CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Blinded, Placebo-Controlled, Phase 1b Study of GS-5718 in Subjects with Cutaneous Lupus Erythematosus (CLE)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	153056 2021-000204-38 NCT04809623
Indication:	Cutaneous Lupus Erythematosus (CLE)
Protocol ID:	GS-US-497-5888
Gilead Medical Monitor:	PPI
Protocol Version/Date:	Original: 11 February 2021 Amendment 1: 01 July 2021

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) application regulations (21 Code of Federal Regulations Part 312); however, sites located in the European Economic Area, the United Kingdom and Switzerland are not included under the IND application and are considered non-IND sites.

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Randomized, Blinded, Placebo Controlled, Phase 1b Study of GS-5718 in Subjects with Cutaneous Lupus Erythematosus (CLE)
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	153056 2021-000204-38 NCT04809623
Study Centers Planned:	Approximately 12 centers worldwide
Objectives:	The primary objective of this study is as follows: • To evaluate the safety and tolerability of GS-5718 in subjects with cutaneous lupus erythematosus (CLE) with or without systemic lupus erythematosus (SLE) The secondary objective of this study is as follows: • To characterize the pharmacokinetics (PK) of GS-5718 in subjects with CLE with or without SLE The exploratory objectives of this study are as follows: CCI

Study Design:	This is a Phase 1b, multicenter, randomized, blinded, placebo controlled, 4-week study, evaluating the safety and tolerability of GS-5718 in subjects with CLE. Eligible subjects, continuing their standard of care therapy, will be randomized in a 2:1 blinded fashion to 1 of 2 arms. The first being 115 mg GS-5718 in addition to standard of care (approximately 8 subjects). The second being placebo in addition to standard of care (approximately 4 subjects). 
Number of Subjects Planned:	Approximately 12 subjects
Target Population:	Adult CLE subjects with active acute CLE (ACLE) or subacute CLE (SCLE) with or without SLE
Duration of Treatment:	Up to 4 Weeks

Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria**: Subjects must meet **all** of the following inclusion criteria to be eligible for participation in this study. Documentation of select criteria (*) **must** be submitted to the study sponsor for review and confirmation of subject eligibility prior to randomization: 1) Are ≥ 18 and ≤ 75 years of age at the time of the initial informed consent 2) Either fulfill EULAR/ACR 2019 classification criteria for SLE* or have biopsy-proven CLE* 3) Must have active ACLE/SCLE* {Klein 2010}; subjects with mixed skin presentations of lupus skin disease (including discoid lupus erythematosus [DLE]) are allowed to enter 4) CLASI activity score[a] of ≥ 6 during screening* and Day 1 [a]Excluding the alopecia component (ie, points for recent hair loss and alopecia do not contribute to the qualifying CLASI-A score) 5) Presence of at least 1 representative lupus skin lesion amenable to punch biopsy and subject willingness to undergo skin biopsy at 2 time points 6) Subjects using protocol-permitted nonbiologic immunosuppressive/immunomodulatory agents for the treatment of CLE/SLE (eg, antimalarials, methotrexate [MTX], or other conventional synthetic disease-modifying antirheumatic drugs [csDMARDs]) must maintain stable dose(s) for ≥ 60 days prior to randomization through Week 4 of the study (see Section 5.4.1 for details) 7) Subjects using protocol-permitted class V-VII topical corticosteroids or oral prednisone ≤ 15 mg/day (or equivalent) must maintain stable dose(s) for ≥ 28 days prior to randomization through Week 4 of the study (see Section 5.4.1) 8) Must have prior intolerance or inadequate response at any time (per investigator judgment) to at least one of the following medications for the treatment of SLE/CLE: a) Topical corticosteroids or topical calcineurin inhibitors b) Oral corticosteroids

	c) A csDMARD, including, but not limited to: chloroquine, quinacrine, hydroxychloroquine, azathioprine, mycophenolate mofetil (MMF), leflunomide, dapsone, or MTX 9) Must have a body mass index (BMI) between 18 and 35 kg/m^2 10) Subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4 11) Able and willing to sign the informed consent form(s), as approved by the institutional review board (IRB)/ethics committee (EC); written, signed, and dated consent must be provided before initiating any screening evaluation **Exclusion Criteria:** Subjects who meet **any** of the following exclusion criteria are not eligible to be enrolled in this study. Consultation with the sponsor medical monitor on select criteria (*) **must** take place prior to randomization: 1) Present with only CCLE skin lesion(s) during screening and Day 1 2) Have highly active SLE (including but not limited to lupus nephritis, neuropsychiatric SLE, vasculitis) that could put the subject at risk per the investigator's judgement 3) Presence of active skin conditions other than cutaneous lupus that may interfere with assessing lupus-specific skin lesion(s) (eg, lupus-nonspecific skin disease, psoriasis, drug-induced lupus) 4) Meet any of the following prior/concomitant medication use criteria relative to the date of randomization: a) Prior use of an interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor at any time b) Exposure to any approved or investigational biologic disease-modifying antirheumatic drug (bDMARD) within 180 days c) Exposure to cyclophosphamide within 60 days d) Exposure to a JAK inhibitor (eg, tofacitinib, baricitinib, upadacitinib) within 60 days e) Use of oral prednisone > 15 mg/day (or equivalent) within 28 days f) Use of Class I-IV topical corticosteroids within 28 days g) Use of topical calcineurin inhibitors within 28 days

	h) Use of injectable corticosteroids within 28 days i) Use of strong CYP3A inhibitors or inducers within 14 days (see Section 5.4.2) 5) Meet any of the following infection criteria: a) Any active infection that is clinically significant (per investigator judgment); baseline SARS-CoV-2 screening should follow local guidelines/institutional practice* b) Positive QuantiFERON at screening; subjects with a positive test are excluded from the study and should be worked up as per local standard of care. Note: QuantiFERON tests with inconclusive results may be repeated one time. If the repeat result is also inconclusive, the subject must be excluded from the study. Note: Subjects with prior latent tuberculosis (TB) who have been treated with a full course of prophylaxis as per local guidelines are eligible. Appropriate documentation of prior treatment is required, a QuantiFERON test is not required.* c) An infection requiring oral anti-infective medication(s) within 28 days prior to randomization d) An infection requiring hospitalization or treatment with intravenous anti-infective medication(s) within 60 days prior to randomization e) Evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies at screening f) Active or chronic or past hepatitis B virus (HBV) infection, as evidenced by positivity for hepatitis B surface antigen (HBsAg) or HBV core antibody (regardless of HBV viral load) at screening g) Evidence of active hepatitis C virus (HCV) infection. Subjects with positive HCV antibody (Ab) at screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA viral load (VL) at screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require a retest at Week 4. h) History of previous life threatening or opportunistic infection 6) Meet any of the following central laboratory confirmed abnormalities at screening:

	a) Hemoglobin < 10.0 g/dL (International System of Units [SI]: < 100.0 g/L) b) Absolute neutrophil count (ANC) < lower limit of normal (LLN) c) Lymphocyte count < 800 cells/mm^3 (SI: < 0.8×10^9 cells/L) d) Platelet count < LLN e) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5 × upper limit of normal (ULN) f) Total bilirubin > 1.0 × ULN g) Estimated CL_{cr} < LLN based on the Cockcroft-Gault equation 7) Subjects who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study or for 14 days after their last dose of study drug 8) Any condition or circumstances which may make a subject unlikely or unable to complete the study or comply with study procedures and requirements (per investigator judgment) 9) Major surgery (requiring regional block or general anesthesia) within 28 days prior to randomization or planned during the subject's study participation 10) Known hypersensitivity to the study drug, its metabolites, or formulation excipients 11) Subject has presence or sequelae of gastrointestinal, liver, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs; this may include a history of weight loss surgery 12) Subject concurrently participates or participated in a drug or drug/device investigational research study within 28 days or 5 half-lives of the investigational product, whichever is longer, prior to randomization 13) Subject has a history of malignancy within the past 5 years prior to screening with the exception of excised and curatively treated nonmetastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of cervix which is considered cured with minimal risk of recurrence 14) History of any lymphoproliferative disease 15) History of organ or bone marrow transplant

	16) Receipt of any live/attenuated vaccine within 28 days prior to randomization or planned during the study or for 28 days after the subject's last dose of study drug 17) Any screening electrocardiogram (ECG) finding deemed clinically significant per investigator judgement
Study Procedures/ Frequency:	Study visits for all subjects will occur according to the schedule below; details available in Appendix 3. • Screening: within 28 days prior to Day 1 • Study Treatment Period: Visits at Day 1 and at Weeks 1, 2, and 4 (or early termination, as applicable) • Follow Up: 28 days after the last dose of study drug
Test Product, Dose, and Mode of Administration:	115 mg GS-5718, oral, once daily
Reference Therapy, Dose, and Mode of Administration:	Placebo to match GS-5718, oral, once daily
Criteria for Evaluation:	
Safety:	Safety will be assessed through adverse event (AE) reporting, clinical laboratory tests, vital sign assessments, physical examinations (complete and symptom-driven), and ECGs at various time points during the study.
Efficacy:	The efficacy endpoints of this study are as follows: • Percent change from baseline in CLASI-A score • Absolute change from baseline in CLASI-A score • Proportion of subjects with a $\geq$ 50% reduction in CLASI-A score relative to baseline • Proportion of subjects with a $\geq$ 4-point reduction in CLASI-A score relative to baseline • Change from baseline in SLEDAI-2K total score and domains (subjects with SLE only) • Change from baseline in Subject's Global Assessment (SGA) of CLE activity using a visual analog scale (VAS) • Change from baseline in Physician's Global Assessment (PGA) of CLE activity using a VAS

Biomarkers:	Blood and urine samples for assessment of markers of inflammation, immune status, pathway activation, and type I interferon signaling may be analyzed. Skin biopsy samples for assessment of markers of inflammation, immune status, pathway activation, and type I interferon signaling may be analyzed. CCI [redacted]
Pharmacokinetics:	For all subjects, intensive PK sampling will be performed at the Week 4 visit. PK blood samples will be collected at predose, and at 0.5, 1, 2, 3, 4, and 6 hours postdose. The predose concentration will be utilized to establish the full 24-hour PK profile at steady-state. Plasma concentrations of GS-5718 will be analyzed and PK will be evaluated. The PK of other metabolites may be explored, as applicable.
Statistical Methods:	The sample size was chosen based on practical considerations. Safety analyses will be based on the Safety Analysis Set, which includes all subjects who received at least 1 dose of study drug. The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least 1 dose of study drug. Continuous endpoints will be summarized descriptively (n, mean, SD, median, first quartile [Q1], third quartile [Q3], minimum, maximum) by treatment arm and visit. Categorical endpoints will be presented in frequency summaries. No formal hypothesis testing will be performed.

This study will be conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

%CV	percentage coefficient of variation
Ab	antibody
ACLE	acute cutaneous lupus erythematosus
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{tau}	area under the concentration versus time curve over the dosing interval
AUROC	area under the receiver operating characteristic curve
bDMARD	biologic disease-modifying antirheumatic drug
BCRP	breast cancer resistance protein
BMI	body mass index
CI	confidence interval
CK	creatine kinase
CL_{cr}	creatinine clearance
CLASI	cutaneous lupus erythematosus disease area and severity index
CCLE	chronic cutaneous lupus erythematosus
CCG	CRF completion guidelines
CLE	cutaneous lupus erythematosus
C_{max}	maximum observed concentration of drug
C_{last}	last observed quantifiable plasma/serum concentration of the drug
CRF	case report form
csDMARD	conventional synthetic disease-modifying antirheumatic drug
C_{tau}	observed drug concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
DAMPs	damage-associated molecular patterns
DLE	discoid lupus erythematosus
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration

FFPE	formalin-fixed paraffin-embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
FU	follow up
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IFN	interferon
IL	interleukin
IL-1R	interleukin-1 receptor
IND	investigational new drug
INR	international normalized ratio
IRAK4	interleukin-1 receptor-associated kinase 4
IRB	institutional review board
IRT	interactive response technology
JAK	janus kinase
LE	lupus erythematosus
LLOQ	lower limit of quantitation
MAD	multiple ascending dose
MMF	mycophenolate mofetil
MTX	methotrexate
NOAEL	no observed adverse effect level
NZB/W	New Zealand Black/New Zealand White
PAMPs	pathogen-associated molecular patterns
PAS	periodic acid-Schiff
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamics
pDCs	plasmacytoid dendritic cells
PGA	Physician's Global Assessment
PI	principal investigator

PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PT	preferred term
PTM	placebo to match
Q1	first quartile
Q3	third quartile
QD	once daily
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
QTcF	QT interval corrected for heart rate using the Fridericia formula
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLE	subacute cutaneous lupus erythematosus
SD	standard deviation
SDV	source data verification
SGA	Subject's Global Assessment
SI	International System of Units
SLE	systemic lupus erythematosus
SLEDAI-2K	systemic lupus erythematosus disease activity index 2000
SOC	system organ class
SOP	standard operating procedure
SSRs	special situation reports
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
TB	tuberculosis
TEAE	treatment-emergent adverse event
TLR	toll-like receptor
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VAS	visual analog scale
VL	viral load

1. INTRODUCTION

1.1. Background

Lupus erythematosus (LE) is a multifactorial, heterogeneous autoimmune disease with genetic and environmental factors implicated in its pathogenesis. LE has broad clinical manifestations, from cutaneous LE (CLE) to systemic LE (SLE), which may involve multiple organ systems {Chen 2019, Ronnblom 2019}. Further, CLE may present in isolation or as a clinical manifestation in the setting of SLE {Kuhn 2008}.

