), or shows an ADA decrease for 3 consecutive visits, or withdraws consent from the study, whichever occurs first (see Section 8.7.3).

[f] According to investigator's discretion.

2. INTRODUCTION

2.1. Background

Systemic lupus erythematosus (SLE) is a systemic chronic autoimmune disease characterized by autoantibody production, inflammation, and tissue damage in multiple organs. It is the prototypic systemic immune complex disease. It is highly prevalent in women and subjects of African descent. Clinical manifestations are protean and vary widely among subjects. They commonly include dermatitis (cutaneous lupus erythematosus [CLE]), arthritis, and nephritis, but the central nervous system and other major organ systems can also be affected.

Standard-of-care therapies used to treat SLE, such as antimalarials, steroids, and immunosuppressants, are only partially effective and have a wide range of toxicities. Durable remission is attained only in a minority of patients, the risk for flares and lupus nephritis (LN) activation and progression to end-stage renal disease is considerable, and the quality of life remains markedly reduced with work disability being very common. Achievement of low lupus disease activity status (LLDAS) is presently advocated as an important goal of the treatment of SLE. LLDAS achievement entails disease control (ie, low level of disease activity as in remission) with limited use of SOC antimalarials and steroids and no immunosuppressant. LLDAS is important, as it associates with the least likely development of long-term organ damage, either due to the disease or the therapies. Among the toxicities, those caused by steroids are of primary concern. Mortality stands out, which is due to cardiovascular disease and believed to result from the combined effect of steroids treatment with the course itself of SLE, which includes vasculitis. The antimalarials, however, also cause concerning toxicities. For example, hydroxychloroquine long-term use results in significantly impairing retinopathy, which has called to limit dosage as much as possible. Thus, there remains an unquestionable unmet medical need for more effective and safer therapies, above all those that, by specifically targeting critical molecules mediating SLE pathogenesis, may offer efficacy with mild or no unsafe consequences.

DS-7011a is an anti-Toll-like receptor 7 (TLR7) antagonistic monoclonal antibody (Mab) developed for the treatment of SLE. It is a humanized, double-mutation (Leu234Ala, Leu235 Ala [LALA])-modified immunoglobulin (Ig) G1 that specifically binds to human and monkey (but not rodent) TLR7 and thus prevents TLR7 natural ligands from binding to and activating TLR7. Humanization decreases the potential for immunogenicity, while the LALA modification decreases the potential for cytotoxicity. In vitro, DS-7011a potently inhibits TLR7-mediated interleukin (IL)-6 production from human peripheral blood mononuclear cells. In mice, an anti-TLR7 Mab successfully treats several lupus models. In monkeys, DS-7011a shows general pharmacokinetic (PK) properties typical of an IgG1, permitting an administration frequency of once every 4 weeks (q4w), and shows no toxicities. Throughout all the toxicology studies, the maximum administered dose (400 mg/kg) was the no-observed-adverse-effect-level (NOAEL).

TLR7 is a nucleic acid sensor. Its natural ligands include exogenous (mainly from viruses) or endogenous (mainly from damaged cells) nucleic acids, especially those complexed with cationic peptides or antibodies. TLR7 ligation results in the production of interferon (IFN)-Type I and other cytokines like IL-6 by inflammatory cells and of antibodies by B-cells. TLR7 has been

extensively implicated in the pathogenesis of mouse lupus models and in SLE in humans, where it critically stimulates the production of inflammatory cytokines and autoantibodies. It may play a prominent role especially in SLE with active CLE and anti-Smith (Sm) and/or anti-ribonucleoprotein (RNP) autoantibodies. DS-7011a acts by binding to TLR7 and blocking its function, causing the inhibition of the production of multiple cytokines, including IFN-Type I, from multiple inflammatory cells, including the plasmacytoid dendritic cells (pDCs) and other inflammatory cells, such as B-cells and cells of the monocyte-macrophage lineage. In B-cells, TLR7 is also a critical mediator of antibody production in co-operation with the B-cell receptor. By blocking TLR7, DS-7011a may thus block critical mechanisms at the core of SLE pathogenesis and therefore be effective for the treatment of the disease.

2.2. Study Rationale

DS-7011a specifically binds to TLR7 and thus prevents TLR7 natural ligands from binding to and activating TLR7. By blocking TLR7, DS-7011a may block critical mechanisms, such as cytokine and autoantibodies production, at the core of SLE pathogenesis and therefore be effective for the treatment of the disease, which still represents an unmet medical need. This study will immediately follow DS-7011a first-in-human (FIH) Phase 1a study in healthy subjects and explore DS-7011a initial safety and efficacy in subjects with SLE to inform "go/no-go" decision to further development phases.

2.3. Dose Selection

DS-7011a will be administered intravenously (IV) 3 times at the dose of 20 mg/kg q4w. This dose was selected based on the safety, tolerability, PK, and pharmacodynamic (PD) results of the DS-7011a FIH Phase 1a study, which was a single ascending-dose study in healthy subjects in which DS-7011a was explored at the doses of 0.1, 0.3, 1, 3, 10, and 20 mg/kg. In said Phase 1a study, the 20 mg/kg dose was found to be similarly safe and well tolerated to lower doses but maximally active pharmacodynamically and thus selected to explore DS-7011a in subjects with SLE in this Phase 1b/2 study. According to preliminary analysis, in said Phase 1a study, the 20 mg/kg dose resulted after a single IV administration in extensive ex vivo inhibition of IL-6 production, which was of early onset and lasting duration and was still 86% on average, more than 65% in each subject, and more than 95% in 40% of subjects after 4 weeks from the administration. The 20 mg/kg dose, which is 1/6 of the NOAEL human equivalent dose, also resulted in C_{max} (719 µg/mL) and area under the plasma concentration time curve up to infinity (AUC_{inf}) (8838 day*µg/mL) that didn't exceed monkey NOAEL (400 mg/kg) C_{max} (14,700 µg/mL [female] or 13,800 µg/mL [male]) and AUC_{inf} (29,300 day*µg/mL [female] or 34,200 day*µg/mL [male]).

2.4. Benefit and Risk Assessment

This Phase 1b/2 study will initially explore the safety, tolerability, PK, PD, immunogenicity, and efficacy of DS-7011a in subjects with SLE. It will immediately follow DS-7011a FIH Phase 1a study in healthy subjects and it will be conducted at the dose of 20 mg/kg (administered as single doses 3 times q4w [Weeks 0, 4, and 8]), which was found to be safe, well tolerated (according to preliminary analysis, it resulted in only one adverse event [AE] of constipation, mild and not drug-related), and maximally active pharmacodynamically in Phase 1a. DS-7011a is not

expected to cause concerning AEs, given the results of the toxicology studies and of Phase 1a study; however, given its mechanism of action, herpes zoster and respiratory tract infections, including COVID-19, will be monitored during this study as possible AEs of special interest (AESIs).

Pharmacology studies indicate DS-7011a may provide patients with SLE with a new targeted therapy positioned to considerably improve on current SOC. As described in the Investigator's Brochure (IB), DS-7011a demonstrated the ability to inhibit the TLR7-stimulated production of multiple cytokines from multiple cell types and the production of antibodies by isolated B-cells.

After initial work in healthy volunteers, DS-7011a will be administered to subjects with SLE 3 times at the dose of 20 mg/kg q4w IV, which is expected to be pharmacologically active based on pharmacology data obtained using a surrogate anti-TLR7 Mab in mice with a lupus model. This expectation has been confirmed by PD data obtained testing DS-7011a in healthy volunteers.

DS-7011a was safe and well tolerated in monkeys after the administration of multiple IV doses. In all studies, NOAEL corresponded to the maximum administered dose.

The data available on potential efficacy and toxicity permit the investigation of DS-7011a in SLE patients with a favorable benefit/risk ratio.

3. OBJECTIVES, HYPOTHESIS, AND ENDPOINTS

The objectives, definitions of associated endpoints as well as applicable outcome measures are described in Table 3.1.

Table 3.1: Description of Objectives and Endpoints

Objectives	Endpoints	Category
Primary		
To explore the safety and tolerability of 3 doses of DS-7011a given IV every 4 weeks (q4w) in subjects with SLE.	Key safety parameters including, but not limited to: AEs, serious adverse events (SAEs), AESIs, such as herpes zoster and respiratory tract infections, including COVID-19, physical examination findings, vital sign recordings (body temperature, blood pressure, heart rate, respiratory rate), results of safety laboratory analyses of blood and urine, electrocardiogram (ECG) findings, and IgM, IgG, and IgA values, vaccine (diphtheria, tetanus, and pneumococcus) titers, and lymphocyte subset (cluster of differentiation [CD]3-, CD4-, CD8-, CD20-, CD16-, and CD56-positive) values.	Safety
Secondary		
To explore the PK properties of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Key PK parameters including, but not limited to: area under the plasma concentration-time curve from time zero to time t (AUC_t), maximum plasma concentration (C_{max}), minimum plasma drug concentration (C_{min}), elimination half-life ($t_{1/2}$), apparent total body clearance of the drug from plasma (CL), apparent volume of distribution at steady state (V_{ss})	PK
To explore the clinical efficacy of 3 doses of DS-7011a given IV q4w in subjects with SLE	Several endpoints indicative of clinical efficacy including: Cutaneous Lupus Area and Severity Index Activity (CLASI-A), Cutaneous Lupus Activity Investigator Global Assessment (CLA-IGA), SLE Disease Activity Index 2000 (SLEDAI-2K), Physician's Global Assessment Systemic Lupus Erythematosus (PGA-SLE), Clinician's Global Impression of Change (CGI-C), Patient Reported Outcomes (PROs) such as quality of life assessments obtained using the Skindex-29+3	Efficacy

Objectives	Endpoints	Category
	and the Short Form 36 (SF-36) Questionnaires, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), Itch Numeric Rating Scale (NRS), and Patient's Global Impression of Change (PGI-C), and laboratory parameters, such as autoantibodies (including antinuclear, anti-dsDNA, anti-Smith [Sm], and anti-ribonucleoprotein [RNP] antibodies), complement factors (C3, C4), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP).	
To explore the immunogenicity of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Anti-drug antibodies (ADAs) against DS-7011a as the immunogenicity endpoint.	Immunogenicity
Exploratory		
To explore the mechanistic efficacy of 3 doses of DS-7011a given IV q4w in subjects with SLE.	Several endpoints indicative of mechanistic efficacy, including, but not limited to: circulating TLR7 and IFN-Type I gene signatures (GS); skin messenger ribonucleic acid (mRNA) coding for proteins under IFN-Type I regulation, such as myxovirus resistance protein (MxA), and for markers of inflammatory cells, such as CD45; and cytokines, including IL-6.	Pharmacodynamics (PD)

3.1. Rationale for Selection of Primary Endpoints and Key Secondary and Exploratory Endpoints

The main scope of this Phase 1b/2 study is to explore DS-7011a safety and tolerability as primary objectives, to explore efficacy, PK, and immunogenicity properties as secondary objectives, and to explore PD properties as exploratory objectives. The rationale for the selection of IgM, IgG, and IgA values, vaccine (diphtheria, tetanus, and pneumococcus) titers, and lymphocyte subset (CD3-, CD4-, CD8-, CD20-, CD16-, and CD56-positive) values should allow an initial insight into DS-7011a immunosuppressive potential. Regarding clinical efficacy endpoints, in addition to overall SLE parameters, the selection of parameters such as the Cutaneous Lupus Area and Severity Index Activity (CLASI-A), which are descriptive of CLE, should favor an initial detection of potential for beneficial clinical activity, given the expectation that TLR7 plays a particularly prominent role in the development of this component of the SLE disease. Regarding clinical laboratory efficacy and PD endpoints, the selection of biomarkers reflects their mechanistic proximity to TLR7 activation (TLR7 GS expression), TLR7 role in SLE pathogenesis (cytokines and autoantibody concentrations), and inflammatory effects that cytokines and autoantibodies have (complement factors and MxA and inflammatory cell marker mRNA). Anti-Sm and anti-RNP autoantibodies will be assessed with particular interest, since their production may especially depend on TLR7 and therefore be blocked by DS-7011a.

4. STUDY DESIGN

4.1. Overall Design

4.1.1. Overview

This Phase 1b/2 study will be double-blind, placebo-controlled, and randomized. It will be the second study in humans with DS-7011a, following an FIH study in healthy subjects. This study will explore the safety, PK, and proof of biological activity of DS-7011a in subjects with SLE, including active CLE. It will enroll up to 24 subjects with SLE in 2 parallel arms randomized to receive 2:1 DS-7011a or placebo. Tentatively, 9 of these 24 subjects will be of African descent. Since SLE appears to be particularly prevalent and difficult to treat in subjects of African descent, it will be interesting to see if DS-7011a may show initial evidence of efficacy in this population. Also, tentatively, 9 of these 24 subjects will be positive for anti-Sm and/or anti-RNP autoantibodies, since TLR7 may play a prominent role especially in SLE with anti-Sm and/or anti-RNP autoantibodies. This will be a multicenter study conducted at approximately 20 to 30 study sites in the US (mostly) and 2 to 4 other countries.

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed.

Randomization will follow a randomization schedule generated by an independent biostatistician. Subjects, investigators, and site staff will be blinded, except for the unblinded site pharmacist or designee who will be responsible for preparing the study drugs. Sponsor's staff or representative (eg, clinical research organization) will also be blinded. If an unblinded clinical function representative is needed for any reason, firewall procedures will be followed to ensure blinding for the study remains intact.

The study will be divided into 3 periods: Screening, Treatment, and Follow-up. The Screening Period will be a maximum of 28 days. Rescreening is permitted during this phase after consultation with the Sponsor if the subject fails initial screening. Subjects will be randomized once considered eligible and will then enter the Treatment Period. Subjects will receive a dose of DS-7011a or placebo q4w 3 times. Dosing will be subordinate to a negative coronavirus disease 2019 (COVID-19) antigenic test, which will be performed on each study day of drug administration. Subjects will be followed until a final visit on Day 113 after the first study drug administration, when DS-7011a exposure and activity are expected to have declined. Additional extended follow-up will be conducted until Day 169 to monitor SAEs, AEs, and AESIs by telephone, unless there is the need to collect blood samples for anti-drug antibodies (ADA).

The subject population is described in Section 5. The overall study schema for this study is presented in Figure 1.1.

4.1.2. End of the Study

The primary completion date is the date when the last subject is examined or receives an intervention for the purposes of final collection of data (database lock) for all outcome analyses (ie, the last subject's Final Visit [Day 113]). The global end of the study is the last subject's

Follow-up Visit (Day 169) (ie, the last subject's last visit overall). The study may be discontinued by the Sponsor for other reasons (ie, administrative, program-level or class-related), in which case the global end of the study would be the date the Sponsor discontinues the study.

The subject's End of Study (EOS) Visit is the date of their last study visit/contact. The scheduled EOS Visit on Day 169 will be by telephone unless there is the need to collect blood samples.

4.1.3. Dose Regimen

DS-7011a will be administered IV 3 times at the dose of 20 mg/kg q4w.

4.1.4. Duration

The study will be divided into 3 periods: Screening, Treatment, and Follow-up. The Screening Period will be a maximum of 28 days.

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed. Overall study duration for a subject is expected to be up to approximately 28 weeks, which includes the 28-day Screening Period, Treatment, and Follow-up. A subject is expected to receive study drug for approximately 3 months (administered as single doses 3 times q4w [Weeks 0, 4, and 8]). Anticipated total duration of the study is approximately 15 months.

4.2. Rationale for Study Design

This Phase 1b/2 study is based on the hypothesis that DS-7011a will be safe and well tolerated and will show initial evidence of efficacy in adult subjects with SLE.

The rationale for running the study is presented in Section 2.2.

The rationale for the study design is to allow an unbiased and controlled interpretation of DS-7011a activity (safety, tolerability, and efficacy) based on the comparison of DS-7011a with placebo treatment, even if the sample size of this study was not calibrated to allow finding a statistically significant difference between DS-7011a- and placebo-treated subjects at pre-stipulated levels of probability and power. Blinding both investigators and study participants to treatment and randomizing assignment to treatment group is expected to avoid bias, while use of placebo provides control.

The rationale for three-month treatment duration is based on the expectation, given published results[2], that it is sufficient to explore DS-7011a initial safety and efficacy in SLE, namely, to impact the CLASI-A endpoint. According to cited results, three-month treatment duration was adequate time for an anti-BDCA2 antibody, which has a mechanism of action with similarities to DS-7011a, to show beneficial impact on CLASI-A and related pharmacodynamic biomarkers.

4.3. Justification for Dose Selection

DS-7011a will be administered IV 3 times at the dose of 20 mg/kg q4w. This dose was selected based on the safety, tolerability, PK, and PD results of the DS-7011a FIH Phase 1a study, which

was a single ascending-dose study in healthy subjects in which DS-7011a was explored at the doses of 0.1, 0.3, 1, 3, 10, and 20 mg/kg. In said Phase 1a study, the 20 mg/kg dose was found to be similarly safe and well tolerated to lower doses but maximally active pharmacodynamically and thus selected to explore DS-7011a in subjects with SLE in this Phase 1b/2 study. According to preliminary analysis, in said Phase 1a study, the 20 mg/kg dose resulted after a single IV administration in extensive ex vivo inhibition of IL-6 production, which was of early onset and lasting duration and was still 86% on average, more than 65% in each subject, and more than 95% in 40% of subjects after 4 weeks from the administration. The 20 mg/kg dose, which is 1/6 of the NOAEL human equivalent dose, also resulted in C_{max} (719 µg/mL) and AUC_{inf} (8838 day*µg/mL) that didn't exceed monkey NOAEL (400 mg/kg) C_{max} (14,700 µg/mL [female] or 13,800 µg/mL [male]) and AUC_{inf} (29,300 day*µg/mL [female] or 34,200 day*µg/mL [male]).

The rationale for the use of placebo is the provision of treatment control, necessary to interpret DS-7011a activity (safety, tolerability, and efficacy), even if the sample size of this study was not calibrated to allow finding a statistically significant difference between DS-7011a- and placebo-treated subjects at pre-stipulated levels of probability and power.

5. STUDY POPULATION

Adult subjects (ages ≥18 years) with SLE including active CLE.

5.1. Inclusion Criteria

Subjects eligible for inclusion in this study have to meet all inclusion criteria for this study:

1. Male and female subjects must be of 18 years or more with definite SLE for at least 6 months prior to Screening, defined according to the 2019 European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) classification criteria for SLE[3], including documented history of positivity for antinuclear antibody (titer ≥1:80).
2. Body mass index (BMI) ≥18 kg/m^2.
3. Presence of active CLE (acute, subacute, and chronic cutaneous lupus) with active skin involvement and a CLASI-A score of 4 or higher at the time of Screening and randomization, as recognized by 2 adjudicators, ie, the investigator in the periphery at the site and a centrally located arbiter contracted ad hoc (in case of disagreement between these 2 adjudicators, a third adjudicator, also centrally located and contracted ad hoc, will solve the disagreement and provide a final decision), despite adequate use of conventional therapies (either topical corticosteroids or antimalarial agents used for at least 12 weeks prior to Screening) or because of the requirement to discontinue these therapies due to side effects or poor tolerability.
4. Subjects must be willing to have skin tape harvests collected from the affected skin area (skin tape stripping done on the target lesion).
5. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at randomization, and she must be willing to use one method of highly effective birth control, as detailed in Section 10.2, and one barrier method, such as condom, diaphragm, or cervical cap with spermicide, upon enrollment, during the Treatment Period, and for 3 months following the last dose of study drug. A female is considered of childbearing potential following menarche and until reaching postmenopausal state, which is defined as no menstrual periods for a minimum of 12 months (a follicle-stimulating hormone [FSH] test may be conducted to confirm postmenopausal state according to investigator's discretion), unless made permanently sterile by surgery (undergone a hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 1 month before the first dose).
6. If male, the subject must be surgically sterile or willing to practice birth control (Section 10.2) upon enrollment, during the Treatment Period, and for 3 months following the last dose of study drug.
7. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 3 months after the final study drug administration.
8. Female subjects must not donate, or retrieve for their own use, ova from the time of Screening and throughout the study Treatment Period, and for at least 3 months after the final study drug administration.