CLE is a chronic autoimmune disease with clinical and serological heterogeneity. Although there are very few population-based studies of CLE prevalence, published data remains relatively consistent with a global incidence rate of 4.3 cases per 100,000 {Durosaro 2009}. Untreated CLE lesions can cause irreversible scarring and/or disfigurement, however early treatment has been associated with improved clinical outcomes {Okon 2013}. Despite the prevalence of CLE and importance of treatment, there are no Food and Drug Administration (FDA) approved therapeutic agents. CLE is an area of high unmet need due to incidence and prevalence of this disease and the absence of an FDA approved therapeutic agent.

Cutaneous LE skin lesions present with varied clinical presentation, morphology and histopathology, and include the following types, acute CLE (ACLE), subacute CLE (SCLE), and chronic CLE (CCLE); CCLE is categorized further into several subtypes of which discoid lupus erythematosus (DLE) is the most common {Chen 2019}. ACLE frequently appears as non-scarring, localized malar erythema or less often, as a generalized rash and is commonly associated with SLE. SCLE, the second most common subtype presents as annular or papulosquamous lesions, often in a photodistributed pattern. It is estimated that approximately half of all patients that present with this form of CLE have concurrent SLE {Szczech 2016}. Discoid lupus erythematosus (DLE), the most common CCLE subtype, presents as erythematous scaling lesions with follicular plugging or hyperkeratosis that often progresses to atrophic scarring and dyspigmentation. About 6-28% of patients with CCLE cases also have SLE {Klein 2010, Little 2020}.

The pathophysiology of CLE represents the complex interplay between environmental precipitating factors, immunological aberrancies, and increased risk due to genetic predisposition, all of which contribute to the development of lupus and continued propagation of disease activity. There are 3 families of interferons, type I interferons (IFN-I), type II interferons (IFN-II), and type III interferons (IFN-III), and these cytokines have been implicated to varying degrees in disease activity. IFN-I are considered to be central in lupus pathogenesis. The largest interferon family, IFN-I induces myeloid dendritic cell maturation and activation, B-cell differentiation and subsequent antibody production, and T cell priming {Jego 2003, Longhi 2009, Psarras 2017}. In addition to these pleiotropic effects linking innate and adaptive immune driven responses, the type I IFN gene signature has also been observed in up to 75% of adult SLE patients {Ronnblom 2019}. This upregulation of IFN-I regulated genes has also been reported in CLE patients, including those without concomitant systemic disease {Braunstein 2012, Sarkar 2018}.

In an attempt to improve disfiguring skin lesions, minimize scarring, and/or modulate immune dysregulation, standard of care for CLE consists of agents repurposed from approved use for the treatment of other dermatologic conditions and SLE. Alongside sun avoidance/protection and smoking cessation, pharmacological standard of care includes topical agents, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic disease-modifying antirheumatic drugs (bDMARDs) targeting immune cell subsets or direct cytokine blockade. However, from the topical preparations of corticosteroids and calcineurin inhibitors to oral antimalarials, methotrexate (MTX), azathioprine, mycophenolate mofetil (MMF), and sulfasalazine to bDMARDs, such as rituximab or belimumab, efficacy and interpatient tolerability remains highly variable with the currently available treatment armamentarium.

More recently, therapies targeting intracellular signaling pathways and inflammatory mediators involved in lupus disease activity have emerged. Although investigational, these include small molecule inhibitors of janus kinase (JAK) enzyme pathways, key contributors to inflammatory cytokine signaling, inhibitors of phosphodiesterase-4, catalysts for the degradation of cyclic adenosine monophosphate, and a monoclonal antibody directed toward blood dendritic cell antigen 2, a receptor selectively expressed on plasmacytoid dendritic cells (pDCs).

GS-5718 employs the intracellular signaling directed mechanism by selectively inhibiting interleukin-1 receptor-associated kinase 4 (IRAK4). IRAK4, a serine-threonine kinase expressed in lymphocytes and innate immune cells, is a critical mediator of the toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling pathways and resulting inflammatory responses. Such signaling through TLRs and IL-1R drives immune cell activation and chronic inflammation, characteristic features of various inflammatory and autoimmune diseases, including LE. GS-5718, a potent and selective inhibitor of IRAK4 activity, thus inhibits inflammatory signaling and proinflammatory cytokine and IFN-I production. This activity represents an opportunity to modulate signaling pathways implicated in lupus disease activity.

1.2. GS-5718

1.2.1. General Information

For further information on GS-5718, refer to the current Investigator's Brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

GS-5718 is a potent and selective inhibitor of IRAK4. The half-maximal inhibitory concentration (IC_{50}) value for GS-5718 inhibition of IRAK4 activity in a time-resolved fluorescence resonance energy transfer-based method was 0.52 nM (PC-451-2135). The selectivity of GS-5718 against 468 human kinases using $KINOME_{scan}$™ (ScanMAX, DiscoveRx, San Diego, CA) was evaluated and found to be 176 times more selective against IRAK1 and > 500 times more selective against all other kinases.

GS-5718 has been evaluated for potency and efficacy using in vitro cellular assays and in vivo models of LE.

In vitro, GS-5718 inhibited TLR7-stimulated expression of a 4 gene type I interferon-stimulated gene panel in human peripheral blood mononuclear cells (PBMCs; PC-451-2150). In pDC, GS-5718 dose-dependently inhibited tumor necrosis factor α (TNF-α) and/or IFN-α produced by stimulation with SLE patient sera in the presence and absence of ex vivo generated ribonucleoprotein or double stranded DNA immune complexes (PC-451-2149).

In the New Zealand Black/New Zealand White (NZB/W) murine model of spontaneous lupus, GS-5718 improved survival and clinical pathology measures (PC-451-2134). These include gross body weight, spleen weight, proteinuria score, titers of autoantibodies to nuclear antigens, and serum chemistry levels (albumin, albumin/globulin ratio, total cholesterol, and amylase). Histologically, GS-5718 improved kidney glomerulus diameter measures, glomerulus score, crescent score, protein cast score, vasculitis score, summed score, PAS score, and spleen lymphoid aggregate diameter measures. GS-5718 changed markers of disease activity such as serum cytokine concentrations, kidney gene expression and splenic immune cell subset frequencies,-toward predisease levels.

The toxicity profile of GS-5718 was assessed in safety pharmacology and repeat dose toxicity studies in rats and monkeys, and in a battery of genotoxicity studies. GS-5718 was nongenotoxic in the studies evaluated and had no effects on the central nervous and respiratory systems of rats. GS-5718-related mild QT prolongation was observed at the high dose level in the cardiovascular safety pharmacology study in monkeys; however, given the small magnitude of change and exposure margin at this dose level (6-fold over the projected steady state free C_{max} at the 115 mg dose in humans), the risk for QT effects at clinically relevant exposures is considered low. There were no GS-5718-related adverse effects in 1-month rat and monkey repeat dose toxicity studies up to the highest dose levels tested. Steady-state AUC exposure margins at the no observed adverse effect level (NOAELs) (relative to the projected steady state AUC at the 115 mg dose in humans) were 11- and 2-fold, in rats and monkeys, respectively. Overall, the nonclinical program has sufficiently characterized the toxicity profile of GS-5718 and supports this study.

1.2.3. Clinical Studies of GS-5718

GS-US-451-5399: This is an ongoing, first-in-human (FIH), Phase 1 study in healthy volunteers to evaluate the safety, tolerability, and pharmacokinetics (PK) of GS-5718 and the effect of food and acid-reducing agents on GS-5718 PK.

1.2.3.1. Clinical Safety

As of November 20, 2020, GS-5718 has been administered to 62 healthy subjects in the FIH study.

GS-5718 in tablet form has been administered to healthy male and female subjects in single ascending doses (up to 150 mg; Part A: Cohorts 1-3 of GS-US-451-5399) and multiple ascending oral doses (up to 150 mg) for 10 days (Part C: Cohorts 6-8 of GS-US-451-5399). Part B of GS-US-451-5399 (Cohort 5) examined food effect and the potential for drug interactions with GS-5718 and a representative acid-reducing agent (omeprazole) with 50 mg single doses of GS-5718. Due to the ongoing nature of the study, it remains blinded to study subjects and the investigator but is unblinded to limited team members of the study sponsor.

GS-5718 has been well tolerated thus far during this study. No deaths, serious treatment-emergent adverse events (TEAEs), or TEAEs leading to study drug discontinuation were reported during the 6 months of the study. There have been no clinically relevant electrocardiogram (ECG) or vital sign abnormalities. When dosed with a single dose of GS-5718 at 150 mg, 1 subject experienced 2 TEAEs (headache and dyspepsia). Both events were Grade 1 in severity. When dosed with multiple doses of GS-5718 at 150 mg daily, 1 subject experienced 2 TEAEs (constipation and maculo-papular rash). The maculo-papular rash was related to the electrodes used for the ECG. Both events were Grade 1 in severity. All TEAEs were self-limited. There were no Grade 3 or 4 TEAEs in any cohorts of this study (Table 1-1).

All treatment emergent laboratory abnormalities are summarized in Table 1-2. There were no Grade 3 or 4 treatment emergent laboratory abnormalities associated with single or multiple administrations of the 150 mg dose. There have been 4 treatment emergent laboratory abnormalities of Grade 3 or higher in any cohort. One subject in Cohort 2 (50 mg single dose) experienced a Grade 3 elevation of creatine kinase (CK) following discharge from the clinic (follow-up visit on Day 12). The subject was asymptomatic. The investigator attributed the elevated CK levels to strenuous exercise reported by the subject. No specific intervention was required. A recheck of CK levels at an unscheduled visit 3 days later (Day 15) showed a trend toward normalization. One subject in Part B of the study (Cohort 5) experienced Grade 3 neutropenia on Day 11 and Day 19. This subject was also noted to have low-normal absolute neutrophil counts (ANC) prior to dosing both at screening and admission (1.67×10^9 cells/mL and 2.02×10^9 cells/L respectively). Two subjects in Cohort 5 experienced Grade 3 CK elevations after discharge on follow-up (Day 30), which the investigator attributed to activity. No specific interventions were required and a recheck of CK levels on unscheduled visits showed a trend toward normalization in both cases.

One subject in Cohort 7 met protocol specified stopping criteria based on a plasma thiocyanate level > 200 µmol/L. The results from a repeat analysis of the sample as well as additional unscheduled collections were all below the protocol-specified stopping criteria limit of 200 µmol/L. There were 2 additional subjects with a plasma thiocyanate level > 200 µmol/L that were detected following administration of study drug. This occurred in 1 subject in Cohort 6 on Day 9 (GS-5718 15 mg or PBO) and in another subject in Cohort 8 on Day 1 (GS-5718 150 mg or PBO). Retesting of the same sample (subject in Cohort 6) or from a backup sample collected at the same time (subject in Cohort 8) showed a plasma retest thiocyanate level below 200 µmol/L. Neither subject discontinued study drug; available data from this study remains blinded.

Collectively, results from the GS-US-451-5399 healthy volunteer study indicates that GS-5718 is generally well tolerated at the doses explored to date.

Table 1-1. GS-US-451-5399 Treatment-Emergent Adverse Events: Overall Summary

Number (%) of Subjects with Any	Cohort 1 15 mg SAD (N=10)	Cohort 2 50 mg SAD (N=10)	Cohort 3 150 mg SAD (N=10)	Cohort 5 50 mg Food/PPI (N=14)	Cohort 6 15 mg MAD (N=10)	Cohort 7 50 mg MAD (N=10)	Cohort 8 150 mg MAD (N=10)	Total (N=74)
TEAE	1 (10.0%)	3 (30.0%)	1 (10.0%)	6 (42.9%)	4 (40.0%)	3 (30.0%)	1 (10.0%)	19 (25.7%)
TEAE with Grade 3 or Higher	0	0	0	0	0	0	0	0
TEAE with Grade 2 or Higher	0	0	0	1 (7.1%)	0	0	0	1 (1.4%)
TEAE Related to Study Drug	0	0	0	4 (28.6%)	0	2 (20.0%)	0	6 (8.1%)
TEAE Related to Study Drug with Grade 3 or Higher	0	0	0	0	0	0	0	0
TEAE Related to Study Drug with Grade 2 or Higher	0	0	0	1 (7.1%)	0	0	0	1 (1.4%)
TE Serious AE	0	0	0	0	0	0	0	0
TE Serious AE Related to Study Drug	0	0	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study Drug	0	0	0	0	0	0	0	0
TEAE Leading to Premature Discontinuation of Study	0	0	0	0	0	0	0	0
All Deaths	0	0	0	0	0	0	0	0
TEAE Leading to Death	0	0	0	0	0	0	0	0

AE = adverse event; MAD = multiple ascending dose, PPI = proton pump inhibitor; SAD = single ascending dose; TEAE = treatment-emergent adverse event

Table 1-2. GS-US-451-5399 Treatment-Emergent Laboratory Abnormalities: Overall Summary

Maximum Postbaseline Toxicity Grade	Cohort 1 15 mg SAD (N=10)	Cohort 2 50 mg SAD (N=10)	Cohort 3 150 mg SAD (N=10)	Cohort 5 50 mg Food/PPI (N=14)	Cohort 6 15 mg MAD (N=10)	Cohort 7 50 mg MAD (N=10)	Cohort 8 150 mg MAD (N=10)	Total (N=74)
Subjects with Postbaseline Value	10	10	10	14	10	9	10	73
Grade 3 or 4	0	1 (10.0%)	0	3 (21.4%)	0	0	0	4 (5.5%)
Grade 3	0	1 (10.0%)	0	3 (21.4%)	0	0	0	4 (5.5%)
Grade 4	0	0	0	0	0	0	0	0
Neutrophils (Decreased)								
Grade 3 or 4	0	0	0	1 (7.1%)	0	0	0	1 (1.4%)
Grade 3	0	0	0	1 (7.1%)	0	0	0	1 (1.4%)
Grade 4	0	0	0	0	0	0	0	0
Creatine Kinase (Increased)								
Grade 3 or 4	0	1 (10.0%)	0	2 (14.3%)	0	0	0	3 (4.1%)
Grade 3	0	1 (10.0%)	0	2 (14.3%)	0	0	0	3 (4.1%)
Grade 4	0	0	0	0	0	0	0	0

MAD = multiple ascending dose, PPI = proton pump inhibitor; SAD = single ascending dose;

1.2.3.2. Pharmacokinetic Profile

Following single-dose administration of 15, 50, or 150 mg GS-5718 under fasting conditions, GS-5718 was absorbed rapidly with the maximum plasma concentration (C_{max}) occurring between 0.75 to 2 hours after dosing (median T_{max}). Following multiple-dose administration of 15, 50, or 150 mg once daily under fed conditions (standard breakfast), the median T_{max} ranged from 3 to 4 hours. Across the dose levels evaluated, GS-5718 exhibited a median $t_{1/2}$ of 25 to 33 hours following single and multiple doses. GS-5718 exposure (AUC and C_{max}) increased in an approximately dose proportional manner across the range of 15 mg to 150 mg. Consistent with the elimination half-life, GS-5718 exposure (AUC and C_{max}) accumulated following multiple, once-daily doses (1.6 to 2.4-fold for AUC and 1.5 to 2.5-fold for C_{max}). Steady-state appears to have been reached by Day 5 to 7.

Administration of GS-5718 with food (high-fat/high-calorie meal) resulted in delayed GS-5718 T_{max} (from 1 to 4 hours) with an approximately 18% reduction in mean C_{max} and no change in mean AUC. Omeprazole (with a 5-day pretreatment at 40 mg once daily dose) reduced mean C_{max} and AUC of GS-5718 by approximately 42% and 22%, respectively, with no change in the T_{max} of GS-5718.

1.2.3.3. Pharmacodynamic Profile

Pharmacodynamics were assessed measuring changes in ex vivo stimulated (TLR7/8, R848) secretion of TNF-α. Several cytokines were evaluated and TNF-α was chosen as primary PD parameter. Preliminary results in changes in TNF-α levels, as measured by the primary PD parameters (AUC_{0-24}, and % Δ $T_{max\%\Delta}$) were determined to be sensitive measures of changes in TNF-α after single dose administration of placebo, 15, 50, or 150 mg GS-5718 under fasting conditions and 50 mg under fed conditions in healthy subjects (Table 1-3). GS-5718 significantly decreased TNF-α AUC_{0-24} and inhibited TNF-α secretion measured as percentage change of TNF-α levels from baseline to 1 hour and to 24-hours postdose compared to placebo. Administration of 50 mg GS-5718 with food did not result in a significant prolonged time to reach % Δ T_{max} compared to administration of 50 mg GS-5718 under fasting conditions (Table 1-3).

Table 1-3. GS-US-451-5399 Preliminary Pharmacodynamic Parameters (inhibition of ex vivo [TLR7/8, R848] stimulated TNF-α) Following Single-Dose Administration of Placebo, or GS-5718 Under Fasting or Fed Conditions in Healthy Subjects

		Placebo	GS-5718 Single Dose (SAD, FE)			
		Fasted	15 mg Fasted	50 mg Fasted	50 mg Fed	150 mg Fasted
TNF-α	$AUC_{0-24hrs}$ geometric mean (% CV)	16392 (29.5)	2127 (39.4)***	757 (62.0)***	828 (62.3)***	614 (70.9)***
	$T_{max\ \%\Delta}$	3.46 (129)	1.30 (82.4)*	4.15 (206)	3.75 (129)	5.62 (281)
	% Δ $T_{max\ \%\Delta}$	-12.8 (-24.8, -0.816)	-97.2 (-98.0, -96.4)***	-97.3 (-98.2, -96.4)***	-97.9 (-99.0, -96.7)***	-98.1 (-100.1, -96.1)***
	% Δ at 1-hour postdose	19.1 (-3.65, 41.9)	-96.7 (-98.0, -95.5)***	-95.9 (-97.5, -94.3)***	-88.1 (-97.2, -79.0)***	-96.7 (-100.2, -93.3)***
	% Δ at 24-hours postdose	13.5 (-13.1, 40.1)	-84.9 (-90.5, -79.4)***	-95.0 (-96.3, -93.7)***	-96.2 (-97.4, -95.0)***	-96.1 (-99.7, -92.5)***

FE = food effect; SAD = single ascending dose; TNF = tumor necrosis factor
$AUC_{(0-24hrs)}$ and T_{max} are reported as geometric mean, % CV
% Δ $T_{max\ \%\Delta}$, % Δ at 1-hour postdose, % Δ at 24-hours postdose are reported as mean, 95% CI
$AUC_{(0-24hrs)}$ is the average AUC of the normalized values from baseline to 24-hours postdose.
$T_{max\ \%\Delta}$ is the time in hours postdose of maximum percent change from baseline value.
% Δ $T_{max\ \%\Delta}$ is the maximum percentage change from baseline value.
*Indicates *P*-Value < 0.05 from Wilcoxon rank-sum test for the treatment when compared to placebo. **Indicates *P*-value < 0.01, ***Indicates *P*-value < 0.001

1.3. Rationale for the Study

GS-5718 is an inhibitor of IRAK4, a serine/threonine kinase at the top of the signaling cascade for TLR and IL-1R mediated inflammatory responses. TLRs are activated via pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) that initiate downstream immune responses. Dysregulated signaling through TLRs and IL-1R can drive uncontrolled immune cell activation and chronic inflammation. This inflammatory state is associated with multiple chronic inflammatory and autoimmune diseases, including SLE and CLE.

Nonclinical studies have revealed a critical role for TLR7 and IRAK4 in murine lupus. TLR7-deficient and IRAK4 kinase inactive knock-in mice have been shown to be protected against the development of lupus-like murine disease {Murphy 2017}. Plasmacytoid dendritic cells isolated from these IRAK4 knock-in mice are completely resistant to TLR7 and TLR9-induced secretion of IFN-α {Kim 2007}. In the in vivo NZB/W preclinical lupus model, GS-5718 statistically improved survival, histologic renal parameters and measures related to lupus activity. GS-5718 also returned PD measures toward predisease levels.

Evidence supports a role for IRAK4 signaling in human studies. The peripheral interferon-stimulated gene signature observed in SLE patients is considered to be TLR7- and TLR9-dependent. Human pDC produce the majority of type I interferons, in particular in response to TLR7 or TLR9 agonism. In in vitro cellular assays, GS-5718 inhibited TLR7- and TLR9-stimulated production of IFN-α in primary human pDC and human whole blood. In human PBMCs, GS-5718 inhibited TLR7-stimulated expression of a 4 gene type I interferon-stimulated gene panel (IFI27, IFI44, IFI44L, and RSAD2). GS-5718 also inhibited IFN-α and TNF-α production from pDC stimulated with sera from patients with SLE.

1.4. Rationale for the Study Design

The goal of this Phase 1b study is to evaluate the safety of GS-5718 over 4 weeks in a population of subjects with CLE with or without SLE. The generated data will inform target engagement and safety in the LE population, which can further inform future studies. CCI

[redacted]

Nonclinical toxicology data support dosing of 115 mg once daily. Nonclinical pharmacology data shows that GS-5718 is a potent and selective inhibitor of IRAK4. In a Phase 1 healthy volunteer study, GS-5718 was generally well tolerated. At all dose levels of GS-5718 studied (15 mg, 50 mg, and 150 mg), there were no serious adverse events (SAEs), TEAEs leading to study drug discontinuation, clinically significant ECG/vital sign abnormalities, or deaths.

Available evidence supports proceeding with a Phase 1b evaluation of GS-5718 in subjects with CLE to assess for safety and tolerability at 1 month.

1.5. Rationale for Dose Selection of GS-5718

This study will evaluate the safety and tolerability of 115 mg once daily GS-5718 for 4 weeks in subjects with CLE. The dose was selected based on short-term safety, PK, and PD results from Study GS-US-451-5399 in healthy subjects. This dose is expected to be well tolerated. Based on Phase 1 PK/PD data, the 115 mg dose is predicted to be above EC_{90} for TNF-α inhibition, a peripheral biomarker for PD response. This dosing regimen is further supported by the 4-week preclinical toxicology studies. In addition to expected safety and tolerability, GS-5718 has demonstrated efficacy in the NZB/W model of spontaneous murine lupus. Taken together, these data support the evaluation of GS-5718 115 mg once daily in subjects with CLE.

1.6. Risk/Benefit Assessment for the Study

There remains a high unmet need for efficacious and safe treatment options for patients with lupus. This Phase 1b study will characterize the safety and tolerability of GS-5718 in this disease state while also establishing the effect of IRAK4 inhibition on clinical outcomes. Based on the clinical data to date, as well as the data from nonclinical efficacy and mechanistic studies, clinical investigation of GS-5718 in patients with lupus is warranted. Safety data from the clinical study available for GS-5718 suggest an acceptable benefit-risk ratio at the proposed 115 mg once daily dose. Furthermore, use of a sponsor-unblinded trial design will permit ongoing monitoring of each subject's clinical status, laboratory values, and reported adverse events (AE).

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments. Refer to Appendix 2 for further details on the risks and risk mitigation strategy.

1.7. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-5718 in subjects with CLE with or without SLE

The secondary objective of this study is as follows:

- To characterize the PK of GS-5718 in subjects with CLE with or without SLE

The exploratory objectives of this study are as follows:

3. STUDY DESIGN

3.1. Endpoints

The primary endpoints of this study are as follows:

- Number of subjects that experience AEs
- Number of subjects that experience laboratory abnormalities

The secondary endpoint of this study is as follows:

- PK parameters of GS-5718, including AUC_{tau} and C_{max}

The exploratory endpoints of this study are as follows:

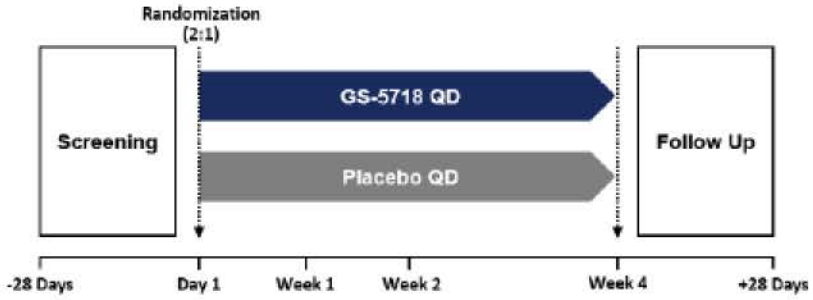
CCI

3.2. Study Design

This is a Phase 1b, multicenter, randomized, blinded, placebo-controlled, 4-week study evaluating the safety and tolerability of GS-5718 in subjects with CLE.

A schematic of this study is provided in Figure 3-1.

Figure 3-1. Study Schema



3.3. Study Treatments

Eligible subjects, continuing their standard of care therapy, will be randomized in a 2:1 blinded fashion to 1 of 2 arms. The first being 115 mg GS-5718 once daily in addition to standard of care (approximately 8 subjects). The second being placebo-to-match (PTM) GS-5718 once daily in addition to standard of care (approximately 4 subjects).

3.4. Duration of Treatment

Randomized subjects will receive GS-5718 or PTM GS-5718 for a maximum of 4 weeks.

3.5. Discontinuation Criteria

3.5.1. Study Drug Interruption

The sponsor medical monitor should be consulted prior to study drug interruption, when medically feasible.

Prior to resuming study drug, the investigator should discuss the case with the sponsor medical monitor.

Study drug interruption should be considered in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.