9. Subjects must agree not to participate in any other investigational study during the study Treatment Period and for 3 months after the last dose of study drug.
10. Subjects must give written informed consent to participation in the study prior to Screening.
11. Subjects must be vaccinated against COVID-19.

5.2. Exclusion Criteria

Subjects meeting any exclusion criterion for this study will be excluded from this study:

1. Active LN on induction therapy, or induction therapy completed within 12 weeks prior to Screening (stable maintenance therapy with mycophenolate or azathioprine allowed).
2. Active neuropsychiatric SLE, including, but not limited to, the following: seizure, new or worsening impaired level of consciousness, psychosis, delirium or confusional state, aseptic meningitis, ascending or transverse myelitis, chorea, cerebellar ataxia, mononeuritis multiplex, or demyelinating syndromes.
3. Primary diagnosis of autoimmune or rheumatic disease other than SLE (secondary Sjögren's syndrome or autoimmune thyroiditis are not exclusionary) or drug-induced lupus.
4. History of chronic, recurrent (3 or more of the same type of infection in 1 year) or recent serious infection (eg, pneumonia, septicemia), including viral infections, as determined by the investigator, or requiring anti-infective treatment within 12 weeks prior to Screening.
5. History of severe herpes infection (eg, herpetic encephalitis, ophthalmic herpes, or disseminated herpes) or signs of herpes or varicella zoster viral infection (chicken pox, shingles, or herpes zoster) within 12 weeks prior to Screening.
6. Positive COVID-19 test (either molecular, based on polymerase chain reaction [PCR], or antigenic) at Screening or symptoms suggestive of SARS-CoV-2 infection (such as fever, chills, cough, shortness of breath, fatigue, myalgia, headache, new loss of taste or smell, sore throat, nasal congestion, rhinitis, nausea, vomiting, or diarrhea) or close contact with an individual with SARS-CoV-2 infection within 2 weeks prior to randomization.
7. History of malignant disease within the 2 years before Screening or ongoing at the time of Screening, except basal cell carcinomas and squamous cell carcinomas of the skin, or completely excised carcinoma in situ of the cervix.
8. Chronic kidney disease with significant proteinuria (ie, >2 g/24 h or urine protein to creatinine ratio >200 mg/g) or decreased renal function (estimated glomerular filtration rate [eGFR] <30 mL/min).
9. New York Heart Association class III or IV congestive heart failure.
10. Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.

11. Treatment with SLE SOC medications, except for the following, which are allowed: oral prednisone (or equivalent at a maximum of 20 mg/d); antimalarials at SOC dose (maximum: hydroxychloroquine 400 mg/d, chloroquine 250 mg/d, quinacrine 100 mg/d); methotrexate (maximum 25 mg/wk); leflunomide (maximum 20 mg/d); mycophenolate (mycophenolate mofetil [MMF] maximum 3000 mg/d or mycophenolic acid sodium [MPS] maximum 2160 mg/d); azathioprine (maximum 200 mg/d); and tacrolimus (maximum 3 mg/d). These medications are allowed as long as they were initiated at least 12 weeks prior to randomization, have been stable for at least 4 weeks prior to randomization, and will remain stable for the duration of the study. Subjects who are not planning to continue these medications during the study must have discontinued them at least 4 weeks prior to randomization.
12. These medications are prohibited as follows:
    - Topical corticosteroids and other topical immunosuppressive agents, including topical calcineurin inhibitors, within 2 weeks prior to randomization (Day 1)
    - Intralesional corticosteroids, IV, intramuscular (IM), and intra-articular corticosteroids within 4 weeks prior to randomization (Day 1)
    - Cyclosporine, voclosporin, pimecrolimus, and sirolimus within 4 weeks prior to randomization (Day 1)
    - Cyclophosphamide within 24 weeks prior to randomization (Day 1)
    - IV Ig or plasmapheresis within 12 weeks prior to randomization (Day 1)
    - All biologic agents, including anti-B-cell antibodies (eg, rituximab, ocrelizumab, and belimumab), other antibodies (eg, anifrolumab, adalimumab, and tocilizumab), Fc constructs (eg, abatacept and etanercept), cytokines, and live vaccines within 12 weeks prior to randomization (Day 1)
13. History of suicide attempt or suicidal ideation within 1 year prior to Screening.
14. History of substance abuse within 6 months prior to Screening or a urine drug test at Screening resulting positive for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates. Medical marijuana may be used per discretion of the investigator.
15. History or positive test result for human immunodeficiency virus (HIV) at Screening.
16. Active hepatitis B virus (HBV) infection determined at Screening as positive test result for hepatitis B surface antigen.
17. Active hepatitis C virus (HCV) infection determined at Screening as HCV ribonucleic acid (RNA) above the limit of detection in subjects with positive HCV antibody titer.
18. History of, or ongoing, active tuberculosis (TB) or untreated latent TB infection (LTBI), determined by a positive QuantiFERON-TB Gold or positive or borderline T-SPOT (Elispot) test performed locally at Screening. Subjects with documented previously completed appropriate LTBI treatment and without evidence of re-exposure will not be required to be tested. Indeterminate QuantiFERON-TB Gold or T-SPOT tests may be repeated once; it will be considered positive if retest results are positive or indeterminate.

19. Any other significant condition (eg, medical, psychiatric, or social) that according to the investigator's judgment would prevent compliance with study protocol and full study participation.
20. Subjects must not be participating in another investigational study or have participated in an investigational study within the past 30 days prior to randomization (Day 1).
21. History of or current inflammatory skin disease other than SLE that in the opinion of the investigator could interfere with the inflammatory skin assessments and confound the disease activity assessments.
22. History of any non-SLE disease that had required treatment with oral or parenteral corticosteroids for more than a total of 2 weeks within the last 24 weeks prior to randomization.

5.3. Screening Failures, Rescreening, and Subject Replacement

Rescreening is permitted after consultation with the Sponsor if a subject fails initial screening. Rescreening may occur only once. The subject identification number will remain the same at the time of rescreening. The initial screening information and the reason why the subject failed this screening will be recorded in EDC. If the subject also fails rescreening, rescreening information and reason for failure will similarly be recorded in EDC.

Subjects who discontinue the study may be replaced after consultation with the Sponsor.

6. STUDY DRUG(S)

6.1. Study Drug(s) Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of the study drug and placebo.

Table 6.1: Study Drug Dosing Information

Study Drug Name	DS-7011a
Dosage Formulation	Provided as sterile solution in vials of 2 mL at a concentration of 100 mg/mL
Dosage Level	20 mg/kg
Route of Administration	Intravenous
Dosing	Intravenous infusions over 1 hour once every 4 weeks on Day 1, Day 29, and Day 57
Duration	Once every 4 weeks for 8 weeks (Weeks 0, 4, and 8)
Packaging	Glass vials/carton Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations.
Labeling	Vials will be labeled as required per local regulatory requirement.
Source	DS-7011a will be supplied by the Sponsor.

DS-7011a will be provided as a sterile solution in vials of 2 mL at a concentration of 100 mg/mL and will be infused diluted in dextrose 5% in water (D5W). Placebo will be prepared using D5W or normal saline as a possible alternative. DS-7011a and placebo will be administered by IV infusion. DS-7011a will be given at the dose of 20 mg/kg q4w IV. The DS-7011a dose was selected based on the safety, tolerability, PK, and PD results of the DS-7011a FIH Phase 1a study. The intent is to select the optimal dose that is found in Phase 1a to be safe, well tolerated, and maximally active pharmacodynamically.

6.2. Preparation, Handling, Storage, and Accountability for Study Drug

6.2.1. Preparation, Handling, and Disposal

The preparation of study drug will be conducted in accordance with the Dose Preparation Instructions (DPI) provided by the Sponsor.

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures (SOP) of the site.

6.2.2. Drug Administration

DS-7011a or placebo will be administered by IV infusion over 1 hour.

6.2.3. Storage

DS-7011a must be stored in a secure, limited access storage area under the recommended storage conditions noted on the label and protected from light. If storage conditions are not maintained per specified requirements, then the Sponsor or contract research organization (CRO) should be contacted.

See the Pharmacy Manual for additional information on storage conditions of study drug/storage conditions of the infusion solution.

6.2.4. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug against the shipping documentation.

The Receipt of Shipment Form should be transmitted as instructed on the form. The original will be retained at the study site.

In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

The investigator is responsible for study drug accountability, reconciliation, and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

All used study drug will be destroyed at the site after reconciliation. Unused study drug will be destroyed at the site unless the Sponsor authorizes the study drug to be returned.

6.3. Measure to Minimize Bias: Randomization and Blinding

6.3.1. Method of Treatment Allocation

Randomization will follow a randomization schedule generated by an independent biostatistician.

6.3.2. Blinding/Unblinding

Subjects, investigators, and site staff will be blinded, except for the unblinded site pharmacist or designee who will be responsible for preparing the study drugs. Sponsor's staff or representative (eg, CRO) will also be blinded. Two cases of unblinding are contemplated: one due to medical emergency and one accidental. In the case of an emergency where, in the opinion of the investigator, discontinuation of study drug is not sufficient, and the study drug must be unblinded in order to further evaluate a course of medical treatment, the Principal Investigator (PI) is authorized to perform the unblinding.

The unblinded subject will discontinue treatment and study participation and will be informed about the treatment assigned. Information about the treatment assignment must be restricted to designated site staff/personnel who are providing immediate care to the subject. Any documentation of the treatment assignment must be maintained separately (ie, in a secured file). The information must not be included in the subject's source files to ensure the treatment assignment will remain blinded to study personnel not involved with the subject's immediate care. In the case of accidental unblinding, the unblinded subject may complete the study.

6.4. Treatment Compliance

Treatment compliance will be directly observable by clinic staff, given that the study drugs are IV infusions. Pertinent data will be recorded in each subject's electronic case report form (eCRF).

6.5. Guidelines for Dose Modification

No dose modifications will be permitted in this study.

6.6. Prior and Concomitant Medications

All therapies received by subjects within 30 days prior to a subject's signing of the informed consent form (ICF) will be recorded as prior therapies.

All therapies used from the time the subject signs the ICF for study participation through the Follow-up Visits will be recorded as concomitant therapies. Concomitant therapies include all prescription, over-the-counter (OTC), and herbal remedies.

COVID-19 vaccine doses received prior to the study will be documented as prior medication, regardless of date of administration.

All prior and concomitant therapies will be recorded in the eCRF.

Changes to allowed (see Exclusion Criterion 11) SLE medications are permitted as long as they result in dose decrease and not increase.

6.7. Prohibited Therapies/Products

The following therapies and products are prohibited starting before randomization, as indicated below, and until the End of Treatment (EOT) Visit (Day 113).

- Topical corticosteroids and other topical immunosuppressive agents, including topical calcineurin inhibitors, whose prohibition starts 2 weeks prior to randomization (Day 1)
- Intralesional corticosteroids, IV, IM, and intra-articular corticosteroids, whose prohibition starts 4 weeks prior to randomization (Day 1)
- Cyclosporine, voclosporin, pimecrolimus, and sirolimus, whose prohibition starts 4 weeks prior to randomization (Day 1)
- Cyclophosphamide, whose prohibition starts 24 weeks prior to randomization (Day 1)
- IV Ig or plasmapheresis, whose prohibition starts 12 weeks prior to randomization (Day 1)
- All biologic agents, including anti-B-cell antibodies (eg, rituximab, ocrelizumab, and belimumab), other antibodies (eg, anifrolumab, adalimumab, and tocilizumab), Fc constructs (eg, abatacept and etanercept), cytokines, and live vaccines within 12 weeks prior to randomization (Day 1)

6.8. Permitted Therapies/Products

The use of acetaminophen of <2 g/d and 1% topical hydrocortisone for contact dermatitis are acceptable concomitant therapies at any time during the study. Stool softeners are allowed during the inpatient stay at the discretion of the investigator. Subjects may drink prune juice for constipation. The following medications are allowed: oral prednisone (or equivalent at a maximum of 20 mg/d); antimalarials at standard-of-care dose (maximum: hydroxychloroquine 400 mg/d, chloroquine 250 mg/d, quinacrine 100 mg/d); methotrexate (maximum 25 mg/wk); leflunomide (maximum 20 mg/d); mycophenolate (mycophenolate mofetil [MMF] maximum 3000 mg/d or mycophenolic acid sodium [MPS] maximum 2160 mg/d); azathioprine (maximum 200 mg/d); and tacrolimus (maximum 3 mg/d). These medications are allowed as long as they were initiated at least 12 weeks prior to randomization, have been stable for at least 4 weeks prior to randomization, and will remain stable for the duration of the study. Subjects who are not planning to continue these medications during the study must have discontinued them at least 4 weeks prior to randomization.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of DS-7011a treatment administration must be recorded. Reasons for treatment discontinuation include:

- Completed
- Death
- AE
- Withdrawal by Subject (**to discontinue study drug**) NOTE: in this section this is only withdrawal for treatment with study drug and is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments).
- Physician Decision
- Lost to Follow-up (see Section 7.4 for details on when a subject is considered Lost to Follow-up)
- Pregnancy
- Protocol Deviation
- Study Termination by Sponsor
- Other

After study drug is permanently discontinued for any reason other than death or lost to follow-up, the subject will be treated as clinically indicated by the investigator or referring physician.

The investigator must discuss with the subject that their decision to permanently discontinue the study drug means the subject still agrees to continue into the Follow-up Period for onsite or modified follow-up visits. Subjects will be followed at regularly scheduled intervals (see Table 1.1).

Procedures for Discontinuation from Study Drug

The subject should be instructed to contact the investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF.
- Due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.

- An EOT evaluation should be performed as described in the Schedule of Events (SoE) (Table 1.1).
- A safety follow-up evaluation should be performed approximately 30 days after the last dose of study drug as described in the SoE (Table 1.1).

The investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose. All procedures specified for the EOT visit will be conducted. See Table 1.1 for specific EOT procedures.

If a subject does not agree to continue to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options

The following modified follow-up options can be offered to the subject who does not agree to study visits at the study site.

- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at EOS)
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records)

Dates of the modified follow-up contact(s) should be recorded. See Section 7.2 for definition of withdrawal by subject from the study (ie, withdrawal of consent).

7.2. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- AE
- Death
- Consent withdrawal (this indicates that the subject withdraws consent and refuses to undergo any further study procedures)
- Lost to Follow-up (see Section 7.4 for details on when a subject is considered Lost to Follow-up)
- Study Termination by Sponsor
- Investigator decision
- Protocol deviation
- Pregnancy (see Section 8.8.1.9)
- Other

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are progressive disease or AE. If reason of death is unknown, every effort should be made to obtain the primary cause of death. Only 1 AE will be recognized as the primary cause of death.

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel contacting an alternative person
- Study personnel accessing and reviewing the subject's medical information from alternative sources

If the subject refuses all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

7.3. Withdrawal Procedures

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the study physician or at the study site.

If a subject withdraws from the study, she/he will be required to have early termination (ET) study procedures performed (refer to Table 1.1). All subjects who are withdrawn from the study should complete the protocol-specified withdrawal procedures.

If a subject is withdrawn from the study, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.

In addition:

- Disclosure of future information is also withdrawn; the Sponsor may retain and continue to use any data collected before such a withdrawal of consent;
- The subject may request destruction of any samples taken and not tested, and the investigator must document this in the site study records;
- Study site personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status.

See SoE (Table 1.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.4. Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

7.5. Retesting of Screening Laboratory Test Results

Retesting of laboratory test results is permitted only once for any subject with Sponsor approval who failed to meet eligibility criteria upon initial screening related to specific inclusion/exclusion criterion. If a subject's laboratory result needs to be retested for any time-dependent module (ie, laboratory, vital signs, etc), the investigator will perform a rescreening visit within 30 days of the original Screening Visit and the appropriate module will be used to accommodate new data that would make the subject eligible to be randomized. The subject identification number will remain the same at the time of retesting.

8. STUDY PROCEDURES

Table 1.1 presents the procedures conducted at specific time points during the study.

8.1. Eligibility Assessment

Eligibility for the study will be accomplished by reviewing the subject's documentation of SLE by EULAR/ACR criteria, demographics, medical history (including smoking and alcohol consumption history), vital signs (blood pressure, heart rate, respiratory rate, and temperature), results of tests (eg, physical examination, ECG, laboratory assessments [a single out-of-the-normal-range value may be repeated once], urine screens for drugs of abuse, cotinine, and alcohol, and serum and urine pregnancy tests), and behavioral characteristics (including the use of non-prohibited substances) and comparing this information with the eligibility criteria (Section 5.1 and Section 5.2).

8.2. Informed Consent

Before a subject participates in the study, it is the investigator's responsibility to obtain the subject's freely given consent, in writing, after adequate explanation of the aims, methods, limited benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive answers to their inquiries, and they should have adequate time to decide whether or not to participate in the study. See Section 10.1.4 for additional details.

8.3. Medical History and Baseline Conditions

Subject's medical and medication histories (as detailed in Section 6.6) will be obtained by the investigator or a qualified designee.

Any untoward medical occurrence (including clinically significant laboratory values/vital signs that are out of range) that is noted prior to the dose of DS-7011a will be recorded.

8.4. Demographics and Baseline Assessments

Demographic and baseline characteristics data will include sex, age, race, ethnicity, body weight (kg), height (cm), and BMI (kg/m^2). Height will be measured at Screening and weight will be obtained at Screening and on Day 1.

The subject's demographics will be compared with the eligibility criteria.

Additional baseline assessments will include:

- Serum pregnancy test
- FSH test (postmenopausal females, according to investigator's discretion)
- Serum virology (HIV, HBV, HCV)
- TB test
- Urine drug screen
- COVID-19 Tests (molecular [based on PCR] or antigenic)
- Chest X-ray

8.5. Randomization

Subjects who meet the eligibility criteria and provide signed informed consent will be randomly assigned on Day 1 to 1 of 2 treatment arms to receive 2:1 DS-7011a or placebo. Study drug will be administered following randomization assignment based on the subject's weight (mg/kg basis) on Day 1.

Subjects who withdraw from the study may be replaced after consultation with the Sponsor. The study will allow up to 3 replacements for a subject with an assigned treatment.

8.6. Efficacy Assessments

8.6.1. Cutaneous Lupus Area and Severity Index Activity

The CLASI-A instrument was developed specifically to evaluate lupus skin manifestations. This evaluation is scored predominantly with objective findings observed in the mucocutaneous system on the day of the visit. CLASI-A, the activity scale of the instrument, includes measurements of erythema, scale and hypertrophy, and mucous membrane disease. Each part of the body is listed separately, from the scalp to the feet, in addition to sections focusing on mucous membrane involvement and alopecia. Scores for each area are assigned based on the most severe lesion within the area of interest. CLASI-A scores of 0 to 9, 10 to 20, and 21 to 70 represent disease severity of mild, moderate, and severe, respectively.[5,6]

8.6.2. Skin Photography

Subjects will undergo regular skin photography assessments throughout the study. For details regarding skin photography submissions, refer to Table 1.1.

The site investigator will obtain detailed photographs of the following body areas: scalp, ears, nose/malar area, rest of face, V-area neck (frontal), posterior neck and shoulders, chest, abdomen, back/buttocks, arms, hands, legs, and feet. In addition, a photograph of the scalp will be included so that non-scarring alopecia could be scored. Information regarding patient hair loss will be submitted by the site clinician and presented to the centralized reviewers. At Screening, the images will be centrally evaluated to confirm the active presence of CLE with active skin involvement. All follow-up time points will be submitted for centralized assessment of the CLASI-A score. The CLASI-A score is generated by the centralized reviewers as the rating of erythema and scale/hypertrophy for each of the 13 defined body areas. Additionally, the clinician will note and examine any current oral/nasal mucous membrane involvement, as well as patient reported hair loss.