- If the subject has any signs or symptoms suggestive of systemic infection, study drug dosing should be interrupted per the judgment of the investigator. Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored. Study drug should continue to be paused until the subject's event has resolved, per investigator judgment.

3.5.2. Study Drug Discontinuation Criteria

The sponsor medical monitor should be consulted prior to study drug discontinuation, when medically feasible.

Study drug should be permanently discontinued in the following circumstances:

- Any opportunistic infection

- Any Grade 2 or higher cardiovascular or hematologic event (or Grade 3 lymphopenia or anemia as described below under "Laboratory Criteria")

- Any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Subject request to discontinue for any reason

- Subject noncompliance, per investigator judgment

- Investigator discretion

- Female subject becomes pregnant during the study

  — NOTE: If the female partner of a male subject becomes pregnant during the study, the investigator, in consultation with the Gilead medical monitor, will determine whether the subject should continue in the study on a case-by-case basis.

- Discontinuation of the study at the request of the study sponsor, a regulatory agency or an institutional review board (IRB)/independent ethics committee (IEC)

- Subject use of prohibited concurrent systemic therapy
- An absolute QTcF > 500 msec or a change from the baseline QTcF value > 60 msec
- Laboratory Criteria: After becoming aware of any of the abnormal laboratory values below, study drug should be paused, and an unscheduled visit (ie, sequential visit) should occur to retest within 3 to 7 days (except creatinine, which should be retested 7 to 14 days apart). Retest may be obtained sooner if medically indicated, per investigator judgment.
- If the laboratory abnormality is confirmed by the retest, then study drug should be permanently discontinued.
  - Hemoglobin < 8.0 g/dL (International System of Units [SI]: < 80.0 g/L)
  - ANC < 1500 cells/mm^3 (SI: < 1.5 × 10^9 cells/L)
  - Lymphocyte count < 500 cells/mm^3 (SI: < 0.5 × 10^9 cells/L)
  - Platelet count < 75,000 cells/mm^3 (SI: < 75 × 10^9 cells/L)
  - Any AST and/or ALT ≥ 3 × ULN independent of signs of liver damage
  - Estimated CL_{cr} < 60 mL/min based on the Cockcroft-Gault equation

Subjects who discontinue study drug dosing at any time should continue with study visits, procedures, and assessments, if deemed medically appropriate by the investigator. Subjects who permanently discontinue study drug for any reason may be replaced (see Section 4.1.1 for more details).

Subjects withdrawing from the study should complete the early termination (ET) and follow-up (FU) visits. Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow up. All contacts and contact attempts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

3.6. End of Study

End of study is defined as when the last subject has completed 4 weeks of study treatment and the FU visit approximately 28 days after the last dose of study drug, as applicable.

3.7. Poststudy Care

The long-term care of subjects poststudy will remain the responsibility of their primary treating physician.

3.8. Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

The biomarker sample collection schedule is described in the Study Procedures Table (Appendix 3). Samples will be collected from all subjects. The biomarker samples will be destroyed no later than 15 years after the end of study or per country requirements.

3.8.2. Biomarker Samples for Optional Future Research

CCI

[redacted]

3.8.3. Biomarker Samples for Optional Genomic Research

CCI

[redacted]

3.8.4. Sample Storage

The stored biological samples may be used by Gilead or its research partner for future testing to provide additional data to answer questions that relate to the main study. At the end of this study, these samples may be retained in storage by Gilead for a period up to 15 years. If subjects provide additional specific consent, residual PK samples may be destroyed no later than 15 years after the end of study or per country requirements.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to enroll approximately 12 evaluable subjects with active ACLE or SCLE.

4.1.1. Subject Replacement

Subjects who permanently discontinue study drug before the end of study treatment may be replaced.

Criteria for subject replacement by the sponsor include but are not limited to the following circumstances:

- Study drug discontinuation prior to the PK sampling visit
- Study drug discontinuation due to an AE categorized as not related to study treatment by the investigator
- Study drug discontinuation due to subject request or subject noncompliance
- Study drug interruption > 3 days
- Use of prohibited concomitant medication or modification of background standard of care medication

4.2. Inclusion Criteria

Subjects must meet **all** of the following inclusion criteria to be eligible for participation in this study.

Documentation of select criteria (*) **must** be submitted to the study sponsor for review and confirmation of subject eligibility prior to randomization:

1) Are ≥ 18 and ≤ 75 years of age at the time of the initial informed consent
2) Either fulfill EULAR/ACR 2019 classification criteria for SLE*

   or

   have biopsy-proven CLE*
3) Must have active ACLE/SCLE* {Klein 2010}; subjects with mixed skin presentations of lupus skin disease (including DLE) are allowed to enter

4) CLASI activity score[a] of ≥ 6 during screening* and Day 1

   [a]Excluding the alopecia component (ie, points for recent hair loss and alopecia do not contribute to the qualifying CLASI-A score)

5) Presence of at least 1 representative lupus skin lesion amenable to punch biopsy and subject willingness to undergo skin biopsy at 2 time points

6) Subjects using protocol-permitted nonbiologic immunosuppressive/immunomodulatory agents for the treatment of CLE/SLE (eg, antimalarials, MTX, or other csDMARDs) must maintain stable dose(s) for ≥ 60 days prior to randomization through Week 4 of the study (see Section 5.4.1 for details)

7) Subjects using protocol-permitted Class V-VII topical corticosteroids or oral prednisone ≤ 15 mg/day (or equivalent) must maintain stable dose(s) for ≥ 28 days prior to randomization through Week 4 of the study (see Section 5.4.1)

8) Must have prior intolerance or inadequate response at any time (per investigator judgment) to at least one of the following medications for the treatment of SLE/CLE:

   a) Topical corticosteroids or topical calcineurin inhibitors

   b) Oral corticosteroids

   c) A csDMARD, including, but not limited to: chloroquine, quinacrine, hydroxychloroquine, azathioprine, MMF, leflunomide, dapsone, or MTX

9) Must have a body mass index (BMI) between 18 and 35 kg/m^2

10) Subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 4

11) Able and willing to sign the informed consent form(s) (ICF), as approved by the IRB/IEC; written, signed, and dated consent must be provided before initiating any screening evaluation

4.3. Exclusion Criteria

Subjects who meet **any** of the following exclusion criteria are not eligible to be enrolled in this study.

Consultation with the sponsor medical monitor on select criteria (*) **must** take place prior to randomization.

1) Present with only CCLE skin lesion(s) during screening and Day 1

2) Have highly active SLE (including but not limited to lupus nephritis, neuropsychiatric SLE, vasculitis) that could put the subject at risk per the investigator's judgment

3) Presence of active skin conditions other than cutaneous lupus that may interfere with assessing lupus-specific skin lesion(s) (eg, lupus-nonspecific skin disease, psoriasis, drug-induced lupus)

4) Meet any of the following prior/concomitant medication use criteria relative to the date of randomization:

   a) Prior use of an IRAK4 inhibitor at any time

   b) Exposure to any approved or investigational bDMARD within 180 days

   c) Exposure to cyclophosphamide within 60 days

   d) Exposure to a JAK inhibitor (eg, tofacitinib, baricitinib, upadacitinib) within 60 days

   e) Use of oral prednisone > 15 mg/day (or equivalent) within 28 days

   f) Use of Class I-IV topical corticosteroids within 28 days

   g) Use of topical calcineurin inhibitors within 28 days

   h) Use of injectable corticosteroids within 28 days

   i) Use of strong CYP3A inhibitors or inducers within 14 days (see Section 5.4.2)

5) Meet any of the following infection criteria:

   a) Any active infection that is clinically significant (per investigator judgment); baseline SARS-CoV-2 screening should follow local guidelines/institutional practice*

   b) Positive QuantiFERON at screening; subjects with a positive test are excluded from the study and should be worked up as per local standard of care.

      Note: QuantiFERON tests with inconclusive results may be repeated one time. If the repeat result is also inconclusive, the subject must be excluded from the study.

      Note: Subjects with prior latent TB who have been treated with a full course of prophylaxis as per local guidelines are eligible. Appropriate documentation of prior treatment is required, a QuantiFERON test is not required.*

   c) An infection requiring oral anti-infective medication(s) within 28 days prior to randomization

d) An infection requiring hospitalization or treatment with intravenous anti-infective medication(s) within 60 days prior to randomization

e) Evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies at screening

f) Active or chronic or past hepatitis B virus infection (HBV), as evidenced by positivity for hepatitis B surface antigen (HBsAg) or HBV core antibody (regardless of HBV viral load) at screening

g) Evidence of active HCV infection. Subjects with positive HCV antibody (Ab) at screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA viral load (VL) at screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require a retest at Week 4

h) History of previous life-threatening or opportunistic infection

6) Meet any of the following central laboratory confirmed abnormalities:

a) Hemoglobin < 10.0 g/dL (International System of Units [SI]: < 100.0 g/L)

b) ANC < LLN

c) Lymphocyte count < 800 cells/mm^3 (SI: < 0.8×10^9 cells/L)

d) Platelet count < LLN

e) ALT or AST $\geq 1.5 \times$ ULN

f) Total bilirubin $> 1.0 \times$ ULN

g) Estimated CL_{cr} < LLN based on the Cockcroft-Gault equation

7) Subjects who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study or for 14 days after their last dose of study drug

8) Any condition or circumstances which may make a subject unlikely or unable to complete the study or comply with study procedures and requirements (per investigator judgment)

9) Major surgery (requiring regional block or general anesthesia) within 28 days prior to randomization or planned during the subject's study participation

10) Known hypersensitivity to the study drug, its metabolites, or formulation excipients

11) Subject has presence or sequelae of gastrointestinal, liver, or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs; this may include a history of weight loss surgery

12) Subject concurrently participates or participated in a drug or drug/device investigational research study within 28 days or 5 half-lives of the investigational product, whichever is longer, prior to randomization

13) Subject has a history of malignancy within the past 5 years prior to screening with the exception of excised and curatively treated nonmetastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of cervix which is considered cured with minimal risk of recurrence

14) History of any lymphoproliferative disease

15) History of organ or bone marrow transplant

16) Receipt of any live/attenuated vaccine within 28 days prior to randomization or planned during the study or for 28 days after the subject's last dose of study drug

17) Any screening ECG finding deemed clinically significant per investigator judgement

4.4. Screen Failures

Retesting of screening laboratory tests may be performed one time prior to screen-failing the subject, if the investigator deems that the initial value was inconsistent with the subject's previous results; due either to error (eg, a mishandled/hemolyzed sample), or to an extenuating circumstance which has since resolved.

Subjects who do not meet eligibility criteria for study entry ("screen failures") may be rescreened once. Written approval from the sponsor medical monitor must be obtained prior to rescreening.

At the time of rescreening, the individual must repeat the informed consent process, sign a new ICF, and repeat all necessary screening procedures. A new screening number will be assigned.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding, and Treatment Codes Access

An interactive response technology (IRT) will be used to manage subject randomization and treatment assignments. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Dosing assignments will be maintained in an investigator- and subject-blinded fashion within the IRT system until study-wide unblinding or emergency unblinding.

5.1.1. Randomization

At the time of initial informed consent, subjects will be assigned a screening number. On Day 1, subjects who meet all eligibility criteria will be randomized to a treatment arm as outlined in Section 3.3 and assigned a subject number.

Once a number has been assigned to a subject, it will not be reassigned to another subject. Replacement subjects will be assigned to the same treatment group as the discontinued subject to be replaced.

5.1.2. Blinding

Investigator, site personnel, site pharmacist(s), and randomized subjects will be blinded to treatment assignment.

Contract research organization personnel will be blinded to treatment assignment.

Gilead personnel will be unblinded and will not communicate unblinded information to blinded sites or subjects as specified in sponsor standard operating procedures (SOPs).

5.1.3. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the IRT for that subject (IRT vendor may be contacted in the case of technology failure). Gilead recommends but does not require that the investigator contact the sponsor medical monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and in the IRT, along with the date on which the treatment assignment was obtained. If a subject's treatment assignment is unblinded, the sponsor must be immediately notified.

Investigator and subject blinding to study treatment is critical to the integrity of this clinical study. Therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

5.2. Description and Handling of GS-5718

5.2.1. Formulation

GS-5718 tablets are available in 15-mg and 100-mg strengths. GS-5718, 15-mg, tablets are round, plain-faced, and film-coated orange. GS-5718, 100-mg, tablets are capsule-shaped, plain-faced, and film-coated orange. In addition to the active ingredient, GS-5718 tablets also contain the following excipients: microcrystalline cellulose, mannitol, crospovidone, fumaric acid, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, FD&C Yellow #6, FD&C Yellow #5, and FD&C Blue #2.

Placebo tablets to match the GS-5718 tablets are available for blinding purposes. PTM GS-5718 tablets are identical in weight, shape, color, and appearance to corresponding GS-5718 tablets. PTM GS-5718 tablets contain lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, FD&C Yellow #6, FD&C Yellow #5, and FD&C Blue #2.