8.6.3. Cutaneous Lupus Activity Investigator Global Assessment

Cutaneous Lupus Activity Investigator's Global Assessment (CLA-IGA) is a five-point score that defines the level of disease severity based on overall lesion characteristics where 0 is "clear" and "4" is severe.[7] Severity is determined by a combination of 3 plaque characteristics (erythema, scale, elevation) based on descriptions of each characteristic. Erythema is the primary characteristic that influences the rating, with plaque elevation, scaling, and other secondary characteristics considered secondarily. Severity of the morphologic features are averaged over the burden of lesions.

8.6.4. Systemic Lupus Erythematosus Disease Activity Index

Systemic Lupus Erythematosus Disease Activity Index – 2000 (SLEDAI-2K) is a simple, one-page activity index that measures disease activity and records features of active lupus as present or not.[8] It has been validated against the SLEDAI, shown to be reliable at different levels of disease activity.[9] The SLEDAI-2K uses a weighted checklist to assign a numeric score based on the presence or absence of 24 symptoms at the time of assessment or during the previous 28 days. Each symptom present is assigned between 1 and up to 8 points based on its usual clinical importance, yielding a total score that ranges from 0 points (no symptoms) to 105 points (presence of all defined symptoms). SLEDAI-2K assessments should be conducted by the same trained evaluator at each visit as much as possible.

A copy of the SLEDAI-2K and glossary is provided in the Study Reference Guide.

8.6.5. Physician's Global Assessment of Systemic Lupus Erythematosus

The Physician's Global Assessment of Systemic Lupus Erythematosus (PGA-SLE) is used to quantify disease activity and is measured using an anchored visual analog scale (VAS).[10] The PGA-SLE will be determined on a continuous VAS that asks the investigator to assess the participant's current disease activity from 0 (no disease) to 3 (maximally severe disease), with the assessment made relative not to the participant's own most severe state but the most severe state possible in SLE per the investigator's assessment. The Safety of Estrogens in Lupus Erythematosus National Assessment SLEDAI Physician's Global Assessment requires investigators to compare the current visit to the previous visit in determining the score. Thus, the assessor should look back at the last assessment and consider whether to move the mark to the right (patient worsening) or to the left (patient improving).

8.6.6. Clinician's Global Impression of Change

Clinician's Global Impression of Change (CGI-C) is a brief rating scale to reflect the clinician's evaluation on the changes in SLE disease severity. The investigators are asked to rate disease progress at each visit based on their clinical judgment as "very much worse", "much worse", "minimally worse", "no change", minimally improved", "much improved", "very much improved".[11]

8.6.7. Patient Reported Outcome Questionnaires

Patient Reported Outcome (PRO) Questionnaires include the following:

- Quality of life questionnaires (Skindex-29+3 and the SF-36 questionnaires)

  The Skindex-29+3 is a self-reported measure of skin-specific symptoms and functioning for CLE populations, and includes items from the Skindex-29, designed for use across dermatologic conditions, and three additional items specific for lupus.[12,13] Subscale scores are generated for each of the three original domains of the Skindex-29, ie, symptoms, functioning, and emotional well-being. In addition, a photosensitivity subscale score is calculated based on two of the additional lupus-specific items related to photosensitivity.[14] For all subscale scores, higher scores indicate lower functioning/worse symptoms.

The SF-36 Health Survey[15] is one of the most widely used patient reported outcomes currently used in SLE.[16] Within a limited number of questions, it captures eight domains relevant to quality of life: (physical functioning, general health, mental health, vitality, role physical, role emotional, bodily pain, and social functioning) and provides 2 summary scores: physical component score (PCS) and mental component score (MCS). Scoring can range from 0 to 100 with higher scores designating better health. The psychometric measurement properties of this instrument have been extensively studied and applied for lupus across multiple cultures and languages. Reliability and responsiveness of SF-36 have been confirmed for SLE.[17,18,19,20,21,22,23]

- Functional Assessment of Chronic Illness Therapy-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) is a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function.[24] It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). As each of the 13 items of the FACIT-Fatigue scale ranges from 0 to 4, the range of possible scores is 0 to 52, with 0 being the worst possible score and 52 the best. To obtain the 0 to 52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. All responses are added with equal weight to obtain the total score. Fatigue is among the most prevalent symptoms of SLE, and can have profound effects on subjects' Health-Related Quality of Life (HRQoL).[24,25] The FACIT-Fatigue has been validated in subjects with SLE and is considered a valid and responsive measure of fatigue in subjects with SLE.[26,27,28,29]

- Itch Numeric Rating Scale

The Itch Numeric Rating Scale (NRS) is a self-rated single item scale designed for assessing worst itch in the past 7 days. The scale utilizes an 11-point NRS, scored from 0 (no itch) to 10 (worst imaginable itch).

- Patient's Global Impression of Change

The Patient's Global Impression of Change (PGI-C) is a self-rated scale that ask respondents to describe the retrospective change in their lupus skin symptoms at a given time point. Responses are captured on a 7-point scale, as follows: "very much worse", "much worse", "minimally worse", "no change", minimally improved", "much improved", "very much improved".[30]

8.6.8. Other Efficacy Assessments

Laboratory parameters:

- Autoantibodies (including antinuclear, anti-dsDNA, anti-Sm, and anti-RNP antibodies)
- Complement factors (C3, C4)
- ESR
- CRP

Blood samples will be collected and analyzed for the following in plasma at Screening and predose on Day 1, predose on Day 29, predose on Day 57, on Day 85, and on Day 113:

- ESR
- CRP
- Complement factors (C3, C4) (collected as serum)
- SLE-related autoantibodies (antinuclear, anti-dsDNA, anti-Sm, anti-RNP) (collected as serum)

8.7. Pharmacokinetic, Pharmacodynamic, Pharmacogenetic, and Immunogenicity Assessments

8.7.1. Pharmacokinetic Assessment(s)

Blood samples will be collected and analyzed for DS-7011a in plasma at the following time points (Table 8.1).

Table 8.1: Schedule of Blood Collection Times

Sample Type	Schedule Time (hours)
Plasma	Day 1 (at predose and at end of infusion), Day 2 (24 hours after administration), Day 8 (1 week after administration), Days 29 and 57 (at predose and at end of infusion), and Days 85 and 113

Allowable time windows for PK blood samples are provided in Section 10.5.

The blood samples will be processed and shipped according to Laboratory Processing Specifications.

The following key PK parameters will be derived, including but not limited to: AUC_t, C_{max}, C_{min}, $t_{1/2}$, CL, and V_{ss}.

8.7.2. Pharmacodynamic and Other Biomarkers

Several endpoints indicative of mechanistic efficacy will be assessed. Circulating TLR7 GS expression will be a biomarker indicative of target engagement, while circulating IFN-Type I (and possibly other cytokines under consideration) GS expression and cytokines will be biomarkers indicative of response to DS-7011a. Other biomarkers indicative of response will be skin mRNA coding for proteins under IFN-Type I regulation, such as MxA, and for markers of inflammatory cells, such as CD45. This mRNA will be extracted from skin tape harvests collected by tape stripping from the skin area affected by CLE.

Blood samples will be collected at predose on Day 1, predose on Day 29, predose on Day 57, on Day 85, and on Day 113 and analyzed for the following:

- TLR7 and IFN-Type I GS (blood also collected on Day 2 and Day 8)
- Cytokines (several, using a multiplex approach, such as IL-6, IL-12/IL-23)

Skin tape harvesting for mRNA will be performed on Days 1, 85, and 113. The following biomarkers will be assessed in the skin:

- mRNA coding for MxA, a protein whose gene expression is under IFN-Type I regulation
- mRNA coding from inflammatory cell markers (CD45 and lymphocyte subset markers, such as CD3, CD20, and CD56)

Skin will be collected by tape stripping of the skin area affected by CLE.

8.7.3. Immunogenicity Assessments

Blood samples will be collected and analyzed for ADAs for DS-7011a in plasma at predose on Day 1, predose on Day 29, predose on Day 57, on Day 85, and on Day 113. The ADA testing will be performed using a validated assay and will involve a tiered assessment including screening, confirmation, and titer determination. ADA samples confirmed positive will be stored for neutralizing ADA. Plasma samples will be collected on Day 169 only from subjects positive for ADA on Day 113. For subjects positive for ADA on Day 169, additional plasma ADA samples will be collected every 3 months (±1 month) up to 1 year from Day 1, or until the subject becomes negative (or, applicable to when preexisting ADA is observed, ADA titer becomes less than baseline), or shows an ADA decrease for three consecutive visits, or withdraws consent from the study, whichever occurs first.

The blood samples will be processed and shipped according to Laboratory Processing Specifications to be provided in a Laboratory Manual.

8.7.4. Pharmacogenetic Assessments

A whole blood sample (in K_2-EDTA) for genotyping will be collected from all subjects at predose on Day 1.

If necessary, this sample may be analyzed for genes involved in the safety, PK, and efficacy of DS-7011a. It will provide information on how individuals metabolize and react to the study drug.

The blood samples will be processed and shipped according to Laboratory Processing Specifications to be provided in a Laboratory Manual.

8.8. Safety Assessments and Reporting

The safety endpoints include the following:

- AEs including treatment-emergent AEs (TEAEs), SAEs, AESIs, such as herpes zoster and respiratory tract infections, including COVID-19
- Physical examination findings
- Vital sign recordings (body temperature, blood pressure, heart rate, respiratory rate)
- ECG findings
- Clinical laboratory evaluations of blood and urine
- Ig values, vaccine titers, and lymphocyte subset values

8.8.1. Adverse Events

8.8.1.1. Methods to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.4. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. COVID-19 assessments are detailed in Section 8.8.2.

8.8.1.2. Time Period for Collecting Adverse Events, including Adverse Events of Special Interest and Serious Adverse Events

For all randomized subjects, all AEs occurring after the subject signs the ICF and through the EOS Visit, whether observed by the investigator or reported by the subject, will be recorded as detailed in Section 10.1.6.2. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Medical conditions (including clinically significant laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to the consent date will be recorded as medical history, and not an AE. Exacerbation of a pre-existing medical condition or symptom, including increase in severity of the symptom will be recorded as an AE.

8.8.1.3. Reporting Procedure for Investigators

All AEs will be recorded in the adverse event CRF page. All SAEs, serious AESIs, and potential Hy's Law cases (Section 8.8.1.7), whether related or not related to study drug will be reported using the paper Serious Adverse Event Report (SAVER) Form. All AEs (serious and nonserious) must be reported with the investigator's assessment of seriousness, severity, and causality to the study drug. Additional information regarding the process for reporting SAEs is provided in the SAE Flow Plan.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

8.8.1.4. Serious Adverse Events Reporting

The following types of events should be reported by the investigator using a paper SAVER form within 24 hours of awareness:

- All SAEs (Section 10.4.2)
- Hepatic events meeting combination abnormalities (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3 × upper limit of normal [ULN] with simultaneous total bilirubin ≥2 × ULN) (potential Hy's Law case), both serious and non-serious (Section 8.8.1.7)
- Serious AESIs (Section 8.8.1.7)
- Overdose (Section 8.8.1.8)
- Pregnancy (Section 8.8.1.9)

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should include the results if available. For deaths, the underlying or immediate cause of death should always be reported as an SAE. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

Call your study monitor for any questions on SAE reporting.

See Section 8.8.1.2 for details on the time period for collecting SAEs.

8.8.1.5. Notifying Regulatory Authorities, Investigators, and Institutional Review Boards/Ethics Committees

Daiichi Sankyo and/or the CRO will inform investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in this or other studies of the study drug, as appropriate per local reporting requirements. Daiichi Sankyo and/or the CRO will comply with any additional local safety reporting requirements. The section of "Reference Safety Information" in the current Investigator's Brochure[1] should be referred to judge "Unexpected."

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per Sponsor's instruction.

In the European Economic Area states, it is the Sponsor's or CRO's responsibility to report SUSARs to all ECs.

8.8.1.6. Follow-up for AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality

of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations or consultation with other health care professionals.

Urgent safety queries must be followed up and addressed promptly. The investigator will submit any updated SAE data to the CRO within 24 hours of receipt of the information. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.8.1.7. Adverse Events of Special Interest

AESIs comprise respiratory tract infections, including COVID-19, and herpes zoster. All AESIs (serious and non-serious) should be reported within 24 hours of the investigator's awareness of the event with an assessment of seriousness, causality, and a detailed narrative. Serious AESIs should be reported by the investigator using the paper SAVER form and non-serious AESIs should be reported by completing the adverse event CRF page.

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST ≥3 × ULN with simultaneous total bilirubin ≥2 × ULN) should always be reported to the Sponsor using a special collection eCRF, with the investigator's assessment of seriousness, causality, and a detailed narrative. These events must be reported within 24 hours of investigator's awareness of the event.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject should have additional clinical and laboratory evaluations in order to determine the nature and severity of the potential liver injury.

8.8.1.8. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported to the Sponsor within 24 hours of awareness.

Overdose will be reported via eCRF. An "excessive and medically important" overdose includes any overdose in which either an SAE or a non-serious AE (Section 8.8.1), or no AE occurs and is considered by the investigator as clinically significant, ie, poses an actual or potential risk to the subject.

Occupational exposures must be reported via EDC.

Overdoses are not expected in this study in which the study drug is monitored at all times by the clinical site staff. The pharmacist and the pharmacy staff are responsible for correctly preparing the study drug for delivery by the staff to the subjects.

8.8.1.9. Pregnancy

It is the responsibility of the investigator or designee to notify the Sponsor of any pregnancy in a female subject or a male subject's female partner that occurs after the subject receives DS-7011a through the EOS Visit. Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the investigator, or designee, must report any pregnancy in a female subject using the Exposure In Utero (EIU)

Reporting form within 24 hours of learning of the pregnancy, as this information is important for drug safety and public health concerns.

The investigator should make every effort to follow the partner of a male subject (upon obtaining written consent from her) until completion of the pregnancy and to document the complete pregnancy outcome information, including normal delivery or induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

For reports of pregnancy in a female partner of a male subject, the EIU Reporting Form (or SAE form if associated with an adverse outcome) should be completed with the details regarding the female partner entered in the narrative section.

8.8.1.10. Pregnancy Testing

Women of childbearing potential who follow the contraception requirements of the study will be included in the study. A serum pregnancy test will be conducted on all females of childbearing potential at Screening so that results are available before enrollment. A urine pregnancy test will be conducted on all females of childbearing potential on Day 1, Day 29, Day 57, Day 85, and Day 113 (Final Visit) to rule out any change in status.

Women claiming postmenopausal status may have an FSH test conducted at Screening according to investigator's decision.

8.8.2. Reporting of Exposure to COVID-19 (SARS-CoV-2)

All confirmed or suspected COVID-19 events must be recorded in the eCRF.

- Subjects who test positive for COVID-19 should be reported as "Confirmed COVID-19," either as an AE or SAE.

The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, ie, the investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.

In the event that the investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious AE in the eCRF.

All study drug interruption or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.

For both serious and non-serious COVID-related AEs, the following information should be provided as applicable:

- Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the eCRF.

- Clinical course of the case, including presenting signs, symptoms, exposure, actions taken with the study drug, medications used for treatment or prophylaxis of COVID-19, and outcome in relevant eCRF (eg, concomitant medication, AE).
- Findings from diagnostic imaging (including computed tomography scan or other chest imaging).

8.8.3. Clinical Laboratory Evaluations

Blood and urine will be collected for clinical chemistry, hematology, and coagulation tests and for urinalysis at Screening, Day 1, and at subsequent visits as detailed in the SoE (Table 1.1). Blood for virology will be collected at Screening. Urine tests for drugs of abuse, cotinine, and alcohol will be conducted at Screening.

A nasal (or pharyngeal or oral) swab for COVID-19 testing will be obtained at Screening and on Days 1, 29, and 57.

Refer to Section 10.3 for the complete list of laboratory parameters.

Abnormal laboratory values occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically significant. New or worsened clinically significant laboratory abnormalities should be recorded as AEs.

8.8.4. Physical Examinations

Physical examinations will be performed at Screening, Day 1, Day 29, Day 57, Day 85, and Day 113 as shown in the SoE (Table 1.1).

A full physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Any abnormality in physical examination should be recorded. New or worsened clinically significant abnormalities should be recorded as AEs.

8.8.5. Vital Signs

Vital signs will be collected at Screening, Day 1, and before each PK/PD blood draw during the study as detailed in the SoE in Table 1.1.

Allowable time windows for vital sign assessments are provided in Section 10.5.

Vital signs will include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, and temperature. Vital signs will be measured after the subject has rested in a supine position for at least 5 minutes, prior to laboratory draws and prior to ECG measurements when they are scheduled at the same time points.

8.8.6. Electrocardiograms

Triplicate ECGs (approximately 1 minute apart) will be taken at Screening, on Day 85 and on Day 113 as shown in the SoE (Table 1.1). ECGs will be obtained after the subject has rested in a supine position for at least 5 minutes. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken at least 5 minutes prior to the blood collection.

Allowable time windows for ECGs are provided in Section 10.5.

At any visit during which a subject exhibits ECG abnormalities (eg, a heart rate ≤50 bpm) based on triplicate ECG readings, additional readings may be performed according to the investigator's discretion. ECG abnormalities that are considered clinically significant and that occur after the study drug administration will be reported as AEs. The following information will be recorded for any visit foreseeing ECG reading: Confirmation if ECG reading was indeed performed or not, date, and values of heart rate, PR interval, RR interval, QT interval, and QTcF interval.

8.8.7. Immunoglobulin (IgM, IgG, and IgA) Values

Blood will be collected for the determination of the circulating values of total IgM, IgG, and IgA, at predose on Day 1 on Day 85, and on Day 113.

8.8.8. Vaccine (Diphtheria, Tetanus, and Pneumococcus) Titers

Blood will be collected on Day 1, on Day 85, and on Day 113 for the determination of the circulating titers of Ab raised by possible prior vaccinations against diphtheria, tetanus, and pneumococcus.

8.8.9. Lymphocyte Subset (CD3-, CD4-, CD8-, CD20-, CD16-, CD56-Positive) Values

Blood will be collected for the determination of the following circulating lymphocyte subsets: CD3-, CD4-, CD8-, CD20-, CD16-, CD56-positive. This collection will be at Screening, at predose on Day 1, and at subsequent visits as detailed in the SoE (Table 1.1) until Day 113.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

This is not a hypothesis testing study.

9.2. Sample Size Determination

The study will enroll up to 24 subjects with SLE in 2 parallel arms randomized to receive 2:1 DS-7011a or placebo. Tentatively, 9 of these 24 subjects will be of African descent. Also, tentatively, 9 of these 24 subjects will be positive for anti-Sm and/or anti-RNP autoantibodies.

The sample size selected is not based on statistical power considerations. The number of subjects in each arm is considered sufficient to achieve the objectives of this study. Initial evidence of DS-7011a efficacy will be inferred by the impact DS-7011a shows on clinical endpoints, mainly CLASI-A, and several mechanistic endpoints. This impact will be evinced by comparing endpoint values between DS-7011a-treated and placebo-treated subjects and between pretreatment (baseline) and post-treatment time points. Concomitant and consistent impact on multiple endpoints will be initial evidence of efficacy, especially if this impact is of large extent. DS-7011a extent of impact will be compared to that reported for antibodies approved (belimumab and anifrolumab) or in late phase of development (BIIB059) for the treatment of SLE[2]. The result of this comparison will inform a DS-7011a "go/no-go" decision to further development.

9.3. Exposure and Compliance

As study drug administration is under the control of the personnel at the clinical study site, compliance to study medication will not be an issue.