5.2.2. Packaging and Labeling

GS-5718 and PTM GS-5718 tablets are packaged in white, high-density polyethylene bottles. Each bottle contains 30 tablets, silica gel desiccant, and polyester packing material. Each bottle is capped with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the United States (US) and other participating countries shall be labeled to meet applicable requirements of the US FDA, European Union (EU) Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

GS-5718 and PTM GS-5718 tablets should be stored below 30 °C (86 °F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability of the study drug and to ensure proper product identification, study drugs should not be stored in a container other than the container in which they are supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling GS-5718 tablets.

5.3. Dosage and Administration of GS-5718

The study medication will consist of 115 mg GS-5718 administered as one 100 mg and one 15 mg tablet for oral administration, and PTM GS-5718 tablets for oral administration. Study drugs will be administered orally once daily with or without food, with the exception of the Week 4 visit (fasting lipids and intensive PK sampling). Each subject should be provided instructions to maintain approximately the same daily time of administration to ensure a similar dosing interval between study drug doses. Study staff should also counsel subjects of the importance of study drug compliance.

For the Week 4 visit, subjects will be instructed to attend the site under fasted conditions (defined as no food or drink, except water for 8 hours prior). Subjects will be instructed to refrain from taking the Week 4 dose at home and to bring their study drug to the site for dosing. Subjects will continue to fast until after collection of the 4-hour PK sample.

For missed dose(s) of study drug, subjects should be instructed to take the missed dose(s) as soon as possible during the same day. If the missed dose is not taken on the original day, subjects should be cautioned not to double the next dose with the missed dose of study drug under any circumstance. In those cases, the missed dose should be returned to the original study drug bottle.

Subjects must be instructed to return the original study drug bottle, including missed dose(s) to the investigator site at the Week 4 visit. If the subject does not return the bottle at this time, the subject must be instructed to do so during the FU visit.

Subject compliance will be defined in the Statistical Analysis Plan.

5.4. Prior and Concomitant Medications

Subjects will maintain their protocol-permitted standard of care throughout the study. All medications taken for the treatment of SLE/CLE will be recorded in the source documents and in the eCRF. All other medications (for non-SLE/CLE indications) taken up to 28 days prior to the screening visit through the end of the study (28 days after the last dose of study drug) must be recorded in the source documents and in the eCRF. At each study visit, the investigator site must capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and nonprescription medications, dietary supplements, vitamins, and minerals.

Currently effective therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medications to treat AEs as deemed necessary by the investigator or the subject's health care provider(s). Should subjects have a need to initiate treatment with any prohibited concomitant medications, the sponsor medical monitor must be consulted prior to the initiation of the new medication, where possible. In instances where a prohibited medication is initiated prior to discussion with the sponsor, the investigator must notify the sponsor as soon as she/he is aware of the use of the excluded medication.

5.4.1. Allowed Concomitant Medications

Protocol-permitted medications taken for the treatment of CLE/SLE should be maintained, as much as possible, at stable doses (defined as no change in prescription) for the respective period of time specified below, prior to randomization through Week 4 (W4; Table 5-1).

For subjects that discontinue study treatment prior to Week 4, any modification to standard of care will be per investigator discretion.

The following medications should be maintained at stable doses for 60 days or greater (≥ 60 days) prior to randomization through Week 4:

- Nonbiologic immunosuppressive/immunomodulatory agents
  - Oral antimalarials (eg, hydroxychloroquine [≤ 400 mg/day], chloroquine [≤ 250 mg/day], quinacrine [≤ 100 mg/day], mepacrine [≤ 200 mg/day], dapsone [≤ 100 mg/day])
  - Oral or injectable MTX (up to 25 mg weekly); subjects on MTX should also be on folic acid supplementation (or equivalent), per local standard of care
  - Other csDMARDs, including azathioprine (≤ 2.5 mg/kg/day, not to exceed 200 mg/day), colchicine, cyclosporine, gold salts, leflunomide (≤ 20 mg/day), minocycline, mycophenolate mofetil (≤ 3 gm/day), mycophenolic acid (≤ 2.16 gm/day), penicillamine, sirolimus, sulfasalazine (≤ 3 gm/day), oral (not topical) tacrolimus

The following medications should be maintained at stable doses for 28 days or greater (≥ 28 days) prior to randomization through Week 4.

- Class V-VII topical corticosteroids; if the investigator wishes to use a Class V-VII topical corticosteroid not listed below, the investigator should obtain approval from the Gilead medical monitor prior to initiation of the medication, where possible
  - Alclometasone dipropionate up to 0.05% concentration
  - Desonide up to 0.05% concentration
  - Fluocinolone acetonide up to 0.03% concentration
  - Fluticasone propionate up to 0.05% concentration
  - Hydrocortisone acetate up to 2.5% concentration
  - Hydrocortisone probutate up to 0.1% concentration
  - Hydrocortisone valerate up to 0.2% concentration

- Oral prednisone ≤ 15 mg/day (or equivalent)
- Vitamins, minerals, and herbal supplements (excluding prohibited herbal/natural supplements as listed in Table 5-3)
- **Vaccines**
  - Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.
    - Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of GS-5718 and its impact on immune responses following vaccination
    - If possible, vaccination against SARS-CoV-2 should be concluded 28 days prior to randomization. Investigators must notify the medical monitor if/when a subject has received a SARS-CoV-2 vaccine within 28 days of randomization or until 28 days after the subject's last dose of study drug.

Table 5-1. Allowed CLE/SLE Medications

Drug Class	Medication	Maintenance Period (Stable Dosing Prior to Randomization)
Nonbiologic Immunosuppressant/Immunomodulator[a]	Antimalarials (eg, hydroxychloroquine, chloroquine, quinacrine, mepacrine, dapsone), azathioprine, colchicine, cyclosporine, oral (not topical) tacrolimus, gold salts, leflunomide, minocycline, methotrexate[b], mycophenolate mofetil, penicillamine, sirolimus, sulfasalazine[b], or other immunomodulatory/immunosuppressive agent	Stable dosing must be maintained for ≥ 60 days prior to randomization through W4
Corticosteroid, Local	Class V-VII topical corticosteroid	Stable dosing must be maintained for ≥ 28 days prior to randomization through W4
Corticosteroid, Systemic	Oral prednisone ≤ 15 mg/day (or equivalent)	Stable dosing must be maintained for ≥ 28 days prior to randomization through W4

a Refer to the dose limits specified in Section 5.4.1.
b Methotrexate and sulfasalazine are BCRP substrates. GS-5718 may increase exposure of BCRP substrates. These medications are allowed but should be used with caution with GS-5718.

5.4.2. Prior and Concomitant Medications That Are Prohibited or To Be Used with Caution

Medications in Table 5-2 and Table 5-3 are prohibited or should be used with caution while participants are taking study drugs. The following medications are prohibited from concomitant use with study drug. The respective washout period (ie, prohibited period) relative to the date of randomization is specified below (Table 5-3).

For subjects that discontinue study drug prior to Week 4, initiation of any of these agents as standard of care will be per investigator discretion.

Prior exposure at any time to any medication in the following drug class is prohibited.

- IRAK4 inhibitors

Exposure to the following medications within 180 days (< 180 days) prior to randomization is prohibited.

- Biologic DMARDs (approved or unapproved)
  - Anti-TNF agents (eg, adalimumab, certolizumab, etanercept, infliximab, golimumab)
  - Non-TNF biologics (eg, anakinra, abatacept, sarilumab, tocilizumab)
  - Anti-B-cell activating factor (eg, belimumab), B-cell depleting agents (anti-CD20, eg, rituximab, ocrelizumab), or anti-CD22 agents (eg, epratuzumab); subjects with prior exposure to a B-cell depleting bDMARD (eg, rituximab, ocrelizumab), must have the presence of $CD19^+$ B cells by flow cytometry at screening

Exposure to the following medication within 60 days (< 60 days) prior to randomization is prohibited.

- Cyclophosphamide
- JAK inhibitors (eg, tofacitinib, baricitinib, upadacitinib)

Exposure to the following medications within 28 days (< 28 days) prior to randomization is prohibited.

- Local corticosteroids
  - Intralesional or intraarticular corticosteroids
  - Class I-IV topical corticosteroids
- Systemic corticosteroids
  - Oral prednisone > 15 mg/day (or equivalent)
  - Intramuscular corticosteroids

- Topical calcineurin inhibitors (eg, tacrolimus, pimecrolimus)
- Any investigational drug, drug/device received or potentially received (within 28 days or 5 half-lives (whichever is longer))
- Live/attenuated vaccine (receipt of a live/attenuated vaccine within 28 days prior to randomization and until 28 days after the subject's last dose of study drug)
  - Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components.

Exposure to the following medications within 14 days (< 14 days) prior to randomization is prohibited.

- Strong CYP3A inhibitors
- Strong CYP3A inducers

Table 5-2. Examples of Prior and Concomitant Medications That Are to Be Used With Caution or That Are Prohibited Because of the Potential for Pharmacokinetic Drug-Drug Interaction With GS-5718[a]

Medication Class	Agents to Be Used With Caution[b]	Prohibited Agents[c]
Strong CYP3A Inhibitors	-	Cobicistat, ritonavir, ketoconazole, voriconazole, clarithromycin, itraconazole, grapefruit, grapefruit juice
Strong CYP3A Inducers	-	Phenytoin, carbamazepine, rifabutin, rifapentine, rifampin, St. John's wort
BCRP Sensitive Substrates	Rosuvastatin (allowed for use but dose should not exceed 20 mg)	-
OCT2, MATE1, MATE2K Sensitive Substrate	Metformin (allowed for use but monitor blood glucose more frequently)	-

BCRP = breast cancer resistance protein; CYP3A = cytochrome P450 3A; MATE1 = multidrug and toxin extrusion 1; MATE2K = multidrug and toxin extrusion 2K; OCT2 = organic cation transporter abbreviation 2

a This table represents examples of the most common concomitant medications and is not meant to be exhaustive. Additional lists on potential perpetrators can be found at https://drug-interactions medicine.iu.edu/MainTable.aspx. If the investigator is unsure if a medication is allowed per protocol, he/she should consult with the sponsor medical monitor.

b Agents should be used with caution < 3 days prior to Day 1 through Week 4

c < 14 days prior to Day 1 through Week 4

Table 5-3. Prohibited Medications

Drug Class	Medication	Prohibited Period (Relative to Randomization)
IRAK4 inhibitor		Prior exposure disallowed
Biologic	Tumor necrosis factor (TNF) inhibitor, non-TNF biologic (eg, anakinra, abatacept, belimumab, rituximab[a], ocrelizumab[a], tocilizumab, sarilumab), or biosimilar (if applicable)	< 180 days prior to randomization through W4
Cyclophosphamide		< 60 days prior to randomization through W4
JAK inhibitors (eg, tofacitinib, baricitinib, upadacitinib)		< 60 days prior to randomization through W4
Investigational	Any investigational drug, drug/device received or potentially received	< 28 days or 5 half-lives (whichever is longer) prior to randomization through W4
Live/attenuated vaccine (eg, intranasal flu, Zostavax, varicella, measles/mumps/rubella (MMR), yellow fever)		< 28 days prior to randomization and until 28 days after the last dose of study drug
Topical Calcineurin Inhibitors	Topical tacrolimus, topical pimecrolimus	< 28 days prior to randomization through W4
Corticosteroid, Local	Intralesional or intraarticular corticosteroid, Class I-IV topical corticosteroid	< 28 days prior to randomization through W4
Corticosteroid, Systemic	Oral prednisone > 15 mg/day (or equivalent), intramuscular corticosteroid	< 28 days prior to randomization through W4

bDMARD = biologic disease-modifying antirheumatic drug; IRAK4 = interleukin-1 receptor-associated kinase 4; JAK = janus kinase; W = Week

a Subjects with prior exposure to a B-cell depleting bDMARD (eg, rituximab), must have the presence of CD19+ B cells by flow cytometry at screening

Consult the medical monitor for any herbal/natural supplements not listed that may have potential drug-drug interactions with study drug or if it is unknown whether there is a potential drug-drug interaction with study drug.

Subjects should be advised to avoid ultraviolet light exposure, utilize sunscreen, and wear protective clothing during the study and for 28 days after the subject's last dose of study drug.

5.5. Study Drug Accountability

The investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition). All unused study drug dispensed to subjects must be returned to the investigator site.

Study drug accountability forms will be provided to each study site to record the following:

- The date received and quantity of study drug received

- The date, subject number, and the study drug kit number dispensed
- The date, quantity of unused study drug returned, along with the initials of the person recording the information

5.5.1. Study Drug Return or Disposal

Gilead recommends that used and unused study drug supplies be destroyed at the site. If the investigator site has an appropriate SOP for drug destruction, as determined by Gilead, the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP must be obtained for electronic trial master file. If study drug is destroyed at the site, the investigator must maintain accurate records for all study drugs destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy must be returned to the sponsor.

If the site does not have an appropriate SOP for drug destruction, used and unused study drug supplies must be sent to the designated disposal facility for destruction. The study monitor will provide instructions for return.

The study monitor will review study drug supplies and associated records at periodic intervals.

For both disposal options listed above, the study monitor must first perform drug accountability.