9.4. Population for Analysis Sets

9.4.1. Pharmacokinetic Analysis Set

The PK analysis will be conducted on the PK Population defined as all subjects who received at least one infusion of study drug and have at least one measurable PK result. PK parameters will include but not be limited to: C_{max}, $C_{min,}$ AUC_t, $t_{1/2}$, CL, and V_{ss}.

9.4.2. Safety Analysis Set

The safety analysis will be conducted on the Safety Analysis Set defined as all subjects who received at least 1 infusion of study drug.

9.4.3. Intent-to-treat Analysis Set

The Intent-to-Treat (ITT) Analysis Set will consist of all subjects who are randomized.

9.4.4. Modified Intent-to-treat Analysis Set

The Modified Intent-to-Treat (mITT) Analysis Set will consist of all randomized subjects who received at least one infusion of study drug.

9.5. Statistical Analysis

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data.

The following sections of the protocol summarize the planned statistical analyses of the primary, secondary, and exploratory endpoints.

9.5.1. Efficacy Analysis

No primary efficacy measures or analysis are planned for this study; all efficacy measures will be secondary analyses.

All secondary efficacy analyses will be based on the mITT Analysis Set. The efficacy endpoints (CLASI-A, CLA-IGA, SLEDAI-2K, PGA-SLE, CGI-C, and PROs) will be summarized by treatment group using descriptive statistics. Comparison between treatment groups for the change from baseline to each visit in CLASI-A, CLA-IGA, SLEDAI-2K, PGA-SLE, CGI-C, and PROs, and laboratory parameters, such as autoantibodies (including antinuclear, anti-dsDNA, anti-Sm, and anti-RNP antibodies), complement factors (C3, C4), ESR, and CRP, will be summarized.

9.5.2. Safety Data Analyses

All safety analyses will be based on the Safety Analysis Set. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Incidence summary of participants with TEAEs will be presented by maximum severity, SAEs, AESIs, AEs assessed as related to study drug, and AEs resulting in discontinuation of study drug. Observations at each visit and changes from baseline in vital sign recordings, results of laboratory analyses, ECG findings, Ig (IgM, IgG, IgA) values, vaccine (diphtheria, tetanus, and pneumococcus) titers, and lymphocyte subset (CD3-, CD4-, CD8-, CD20-, CD16-, CD56-positive) values will be numerically summarized by treatment group over time. Physical examination findings at each evaluation will be listed.

Listings of all safety endpoints will be generated.

Any medication (other than study drugs) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) drug dictionary.

9.5.2.1. Treatment-Emergent Adverse Events

TEAEs are defined as new AEs that occur after the first dose of study drug or as AEs that were present prior to the dose of study drug but which worsened in severity after the start of study drug. An AE will be assigned to the study day in which it started, even if it resolved on a subsequent day. The incidence of TEAEs will be summarized by treatment group.

TEAEs will be further summarized by intensity (Section 10.4.4) and relationship to study drug (Section 10.4.5). Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and related treatment-emergent SAEs will be tabulated, and TEAEs leading to discontinuation of study drug will be tabulated.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term (PT), system organ class (SOC), intensity, and relationship to study drug will be provided. Deaths, SAEs, and AEs associated with study drug discontinuation will be listed.

AEs due to COVID-19 will be also summarized and listed.

9.5.2.2. Vital Signs

Descriptive statistics will be provided for vital signs measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline.

A listing of vital sign data will be generated.

9.5.2.3. Electrocardiograms

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) as well as any increase in QTc from baseline as follows: QTcF >60 ms above baseline in the 12-lead ECG, confirmed (persistent for >5 minutes) on repeated 12-lead ECGs.

A listing of ECG data will be generated.

9.5.2.4. Safety Laboratory Results

Descriptive statistics will be provided for the clinical laboratory results (blood chemistry, hematology, coagulation, urinalysis, urine protein, Ig, lymphocyte subsets, and vaccine titers) by scheduled time of evaluation and by treatment group, as well as for the change from baseline. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the last assessment visit.

9.5.3. Pharmacokinetics Analysis

PK analysis and statistical analysis of PK endpoints will be conducted in accordance with the protocol, SAP, and the Daiichi Sankyo Analysis Guidelines. Plasma concentrations of DS-7011a will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate SAP.

9.5.3.1. Pharmacokinetic Parameters

Key PK parameters for DS-7011a collected from the study will be analyzed by non-linear mixed-effect modeling. Results from the analysis will be reported separately. Other parameters may be calculated, as appropriate, upon review of the data. The estimated PK parameters will be calculated for each study participant using the actual sample collection times recorded during the study.

The following PK parameters will be estimated.

PK Parameter	Definition
C_{max}	Maximum plasma concentration

PK Parameter	Definition
C_{min}	Minimum plasma concentration
AUC_t	Area under the plasma concentration-time curve up to time t, calculated by linear trapezoidal method when concentrations are increasing and by logarithmic trapezoidal method when concentrations are decreasing (Linear Up/Log Down Trapezoidal Method)
$t_{½}$	Terminal elimination half-life, where $t_{½} = (ln2)/K_{el}$
CL	Total body clearance, where $CL = Dose/AUC_{inf}$
V_{ss}	Volume of distribution at steady state, where Vss = CL*MRT (IV only), where MRT is the mean residence time of drug in plasma

9.5.3.2. Statistical Analysis of Pharmacokinetic Endpoints

PK parameters (with the exception of T_{max}) will be summarized by treatment arm using the following descriptive statistics: sample size, arithmetic mean, standard deviation (SD), coefficient of variation, minimum, median, maximum, and geometric mean. For T_{max}, the following descriptive statistics will be provided: sample size, minimum, median, and maximum.

Plasma concentrations of DS-7011a will be listed for each subject and time point and summarized with number of subjects, the number of non-missing observations (n), arithmetic mean, SD, coefficient of variation (CV%, calculated by SD/mean × 100), median, minimum, and maximum values for each nominal sampling time. Similarly, plasma concentrations of DS-7011a will be summarized by ADA status.

Mean plasma concentration versus nominal time profiles will be presented for each dose level on both linear and semilogarithmic scales. Individual plasma concentration versus actual time profiles will be grouped by dose level and presented on both linear and semilogarithmic scales. Mean plasma concentrations of DS-7011a will be similarly presented by ADA status.

Additionally, scatterplots of plasma concentrations of DS-7011a and key endpoints (eg, TLR7 GS expression, IFN-Type I GS expression, skin MxA expression, and change in CLASI-A) for this Phase 1b/2 study in subjects with SLE will be presented.

9.5.4. Immunogenicity Analysis

Immunogenicity will be assessed through characterization of the incidence and titer of ADA.

The number and percentage of subjects will be calculated for the presence or absence of ADA, defining subjects who are positive for ADA at least at 1 time point as positive and subjects who are negative for ADA at all time points as negative.

9.5.5. Pharmacodynamic Analysis

Pharmacodynamic measures will be evaluated as exploratory analyses.

The pharmacodynamic endpoints (mechanistic endpoints) will be summarized by treatment group using descriptive statistics. Comparison between treatment groups for the change from baseline to each visit in several endpoints indicative of mechanistic efficacy, including, but not limited to: circulating TLR7 and IFN-Type I GS; skin mRNA coding for proteins under IFN-Type I regulation, such as MxA, and for markers of inflammatory cells, such as CD45; and cytokines, will be summarized.

10. APPENDICES – SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the Investigator's Brochure, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the independent institutional review board (IRB) for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the statistical analysis plan (SAP). Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB.

The investigator should notify the IRB of deviations from the protocol or serious adverse events (SAEs) occurring at the study site and other adverse event (AE) reports in accordance with local procedures.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing the final clinical study report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those investigators who have enrolled and treated at least one subject. However, where an investigator has special knowledge of the field or of the study, the Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

10.1.2. Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;
- Other applicable local regulations.

In addition, the investigator will inform the Sponsor in writing within 24 hours of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance of which the investigator becomes aware.

10.1.3. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, the IRB, and regulatory authorities of such information, and when needed will amend the protocol and/or subject information.

The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB. The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised informed consent form (ICF).

10.1.4. Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The ICF and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed ICF should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

For study sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

10.1.5. Subject Confidentiality

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The identifying features or a subject's facial features during photography will be redacted as needed to ensure that the subject's anonymity is maintained. On the electronic case report forms (eCRFs) or other documents submitted to the Sponsor, subjects should be identified by a unique subject identification as designated by the Sponsor. Documents that are not for submission to the Sponsor (eg, signed ICF) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the independent IRB/ethics committee (EC) direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

10.1.6. Data Integrity and Quality Assurance

10.1.6.1. Monitoring and Inspections

The Sponsor monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at the study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries in the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, standard operating procedures (SOPs), GCP, and applicable regulations to the investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings.

In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

10.1.6.2. Data Collection

An eCRF must be completed for each randomized subject. Screen failure information will be collected at the clinical site in a log. All data collected for randomized subjects during the study will be recorded in the individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF, and any corrections made will be automatically documented via an "audit trail".

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the investigator via the electronic data capture (EDC) system's electronic signature. This signature will indicate that the investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

10.1.6.3. Data Management

Each subject will be identified in the database by a unique subject identifier.

To ensure the quality of clinical data across all subjects and study sites, a contract research organization (CRO) clinical and data management review will be performed on subject data according to specifications developed by the Sponsor. Data will be vetted both electronically by programmed data rules within the application and manually. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness, and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). SAEs in the clinical database will be reconciled with the safety database.

10.1.6.4. Study Documentation and Storage

The investigator will maintain a signature list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to obtain informed consent and make entries and/or corrections on eCRFs will be included on the signature list.

Investigators will maintain a confidential Screening log of all potential study candidates that includes limited information of the subjects, and date and outcome of the screening process.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers upon enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data). In this study, the study eCRF may be used as source documents.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed ICFs, investigator's agreement, clinical supplies receipts, distribution, and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (site specific Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by local laws or regulations or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to provide further instruction.

10.1.6.5. Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (site specific Trial Master File) of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities.

Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent IRB and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records, and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable laws or regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/Institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

10.1.7. Finances

Prior to starting the study, the Principal Investigator and/or Sponsor will sign a clinical study agreement with the CRO. This agreement will include the financial information agreed upon by the parties.

10.1.8. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.9. Publication and Public Disclosure Policy

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

10.1.10. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

The Sponsor must be notified in writing of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) within 24 hours and in accordance with the clinical study agreement between the parties.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study drug, and had at least one administration of study drug, data should be collected for safety purposes.

If applicable, the investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

10.1.11. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

Study termination may also be requested by (a) competent authority/ies.

10.1.12. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative from the Sponsor.

For product complaints, refer to the Pharmacy Manual for instructions and details.

10.2. Appendix 2: Highly Effective Contraception

Methods considered to be highly effective contraception include:[4]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence

10.3. Appendix 3: Central and/or Local Laboratory

The clinical laboratory tests listed in Table 10.1 are to be performed in this study.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry (central laboratory)	albumin albumin globulin (A/G) ratio alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bicarbonate/CO_2 bilirubin (total) bilirubin (direct) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine cholesterol (total)	creatine phosphokinase gamma-glutamyl transaminase (GGT) glucose (non-fasting/fasting) lactate dehydrogenase lipase lipoprotein, high density (HDL) lipoprotein, low density (LDH) magnesium (Mg) phosphorus potassium (K) protein (total) sodium (Na) triglycerides uric acid creatinine clearance
Hematology (central laboratory)	hemoglobin hematocrit platelet count red blood cell (RBC) count white blood cell (WBC) count mean corpuscular hemoglobin mean corpuscular hemoglobin concentration mean corpuscular volume	differential WBC count: basophils eosinophils lymphocytes monocytes neutrophils lymphocyte subsets (CD3-, CD4-, CD8-, CD20-, CD16-, CD56-positive)
Coagulation (central laboratory)	prothrombin time/international normalized ratio	
Urinalysis (abbreviated) (central laboratory)	bilirubin glucose ketone bodies occult blood pH protein	creatinine urobilinogen sediments casts RBC WBC

Test	Analytes	
Virology (local laboratory)	hepatitis B surface antigen (HBsAg) and reactive antibody hepatitis C virus ribonucleic acid (RNA) hepatitis C virus reactive antibody	human immunodeficiency virus 1 and 2 (HIV 1, HIV 2) antigen and reactive antibody SARS-CoV-2 RNA, as detected by COVID-19 molecular test, which is based on polymerase chain reaction (PCR) SARS-CoV-2 antigen, as detected by COVID-19 antigenic test
Pregnancy testing (local laboratory)	serum and urine beta-human chorionic gonadotropin (β-hcg); follicle-stimulating hormone (FSH) for postmenopausal women	
Urine drug screen (local laboratory)	amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, alcohol and opiates	
Ongoing or active tuberculosis (local laboratory)	QuantiFERON-TB Gold or T-SPOT (Elispot) test	
Immunoglobulins (central laboratory)	IgG, IgA, IgM	
Vaccine titers (central laboratory)	diphtheria, tetanus, and pneumococcus viruses	
Pharmacokinetics (central laboratory)	plasma DS-7011a	
Biomarkers	1) circulating TLR7 and IFN-Type I GS (central laboratory) 2) SLE-related autoantibodies (including antinuclear, anti-dsDNA, anti-Sm, and anti-RNP antibodies) (local laboratory at Screening and central laboratory thereafter), 3) complement factors (C3 and C4) (local laboratory at Screening and central laboratory thereafter) 4) cytokines (central laboratory) 5) ESR and CRP (local laboratory) 6) skin mRNA coding for proteins under IFN-Type I regulation, such as MxA, and markers of inflammatory cells, such as CD45 (central laboratory) - Skin Tape Harvesting	
Immunogenicity (central laboratory)	anti-drug antibodies	
Pharmacogenetics (central laboratory)	blood sample for genotyping	

10.4. Appendix 4: General Information – Adverse Events

10.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. 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 medicinal product, whether or not considered related to the medicinal product.

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

10.4.1.1. Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

10.4.1.2. Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

10.4.2. Serious Adverse Event

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

- Results in death.
- Is life-threatening.
  - The term "life-threatening" in the definition of "serious" 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity.
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event.
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3. Difference between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.4.4. Intensity of Adverse Events

The definition used to assess the intensity of AEs:

Mild: Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject's usual function.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function.

10.4.5. Causality Assessment

The investigator should assess causal relationship between an AE and the study drug based on his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

  Or

  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study (or its chemical group) or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.4.6. Action Taken Regarding Study Drug

- Study Drug Not Given: The AE occurred before study drug administration.
- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.

- Drug Interrupted: The study drug was temporarily stopped.
- Dose Increased: The dosage of study drug was increased.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

10.4.7. Other Action Taken for Event

- None.
  - No treatment is required.
- Medication is required.
  - Prescription and/or over-the-counter medication is required to treat the AE.
- Hospitalization or prolongation of hospitalization is required.
  - Hospitalization is required or prolonged because of the AE, whether or not medication is required.
- Other.

10.4.8. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no sequelae observed.
- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered.
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

10.5. Appendix 5: Allowable Time Windows for Vital Signs, ECGs, and PK/PD Blood Draws

Table 10.2: Allowable Time Windows for Vital Signs, ECGs, and PK/PD Blood Draws

Vital Signs/ECG Procedures (in order of collection)	Allowable Time Window	
	Screening and Day 1	**Day 1 and up to Follow-up Visit/End of Study Visit**
Vital signs relative to drug administration should be taken:	No more than 5 minutes before the blood collection for safety measurements (inclusive of at least 5 minutes of supine rest with 5 additional minutes allowed).	Vital signs should be taken no more than 10 minutes before PK/PD blood draws (inclusive of at least 5 minutes of supine rest with 1 additional minute allowed). The time between the completion of vital signs and the blood draw may be expanded to 20 minutes when an ECG is scheduled to precede the PK/PD blood draw.
Triplicate 12-lead ECGs should be taken:	No more than 15 minutes before the blood collection for safety measurements (inclusive of at least 5 minutes of quiet rest in the supine position). Allow approximately 2 minutes between triplicate ECGs with 1 additional minute allowed between each of the triplicate ECGs.	When a PK/PD blood collection is scheduled concomitantly with an ECG, then ECG should be taken no more than 15 minutes before the PK/PD blood draws (inclusive of the at least 5 minutes of supine rest with 1 additional minute allowed).

PK/PD Procedures (in order of collection)	Allowable Time Window
PK/PD blood samples	
Days 1, 29, and 57: predose	15 minutes
Day 2 (24 hours after treatment administration)	±60 minutes
Day 8 (1 week after treatment administration)	±1 day
Days 1, 29, and 57: end of infusion	+5 minutes
Days 85, 113, and 169	±3 days
TLR7 and IFN-Type I drawn predose on Day 1 with PD blood sample, on Days 2, 8, 29, 57, 85, and 113	Not applicable

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_t	area under the plasma concentration-time curve from time zero to time t
AUC_{inf}	area under the plasma concentration time curve up to infinity
BMI	body mass index
CD	cluster of differentiation
CDC	Center for Disease Control and Prevention
CFR	Code of Federal Regulations
CGI-C	Clinician's Global Impression of Change
CL	apparent total body clearance of the drug from plasma
CLA-IGA	Cutaneous Lupus Activity Investigator's Global Assessment
CLASI-A	Cutaneous Lupus Area and Severity Index Activity
CLE	cutaneous lupus erythematosus
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CV%	coefficient of variation
DPI	Drug Preparation Instructions
dsDNA	double-stranded deoxyribonucleic acid
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate; CKD-EPI mL/min/1.73 m^2=142*[(min(C/0.7;1))exp-0.241]*[(max(C/0.7;1))exp-1.200]*0.9938exp25*A
EIU	Exposure In Utero
EOS	End of Study (Visit)
EOT	End of Treatment

Abbreviation	Definition
ESR	erythrocyte sedimentation rate
ET	early termination
EU	European Union
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GS	gene signature
HbsAg	hepatitis B surface antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	health insurance portability and accountability act
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
Ig	immunoglobulin
IL	interleukin
IL-6	interleukin-6; a diagnostic test for inflammation and various illnesses
IFN	interferon
IM	intramuscular
IRB	institutional review board
ITT	Intent-to-Treat
IV	intravenous
K_2-EDTA	dipotassium ethylenediaminetetraacetate
LALA	Leu234Ala, Leu235 Ala
LLDAS	low lupus disease activity status
LN	lupus nephritis
LTBI	latent TB infection
Mab	monoclonal antibody
MCS	mental component score

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMF	mycophenolate mofetil
MPS	mycophenolic acid sodium
MxA	myxovirus resistance protein
RNA	ribonucleic acid
mRNA	messenger ribonucleic acid
ms	milliseconds
NOAEL	no-observed-adverse-effect-level
NRS	numeric rating scale
OTC	over-the-counter
PCR	polymerase chain reaction
PCS	physical component score
PD	pharmacodynamic
pDC	plasmacytoid dendritic cell
PGA-SLE	Physician's Global Assessment Systemic Lupus Erythematosus
PGI-C	Patient's Global Impression of Change
PI	Principal Investigator
PK	pharmacokinetic
PRO	Patient Reported Outcome
PT	preferred term
q4w	every 4 weeks
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RNA	ribonucleic acid
RNP	ribonucleoprotein
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SD	standard deviation
SF-36	Short Form 36
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index – 2000
SLE	systemic lupus erythematosus
Sm	Smith
SOC	system organ class
SOC	standard of care

Abbreviation	Definition
SoE	Schedule of Events
SOP	standard operating procedures
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TLR7	toll-like receptor 7 (pattern recognition receptors)
T_{max}	time to reach maximum plasma concentration
$t_{½}$	elimination half-life
ULN	upper limit of normal
US	United States
VAS	visual analog scale
V_{ss}	apparent volume of distribution at steady state
WHO	World Health Organization

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