6. STUDY PROCEDURES

Written informed consent must be obtained prior to the conduction of any study procedure. It is the responsibility of the investigator to ensure that each subject meets all eligibility criteria prior to randomization.

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 3.

Unscheduled visits should be performed, as needed, at the discretion of the investigator. The assessments performed during an unscheduled visit are also at the discretion of the investigator.

The investigator must document any deviation from the protocol procedures and notify the study sponsor.

6.1. Subject Enrollment and Treatment Assignment

Entry into screening does not guarantee enrollment into the study. In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study wide at any time.

6.2. Baseline Photography

Baseline, pretreatment photographs must be obtained from an identified cutaneous lesion or area of active disease and provided to the sponsor in a deidentified manner.

The confidentiality of all subjects will be maintained, and photographs of the subjects will not be published nor made public without ensuring complete deidentification of the subject (eg, blocking portions of his/her face or body).

6.3. On-Study Photography

Photography of areas of skin involvement must be performed at the time points indicated in the Study Procedures Table (Appendix 3). A separate manual will be provided detailing methods of photography.

6.4. Skin Biopsies

Skin biopsies will be performed at the time points indicated in the Study Procedures Table (Appendix 3). A separate manual will be provided detailing instructions for the collection of skin biopsy samples.

Each biopsy should be performed at the end of the respective visit after all other study procedures have been completed, as much as possible.

6.5. Efficacy Assessments

Efficacy assessments will be performed at the time points indicated in the Study Procedures Table (Appendix 3).

6.5.1. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

The CLASI is a standardized, validated measure of cutaneous lupus disease activity and damage, widely used in clinical trials. CLASI-A scores range from 0 to 70, with higher scores indicating more severe disease activity.

6.5.2. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

The SLEDAI-2K is a validated measure of global disease activity, commonly used in SLE clinical trials. The SLEDAI-2K assesses the presence/absence of disease activity across 9 organ systems, with total scores that range from 0 to 105; higher scores indicating more severe disease activity. The SLEDAI-2K is only to be administered to subjects with concurrent SLE.

6.5.3. Physician's Global Assessments of CLE Disease Activity

The PGA of CLE disease activity will be recorded on a 0 to 100 mm VAS, with 0 indicating "no CLE disease activity" and 100 indicating "maximum CLE disease activity". The evaluating physician and the subject should complete the global assessments independently of each other.

6.5.4. Subject's Global Assessments of CLE Disease Activity

The SGA of CLE disease activity will be recorded on a 0 to 100 mm VAS, with 0 indicating "I have no CLE" and 100 indicating "I have the worst CLE."

6.6. Assessments for Early Discontinuation from Study

If a subject discontinues study dosing (eg, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow up and procedures (see Section 3.5.2). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study where the subject is administered a study drug, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. Adverse events may also include pretreatment or posttreatment complications that occur as a result of protocol-specified procedures or special situations (Section 7.1.3).

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (Section 7.1.3)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the ICF is signed and not related to a protocol-associated procedure is not an AE but rather considered to be preexisting and should be documented in the medical history eCRF.

Preexisting events that increase in severity or change in nature after study drug initiation or during or as a consequence of participation in the clinical study will also be considered AEs.

7.1.2. Serious Adverse Events

An SAE is defined as an event that, at any dose, results in the following:

- Death
- A life-threatening situation (Note: 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 that hypothetically might have caused death if it were more severe.)
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: Such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

7.1.2.1. Protocol-Specific Adverse Event Definitions

Protocol-specific AE reporting exemptions:

- Laboratory abnormalities that are not deemed clinically significant and are not associated with symptoms are not considered AEs
- ECG changes that are not deemed clinically significant and are not associated with symptoms are not considered AEs

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

Special situation reports (SSRs) include all reports of medication error, abuse, misuse, overdose, occupational exposure, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, counterfeit of falsified medicine, and pregnancy regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration or administration of a study drug while the medication is in the control of a health care professional, patient, or consumer. Medication errors may be classified as a medication error without an AE, which includes situations of missed dose, medication error with an AE, intercepted medication error, or potential medication error.

Abuse is defined as persistent or sporadic intentional excessive use of a study drug by a subject.

Misuse is defined as any intentional and inappropriate use of a study drug that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a study drug given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy, except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Occupational exposure is defined as exposure to a study drug as a result of one's professional or nonprofessional occupation.

Drug interaction is defined as any drug/drug, drug/food, or drug/device interaction.

Unexpected benefit is defined as an unintended therapeutic effect where the results are judged to be desirable and beneficial.

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a Gilead study drug.

Counterfeit or falsified medicine: Any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to study drug using clinical judgment and the following considerations:

- No: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).
- Yes: There is reasonable possibility that the AE may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No: Evidence exists that the AE has an etiology other than the study procedure.
- Yes: The AE occurred as a result of protocol procedures.

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE). For each episode, the highest grade attained should be reported as defined in the CTCAE.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying condition; this may or may not be in agreement with the grading of the laboratory abnormality.

If a CTCAE criterion does not exist for the respective AE, the investigator should use the following grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE.

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After informed consent, but prior to initiation of study drug, the following types of events must be reported on the applicable eCRFs: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following the subject signing the informed consent, all AEs, regardless of cause or relationship, until 28 days after last administration of study drug must be reported in the eCRFs as instructed.

All AEs should be followed until resolution or until the AE is stable, if possible. Gilead may request that certain AEs be followed beyond the protocol-defined follow-up period.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (ie, signing the ICF) and throughout the duration of the study, including the posttreatment FU visit, must be reported on the applicable eCRFs to Global Patient Safety (GLPS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after the ICF is signed.

Any SAEs and deaths that occur after the posttreatment FU visit but within 28 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol-defined follow-up period; however, if the investigator learns of any SAEs that occur after the protocol-defined follow-up period has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead GLPS.

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

All study drug SSRs that occur from study drug initiation and throughout the duration of the study, including the posttreatment FU visit, must be reported to Gilead GLPS (Section 7.4.2). Adverse events and SAEs resulting from SSRs must be reported in accordance to the AE and SAE reporting guidance (Section 7.3).

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment FU visit, must be reported to Gilead GLPS utilizing the paper SSR (Section 7.4.2).

7.3.5.2. Non-Gilead Concomitant Therapy Report

Special situations involving non-Gilead concomitant medications does not need to be reported on the SSR form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

All clinical sequelae in relation to these SSRs will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

7.4. Reporting Process for Serious Adverse Events and Special Situation Reports

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Electronic Serious Adverse Event Reporting Process

- Site personnel will record all SAE data on the applicable eCRFs and from there transmit the SAE information to Gilead GLPS within 24 hours of the investigator's knowledge of the event from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If it is not possible to record and transmit the SAE information via eCRF, record the SAE on the paper SAE reporting form and transmit within 24 hours:

Gilead GLPS
Email: PPI
or
Fax: PPI

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SAE reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

7.4.2. Special Situations Reporting Process

7.4.2.1. Electronic Special Situations Reporting Process

- Site personnel will record all SSR data on the applicable eCRFs and from there transmit the SSR information to Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required posttreatment follow-up period.

- If for any reason it is not possible to record the SSR information electronically, record the SSR on the paper special situation reporting form and transmit to:

Gilead GLPS
Email: PPI
or
Fax: PPI

- If an SSR has been reported via a paper form because the eCRF database has been locked, no further action is necessary. If the database is not locked, any SSR reported via paper must be transcribed as soon as possible on the applicable eCRFs and transmitted to GLPS.

See Section 7.4.2.2. for instructions on reporting special situations with Gilead concomitant medications.

7.4.2.2. Reporting Process for Gilead Concomitant Medications

- Special situations that involve Gilead concomitant medications that are not considered study drug must be reported within 24 hours of the investigator's knowledge of the event to Gilead GLPS utilizing the paper special situations report form to:

Gilead GLPS
Email: PPI
or
Fax: PPI

- Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.
- Special situations involving non-Gilead concomitant medications do not need to be reported on the SSR form; however, special situations that result in AEs due to a non-Gilead concomitant medication, must be reported as an AE.

7.4.2.3. Pregnancy Reporting Process

- The investigator should report pregnancies in female study subjects and/or female partners of male subjects that are identified after initiation of study drug and throughout the study, including the posttreatment follow-up period, to Gilead GLPS using the pregnancy report form within 24 hours of becoming aware of the pregnancy. Contact details for transmitting the pregnancy report form are as follows:

  Gilead GLPS
  Email: PPI
  or
  Fax: PPI

- The pregnancy itself is not considered an AE, nor is an induced elective abortion to terminate a pregnancy without medical reasons.
- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.
- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome after study must be reported to the Gilead GLPS.
- The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS.
- Gilead GLPS contact information is as follows:
  - Email: PPI
  - Fax: PPI
- Refer to Appendix 4 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs which may be in the form of line listings, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the IB or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study drug. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.6. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not to be recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

All clinical toxicities and clinically significant laboratory toxicities will be managed according to the guidelines detailed in Section 3.5 and Appendix 5, respectively.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the safety and tolerability of GS-5718 in subjects with CLE with or without SLE

The secondary objective of this study is as follows:

- To characterize the PK of GS-5718 in subjects with CLE with or without SLE

The exploratory objectives of this study are as follows:

8.1.2. Primary Endpoints

- Number of subjects experiencing AEs
- Number of subjects experiencing laboratory abnormalities

8.1.3. Secondary Endpoints

- PK parameters of GS-5718, including AUC_{tau} and C_{max}

8.1.4. Exploratory Endpoints

8.1.5. Final Analysis

The final analysis will be performed after all subjects have completed the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all subjects randomized into the study. This is the primary analysis set for safety and efficacy listings.

8.2.1.2. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least 1 dose of study drug.

8.2.1.3. Safety

The primary analysis set for safety analyses is defined as Safety Analysis Set, which includes all subjects who received at least 1 dose of study drug.

All data collected during treatment plus 28 days after last dose of study drug will be included in the safety summaries.

8.2.1.4. Pharmacokinetics

The PK Analysis Set includes all subjects who were randomized and received at least 1 dose of study drug and have at least 1 nonmissing concentration value reported by the PK laboratory for the corresponding analytes.

8.2.1.5. Biomarkers

The primary analysis set for biomarker analyses will be the Biomarker Analysis Set, which includes all randomized subjects who received at least 1 dose of study drug and have at least 1 baseline measurement available for the specific parameter of interest.

8.2.2. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

Laboratory data that are continuous in nature but are less than the LLOQ or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus 1 significant digit, respectively (eg, if the result of a continuous laboratory test is < 20, a value of 19 will be assigned; if the result of a continuous laboratory test is < 20.0, a value of 19.9 will be assigned).

Missing data can have an impact upon the interpretation of the study data. As this study is of short duration, it is anticipated that missing data will be minimal. In general, values for missing data will not be imputed; however, a missing pretreatment laboratory result would be treated as normal (ie, no toxicity grade) for the laboratory abnormality summary.

8.3. Demographic and Baseline Characteristics Analysis

Demographic and baseline measurements will be summarized using standard descriptive methods.

Demographic summaries will include sex, race/ethnicity, and age.

Baseline data will include but is not limited to, a summary of time from CLE diagnosis, ACLE versus SCLE disease subtype, presence of additional types of CLE, SLE diagnosis, CLASI-A score at baseline, CLASI-Damage (CLASI-D) score at baseline.

8.4. Efficacy Analysis

8.4.1. Exploratory Analysis

CCI [redacted]

8.5. Safety Analysis

All safety data collected on or after the date when study drug was first dispensed up to the date of last dose of study drug plus 28 days will be summarized by treatment group (according to the study drug received). Data for the pretreatment and treatment-free follow up will be included in data listings.

8.5.1. Extent of Exposure

A subject's extent of exposure to study drug data will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by treatment group.

8.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC), high-level group term, high-level term, preferred term (PT), and lower-level term will be attached to the clinical database.

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent AE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus 28 days.

Summaries (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by treatment group. Additionally, AEs by severity, AEs related to study drug, serious AEs, AEs leading to study and drug discontinuation will be summarized.

8.5.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Data and change from baseline at all scheduled time points will be presented.

Graded laboratory abnormalities will be defined using CTCAE scale.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time postbaseline up to the date of last dose of study drug plus 28 days, will be summarized by treatment group.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 28 days will be included in a data listing.

8.5.4. Other Safety Evaluations

8.5.4.1. Vital Signs and ECG

Vital signs and ECG data will be summarized by treatment group.

8.6. Adjustments for Multiplicity

There will be no adjustment for multiplicity.

8.7. Pharmacokinetic Analysis

Plasma concentrations and PK parameters (AUC_{tau}, C_{max}, T_{max}, C_{last}, T_{last}, and C_{tau}) will be listed and summarized for GS-5718 using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, percentage coefficient of variation (%CV), SD, median, minimum, and maximum). Plasma concentrations of GS-5718 over time will be plotted in semi-logarithmic and linear formats as mean ± SD.

8.8. Biomarker Analysis

For analysis of the biomarkers collected at baseline and postbaseline visits, the baseline level and the modulation pattern upon treatment, including percent and absolute change over time from baseline level, will be evaluated for treated and for placebo subjects. Descriptive statistics will be provided at each sampling time by treatment group. Additionally, graphical summaries, eg, mean ± SD, median ± interquartile range (Q1, Q3), box plots, and scatter plots to explore correlations between different biomarkers may also be generated, as needed. These graphs may be generated for raw values as well as percent and absolute change from baseline, as appropriate.

CCI [redacted]

CCI [redacted]

8.9. Sample Size

Sample size was determined based on practical considerations and no sample size calculation was performed. A sample size of 12 evaluable subjects (8 subjects randomized to GS-5718 and 4 subjects randomized to placebo) should provide a suitable assessment of the descriptive safety and PK profile.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) E6(R2) addendum to its guideline for GCP and applicable laws and regulations.

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide prompt and accurate documentation of their financial interest or arrangements with Gilead or proprietary interests in the study drug during the course of a clinical study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.3. Institutional Review Board/Independent Ethics Committee Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC on any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.4. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study before undertaking any study-related procedures. The investigator must use the most current IRB- or IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the subject, the person conducting the consent discussion, and an impartial witness (if required by IRB or IEC or local requirements).

The ICF will inform subjects about all planned testing and/or planned sample retention. The results of the tests done on the samples will not be given to the subject nor the investigator.

9.1.5. Confidentiality

The investigator must ensure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as year of birth) will be recorded on any form or biological sample submitted to Gilead, IRB/IEC, or the laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions

NOTE: The investigator must keep a screening log with details for all subjects screened and enrolled in the study, in accordance with the site procedures and regulations. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, CRFs/eCRFs, study drug information, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.6. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRFs/eCRFs, IRB/IEC, governmental approval with correspondence, the ICF(s), drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification
- Documentation that subject meets eligibility criteria, ie, medical history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent

- Dates of all visits
- Documentation that protocol-specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity) and documentation that adequate medical care has been provided for any AE
- Concomitant medications (start and end date; dose if relevant; dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

All clinical study documents must be retained by the investigator for at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, for 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.7. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in the electronic data capture (EDC) system. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures, unless collected by a nonelectronic data capture vendor system (eg, central laboratory). The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Data entry should be performed in accordance with the CRF Completion Guidelines (CCGs) provided by the sponsor. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued in the EDC system as data discrepancies are identified by the monitor or Gilead staff who routinely review the data for

completeness, correctness, and consistency. The site investigator, site coordinator, or other designee is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry and providing the reason for the update (eg, data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. At a minimum, prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her login credentials to confirm that the forms have been reviewed and that the entries accurately reflect the information in the source documents. At the conclusion of the study, Gilead will provide the site investigator with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.6.

9.1.8. Investigator Inspections

The investigator will make available all source documents and other records for this study to Gilead's appointed study monitors, to IRBs/IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.5).

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical study payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

The monitor is responsible for routine review of the CRF/eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries in the CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on-site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.4. Study Discontinuation

Both Gilead and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the subjects, appropriate regulatory authorities, and IRB/IEC. In terminating the study, Gilead and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

9.5. Source Data

The source data for this study may include, but are not limited, to original documents like hospital records (including electronic medical records), clinical charts, subject diaries, pharmacy dispensing records, data from central laboratories and photographs.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
33 LAKESIDE DRIVE
FOSTER CITY, CA 94404, USA

STUDY ACKNOWLEDGMENT

A Randomized, Blinded, Placebo-Controlled, Phase 1b Study of GS-5718 in Subjects with Cutaneous Lupus Erythematosus (CLE)

GS-US-497-5888, Amendment 1, 01 July 2021

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPI
PPI (Printed)
Medical Monitor

PPI

02-JUN-2021
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Pandemic Risk Assessment and Mitigation Plan

During an ongoing pandemic, potential risks associated with subjects being unable to attend study visits have been identified for this study.

These risks can be summarized as follows:

1) Study drug supplies to subjects and sites:

   a) Subjects may be unable to return to the site for a number of visits to get the study drug, or the site may be unable to accept any subject visits. Without study drugs, the subject would not be able to stay on the study drug as planned per protocol.

   - Mitigation plan: Study drug supplies may be provided to the subject from the site without a clinic visit, once it is confirmed that the subject may safely continue on study drug as determined by the principal investigator (PI). A virtual study visit, via phone or video conferencing, must be performed prior to remote study drug resupply. At the earliest opportunity, the site will schedule in-person subject visits and return to the protocol's regular schedule of assessments. A qualified courier may be utilized to ship the study drug from sites to study subjects if permitted by local ethic committee (EC)/institutional review boards (IRB)/Regulatory Authority as applicable and with sponsor's approval.

   b) Shipments of study drug could be delayed because of transportation issues. Without study drug subject would not be able to stay on the study drug as planned per protocol.

   - Mitigation plan: The sites' study drug inventory should be closely monitored. Site staff should notify the sponsor or delegate if they foresee shortage in study drug inventory or if there is any interruption in local shipping service. The sponsor will continue to monitor inventory at the study drug depot and study sites. Manual shipments will be triggered as necessary.

2) Subject safety monitoring and follow-up:

   a) Subjects may be unable or unwilling to come to the study site for their scheduled study visits as required per protocol.

   - Mitigation plan: For subjects who may be unable or unwilling to visit the study site for their scheduled study visits as required per protocol, the PI or qualified delegate will conduct a virtual study visit, via phone or video conferencing, to assess the subject within target visit window date whenever possible. During the virtual study visit, the following information at minimum will be reviewed:

     i) Confirm if subject has experienced any AEs/SAEs/special situations (including pregnancy) and follow up on any unresolved AE/SAEs.

     ii) Review current list of concomitant medications and document any new concomitant medications.

iii) If applicable, confirm electronic diary questionnaires and patient-reported outcomes have been completed and transmitted.

iv) If applicable, confirm subjects study drug supply is sufficient to last until the next planned visit date. If study drug resupply is needed it will be provided as described above in (1).

v) If applicable, remind subject to maintain current dosing and to keep all dispensed study drug kits for return at the next on-site visit.

b) Subjects may be unable or unwilling to travel to the site for planned assessments (eg, safety blood draws); hence samples may not be sent for central laboratory analyses.

- Mitigation plan: Local labs may be utilized as appropriate to monitor subject safety until the subject can return to the site for their regular follow up per protocol. Any laboratory assessments conducted at a local laboratory due to the pandemic will be documented accordingly. Pregnancy testing may be performed using a home urine pregnancy test if local laboratory pregnancy testing is not feasible.

- The study sponsor must be notified if the subject is unable to complete the PK sampling as outlined in Appendix 3.

c) Subjects may be unable or unwilling to attend the study visit to sign an updated informed consent form (ICF) version.

- Mitigation plan: The site staff will follow their approved consent process and remain in compliance with local EC/IRB and national laws and regulations. Remote consent will be allowed if has been approved by the local EC/IRB. The consent process will be documented and confirmed by normal consent procedure at the earliest opportunity.

3) Protocol and monitoring compliance:

a) Protocol deviations may occur, in case scheduled visits cannot occur as planned per protocol.

- Mitigation plan: If it is not possible to complete a required procedure, an unscheduled visit should be conducted as soon as possible when conditions allow. The situation should be recorded and explained as a protocol deviation. Any missed subject visits or deviation to the protocol due to the pandemic must be reported in the eCRF and described in the clinical study report. Any virtual study visits that are conducted in lieu of clinic visits due to the pandemic will be documented as a protocol deviation related to the pandemic.

b) Monitors may be unable to carry out on-site source data review or source data verification (SDV), or study drug accountability or assess protocol and GCP compliance. This may lead to delays in SDV, an increase in protocol deviations, or under reporting of AEs.

- Mitigation plan: The study monitor is to remain in close communication with the site to ensure data entry and query resolution. Remote SDV may be arranged in accordance with Gilead policy and as permitted by local regulation. The study monitor is to reference the Study Monitoring Plan for guidance on how to conduct a remote monitoring visit and remote SDV (if applicable). The study staff is to save and document all relevant communication in the study files. The status of sites that cannot accept monitoring visits and/or subjects on site, must be tracked centrally and updated on a regular basis.

4) Missing data and data integrity:

   a) There may be an increased amount of missing data due to subjects missing visits/assessments. This could have an impact on the analysis and the interpretation of clinical trial data.

   - Mitigation plan: Implications of a pandemic on methodological aspects for the study will be thoroughly assessed and documented, and relevant actions will be taken as appropriate (ie, modification of the statistical analysis plan) and in compliance with Regulatory Authorities' guidance. Overall, the clinical study report will describe the impact of the pandemic on the interpretability of study data.

Risks will be assessed continuously, and temporary measures will be implemented to mitigate these risks as part of a mitigation plan, as described above. These measures will be communicated to the relevant stakeholders as appropriate and are intended to provide alternate methods that will ensure the evaluation and assessment of the safety of subjects who are enrolled in this study.

Since these potential risks are considered mitigated with the implementation of these measures, the expected benefit-risk assessment of GS-5718 in study subjects remains unchanged.

Appendix 3. Study Procedures Table

Procedure	Screening V0	Study Treatment Period				Early Termination[b]	Follow Up	Instructions
		Day 1	Week 1	Week 2	Week 4			
	−28[a]	0[a]	+7 Days[a] (±2 Days)	+14 Days[a] (±2 Days)	+28 Days[a] (±2 Days)	Any	+28 Days[a] (±5 Days)	
Informed Consent	X							Written, signed, and dated informed consent must be obtained prior to screening
Inclusion/Exclusion Criteria	X	X						Documentation of select criteria must be submitted to the study sponsor for review and confirmation of subject eligibility
Medical History, Demographics, Substance Use	X							Medical history will include demographics, a review of surgical history, and CLE/SLE history
Prior and Concomitant Medications	X	X	X	X	X	X	X	
Height	X							Subjects should be instructed to remove shoes prior to baseline height measurement
Weight	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	Blood pressure, Pulse, Respiratory Rate, Temperature
12-Lead ECG	X			X	X	X	X	Resting ECG, performed and assessed locally; for subjects with chest lesions, study assessments should precede ECG, as applicable
Complete Physical Examination	X							
Symptom-Driven Physical Examination		X	X	X	X	X	X	Performed, as needed, based on signs and symptoms
CLASI Assessment	X	X	X	X	X	X	X	Subjects must have a CLASI activity (CLASI-A) score of ≥ 6 (excluding the alopecia component) during screening and Day 1

Procedure	Screening V0	Study Treatment Period				Early Termination[b]	Follow Up	Instructions
		Day 1	Week 1	Week 2	Week 4			
	−28[a]	0[a]	+7 Days[a] (±2 Days)	+14 Days[a] (±2 Days)	+28 Days[a] (±2 Days)	Any	+28 Days[a] (±5 Days)	
Photography of Skin Lesion(s)	X	X	X	X	X	X	X	Subject identifying features should be obscured, as much as possible. Follow-up photographs **must** target the same area of clinically active disease evaluated and photographed at baseline.
SLEDAI-2K Assessment		X		X	X	X	X	To be completed for subjects with concurrent SLE
Subject's Global Assessment	X	X	X	X	X	X	X	Subject's global assessment of CLE disease activity (visual analogue scale)
Physician's Global Assessment	X	X	X	X	X	X	X	Physician's global assessment of CLE disease activity (visual analogue scale)
Chemistry	X	X	X	X	X	X	X	See Appendix 6
Hematology	X	X	X	X	X	X	X	See Appendix 6
Fasting Lipids		X			X			No food or drinks, except water for at least 8 hours prior to blood sample collection
Serum Pregnancy Test	X							Females of childbearing potential only (see Appendix 4)
Urine Pregnancy Test		X	X	X	X	X	X	Females of childbearing potential only (see Appendix 4)
FSH Test	X							Females of nonchildbearing potential only (see Appendix 4)
Urine drug and Alcohol screen	X							
Urinalysis	X	X	X	X	X	X	X	
Urine Biomarkers		X		X	X	X	X	Day 1 sample to be taken predose
Urine Spot Protein/Creatinine Ratio		X		X	X	X	X	
QuantiFERON®-TB Gold In-Tube test	X							Not required for subjects with prior latent TB who have been treated with a full course of prophylaxis

Procedure	Screening V0	Study Treatment Period				Early Termination[b]	Follow Up	Instructions
		Day 1	Week 1	Week 2	Week 4			
	−28[a]	0[a]	+7 Days[a] (±2 Days)	+14 Days[a] (±2 Days)	+28 Days[a] (±2 Days)	Any	+28 Days[a] (±5 Days)	
HIV, HBV, and HCV Serology	X							
HCV Serology					X			Only applicable for subjects with baseline positive HCV antibody and negative HCV RNA VL
Skin Biopsy FFPE (4 mm)		X			X			A separate manual will be provided for skin biopsy instructions. Skin biopsies should be performed at the end of the respective visit after all other study procedures have been completed, as much as possible. Day 1 biopsies are to be taken predose.
Skin Biopsy RNA later (2-4 mm)		X			X			
PaxGene RNA Sample		X	X	X	X	X	X	Day 1 sample to be taken predose
Immunophenotyping Whole Blood		X		X	X	X	X	
TBNK Whole Blood		X		X	X	X	X	
Antinuclear Antibody by IFA	X							
ENA panel (anti-Sm, -RNP, -Ro, -La) and antiphospholipid antibodies		X						
Anti-dsDNA antibody		X		X	X	X	X	Day 1 sample to be taken for all subjects. Samples thereafter only applicable for subjects with concurrent SLE.
Complement Panel (C3, C4, CH50)		X		X	X	X	X	Day 1 sample to be taken predose
Quantitative Serum Immunoglobulin Test		X			X	X	X	
Serum Biomarker		X	X	X	X	X	X	Day 1 sample to be taken predose
Plasma Biomarker		X	X	X	X	X	X	Day 1 sample to be taken predose
Viably Frozen PBMC		X		X	X	X	X	Day 1 sample to be taken predose

Procedure	Screening V0 −28[a]	Study Treatment Period: Day 1 0[a]	Week 1 +7 Days[a] (±2 Days)	Week 2 +14 Days[a] (±2 Days)	Week 4 +28 Days[a] (±2 Days)	Early Termination[b] Any	Follow Up +28 Days[a] (±5 Days)	Instructions
CCI								
Intensive Plasma PK					X[d]			Subjects will be instructed to fast prior to this clinic visit and take the dose at the clinic on the intensive PK sampling day
Randomization (IRT)		X						
Study Drug Dispensed		X						Final Day 1 procedure
Study Drug Accountability		X			X	X		
Adverse Event(s)	X	X	X	X	X	X	X	AE reporting begins after the subject signs the ICF until 28 days after the last dose of study drug, regardless of causality

CLE = cutaneous lupus erythematosus; dsDNA = double-stranded deoxyribonucleic acid; ECG = electrocardiogram; ENA = extractable nuclear antigen; FFPE = formalin-fixed paraffin-embedded; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IFA = indirect fluorescent antibody; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; RNA = ribonucleic acid; SLE = systemic lupus erythematosus; TB = tuberculosis; TBNK = T cell/B cell/Natural Killer cell; VL = viral load

a All visits are anchored to Day 1 (eg, screening is up to 28 days prior to Day 1, the Week 1 visit is 7 days after Day 1, with a window of plus or minus 2 days)

b The early termination (ET) visit can satisfy the follow up (FU) visit if it takes place ≥ 28 days following the last dose of study drug

c CCI

d Intensive plasma PK sampling will occur prior to the dose (≤ 5 min before dose) (at the Week 4 visit) and at 0.5, 1, 2, 3, 4, and 6 hours postdose (collection window: ±5 minutes for the 0.5 and 1 hour PK sample; ± 15 minutes for the other time points)

Appendix 4. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

A) Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming postmenopausal unless the subject is permanently sterile or has medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle-stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

B) Definition of Male Fertility

For the purposes of this study, a male born subject is considered fertile after the initiation of puberty unless the subject is permanently sterile by bilateral orchidectomy or medical documentation.

2) Contraception Requirements for Female Subjects

A) Study Drug Effects on Pregnancy and Hormonal Contraception

GS-5718 is contraindicated in pregnancy as its teratogenicity/fetotoxicity profile is unknown. GS-5718 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, hormonal contraception is not recommended as a contraceptive method either solely or as a part of a contraceptive regimen.

B) Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the Admission (Day −1) visit prior to enrollment. Pregnancy tests will be performed at monthly intervals thereafter until the end of contraception requirement.

Duration of required contraception for female subjects in this clinical trial should start from screening visit until 14 days after the last dose of study drug.

Female subjects must agree to one of the following contraceptive methods:

Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below:
- Non-hormonal intrauterine device (IUD)
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Inclusion of methods of contraception in this list of permitted methods does not imply that the method is approved in any country or region. Methods should only be used if locally approved.

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until the end of contraception requirement.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male subject's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment until 14 days after last dose of study drug. If the female partner of childbearing potential is not pregnant, additional contraception recommendations should also be considered.

Male subjects must also refrain from sperm donation during treatment and until the end of contraception requirement.

4) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), withdrawal (coitus interruptus), hormonal contraception, spermicides only, and lactational amenorrhea method. A female condom and a male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

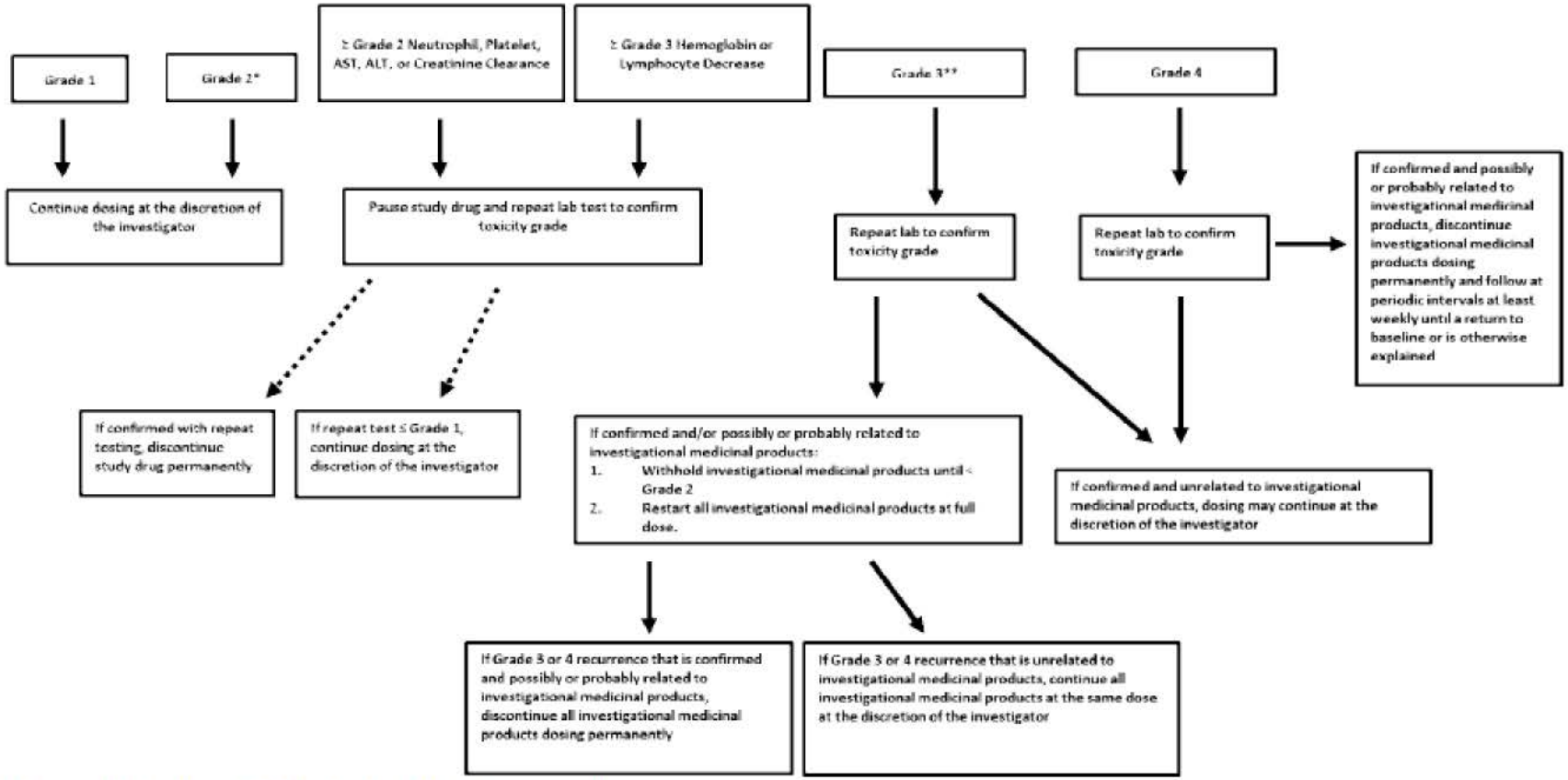
Female subjects will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 14 days after last study drug dose. Study drug must be discontinued immediately.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study to 14 days after last the study drug dose must also report the information to the investigator who, in consultation with the Gilead medical monitor, will determine whether the subject should continue in the study on a case-by-case basis.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.4.2.3.

Appendix 5. Management of Laboratory Adverse Events

Refer to the clinical and laboratory study drug discontinuation criteria outlined in Section 3.5.



* Not applicable for Neutrophil, Platelet, AST, ALT, or Creatinine Clearance
** Not applicable for Neutrophil, Platelet, AST, ALT, Creatinine Clearance, Hemoglobin decrease or Lymphocyte decrease

Appendix 6. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Lipid Profile	Other Tests
Differentials (absolute and percentage), including but not limited to: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Hematocrit Hemoglobin Platelet count Red blood cell count Red blood cell indices Reticulocyte count White blood cell count	Alanine aminotransferase Alkaline phosphatase Aspartate aminotransferase Bilirubin, direct and indirect Bilirubin, total Gamma-glutamyl transpeptidase Total protein Albumin Blood urea nitrogen Bicarbonate Calcium Chloride Creatine Kinase Creatinine Creatinine clearance Cystatin C Glucose Magnesium Phosphorus Potassium Sodium Uric acid (at screening only)	Appearance Blood Bilirubin Color Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urine protein to creatinine ratio Urobilinogen	High-density lipoprotein Low-density lipoprotein Total cholesterol Triglycerides	Autoantibody tests: Anti-nuclear antibody Anti-double-stranded DNA Antiphospholipid antibodies Anti-RNP Anti-Sm Anti-SSA/Ro Anti-SSB/La Complement levels (C3, C4, and CH50) Follicle-stimulating hormone (as applicable) Plasma PK QuantiFERON®-TB Gold In-Tube test* Quantitative immunoglobulins (IgG, IgM, and IgA) Urine drug screen for: Alcohol Amphetamines Barbiturates Benzodiazepines Opiates CCI [redacted]
		Pregnancy	**Virology**	
		In females of childbearing potential: Serum pregnancy test Urine pregnancy test	Hepatitis B surface antigen Hepatitis B virus core antibody Hepatitis C Virus antibody (if positive, then reflex HCV RNA) Human immunodeficiency virus antibody	

* Not required for subjects with prior latent TB who have been treated with a full course of prophylaxis.

All labs will be assayed and calculated by a sponsor-designated laboratory unless otherwise specified, in accordance with the time points detailed in the Study Procedures Table (Appendix 3)

Unscheduled laboratory tests may be performed at the discretion of the investigator; if the test(s) is performed to evaluate laboratory results to resume study drug, samples must also be submitted to the sponsor-designated laboratory.

Appendix 7. EULAR/ACR 2019 Classification Criteria for Systemic Lupus Erythematosus

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight
Constitutional	
Fever	2
Hematologic	
Leukopenia	3
Thrombocytopenia	4
Autoimmune hemolysis	4
Neuropsychiatric	
Delirium	2
Psychosis	3
Seizure	5
Mucocutaneous	
Non-scarring alopecia	2
Oral ulcers	2
Subacute cutaneous OR discoid lupus	4
Acute cutaneous lupus	6
Serosal	
Pleural or pericardial effusion	5
Acute pericarditis	6
Musculoskeletal	
Joint involvement	6
Renal	
Proteinuria >0.5g/24h	4
Renal biopsy Class II or V lupus nephritis	8
Renal biopsy Class III or IV lupus nephritis	10

Immunology domains and criteria	Weight
Antiphospholipid antibodies	
Anti-cardiolipin antibodies OR	
Anti-β2GP1 antibodies OR	
Lupus anticoagulant	2
Complement proteins	
Low C3 OR low C4	3
Low C3 AND low C4	4
SLE-specific antibodies	
Anti-dsDNA antibody* OR	
Anti-Smith antibody	6

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Appendix 8. Cutaneous LE Disease Area and Severity Index (CLASI)

Cutaneous LE Disease Area and Severity Index (CLASI) ©

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

activity ⟷ damage

Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

Dyspigmentation

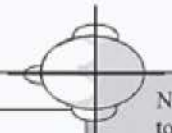
Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia

Recent Hair loss (within the last 30 days / as reported by patient)	
1-Yes 0-No	



NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score (For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)		Total Damage Score (For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)	

Appendix 9. Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

Study No.: _____ Patient Name: _____ _____ Visit Date: ___

(Enter weight in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 10 days.)

Weight	SLEDAI SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / $x10^9$/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / $x10^9$/L, exclude drug causes.

TOTAL SLEDAI SCORE _____

Appendix 10. Physician's Global Assessment of CLE Disease Activity

A horizontal visual analog scale will be used to record the physician's assessment of the patient's CLE disease activity.

Instructions:

Place a mark on the line below to indicate the subject's current CLE disease activity (independent of the subject's self assessment):

Appendix 11. Subject's Global Assessment of CLE Disease Activity

A horizontal, visual analog scale will be used to provide the subject's overall assessment of CLE disease activity.

Instructions:

Place a mark on the line below to indicate how active your skin condition (CLE) has been over the last week: