CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib and GS-9876 in Female Subjects with Moderately-to-Severely Active Cutaneous Lupus Erythematosus (CLE)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404
IND Number:	134040
EudraCT Number:	Not applicable
ClinicalTrials.gov Identifier:	NCT03134222
Indication:	Cutaneous lupus erythematosus
Protocol ID:	GS-US-436-4092
Gilead Clinical Program Manager:	Name: PPD Telephone: PPD Fax: PPD
Gilead Medical Monitor:	Name: PPD Telephone: PPD Fax: PPD Mobile: PPD
Protocol Version/Date:	Original: 19 December 2016 Amendment 1: 23 February 2017 Amendment 2: 30 June 2017 Administrative Amendment 3: 4 January 2018 Amendment 4: 15 October 2018

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PROTOCOL SYNOPSIS

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

Study Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib and GS-9876 in Female Subjects with Moderately-to-Severely Active Cutaneous Lupus Erythematosus (CLE)
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	134040 Not applicable NCT03134222
Study Centers Planned:	Approximately 20 centers in the United States (US) and Canada
Objectives:	The primary objective of this study is as follows: • To evaluate the efficacy of filgotinib and GS-9876 in female subjects with moderately-to-severely active cutaneous lupus erythematosus (CLE) The secondary objective of this study is as follows: • To evaluate the safety and tolerability of filgotinib and GS-9876 in moderately-to-severely active CLE The exploratory objectives of this study are as follows: [redacted]

Study Design: This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of filgotinib and GS-9876 in female subjects with moderately-to-severely active CLE.

Eligible subjects will be randomized 2:2:1 in a blinded fashion to 1 of 3 arms and receive daily oral doses of the following study drugs starting on Day 1 for 12 weeks:

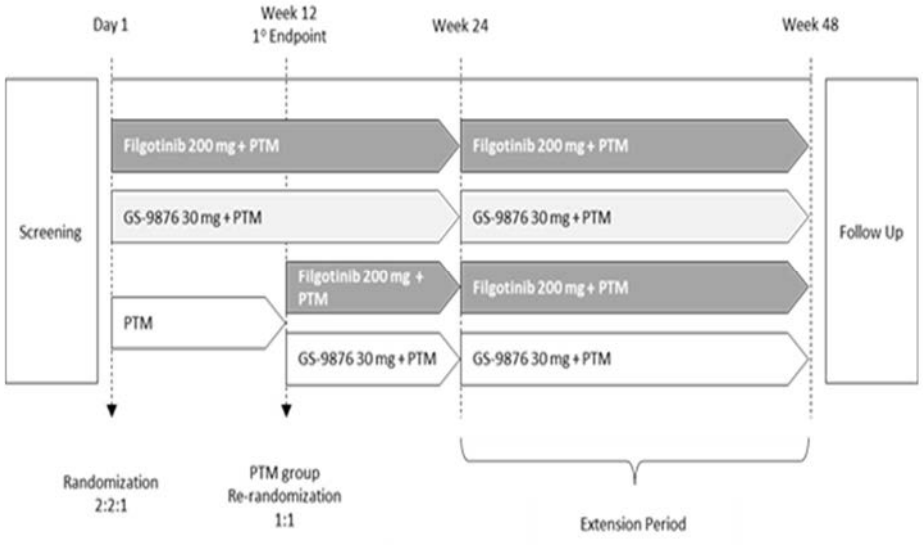
Arm	Study Drugs
Filgotinib 200 mg (n=20)	**filgotinib 200 mg** + PTM GS-9876 30 mg
GS-9876 30 mg (n=20)	**GS-9876 30 mg** + PTM filgotinib 200 mg
Placebo (n=10)	PTM filgotinib 200 mg + PTM GS-9876 30 mg

PTM = placebo to match

On Day 1, randomization will be stratified by two factors: (i) disease subtype (chronic cutaneous lupus erythematosus [CCLE] (eg, discoid lupus erythematosus [DLE]) vs subacute cutaneous lupus erythematosus [SCLE]) and (ii) concurrent background disease-modifying antirheumatic drug [DMARD] use vs no use.

At Week 12, upon completion of all scheduled assessments, subjects on placebo will be re-randomized 1:1 to receive filgotinib 200 mg + PTM GS-9876 30 mg once daily or GS-9876 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study in a blinded fashion. Dosing and assessments for all subjects will continue through Week 24.

Subjects who have not permanently discontinued study drug dosing during the first 24-week period may enter the subsequent 24-week extension period where they will continue to receive their assigned dose of study drug, in a blinded fashion.



Substudies:	CCI [redacted]
Number of Subjects Planned:	Approximately 50 female subjects
Target Population:	Adult female subjects with moderately-to-severely active CLE
Duration of Treatment:	A maximum of 48 weeks of study drug
Diagnosis and Main Eligibility Criteria:	**Main Eligibility Criteria:** • Female, ≥ 18 ≤ 75 years of age at the time of consent • Must have a diagnosis of CLE, per investigator evaluation, with the following: — Moderately-to-severely active CLE (Cutaneous Lupus Disease Area and Severity Index [CLASI] activity score ≥ 10) at screening and Day 1 — Prior intolerance or inadequate response to at least one of the listed medications for the treatment of CLE (Sections 4.2 and 4.3): • Stable dose (defined as no change in prescription for at least 28 days prior to Day 1) of antimalarials and/or topical or oral corticosteroids is permitted during the study (see Section 5.6.1 for dose restrictions and other details). Subjects who are not planning to continue these medications during the study must have discontinued them at least 28 days prior to Day 1 • Must not have used prohibited medications per Section 5.6.2
Study Procedures/ Frequency:	Study visits for all subjects will occur at: • **Screening:** Within 28 days prior to Day 1 • **Study Dosing Period:** Day 1 and at Weeks 2, 4, 8, 12, 14, 16, 20, and 24 or early termination (ET; if applicable)

Subjects who have not permanently discontinued study drug dosing during the first 24-week period may be eligible to enter the 24-week extension period:

- **24-week Extension Period:** Weeks 30, 36, 42, and 48 or ET (if applicable)
- **Follow-Up (FU) Visit:** A FU visit will be conducted 4 weeks after the last dose of study drug. Subjects who discontinue study drug ≥ 4 weeks prior to their last visit will not be asked to return for a FU visit

Screening Assessments:

Subjects who provide written informed consent will be screened for eligibility, and undergo the following tests/procedures: complete medical history (including demographics, surgical history, and CLE history with documentation of prior skin biopsy results, if available), review of medication use, complete physical examination, height, weight, Physician's Global Assessment (PGA), CLASI, vital signs (blood pressure, heart rate, respiratory rate, and temperature), 12-lead electrocardiogram (ECG), clinical labs (chemistry, hematology, coagulation, urinalysis, and urine protein to creatinine ratio), hepatitis B virus (HBV) test, hepatitis C virus (HCV) test, human immunodeficiency virus type 1 and type 2 (HIV-1, HIV-2) test, QuantiFERON® TB Gold in Tube test (if applicable) and chest x-ray (if not obtained within 3 months prior to screening), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin A1c (HbA_{1c}), thyroid stimulating hormone (TSH) test, urine drug and alcohol screen, serum pregnancy test (females of child-bearing potential only, as defined per protocol), follicle stimulating hormone (FSH) test (females of non-childbearing potential only, as defined per protocol),), and adverse event (AE) collection.

Day 1 through Week 24 (Study Dosing Period) Assessments:

Eligible subjects will be randomized on Day 1. Subjects will return to the study center at Weeks 2, 4, 8, 12, 14, 16, 20, and 24 and undergo the following tests/procedures: medical history updates (Day 1 only), review of medication use, symptom-driven physical examinations, PGA, CLASI, Subject's Global Assessment and other subject-reported measures (visual analogue scales [VAS], 36-item Short Form Health Survey [SF-36], Dermatology Quality of Life Index [DLQI], and Treatment Satisfaction Questionnaire for Medication [TSQM]), weight, vital signs, 12-lead ECG (Week 24 only), clinical labs (chemistry, hematology, coagulation, urinalysis, and urine protein to creatinine ratio), HCV monitoring (Weeks 12 and 24; if applicable), CRP, ESR, fasting lipids (Day 1 and Weeks 12 and 24), urine pregnancy test (females of child-bearing potential only), quantitative serum immunoglobulin test (Day 1 and Weeks 8 and 20), autoantibody panel and complement levels (Day 1 and Weeks 12 and 24), detailed target lesion assessment, representative photographs of areas

with skin involvement (identifying subject features should be obscured, as much as possible), detailed mucous membrane assessment (Day 1 and Weeks 2, 12, 14, and 24), and AE collection.

At Week 12, upon completion of all scheduled assessments, subjects on placebo will be re-randomized 1:1 in a blinded fashion to receive filgotinib 200 mg + PTM GS-9876 30 mg once daily or GS-9876 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study.

Subjects who discontinue study drug dosing at any time may continue with study visits, procedures, and assessments, if deemed medically appropriate by the investigator, but will not be eligible for entering the 24-week extension period.

Weeks 30 through 48 (24-week Extension Period) Assessments:

Subjects who have not permanently discontinued study drug dosing in the first 24-week period may enter the subsequent 24-week extension period where they will continue to receive their assigned dose of study drug, in a blinded fashion. Subjects will return to the study center at Weeks 30, 36, 42, and 48, and undergo the following tests/procedures: review of medication use, symptom-driven physical examinations, PGA, CLASI, Subject's Global Assessment and other subject-reported measures, weight, vital signs, 12-lead ECG (Weeks 36 and 48), clinical labs (chemistry, hematology, coagulation, urinalysis, and urine protein to creatinine ratio), HCV monitoring (Weeks 36 and 48; if applicable), CRP, ESR, fasting lipids (Week 42 only), urine pregnancy test (females of child-bearing potential only), quantitative serum immunoglobulin test (Week 42 only), autoantibody panel and complement levels (Week 42 only), detailed target lesion assessment, representative photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible), detailed mucous membrane assessment (Weeks 36 and 48), and AE collection.

Early Termination Visit Assessments:

Subjects who discontinue the study prematurely (prior to Week 24 or prior to Week 48 for subjects entering the 24-week extension period), will return to the study center for the early termination (ET) visit and undergo the following test/procedures: review of medication use, symptom-driven physical examination, PGA, CLASI, Subject's Global Assessment and other subject-reported measures, weight, vital signs, 12-lead ECG (if not completed within the prior 12 weeks), clinical labs (chemistry, hematology, coagulation, urinalysis, and urine protein to creatinine ratio), HCV monitoring (if applicable, if not completed within the prior 12 weeks), CRP, ESR, urine pregnancy test (females of child-bearing potential only), complement levels, detailed target lesion assessment, representative photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible), and AE collection.

	Follow-up Visit Assessments: Subjects will return to the study center for a FU visit 4 weeks after their last dose of study drug. The follow-up visit will include: review of medication use, a symptom-driven physical examination, PGA, CLASI, Subject's Global Assessment and other subject-reported measures (except for the TSQM), weight, vital signs, clinical labs (chemistry, hematology, coagulation, urinalysis, and urine protein to creatinine ratio), urine pregnancy test (females of childbearing potential only), complement levels, detailed target lesion assessments, representative photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible), and AE collection. *Subjects who discontinue study drug ≥ 4 weeks prior to their final study visit will not be asked to return for a FU visit.* **Pharmacokinetic Assessments:** Blood samples for PK analysis will be collected at Week 2 (at least 30 minutes and up to 3 hours postdose), anytime at Week 4, and within 2 hours prior to study drug administration at Weeks 12 and 24. **Biomarker Assessments:** Blood samples will be collected at screening, predose on Day 1 and at Weeks 2, 4, 12, 24, 48 (for subjects who enter the 24-week extension period), FU, and ET visit (if applicable). **Concomitant Medication Management:** Stable medications at Day 1 (per Section 5.6.1) are to be continued during the study. Refer to Section 5.6.2 for a list of prohibited medications.
Test Product, Dose, and Mode of Administration:	Filgotinib 200 mg tablet, oral, once daily GS-9876 30 mg tablet, oral, once daily
Reference Therapy, Dose, and Mode of Administration:	Placebo to match filgotinib 200 mg tablet, oral, once daily Placebo to match GS-9876 30 mg tablet, oral, once daily
Criteria for Evaluation:	
Safety:	Safety will be assessed through 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 primary endpoint is: • Change in CLASI activity score from baseline to Week 12 The secondary endpoints are: • Proportion of subjects at Week 12 with decrease of ≥ 5 points in CLASI activity score from baseline • Proportion of subjects at Week 12 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase) • Proportion of subjects at Week 24 with decrease of ≥ 5 points in CLASI activity score from baseline • Proportion of subjects at Week 24 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)
Pharmacokinetics:	Plasma concentrations of filgotinib, its metabolite (GS-829845), and GS-9876 will be analyzed.
Biomarkers:	Blood samples for assessment of markers of inflammation, immune status, and janus kinase (JAK)-signal transduction and activation of transcription (STAT) and spleen tyrosine kinase (SYK) pathway activation may be analyzed. Histopathologic, immunohistochemistry (IHC), and gene expression assessments may be performed on available biopsies. CCI [redacted]
Statistical Methods:	The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug. The primary endpoint is the change in CLASI activity score from baseline to Week 12. The primary analysis will consist of superiority test of filgotinib 200 mg versus placebo and GS-9876 30 mg versus placebo, respectively. All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment arm and by study part. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment arm.

The primary analysis will be conducted when all enrolled subjects either complete their Week 12 visit or prematurely discontinue from the study. The final analysis will be performed when all subjects complete the study or prematurely discontinue from the study.

Sample Size:

With a sample size of 50 subjects (20 in each active treatment arm and 10 in the placebo arm), there is a 79% power to detect a 2-point difference between each active arm and the placebo arm in the primary endpoint using a 2-sided 0.1-level test, assuming a common standard deviation of 2 and a 10% drop-out rate per arm.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

ACLE	acute cutaneous lupus
ACR20	American College of Rheumatology 20% improvement
AE	adverse event
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
ANA	antinuclear antibody
ANC	absolute neutrophil count
APLA	antiphospholipid antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUROC	area under the receiver operating characteristic curve
BAP	biomarker analysis plan
BCR	B-cell receptor
BCRP	breast cancer resistance protein
bDMARD	biologic disease-modifying antirheumatic drugs
BLQ	below the limit of quantitation
CCLE	chronic cutaneous lupus erythematosus
CD	cluster determinant
CD	Crohn's disease
CES	carboxylesterases
CIA	collagen-induced arthritis
CK	creatinine kinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CL_{cr}	creatinine clearance
CLE	cutaneous lupus erythematosus
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	contract research organization
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DLE	discoid lupus erythematosus
DLQI	Dermatology Life Quality Index
DMARD	disease-modifying antirheumatic drug
DMC	data monitoring committee

DNA	deoxyribonucleic acid
dsDNA	double stranded DNA
DSPH	(Gilead) Drug Safety and Public Health
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic case report form
ENA	extractable nuclear antigen
eSAE	electronic serious adverse event form
ESR	erythrocyte sedimentation rate
ET	early termination
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow-up
GCP	good clinical practice
GI	gastrointestinal
Gilead	Gilead Sciences, Inc.
GLP	Galapagos
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
hERG	human ether-a-gogo related gene
HIV	human immunodeficiency virus
HR	heart rate
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN	Interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Independent Review Board
IUD	intrauterine device
IWRS	interactive web response system

JAK	janus kinase
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
MCV	mean corpuscular volume
MMRM	mixed model for repeated measures
MTX	Methotrexate
NOAEL	no observed adverse effect level
NOELs	no observed effect levels
NSAID	nonsteroidal anti-inflammatory drug
OATs	organic anion transporters
P protein	phosphorylated protein
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PGA	Physician's Global Assessment
P-gp	P-glycoprotein
PK	pharmacokinetics
PT	preferred term
PT	prothrombin time
PTM	placebo to match
PXR	pregnane X receptor
Q1	first quartile
Q3	third quartile
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
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the Fridericia formula
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	statistical analysis plan
SCLE	subacute cutaneous lupus erythematosus
SD	standard deviation
SF-36	36 Item Short Form Health Survey
SLE	Systemic lupus erythematosus
SLEDAI-2K	systemic lupus erythematosus disease activity index 2000
SOC	system organ class
SjS	Sjogren's syndrome

Sm	Smith antigen
SSA	Sjogren's-syndrome-related antigen A
SSB	Sjogren's-syndrome-related antigen B
STAT	signal transduction and activation of transcription
SUSAR	suspected unexpected serious adverse reaction
SYK	spleen tyrosine kinase
TB	tuberculosis
TEAEs	treatment emergent adverse events
TLR	Toll-like receptor
TNFα	tumor necrosis factor alpha
TSH	thyroid-stimulating hormone
TSQM	Treatment Satisfaction Questionnaire for Medication
TYKs	tyrosine kinases
UGT	uridine disphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
vfPBMCs	viably frozen peripheral blood mononuclear cells
VL	viral load
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Cutaneous lupus erythematosus (CLE) is a chronic autoimmune disorder, most commonly diagnosed in women 20-50 years of age. Approximately 1/3 of women who are diagnosed with CLE also develop systemic lupus erythematosus (SLE) {Wieczorek 2014}. In a study of over 1,000 patients with CLE in Sweden, it was found that 24% of the patients carried a diagnosis of SLE, while another 18% gained a diagnosis of SLE over a 2 year period {Gronhagen 2011}. Thus, treatment and monitoring of CLE includes ongoing assessment for and/or treatment of SLE, which is also highly female-predominant.

Cutaneous lupus is histologically characterized by interface dermatitis, in which lymphocytes infiltrate the basal epidermis and induce apoptosis of keratinocytes, resulting in hydropic degeneration with colloid bodies. Inflammation in CLE is mediated in part by type I interferons as well as Toll-like receptor (TLR)-dependent and -independent mechanisms. Subtypes of CLE include: chronic cutaneous lupus erythematosus (CCLE), subacute cutaneous lupus erythematosus (SCLE), and acute cutaneous lupus erythematosus (ACLE). The most common subtype of CLE is CCLE, and in particular discoid lupus erythematosus (DLE) which accounts for approximately half of all CLE {Jarrett 2016}. A diagnosis of ACLE in isolation will not qualify a subject for entry into this study.

Overall, therapeutic options for CLE are limited {Winkelmann 2013}. There are few approved disease-modifying antirheumatic drugs (DMARDs) for CLE, and very limited clinical trial data in CLE for the biologic and synthetic DMARDs that have been approved for other indications. Avoidance of sunlight and topical sunscreen often help to limit disease flares, due to the photosensitive nature of the disease. Topical preparations of corticosteroids (eg, clobetosol), or injectable corticosteroids are commonly used, as well as topical immunosuppressants (eg, tacrolimus). Antimalarials (eg, chloroquine or hydroxychloroquine) are among the most common oral medications used. Other drugs used for CLE include: methotrexate (MTX), azathioprine, biologic disease-modifying antirheumatic drugs (bDMARDs; such as rituximab or belimumab), cyclophosphamide, cyclosporine, dapsone, gold salts, intravenous immunoglobulin (IVIG), mycophenolate, retinoids, and thalidomide, but efficacy with these agents is variable and toxicities can be dose limiting.

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective oral inhibitor of janus kinase (JAK) 1 being developed by Gilead Sciences, Inc. (Gilead) and Galapagos (GLP) NV. Janus kinase 1 is believed to play an integral part in the pathogenesis of various autoimmune diseases, due its role in inflammatory cytokine signaling.

GS-9876 is a potent and selective oral inhibitor of spleen tyrosine kinase (SYK) being developed by Gilead for the treatment of inflammatory diseases. Spleen tyrosine kinase is a cytoplasmic tyrosine kinase (TYK) primarily expressed in cells of the hematopoietic lineage, where it functions as a key signaling molecule mediating immunoreceptor signaling. Given its central role in immune cell signaling, inhibition of SYK is expected to affect multiple steps in the pathogenesis of several autoimmune diseases resulting in pleiotropic anti-inflammatory effects.

1.2. Filgotinib

1.2.1. General Information

For further information on filgotinib, refer to the current investigator's brochure (IB).

1.2.2. Nonclinical Pharmacology and Toxicology

Filgotinib is a highly selective, adenosine triphosphate (ATP)-competitive inhibitor of JAK1. In cellular assays, it inhibits JAK/signal transduction and activator of transcription (STAT)-driven processes with half maximal inhibitory concentration (IC_{50}) values from 179 nM upwards; in human whole blood assays, filgotinib exhibits approximately 30-fold selectivity over JAK2. Filgotinib demonstrated significant efficacy in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulphate sodium (DSS)-induced colitis model. Filgotinib's metabolite, GS-829845, exhibits a similar JAK1 selectivity profile, but is approximately 10 to 20-fold less potent than filgotinib.

In rats, filgotinib and GS-829845 had no effects on the respiratory system and CNS and no relevant effects on cardiovascular parameters (human ether-a-gogo related gene [hERG] and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845, at exposures 7-fold that of the C_{max} in human subjects dosed with filgotinib 200 mg once daily.

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib and GS-829845 were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the testes of both species, and in the incisor teeth of rats. Effects on the lymphoid system were fully reversible.

Filgotinib and GS-829845 are non-genotoxic.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg once daily of filgotinib in subjects with RA. Administration of filgotinib did not affect female fertility, however, impaired male fertility was observed in rats at exposures approximately 15-fold the human exposure at 200 mg of filgotinib in subjects with RA. The metabolite, GS-829845, did not have any effects on fertility parameters.

1.2.3. Clinical Trials of Filgotinib

A detailed description of all clinical studies can be found in the filgotinib IB.

1.3. GS-9876

1.3.1. General Information

For further information on GS-9876, refer to the current IB.

1.3.2. Nonclinical Pharmacology and Toxicology

1.3.2.1. Nonclinical Pharmacology and Safety Pharmacology

GS-9876 is a selective and potent ATP-competitive inhibitor of SYK with an IC_{50} value of 9.5 nM. Overall, GS-9876 is at least 7-fold more selective biochemically for SYK relative to all other protein kinases assayed. Functionally, GS-9876 inhibited anti-immunoglobulin (Ig) M-induced B-cell receptor (BCR)/SYK-mediated phosphorylation and activation of multiple downstream signaling pathways in primary human B-cells, suppressed anti-IgM mediated cluster determinant (CD) 69 and CD86 activation marker expression on B-cells, and proliferation of peripheral B cells. GS-9876 inhibited immune-complex stimulated tumor necrosis factor alpha (TNFα) and IL-1β release from primary human monocytes. In human blood, GS-9876 inhibited SYK autophosphorylation, anti-IgD/BCR-induced CD69 expression on B-cells, and anti-FceRI-stimulated CD63 expression on basophils with geometric mean half-maximal effective concentration (EC_{50}) values ranging from 171 nM to 301 nM.

In a MRL/lpr murine model of lupus, SYK inhibition showed a dose-responsive decrease in anti-dsDNA antibody titers and inhibition of proteinurea with an estimated SYK trough target inhibition of 50%. FACS analysis of splenic lymphocyte populations at study termination showed significant changes in lymphocyte subsets and activation markers with SYK inhibition including significant reductions in the percentage of follicular ($CD19^+/CD21^+/CD23^+$) and mature ($CD19^+/IgM^-/IgD^+$) B cells, as well as activated plasma cells ($CD19^+/CD138^+/CD69^+$). Activated T_{helper} cells ($CD4^+CD69^+$) and central memory T cells ($CD4^+/ CD44^+/CD62L^+$) were also reduced. A trend toward improved renal histopathology was observed with SYK inhibition.

In two independent rat CIA models in animals with established disease, GS-9876 caused significant and dose-dependent amelioration of clinical disease and histopathologic signs. Histological evaluation of joints demonstrated that GS-9876 reduced pannus formation, cartilage damage, bone resorption, and periosteal bone formation. Significant efficacy was seen with GS-9876 doses that produced C_{ave} exposures that were calculated to inhibit SYK phosphorylation by EC_{50}. GS-9876 was well tolerated at all doses and there were no treatment-related adverse effects on body weight, food and drink intake, in-life observations or clinical pathology parameters.

Safety pharmacology studies showed no clinically-relevant effects on the respiratory, and CNS systems after single oral doses up to 300 mg/kg. Cardiovascular effects in telemetered cynomolgus monkeys at ≥ 20 mg/kg included prolonged QTc interval from 5 through 25 hours postdose, slightly higher systolic, diastolic, and mean arterial pressure with lower heart rate through 6 hours postdose, and higher heart rate from 9 through 25 hours postdose. While differences in QTc interval were generally small, the changes were of sufficient magnitude to be considered biologically relevant. There were no inhibitory effects on the hERG potassium current when GS-9876 was tested up to a free drug concentration of 30 μM, which is approximately 207-fold above the observed steady state C_{max} at a 30 mg once daily dose. Further, no cardiovascular effects were observed in telemetered cynomolgus monkeys administered GS-9876 for 39 weeks at doses up to 15 mg/kg/day. The potential for GS-9876 to prolong the QTc interval was assessed with intensive time-matched electrocardiogram (ECG) monitoring in Gilead clinical studies GS-US-379-1372 and GS-US-379-1900, and no clinically significant changes in time-matched QTc intervals or in serial vital sign measurements were observed.

1.3.2.2. Nonclinical Toxicology

In repeat-dose studies, toxicity was assessed in rats and monkeys administered GS-9876 orally for up to 39 weeks. Dose-dependent effects on lymphocytes in both rats and monkeys were consistent with the expected pharmacology of SYK inhibition. Effects observed in rats and monkeys were increased erythrocyte turnover in rats at ≥ 10 mg/kg/day, and hemorrhage and thrombosis in monkeys at ≥ 20 mg/kg/day. At higher doses in rats (≥ 30 mg/kg/day), mortality associated with bacterial infections was seen, likely resulting from the immunomodulatory activity of GS-9876. Additional findings included lymphoid depletion in the thymus, changes in the pancreas, with secondary effects related to the immunomodulatory activity of GS-9876, and opportunistic bacterial infection, observed in several tissues. The no-observed-adverse-effect level (NOAEL) in rats was 10 mg/kg/day after 26 weeks dosing. For the highest proposed clinical dose of 30 mg once daily, estimated exposure margins are 2.4-/5.9- fold based on exposures at the NOAELs in the 26 week study in male/female rats, respectively.

In the 28-day monkey study, there were no adverse effects at doses up to 10 mg/kg/day, with hemorrhagic/thrombotic effects noted at 20 mg/kg/day. In the 39-week monkey study, there was no evidence of effects on hemostasis, and the NOAEL was 15 mg/kg/day, associated with an $AUC_{0\text{-}24hr}$ of 8040 ng•h/mL. One animal administered 15 mg/kg/day was sacrificed for humane reasons with persistent fecal changes, weight loss, deteriorating clinical condition, and large bowel inflammation. The moribund condition of this animal was not considered directly related to GS-9876 administration. For the 30 mg dose in planned Study GS US-436-4092, the estimated exposure margins is 2.2-fold based on exposures at the NOAEL in the 39-week study in monkeys , and 1.2-fold based on exposures at the mid dose of 10 mg/kg/day. In clinical studies GS-US-379-1372 and GS US-379-1900 no changes in platelets numbers, prothrombin time (PT), partial thromboplastin time (PTT), international normalized ration (INR) or bleeding time were observed.

In the pivotal developmental toxicity studies in pregnant rats and rabbits, there were no fetal malformations. At doses associated with significant maternal toxicity (reduced body weight gain and food consumption in rats and rabbits, and mortality and one abortion in rabbits), increases in post-implantation loss and late resorptions, reduced fetal body weights and fetal variations (delayed ossification) were noted in rats, with reduced fetal body weights in rabbits. In rats, the maternal NOAEL and embryo-fetal development NOEL was 30 mg/kg/day. In rabbits, the maternal NOAEL was not determined < 10 mg/kg/day and the embryo-fetal development NOEL was 10 mg/kg/day. For the 30 mg dose in planned Study GS-US-436-4092, estimated exposure margins are 23- and 1.0-fold compared to exposures at the fetal NOELs in rats and rabbits, respectively.GS-9876 was negative in the bacterial reverse mutation (Ames) assay, in vitro chromosomal aberration assay, and in vivo rat micronucleus assay and is therefore considered to be nongenotoxic. In the in vitro chromosome aberration assay in human lymphocytes, slight, but statistically significant increases in the number of polyploid cells was observed at the highest GS-9876 dose level evaluated. GS-9876 did not induce structural chromosome breakage when evaluated in the in vitro assay.

Table 1. Margins for GS-9876 Based on Systemic Exposure Relative to the Observed Human Exposure at 30 mg once daily (AUC)

Species	Duration	Route	NOAEL (mg/kg/day)	AUC_{0-24} (ng•h/mL)[a]	Margin[b]
Rat	Once daily x 26 weeks	Oral	10	8,800/21,800 (male/female)	2.4/5.9 (male/female)
Cynomolgus Monkey	Once daily x 39 weeks	Oral	15	8,040	2.2

NOAEL = no observed adverse effect level.
a Week 26 male and female rat AUC and week 39 Cynomolgus monkey AUC (combined sex)
b Margins of exposure were calculated using observed steady-state exposure (AUC_{tau}) in humans of 3708 ng•h/mL at 30 mg once daily in study GS-US-379-1900

1.3.2.3. Nonclinical Drug Metabolism and Pharmacokinetics

GS-9876 exhibits high absorption in rats, dogs and monkeys. Plasma protein binding is moderate in all species with the mean free fraction in humans of 20.4%.

After oral dosing to albino and pigmented rats, recovery of [^{14}C]GS-9876-derived radioactivity was high (≥ 97.8%) and the main route of elimination of GS-9876 was hepatobiliary with ≤ 5.1% orally dosed radioactivity found in urine and 69.4% in bile.

In vitro, GS-9876 exhibits high metabolic stability with human hepatocytes, liver fractions and individual metabolizing enzymes. GS-9876 had little inhibitory effect on the activities of the major human drug metabolizing CYP enzymes and was a weak inhibitor of human UGT1A1. GS-9876 is a weak inhibitor of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and is a substrate for those efflux transports. It is a weak inhibitor of the hepatic uptake transporters organic ion transporter (OAT) P1B1 and OATP1B3 but is a substrate for neither. Drug-drug interactions in vivo are unlikely through inhibition of human CYP enzymes, UGT1A1, or efflux or uptake transporters. The potential of GS-9876 to cause drug-drug interactions through induction is low as there is little activation of pregnane x receptor (PXR) or aryl hydrocarbon receptor (AhR) in vitro.

1.3.3. Clinical Trials of GS-9876

A detailed description of all clinical studies with GS-9876 may be found in the most current IB.

Completed Clinical Trials

GS-US-379-1372**:** This was a first-in-human, Phase 1, single-dose ranging study of GS-9876 in healthy adult volunteers to evaluate the safety, tolerability, PK, pharmacodynamics (PD), food effect, and drug-drug interaction potential using omeprazole. No risks were identified and no grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, laboratory parameters, or ECGs.

GS-US-379-1900: This was a single- and multiple-dose Phase 1 study of GS-9876 in healthy volunteers to evaluate the safety, tolerability, PK and PD of GS-9876. No risks were identified, all AEs were Grade 1 in severity. No dose relationships were observed between GS-9876 and

any AE. No AE was assessed by the investigator as related to study drug .There were no clinically significant changes in vital signs, physical findings, laboratory parameters, or ECGs.

GS-US-379-1582: This was a proof of concept trial in subjects with RA to evaluate efficacy, safety, tolerability and PK of GS-9876. GS-9876 was well-tolerated and no safety signals were identified.

Ongoing Clinical Trials

GS-US-379-1932: This is a Phase 1, open-label study in subjects with impaired renal function to evaluate the PK of GS-9876.

GS-US-445-4189: This is a Phase 2, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of filgotinib, GS-9876, and GS-4059 in adult subjects with active Sjogren's Syndrome.

GS-US-437-4093: This is a Phase 2, randomized, double-blind, study in subjects with lupus membranous nephropathy (LMN) to evaluate the safety and efficacy of GS-9876 and filgotinib.

1.4. Rationale for This Study

Although CLE affects approximately 70 per 100,000 persons in the United States (US), therapeutic options for CLE are limited {Winkelmann 2013}. There are few approved DMARDs for CLE (eg, hydroxychloroquine and MTX), and very limited clinical trial data in CLE for the various newer biologic and synthetic DMARDs that have been approved for other indications. Some individuals with CLE have an inadequate response or intolerance to available therapies. The most common oral therapy for CLE, hydroxychloroquine, has a rare, but serious cumulative risk of irreversible retinopathy which potentially limits its long-term use. There is an unmet need for orally administered therapies with novel and targeted mechanisms of action that can safely and effectively improve the disease.

Filgotinib is an orally administered, small molecule inhibitor of JAK1, an intracellular TYK dysregulated in subjects with inflammatory disorders. Filgotinib has demonstrated clinical activity and a favorable safety and tolerability profile in Phase 2 studies in subjects with moderately to severely active RA. Janus kinase 1 activation is required for type I interferon (IFN) signaling, which is thought to be central to both systemic and cutaneous lupus. Further, in vivo studies using a JAK1/JAK2 inhibitor (ruxolitinib) attenuated the development of skin lesions in the MRL/lpr mouse model of lupus {Chan 2015}.

Given its central role in immune cell signaling, inhibition of SYK is expected to have pleiotropic anti-inflammatory effects and affect multiple steps in CLE pathogenesis. B cells have been implicated in the pathogenesis of CLE as demonstrated by an increased number of B cells in the peripheral blood and lesions of individuals with DLE {Wouters 2004}. B cell depletion demonstrates an effect in individuals with certain types of CLE {Vital 2015}. As a critical mediator of BCR signaling, SYK inhibition suppresses BCR-stimulated proliferation, co-stimulatory molecule expression, and autoantibody production {Braselmann 2006, Coffey 2012}. Phosphorylated SYK and SYK-associated genes are highly expressed in several cell types in CLE skin including keratinocytes and infiltrating immune cells. Further, inhibiting SYK in

vitro decreases keratinocyte expression of pro-inflammatory cytokines {Braegelmann 2016}. Spleen tyrosine kinase inhibition in two lupus-prone mouse models (MRL/lpr and BAK/BAX) suppresses skin disease {Deng 2010}.

The data suggest that inhibition of SYK or of JAK1 may decrease several processes implicated in CLE pathophysiology including B-cell and T-cell activation.

1.4.1. Rationale for Endpoint and Timing

Change in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score will be the primary measure of efficacy compared to placebo. The CLASI is a standardized measure of cutaneous-lupus disease activity and damage widely used in clinical studies {Klein 2010}. Secondary measures will include physician and subject reported outcomes. Quality of life will be measured using validated questionnaires including the Dermatology Quality of Life Instrument (DLQI) {Holm 2016} and the 36 Item Short Form Health Survey (SF-36). Satisfaction with the study drugs will be measured using the Treatment Satisfaction Questionnaire for Medication (TSQM).

Given the chronic nature of CLE, the primary endpoint (change in the CLASI activity score) will be assessed at Week 12 to provide adequate time for clinical response in skin scores. The selection of this time point is based on prior studies of CLE and other dermatological inflammatory conditions such as plaque psoriasis {Schmitt 2014} and on the speed of action of filgotinib (approximately 80-90% of total clinical benefit achieved by week 12), as demonstrated in Phase 2b studies of subjects with active RA (protocols GLPG0634-CL-203 and GLPG0634-CL-204). Review of the published information on prior randomized studies in CLE demonstrates a range of drug administration duration between 8 weeks for hydroxychloroquine {Ruzicka 1992} and 6 months for MTX {Carneiro 1999}, supporting the idea that a 12 week primary endpoint is both clinically and ethically appropriate and allows an acceptable time to assess initial response to therapy.

1.4.2. Rationale for Dose

Enrolled subjects will be randomized to receive once daily oral filgotinib (200 mg), GS-9876 (30 mg), or matched placebo tablets. The regimens of filgotinib and GS-9876 are based on safety data from clinical studies and supported by non-clinical safety data. Clinical efficacy data further support the filgotinib dose.

Results from Phase 2a studies (GLPG-CL-201 and GLPG-CL-202) and Phase 2b studies (GLPG-CL-203 and GLPG-CL-204) showed that 200 mg once daily filgotinib was well tolerated and demonstrated clinical efficacy (ACR20/50/70 and DAS28[CRP]) in subjects with RA. Exposure-response analysis of data from Phase 2 studies indicated a dose-dependent increase in efficacy, with a plateau at the 200 mg total daily dose on the dose-response curve. These results are consistent with the relationship observed between filgotinib exposures and pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 (~78%) was achieved at or above the 200 mg total daily dose {Namour 2015}. Safety data collected across Phase 2 clinical studies showed no dose-dependent trends in the incidence

of AEs or SAEs. Based on the overall risk-benefit observed in Phase 2b studies, as well as the clinical overlap of RA and CLE, 200 mg once daily filgotinib is expected to be a safe dose to evaluate efficacy in subjects with CLE.

A 30 mg once daily dose of GS-9876 will be investigated in this study. In the multiple ascending dose study (GS-US-379-1900), GS-9876 doses of up to 50 mg once daily for 7 days were well tolerated in healthy volunteers. A trial of GS-9876 30 mg once daily is also under investigation in subjects with RA (GS-US-379-1582). Based on the similarity in risk-benefit profiles between RA and CLE, a 30 mg once daily dose is expected to have an acceptable safety profile and have the potential to be efficacious in CLE.

The totality of available data support the use of filgotinib 200 mg once daily and GS-9876 30 mg once daily for Phase 2 evaluation.

1.5. Risk/Benefit Assessment for the Study

Based on the clinical data to date, as well as the data from nonclinical efficacy and mechanistic studies, there is a positive benefit-risk ratio for the development of filgotinib and GS-9876 in this underserved disease. This is particularly true for patients with CLE, who are at an increased risk of developing or having concomitant systemic disease, notably in the form of SLE.

Filgotinib has been administered in Phase 2b studies of subjects with RA and Phase 2b studies of subjects with CD at daily doses ranging from 50-200 mg. In general, filgotinib has been safe and well-tolerated in all populations studied. No clinically relevant impact on cardiovascular parameters (including vital signs and ECGs), respiratory or neurologic function has been observed in trials of filgotinib. In the Phase 2b studies in RA, the most common AEs were in the Infections and Infestations SOC, and infections were reported more commonly in the filgotinib groups. Pneumonia is an identified risk for filgotinib and serious infection is considered an important potential risk. Reference is made to the IB for further information.

As filgotinib is an immunomodulatory agent, malignancy is closely monitored in clinical studies. Although an association of NHL and other malignancies with filgotinib has not been established, “NHL and other malignancies” is considered to be an important potential risk. Reference is made to the IB for further information.

Nonclinical studies in rats and dogs identified lymphoid tissues and testes as target organs for filgotinib in long-term repeat-dose toxicity studies. Although decreased lymphocyte numbers observed in nonclinical studies have not been seen in clinical studies, hematological assessments will be performed throughout the present study to ensure this potential risk is appropriately monitored. In both rats and dogs, microscopic findings in the testes included germ cell depletion and degeneration with reduced sperm content and increased cell debris in the epididymis, and reduced fertility in male rats. When using the AUC at the NOELs for dogs in the 26 and 39-week chronic toxicity studies, and in the 39-week targeted exposure toxicity study, the exposure margins compared with the proposed clinical dose of 200 mg once daily are 2.3, 1.8, and 3.4-fold, respectively. Reference is made to the IB for further information about nonclinical and clinical testicular findings.

GS-9876 is a highly selective SYK inhibitor with once daily dosing. Nonclinical studies show that SYK inhibition may have therapeutic value in the treatment of multiple autoimmune diseases such as RA, SLE, autoimmune cytopenias, as well as allergic and autoinflammatory diseases. Clinical experience with GS-9876 is limited.

In repeat dose toxicity studies of GS-9876 (in rats for up to 26 weeks and in cynomolgus monkeys for up to 39 weeks), the primary observed effects were reversible, dose-dependent decreases in circulating lymphocytes, and decreased lymphocytes in various tissues (spleen, lymph nodes, thymus, and/or bone marrow), consistent with the expected pharmacology of SYK inhibition {Barr 2012}. Additionally, effects on erythrocyte turnover were seen in rats, and effects on hemostasis (hemorrhage and thrombosis) were seen in monkeys. In clinical studies of GS-9876 in healthy volunteers, no safety signals were identified and no grade 3 or 4 AEs were reported. There were no clinically significant changes in vital signs, physical findings, laboratory parameters, or ECGs. Given the role of SYK in platelet activation and aggregation, bleeding time was evaluated in the study subjects; no clinically relevant prolongation was noted.

Filgotinib is contraindicated in pregnancy; highly effective contraception is to be used across all clinical studies to mitigate this risk.

Preclinical and clinical data support the further clinical development of filgotinib and GS-9876 due to their potential benefit as novel therapies in CLE, with an acceptable level of risk consistent with immunomodulation in this patient population. Controlled trials will be utilized to minimize risk to subjects, while gaining understanding of drug efficacy. The development of GS-9876 and filgotinib are expected to provide valuable alternatives to existing treatments for CLE and related diseases.

1.6. Compliance

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

2. OBJECTIVES

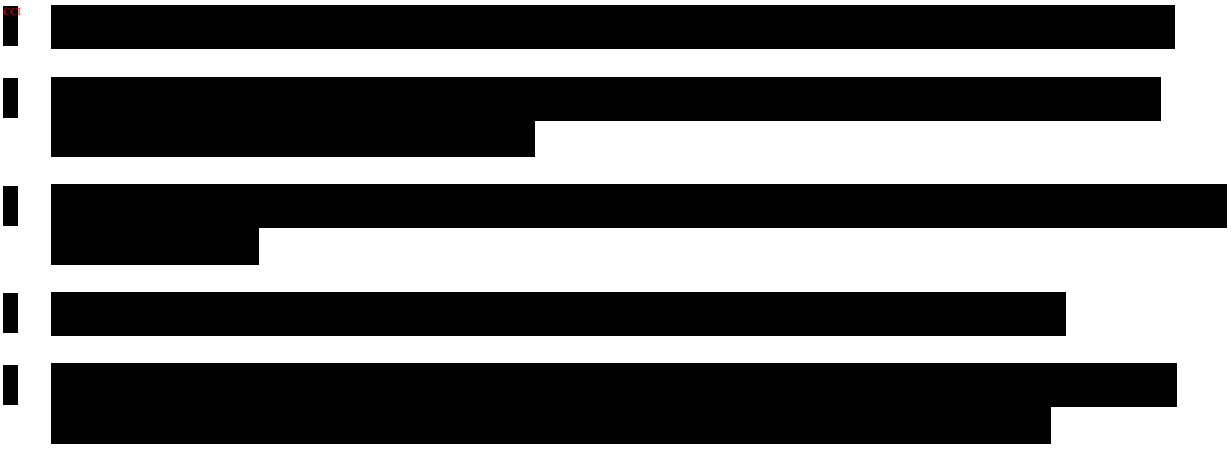
The primary objective of this study is as follows:

- To evaluate the efficacy of filgotinib and GS-9876 in female subjects with moderately-to-severely active CLE

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of filgotinib and GS-9876 in moderately-to-severely active CLE

The exploratory objectives of this study are as follows:



3. STUDY DESIGN

3.1. Endpoints

The primary endpoint of this study is:

- Change from baseline in CLASI activity score from baseline to Week 12

The secondary endpoints of this study are:

- Proportion of subjects at Week 12 with decrease of ≥ 5 points in CLASI activity score from baseline
- Proportion of subjects at Week 12 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)
- Proportion of subjects at Week 24 with decrease of ≥ 5 points in CLASI activity score from baseline
- Proportion of subjects at Week 24 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)

The exploratory endpoints of this study include:

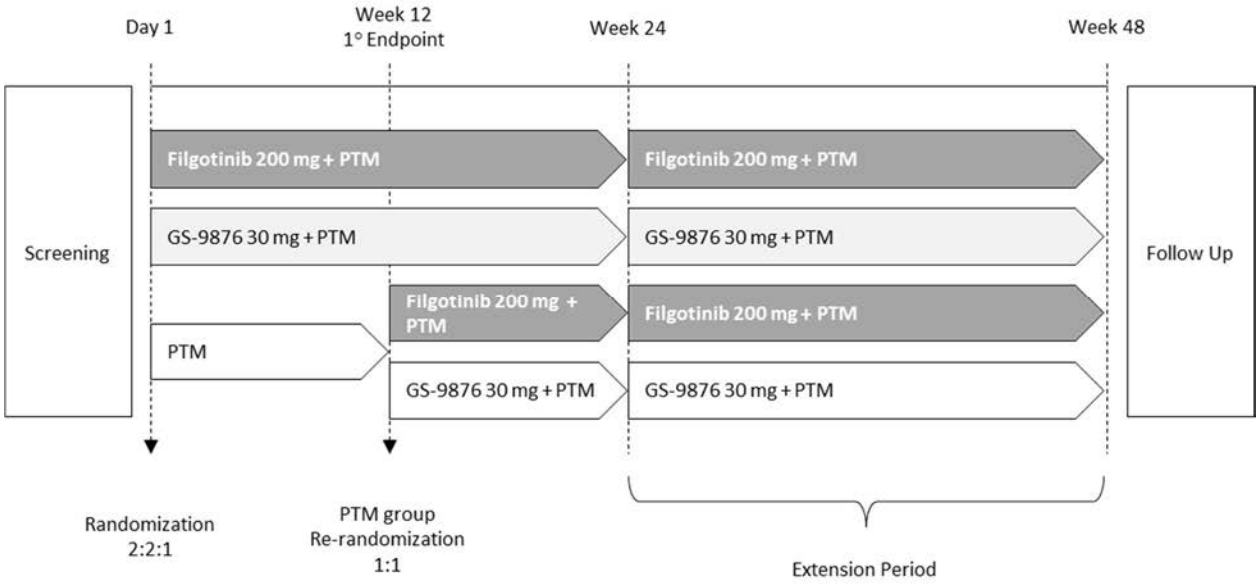
CCI [redacted]

3.2. Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of filgotinib and GS-9876 in female subjects with moderately-to-severely active CLE.

A schematic of this study is provided in Figure 1.

Figure 1. Study Schema



3.3. Study Treatments

Eligible subjects will be randomized 2:2:1 in a blinded fashion to 1 of 3 arms and receive daily oral doses of the following study drugs starting on Day 1 for 12 weeks:

Arm	Study Drugs
Filgotinib 200 mg (n=20)	filgotinib 200 mg + PTM GS-9876 30 mg
GS-9876 30 mg (n=20)	GS-9876 30 mg + PTM filgotinib 200 mg
Placebo (n=10)	PTM filgotinib 200 mg + PTM GS-9876 30 mg

PTM = placebo to match

On Day 1, randomization will be stratified by two factors: (i) disease subtype (CCLE [eg DLE] vs SCLE) and (ii) concurrent background DMARD use vs no use.

At Week 12, upon completion of all scheduled assessments, subjects on placebo will be re-randomized 1:1 to receive filgotinib 200 mg + PTM GS-9876 30 mg once daily or GS-9876 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study in a blinded fashion. Dosing and assessments for all subjects will continue through Week 24.

Subjects who have not permanently discontinued study drug dosing in the first 24-week period may enter the subsequent 24-week extension period where they will continue to receive their assigned dose of study drug, in a blinded fashion.

3.4. Duration of Treatment

Randomized subjects will receive a maximum of 48 weeks of study drug.

3.5. Subject Discontinuation Criteria

3.5.1. Study Drug Interruption Considerations

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

Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the Gilead medical monitor*:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the Gilead medical monitor
- If the subject has any signs or symptoms suggestive of infection (regardless of severity), study drug dosing should be immediately interrupted, and the medical monitor notified. 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 judgment of the investigator.
- Refer to Section 7.5 for details on study drug interruption due to AEs that are related to the study drug(s)

NOTE: During the time of study drug interruption for any of the above, the subject may continue to have study visits and to take part in procedures and assessments, if deemed medically appropriate by the investigator.

3.5.2. Study Drug Discontinuation Criteria

The Gilead medical monitor should be consulted prior to study drug discontinuation whenever feasible.

Study drug should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active hepatitis C virus (HCV) during the study, as evidenced by HCV RNA positivity
- 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
- [redacted]
- Female subject becomes pregnant during the study; refer to Section 7.7.2.1
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board (IRB)/ independent ethics committee (IEC)
- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the Gilead medical monitor
- Laboratory Criteria: After becoming aware of any of the following abnormal laboratory values, 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 and further care of the subject's CLE should be as directed per the investigator.

  a) Neutrophil counts < 750 neutrophils/mm^3 (SI: < 1.0 x 10^9 cells/L)

b) Hemoglobin values < 8.0 g/dL (SI: < 80 g/L)

c) Platelet counts < 75,000 platelets/mm^3 (SI: < 75.0 x 10^9 cells/L)

d) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal range (ULN) AND total bilirubin > 2 x ULN or accompanied by symptoms consistent with hepatic injury

e) AST and/or ALT elevations > 3 x ULN accompanied by elevated international normalized ratio (INR) >1.5[1]

f) AST or ALT > 5 x ULN[1]

g) Estimated creatinine clearance (CL_{cr}) < 40 mL/min based on the Cockcroft-Gault formula

Subjects who discontinue study drug dosing at any time may continue with study visits, procedures, and assessments, if deemed medically appropriate by the investigator, but will not be eligible for entering the 24-week extension period. Subjects who permanently discontinue study drug for any reason will not be replaced.

Subjects withdrawing from the study should complete the early termination (ET) and 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 24 weeks of dosing (or 48 weeks of dosing if entering the extension period) plus the FU visit 4 weeks after the last dose of study drug (if applicable).

3.7. Post Study Care

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

[1] In each case, there is a need for additional investigations, such as review of ethanol, recreational drug and dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging should be promptly discussed with the study medical monitor.

3.8. Biomarker Testing

3.8.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs, and to increase knowledge and understanding of the biology of CLE or related diseases. The specific analyses may include, but will not be limited to, the assays listed below.

- Plasma and serum samples for analysis of circulating factors including but not limited to cytokines, microRNA, and metabolites
- Whole blood samples and vfPBMCs to assess cell phenotype and function
- PAXgene blood samples for leukocyte gene expression analysis
- [redacted]

The biomarker sample collection schedule is described in the Study Procedures Table (Appendix 2). Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens collected. The testing outlined above is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

Specimens will be collected from all subjects. The biomarker samples will be destroyed no later than 15 years after the end of study. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

3.8.1.1. Biomarker Samples for Optional Future Research

CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to enroll approximately 50 subjects with moderately-to-severely active CLE.

4.2. Inclusion Criteria

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

1) Female, ≥ 18 to ≤ 75 years of age at the time of initial written informed consent

2) Must have a diagnosis of CLE (CCLE (eg, DLE) or SCLE), per investigator evaluation, with the following:

   a) Moderately-to-severely active CLE {Klein 2010}, with a CLASI activity score ≥ 10 at screening and Day 1

   b) Prior intolerance or inadequate response (per investigator judgment) to at least one of the following medications *for the treatment of CLE:*

      - Topical corticosteroids or topical tacromilus, administered for ≥ 3 months
      - Oral corticosteroids ≥ 10 mg/day taken for ≥ 3 months
      - A conventional synthetic disease-modifying antirheumatic drug (csDMARD), including, but not limited to: chloroquine, quinicrine, hydroxychloroquine, azathioprine, mycophenolate, leflunomide, dapsone, or MTX, administered for ≥ 3 months
      - A bDMARD (such as belimumab or abatacept) administered for ≥ 3 months, or ≥ 1 dose of a cell-depleting bDMARD, such as rituximab. Subjects with prior exposure to a B-cell depleting bDMARD (at any time) must have presence of CD19+ B cells by flow cytometry at screening

3) Subjects using antimalarials and/or topical and/or oral corticosteroids (≤ 10 mg prednisone) must agree to one of the follow (a or b):

   a) Continue stable doses from 28 days prior to Day 1 through Week 12 of the study (see Section 5.6.1 for dose restrictions and other details)

   b) Discontinue these medications at least 28 days prior to Day 1

4) Females of childbearing potential (as defined in Appendix 5) must have a negative pregnancy test at screening and Day 1

5) Subjects of childbearing potential (as defined in Appendix 5) who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5

6) Lactating subjects must agree to discontinue nursing starting from the time of written consent through the study and for 36 days after their last dose of study drug

7) Subjects must agree not to undergo in vitro fertilization or donate their eggs for reproductive purposes, starting at the time of written consent through the study and for 36 days after their last dose of study drug

8) Meet either of the following tuberculosis (TB) screening criteria (a or b):

   a) No evidence of active or latent TB:

      - Negative history of TB infection and
      - Negative QuantiFERON® TB-Gold In-Tube test (Note: QuantiFERON® tests with inconclusive results may be repeated one time. If the repeat result is also inconclusive, the subject is excluded from the study) and
      - Negative chest X-ray results (radiographs taken at Screening or within 90 days prior to screening with films or report available for investigator review)

   b) Subjects with prior **latent** TB who have been treated with a full course of prophylaxis as per local guidelines (Note: appropriate documentation of previous treatment is required. In these cases, a QuantiFERON® TB-Gold In-Tube test is not needed, but a chest radiograph must be obtained at screening or within 3 months prior to screening [report or films must be available]. In addition, these cases must be approved by the Gilead medical monitor prior to enrollment)

   NOTE: subjects with a new diagnosis of latent TB or prior untreated/partially treated latent TB are NOT allowed (ie, subjects who require prophylactic therapy for TB during the study). Subjects with current or prior **active** TB are excluded (regardless of treatment).

9) Are able and willing to sign the informed consent as approved by the IRB/IEC. Written consent must be provided before initiating any screening evaluations. Subjects must have read and understood the ICF, must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments; subjects who cannot read or understand the ICF may not be enrolled by a guardian, representative, or any other individual

4.3. Exclusion Criteria

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

1) Have active SLE or Sjogren's syndrome (SjS) that requires use of a prohibited medication (refer to Section 5.6.2). Systemic lupus erythematosus or SjS that is readily managed with protocol-permitted medications is allowed, per investigator judgment

2) Have another highly active inflammatory/autoimmune/rheumatic disease (such as highly active RA, nephritis, or CNS inflammation) which would compromise subject safety or interfere with the conduct of the study (per investigator judgment). Stable conditions, eg, stable thyroiditis, are permitted

3) Previous dosing within 3 months of screening with a JAK inhibitor or SYK inhibitor (marketed or investigational)

4) Previous history of cyclophosphamide use (at any time)

5) Known hypersensitivity to the study drugs, their metabolites, or formulation excipients

6) Major surgery (requiring regional block or general anesthesia) within 30 days prior to screening, or planned during the study

7) Active infection that is clinically significant, per investigator judgment, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 60 days prior to screening; or any infection requiring oral anti-infective therapy within 30 days prior to screening

8) Subjects who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study or for 36 days after their last dose of study drug

9) A positive test result for human immunodeficiency virus (HIV)-1 and 2 antibody at or prior to screening

10) Positive for HCV antibodies at screening. Subjects with positive HCV antibody (Ab) will 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 ongoing monitoring as outlined in the schedule of assessments

11) Positive for hepatitis B surface antigen (HBsAg) or HBV core antibodies at screening (regardless of HBV VL)

12) History of malignancy within the last 5 years prior to screening (except for successfully treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence)

13) History of lymphoproliferative disorder or current lymphoproliferative disease

14) History of organ or bone marrow transplant

15) Use of prohibited concomitant medications per Section 5.6.2

16) Any chronic, uncontrolled medical condition which would put the subject at increased risk during study participation, such as uncontrolled: diabetes, hypertension, morbid obesity, thyroid, adrenal, pulmonary, hepatic, renal, neurologic or psychiatric disease, or other disease of concern, as per judgment of investigator

17) Administration of a live/attenuated vaccine within 4 weeks prior to Day 1, or planned during the study or for 12 weeks after subject's last dose of study drug

18) History of opportunistic infection or immunodeficiency syndrome, which would put the subject at risk, per investigator judgment

19) Currently on systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis [PCP], cytomegalovirus [CMV], Herpes zoster, and atypical mycobacteria). Past history of disseminated Staphyloccoccus aureus or disseminated Herpes simplex infection

20) History of symptomatic Herpes zoster or herpes simplex within 12 weeks of screening, or any history of disseminated Herpes simplex, Herpes zoster, ophthalmic zoster, or central nervous system zoster

21) Blood loss, donation (> 500 mL), or blood product transfusion within 12 weeks of Day 1

22) Known bleeding disorder or hypercoagulable state; antiphospholipid antibody (APLA) syndrome with prior clinically significant event (per judgment of investigator); or on chronic anticoagulation/anti-platelet therapy such as warfarin, heparin, etc, as outlined in Section 5.6.2 (NOTE: stably prescribed chronic aspirin therapy ≤ 325 mg/day for cardiovascular prophylaxis is allowed)

23) Current drug or alcohol abuse, per judgment of investigator

24) Any condition or circumstances which in the opinion of the investigator may make a subject unlikely or unable to complete the study or comply with study procedures and requirements

25) Participation in any clinical study of an investigational drug within 4 weeks or 5 half-lives prior to screening, whichever is longer. Exposure to investigational biologics should be discussed with the Gilead medical monitor

26) Tests performed at the central laboratory at screening that meet any of the criteria below (at the investigator's discretion, out of range lab values may be retested one time to rule out laboratory error):

    i) Hemoglobin < 8.0 g/dL (International System of Units [SI]: < 80 g/L);

    ii) Absolute neutrophil count (ANC) < 1.5 x 10^3 cells/mm^3 (SI: < 1.5 x 10^9 cells/L);

    iii) Platelet count < 100 x 10^3 cells/mm^3 (SI: < 100 x 109 cells/L);

    iv) ALT or AST ≥ 1.5 x upper limit of normal ULN;

    v) Total bilirubin level ≥ 2 x ULN unless the subject has a diagnosis of Gilbert's disease with clear documentation

    vi) Estimated CL_{cr} < 60 mL/min based on the Cockcroft-Gault equation.

4.4. Screen Failures

Subjects who do not meet eligibility criteria for study entry ("screen failures") may be rescreened one time in select cases. For example,

- To adequately washout a concomitant medication
- Administrative reasons (eg, exceeding the screening window due to issues with appointment scheduling or obtaining results of laboratory data)

Written approval must be obtained from the sponsor prior to rescreening. Rescreening may not be used to recheck a subject who is likely unsuitable for the study (for example, to check whether a chronically abnormal laboratory test is closer to normal range).

Subjects who are permitted to rescreen must repeat the informed consent process and sign a new informed consent form. A new screening number will be assigned. The following test/procedure will not need to be repeated (unless required per investigator judgment) if results are available within the appropriate timeframe:

- Chest x-ray, if performed within 3 months prior to the rescreening visit

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be employed 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. Subjects will be assigned a screening number at the time of consent.

5.1.1. 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 IWRS system for that subject. Gilead recommends but does not require that the investigator contact the Gilead 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 on the eCRF, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Gilead medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and 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.

Gilead Drug Safety and Public Health (DSPH) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description of Filgotinib and PTM Filgotinib

5.2.1. Formulation of Filgotinib and PTM Filgotinib

Filgotinib 200 mg tablets are beige, debossed with "GSI" on one side and "200" on the other, capsule-shaped, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo to match filgotinib 200 mg tablets are identical to the active tablets in appearance. Placebo to match filgotinib 200 mg tablets contains the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

5.2.2. Packaging and Labeling of Filgotinib and PTM Filgotinib

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

Study drugs to be distributed to centers in North America shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations as applicable.

5.3. Description of GS-9876 and PTM GS-9876

5.3.1. Formulation of GS-9876 and PTM GS-9876

GS-9876 will be supplied as 30 mg tablets that are round, plain-faced and film-coated blue. Each tablet contains 30 mg of GS-9876 free base as the succinate form (GS-9876-02). The GS-9876 tablets contain commonly used excipients including microcrystalline cellulose, mannitol, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and FD&C blue #2/indigo carmine aluminum lake.

Placebo to match tablets will be supplied that are identical in physical appearance to the GS-9876 30 mg tablets and contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and FD&C blue #2/indigo carmine aluminum lake.

5.3.2. Packaging and Labeling of GS-9876 and PTM GS-9876

GS-9876 and PTM GS-9876 tablets are packaged in white, HDPE bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in North America will be labeled to meet applicable requirements of the FDA and/or other local regulations.

5.4. Storage and Handling of Study Drugs

Filgotinib, PTM filgotinib, GS-9876, and PTM GS-9876 tablets should be stored at controlled room temperature of 25 ºC (77 ºF); excursions are permitted between 15 ºC and 30 ºC (59 ºF and 86 ºF). Storage conditions are specified on the label.

Until dispensed to the subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drugs and to ensure proper product identification, the drug products should not be stored in a container other than the containers in which they are supplied. 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 when handling.

5.5. Dosage and Administration of Study Drugs

Study drugs will be administered once daily with or without food. Each subject should be given instructions to maintain approximately the same daily time of administration to ensure a similar dosing interval between study drug doses.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication 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 circumstances. In those cases, the missed dose should be returned to the study drug bottle.

5.6. Prior and Concomitant Medications

All medications taken for the treatment of CLE will be recorded in the source documents and on the eCRF. All other medications (for non-CLE indications) taken up to 30 days prior to the screening visit through the end of the study (4 weeks after the last dose of study drug) will be recorded in the source documents and on the eCRF. At each study visit, the study center will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, dietary supplements, vitamins, and minerals.

Effective current 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 providers. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Gilead medical monitor should be consulted prior to initiation of the new medication, where possible. In instances where an excluded medication is initiated prior to discussion with the sponsor, the investigator must notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.6.1. Allowed Concomitant Medications

5.6.1.1. Concomitant Medications for CLE

The allowed concomitant medication(s) for CLE should be maintained, as much as possible, at stable doses (defined as no change in prescription) 28 days prior to Day 1 through Week 12:

- Class V-VII topical corticosteroids for CLE as listed below (administered per investigator judgment). 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 corticosteroids for CLE ≤ 10 mg prednisone/day (or equivalent). Subjects who are not planning to continue oral corticosteroids during the study must have discontinued them at least 28 days prior to Day 1
- Oral antimalarials (eg, chloroquine ≤ 250 mg/day, hydroxychloroquine ≤ 400 mg/day, or quinacrine ≤ 100 mg/day) for CLE (administered per investigator judgment). Subjects who are not planning to continue oral antimalarials during the study must have discontinued them at least 28 days prior to Day 1
- Oral dapsone ≤ 100 mg/day. Subjects who are not planning to continue dapsone during the study must have discontinued the drug at least 28 days prior to Day 1
- Oral or injectable MTX ≤ 20 mg per week (subjects on MTX should also be on folic acid supplementation [or equivalent], per local standard of care). All local standard-of-care practices for the administration of MTX, including laboratory testing, follow-up care, and contraindications should be performed throughout the study. The concomitant use of medicines which may increase the risk of hepatotoxicity and/or nephrotoxicity with MTX (such as NSAIDs, salicylates, or other folate antagonists) should be avoided, as much as possible, in accordance with clinical practice

After completion of the Week 12 visit, the dose and/or frequency of these medications may be reduced one or more times per investigator judgment. In these cases, the dose and/or frequency may be increased again as needed, but should not exceed the subject's Day 1 dose and frequency.

Subjects who require concomitant medications at doses and/or frequencies that are higher than their Day 1 dose for ≥ 14 consecutive days are to be withdrawn from study drug but may continue with study visits per investigator judgment.

Dose adjustment for toxicity management is allowed at any time. A toxicity requiring dose adjustment should be reported as an AE or SAE and managed as outlined in Section 7.5.

5.6.1.2. Other Concomitant Medications

The following concomitant medications should be maintained, as much as possible, at stable prescription for at least 28 days prior to Day 1 and throughout the duration of the study.

- Cevilimine or pilocarpine, as prescribed by investigator
- Azathioprine up to a maximum of 2 mg/kg bodyweight/day or 300 mg/day, whichever is lower
- Vitamins, minerals, and herbal supplements
- Hormonal contraceptives or female hormone replacement therapy

- Other chronic therapies including, but not limited to, antihypertensives, thyroid replacement, analgesics, daily aspirin for cardiovascular prophylaxis (≤ 325 mg/day), and chronic nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesics

5.6.2. Prohibited Concomitant Medications

The prohibited medications are as follows:

Table 2. Prohibited Medications

Drug Class	Agents Disallowed	Prohibited Period
Biologic Immunomodulator	Anti-tumor necrosis factor drugs infliximab, adalimumab, belimumab, golimumab, certolizumab, rituximab (CD19+ B cells must be present), dupilumab, or biosimilar agent (if applicable)	90 days prior to screening through the end of study participation
	Any other investigational immunomodulatory biologic agent or biosimilar (if applicable)	90 days or 5 half-lives prior to screening (whichever is longer) through the end of study participation
Prohibited CLE Medications		
Corticosteroids	Oral corticosteroids > 10 mg prednisone equivalent/day	28 days prior to Day 1 through the end of study participation
	Injectable corticosteroids	28 days prior to Day 1 through the end of study participation
	Class I-IV topical corticosteroids	28 days prior to Day 1 through the end of study participation
Non-biologic Immunomodulator	Azathioprine (> 2 mg/kg bodyweight/day or 300 mg/day, whichever is lower), colchicine, cyclosporine, dapsone (>100 mg/day), tacrolimus (oral or topical), gold salts, minocycline, MTX > 20 mg/week (subcutaneous or oral), mycophenolate, penicillamine, sirolimus or other immunomodulatory/immunosuppressive therapies (with the exception of oral antimalarials as permitted in Section 5.6.1.1)	28 days prior to Day 1 through the end of study participation
Strong P-gp Inducers[a]		
Anticonvulsants	Phenobarbital, phenytoin, or carbamazepine	21 days prior to Day 1 through the end of study participation
Antimycobacterials	Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort or danshen (salvia miltiorrhiza)	

Drug Class	Agents Disallowed	Prohibited Period
CYP3A4 Inhibitors[b]		
Strong CYP3A4 Inhibitors	Clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, telaprevir, boceprevir, grapefruit juice, idelalisib, Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir), troleandomycin, or mibefradil	14 days prior to Day 1 through the end of study participation
Moderate CYP3A4 Inhibitors	Fluconazole, erythromycin, diltiazem, dronedarone, aprepitant, casopitant, imatinib, verapamil, tofisopam, ciprofloxacin, cimetidine, cyclosporine, Schisandra sphenanthera, crizotinib, netupitant, nilotinib, or isavuconazole	14 days prior to Day 1 through the end of study participation
CYP3A4 Inducers[c]		
Strong CYP3A4 Inducers	Carbamazepine, phenytoin, rifampin, fosphenytoin, pentobarbital, primidone, rifabutin, rifapentine, phenobarbital, mitotane, avasimibe, St. John's Wort, enzalutamide	14 days prior to Day 1 through the end of study participation
Moderate CYP3A4 Inducers	Bosentan, thioridazine, nafcillin, modafinil, semagacestat, genistein	14 days prior to Day 1 through the end of study participation
Other		
JAK Inhibitor	Ruxolitinib or tofacitinib (or investigational)	3 months prior to screening through the end of study participation
SYK Inhibitor	Fostamatinib or entospletinib (or investigational)	3 months prior to screening through the end of study participation
Anti-platelet	Adenosine diphosphate (ADP) receptor inhibitors, phosphodiesterase inhibitors, PAR-1 antagonists, glycoprotein 2b/3a inhibitors	One year prior to screening through the end of study participation
	Aspirin > 325 mg/day	14 days prior to Day 1 through the end of study participation
Anti-coagulant	Warfarin, any Vitamin K antagonist, any novel oral anticoagulant, any heparin or low molecular heparins, or inhibitors of factor Xa	One year prior to screening through the end of study participation

a May result in a decrease in the concentrations of filgotinib. Filgotinib is a P-gp substrate. A single dose of 200 mg itraconazole (a potent P-gp inhibitor) increased filgotinib C_{max} by 63.9% and AUC_{inf} by 44.6% but had no effect on the major, active metabolite GS-829845.
b May result in an increase in the concentrations of GS-9876
c May result in a decrease in the concentrations of GS-9876

5.7. Vaccine Guidelines

Prior to study participation, it is recommended that the subject's vaccinations be brought up to date according to local vaccination standards.

Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 4 weeks of Day 1, throughout the study, and for 12 weeks after the last dose of study drug.

Subjects should be advised to avoid routine household contact with persons vaccinated with live/attenuated vaccine components. General guidelines suggest that a study subject's exposure to household contacts should be avoided for the below stated time periods:

- Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination
- Oral polio vaccination - avoid contact for 6 weeks following vaccination
- Attenuated rotavirus vaccine - avoid contact for 10 days following vaccination
- Inhaled flu vaccine - avoid contact for 1 week following vaccination

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 filgotinib or GS-9876 and their impact on immune responses following vaccination.

5.8. Accountability of Study Drugs

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

Study drug accountability records will be provided to each study site to:

- Record the date received and quantity of study drug
- Record the date, subject number, subject initials, the study drug number dispensed
- Record the date, quantity of used and unused study returned, along with the initials of the person recording the information.

5.8.1. Study Drug Return or Disposal

For additional information about study drug accountability, return, and disposal, refer to Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the screening evaluations. The screening number and subject ID will be assigned for each subject by IWRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization. A subject will be considered enrolled once they have been randomized.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened up to 28 days prior to randomization (Day 1) to determine eligibility for participation in the study.

The following will be performed and documented at screening:

- Obtain written informed consent
- Review of inclusion/exclusion criteria
- Obtain medical history (including demographics, surgical history, and CLE history with documentation of prior skin biopsy results, if available)
- Complete PE
- Height
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA
- CLASI
- Standard 12-lead ECG
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)

- Endocrine Tests (HbA_{1c} and TSH)
- Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Serum Pregnancy Test (for females of childbearing potential) or FSH test (for females of nonchildbearing potential)
- Virology Tests (HIV-1, HIV-2, HBV, and HCV)
- QuantiFERON® TB Gold in Tube Test (if applicable)
- Biomarker Samples
    - Whole Blood, Cytochex
    - Whole Blood, Heparin
    - Serum and plasma biomarker samples
    - vfPBMC sample
    - PAXgene RNA sample

- Obtain urine samples for:
    - Urinalysis
    - Urine Drug and Alcohol test
    - Urine protein to creatinine ratio
- Chest x-ray (if not obtained within 3 months prior to screening, with films or report available for investigator review)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for randomization into the study on Day 1.

Subjects who do not meet the eligibility criteria will be excluded from randomization and may be considered for rescreening one time for the study in consultation with the sponsor or its designee. Refer to Section 4.4 for additional details.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all SAEs, as well as any AEs related to protocol-mandated procedures on the AE eCRF and any concomitant medications in the concomitant medication eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7.6 Adverse Events and Toxicity Management for details.

6.2.2. Day 1 Assessments

Day 1 assessments, including study drug administration, will be done at the study center. The following will be performed and documented prior to dosing:

- Updates to medical history

- Weight
- Symptom-driven physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA
- CLASI
- Detailed target lesion assessment (see Section 6.9.2.3 for details)
- Photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible)
- Detailed mucous membrane assessment (see Section 6.9.2.4 for details)
- Subject questionnaires:
  - Subject's global assessment of CLE disease activity
  - Subject assessment of autoimmune disease-related dry eyes/mouth
  - Subject assessment of autoimmune disease-related body pain
  - Subject assessment of autoimmune disease-related joint pain/stiffness
  - Subject assessment of autoimmune disease-related fatigue
  - Subject assessment of CLE on sexual activity
  - SF-36
  - DLQI
  - TSQM
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - Fasting lipids (overnight fast [no food or drinks, except water] of at least 8 hours required prior to blood sample collection)
  - CRP and ESR
  - Quantitative Serum Immunoglobulin Test
  - Autoantibody Panel and Complement Levels

- Biomarker Samples (predose)
  - Whole Blood, Cytochex
  - Whole Blood, Heparin
  - Serum and plasma biomarker samples
  - vfPBMC sample
  - PAXgene RNA sample

CCI [redacted]

- Obtain urine sample for:
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential)
  - Urine protein to creatinine ratio

CCI [redacted]

- After the subject's eligibility for the study has been confirmed, the subject will be randomized to 1 of 3 arms
- Study drug dispensation
- Review and record all adverse events and concomitant medications

6.3. Randomization

Upon qualification for the study, subjects will be randomized in a 2:2:1 ratio using a computerized IWRS system on the Day 1 visit.

For each subject at each dispensation visit, the clinic will contact the IWRS system for the appropriate kit number to be dispensed. The kit will contain the relevant study drug for the period until the next dispensation visit.

Refer to Sections 3.3 and Section 6.1 for additional details.

6.4. Week 2 through Week 24 (Study Dosing Period)

The following assessments will be completed as specified in the Study Procedures Table (Appendix 2).

- Weight

- Symptom-driven physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA
- CLASI
- Detailed target lesion assessment (see Section 6.9.2.3 for details)
- Photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible)
- Detailed mucous membrane assessment (Weeks 2, 12, 14, and 24; see Section 6.9.2.4 for details)
- Subject questionnaires:
  - Subject's global assessment of CLE disease activity
  - Subject assessment of autoimmune disease-related dry eyes/mouth
  - Subject assessment of autoimmune disease-related body pain
  - Subject assessment of autoimmune disease-related joint pain/stiffness
  - Subject assessment of autoimmune disease-related fatigue
  - Subject assessment of CLE on sexual activity
  - SF-36
  - DLQI
  - TSQM
- Standard 12-lead ECG (Week 24 only)
- HCV monitoring (Weeks 12 and 24; if applicable)
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - Fasting Lipids (Weeks 12 and 24; overnight fast [no food or drinks, except water] of at least 8 hours required prior to blood sample collection)
  - CRP and ESR
  - Quantitative Serum Immunoglobulin Test (Weeks 8 and 20)
  - Autoantibody Panel and Complement Levels (Weeks 12 and 24)

- Biomarker Samples (Weeks 2, 4, 12, and 24)
  - Whole Blood, Cytochex
  - Whole Blood, Heparin
  - Serum and plasma biomarker samples
  - vfPBMC sample
  - PAXgene RNA sample
- Pharmacokinetic Samples (Week 2 [at least 30 minutes and up to 3 hours after dosing],Week 4 [anytime], Week 12 [within 2 hours prior to study drug administration], and Week 24 [within 2 hours prior to study drug administration])

- Obtain urine sample for:
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential)
  - Urine protein to creatinine ratio

- [redacted]
- Re-randomization 1:1 upon completion of Week 12 assessments (subjects on placebo only, will be performed in a double-blind fashion via IWRS)
- Study drug dispensation (not applicable at Weeks 2 and 14 and not applicable at Week 24 for subjects who do not enter the 24-week extension period)
- Study drug accountability
- Review and record all adverse events and concomitant medications

6.5. Week 30 through Week 48 (24-week Extension Period)

The following assessments will be completed at each visit or as specified. All assessments are summarized in the Study Procedures Table (Appendix 2).

- Weight
- Symptom-driven physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA

- CLASI
- Detailed target lesion assessment (see Section 6.9.2.3 for details)
- Photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible)
- Detailed mucous membrane assessment (Weeks 36 and 48; see Section 6.9.2.4 for details)
- Subject questionnaires:
  - Subject's global assessment of CLE disease activity
  - Subject assessment of autoimmune disease-related dry eyes/mouth
  - Subject assessment of autoimmune disease-related body pain
  - Subject assessment of autoimmune disease-related joint pain/stiffness
  - Subject assessment of autoimmune disease-related fatigue
  - Subject assessment of CLE on sexual activity
  - SF-36
  - DLQI
  - TSQM
- Standard 12-lead ECG (Weeks 36 and 48)
- HCV monitoring (Weeks 36 and 48; if applicable)
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - Fasting Lipids (Week 42 only; overnight fast [no food or drinks, except water] of at least 8 hours required prior to blood sample collection)
  - CRP and ESR
  - Quantitative Serum Immunoglobulin Test (Week 42 only)
  - Autoantibody Panel and Complement Levels (Week 42 only)
  - Biomarker Samples (Week 48 only)
    - Serum and plasma biomarker samples
    - PAXgene RNA sample
- Obtain urine sample for:
  - Urinalysis

  - Urine pregnancy test (for females of childbearing potential). When visits are greater than 4 weeks apart, women should continue to have urine pregnancy tests every 4 weeks using at home pregnancy test kits that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and eCRF. If any urine pregnancy test is positive, study drug should be immediately interrupted and the subject should return to the study center for a serum pregnancy test
  - Urine protein to creatinine ratio
- Study drug dispensation (not applicable at Week 48)
- Study drug accountability
- Review and record all adverse events and concomitant medications

6.6. Follow-up Assessments

A FU visit will be conducted 4 weeks after the last dose of study drug. Subjects who discontinue study drug ≥ 4 weeks prior to their last visit will not be asked to return for a FU visit.

- Weight
- Symptom-driven physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA
- CLASI
- Detailed target lesion assessment (see Section 6.9.2.3 for details)
- Photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible)
- Subject questionnaires:
  - Subject's global assessment of CLE disease activity
  - Subject assessment of autoimmune disease-related dry eyes/mouth
  - Subject assessment of autoimmune disease-related body pain
  - Subject assessment of autoimmune disease-related joint pain/stiffness
  - Subject assessment of autoimmune disease-related fatigue
  - Subject assessment of CLE on sexual activity

  - SF-36
  - DLQI
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - Complement Levels
  - Biomarker Samples
    - Serum and plasma biomarker samples
    - PAXgene RNA sample
- Obtain urine sample for:
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential)
  - Urine protein to creatinine ratio
- Review and record all adverse events and concomitant medications

6.7. Early Termination Assessments

Subjects who discontinue the study prior to Week 24 (or prior to Week 48 for subjects entering the 24-week extension period) will return to the study center for the ET visit.

- Weight
- Symptom-driven physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- PGA
- CLASI
- Detailed target lesion assessment (see Section 6.9.2.3 for details)
- Photographs of areas with skin involvement (identifying subject features should be obscured, as much as possible)
- Subject questionnaires:
  - Subject's global assessment of CLE disease activity

  - Subject assessment of autoimmune disease-related dry eyes/mouth
  - Subject assessment of autoimmune disease-related body pain
  - Subject assessment of autoimmune disease-related joint pain/stiffness
  - Subject assessment of autoimmune disease-related fatigue
  - Subject assessment of CLE on sexual activity
  - SF-36
  - DLQI
  - TSQM
- Standard 12-lead ECG (if not completed within the prior 12 weeks)
- HCV monitoring (if applicable, if not completed within the prior 12 weeks)
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR
  - Complement Levels
  - Biomarker Samples
    - Whole Blood, Cytochex
    - Whole Blood, Heparin
    - Serum and plasma biomarker samples
    - vfPBMC sample
    - PAXgene RNA sample
- Obtain urine sample for:
  - Urinalysis
  - Urine pregnancy test (for females of childbearing potential)
  - Urine protein to creatinine ratio
- Study drug accountability
- Review and record all adverse events and concomitant medications

6.8. Unscheduled Visit Assessments

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments performed are at the investigator's discretion.

6.9. Study Assessments

6.9.1. Priority of Assessments

Subject-reported outcomes are recommended to be completed before any other study procedures. Invasive study procedures such as blood draws and biopsies should be done at the end of a study visit, as much as possible. Investigator questionnaires/assessments should be performed prior to reviewing subject-reported outcomes for that visit, as much as possible.

6.9.2. Efficacy

Efficacy assessments will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

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

The CLASI is assessed using a one-page tool which lists each part of the body separately and results in separate scores for skin damage and disease activity.

6.9.2.2. Physician's Global Assessments of CLE Disease Activity

The Physician's Global Assessment of CLE Disease Activity will be recorded on a 0-100 mm visual analogue scale (VAS; Appendix 7), 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.

6.9.2.3. Detailed Target Lesion Assessments

The investigator will identify a highly clinically active lesion on Day 1. The lesion will be measured and assessed for edema (0 = absent, 1 = slight, just palpable, 2 = visible and palpable). The area that was assessed will be recorded in the source documents.

6.9.2.4. Detailed Mucous Membrane Assessments

Mucous membranes will be assessed for lesions at the buccal mucosa, the hard and soft palates, and the nasal mucosal areas for erythema, keratosis, and erosions and scored as indicated below.

Area of Lesion Assessment	Erythema	Keratosis	Erosions
Buccal Mucosa	0 = absent 1 = present	0 = absent 1 = present	0 = absent 1 = erosion 2 = ulceration
Hard and Soft Palates	0 = absent 1 = present	0 = absent 1 = present	0 = absent 1 = erosion 2 = ulceration
Nasal Mucosal Areas	0 = absent 1 = present	0 = absent 1 = present	0 = absent 1 = erosion 2 = ulceration

6.9.2.5. Subject's Global Assessment of CLE Disease Activity

The Subject's Global Assessment of CLE Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "I have no CLE" and 100 indicating "I have the worst CLE."

6.9.2.6. Subject Assessment of Autoimmune Disease-Related Dry Eyes/Mouth

The Subject Assessment of Autoimmune Disease-Related Dry Eyes/Mouth will be recorded on a 0-100 mm VAS (Appendix 8), with 0 indicating "I have no dry eye/mouth due to my autoimmune condition" and 100 indicating "I have the worst dry eye/mouth due to my autoimmune."

6.9.2.7. Subject Assessment of Autoimmune Disease-Related Body Pain

The Subject Assessment of Autoimmune Disease-Related Body Pain will be recorded on a 0-100 mm VAS (Appendix 8), with 0 indicating "I have no body pain due to my autoimmune condition" and 100 indicating "I have the worst body pain due to my autoimmune condition."

6.9.2.8. Subject Assessment of Autoimmune Disease-Related Join Pain/Stiffness

The Subject Assessment of Autoimmune Disease-Related Joint Pain/Stiffness will be recorded on a 0-100 mm VAS (Appendix 8), with 0 indicating "I have no joint pain/stiffness due to my autoimmune condition" and 100 indicating "I have the worst joint pain/stiffness due to my autoimmune condition."

6.9.2.9. Subject Assessment of Autoimmune Disease-Related Fatigue

The Subject Assessment of Autoimmune Disease-Related Fatigue will be recorded on a 0-100 mm VAS (Appendix 8), with 0 indicating "I have no fatigue due to my autoimmune condition" and 100 indicating "I have the worst fatigue due to my autoimmune condition."

6.9.2.10. Subject Assessment of CLE on Sexual Activity

The Subject Assessment of CLE on Sexual Activity will be recorded on a 0-100 mm VAS (Appendix 8), with 0 indicating "my CLE does not affect my sexual activity" and 100 indicating "my CLE completely stops my sexual activity."

6.9.2.11. 36-Item Short Form Healthy Survey

The SF-36 is a health related quality of life instrument consisting of 36 questions belonging to 8 domains in 2 components and covers a 4-week recall period:

- Physical well-being, 4 domains: physical functioning (10 items), role physical (4 items), bodily pain (2 items), and general health perceptions (5 items)
- Mental well-being, 4 domains: vitality (4 items), social functioning (2 items), role emotional (3 items), and mental health (5 items).

The remaining item (health transition) is not part of the above domains but is kept separately. These scales will be rescaled from 0 to 100 (converting the lowest possible score to 0 and the highest possible score to 100), with higher scores indicating a better quality of life. The SF-36 is not disease specific and has been validated in numerous health states.

6.9.2.12. Dermatology Quality of Life Index (DLQI)

The DLQI is a 10-question questionnaire used to measure the impact of skin disease on the quality of life of an affected person. Subjects will assess the impact of skin disease based on the previous week. Dermatology Quality of Life Index topics include symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Each question is scored from 0 to 3 (0 = not at all, not relevant, or question unanswered; 1 = a little, 2 = a lot, 3 = very much).

6.9.2.13. Treatment Satisfaction Questionnaire for Medication

The TSQM is a composite measure based on the subject's rating of medication effectiveness, side effects, and convenience.

At Day 1, this questionnaire will be used to assess prior medications used to treat the subject's CLE. At all other time points, the TSQM will be used to assess the subject's opinion of the study drugs. Site staff should remind the subject of which CLE drugs they should be evaluating at each visit.

6.9.3. Safety

Safety will be assessed via AEs, concomitant medications, physical examinations (complete and symptom-driven), vital signs, ECGs, and clinical laboratory results.

6.9.4. Clinical Laboratory Evaluations

The hematology, serum chemistry, and coagulation laboratory analyses will be performed at a central laboratory. Reference ranges will be supplied by the central laboratory and will be used by the investigator to assess the laboratory data for clinical significance and pathological changes.

Blood samples will be collected by venipuncture [redacted] in the arm at the time points indicated in the Study Procedures Table (Appendix 2). In addition, urine samples for the clinical laboratory assessments will be collected. An overnight fast (no food or drinks, except water) of at least 8 hours will be required prior to collection of blood samples for lipid testing.

- Refer to Appendix 6 for table of clinical laboratory tests.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator (refer to Section 7.5). More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and/or withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) (see Section 3.5 for additional information).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.9.5. Vital Signs

Vital signs will be measured at the time points indicated in the Study Procedures Table (Appendix 2).

Vital signs should be taken after the subject has been resting in the seated or supine position for at least 5 minutes and will include pulse rate, respiratory rate, systolic and diastolic blood pressure, and temperature.

6.9.6. Physical Examination

A physical examination should be performed at the time points indicated in the Study Procedures Table (Appendix 2). Any changes from screening will be recorded. Weight will be measured at all visits. Height will be measured at screening only. Subjects should be instructed to remove shoes prior to measurement of height.

At screening, a complete physical examination will be performed. A complete physical examination will include source documentation of general appearance and the following body systems: head, neck, and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes; abdomen; skin, hair, nails; musculoskeletal; and neurological. Symptom-driven physical examinations will be performed at all other visits based on reported signs and symptoms.

6.9.7. Other Safety Assessments

6.9.7.1. 12-lead Electrocardiogram

A resting 12-lead ECG will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

The ECG should be obtained after the subject has been resting in the supine position for at least 5 minutes and will include heart rate (HR), inter-beat (RR), QRS, uncorrected QT, morphology, and rhythm analysis. QT interval corrected for HR according to Fridericia (QTcF) will be derived during the statistical analysis. Electrocardiograms will be interpreted by the investigator (or qualified designee) for clinical significance and results will be entered into the eCRF.

6.10. Pharmacokinetics Assessments

Blood samples for PK analysis will be collected at Week 2 (at least 30 minutes and up to 3 hours postdose), anytime at Week 4, and within 2 hours prior to study drug administration at Weeks 12 and 24.

Plasma concentrations of filgotinib, its metabolite (GS-829845), and GS-9876 will be analyzed.

6.11. Biomarker Assessments

Blood samples will be collected at screening, predose on Day 1 and at Weeks 2, 4, 12, 24, 48 (for subjects entering the 24-week extension period), FU, and ET (if applicable).

Blood samples may be analyzed for assessment of markers of inflammation, immune status, and JAK-STAT and SYK pathway activation.

CCI [redacted]

6.12. Photography

Photography of areas of skin involvement should be performed at the time points indicated in the Study Procedures Table (Appendix 2). Photographs may be used in exploratory analyses to evaluate association of images with other measures of CLE activity, such as CLASI data.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, 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 medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

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 adverse event and must be reported.
- Pre-existing 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 (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

A **serious adverse event** (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (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.)
- In-patient 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 a 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. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

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 investigational medicinal product (IMP) therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the IMP rather than by another etiology.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event 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 adverse event has an etiology other than the study procedure.

- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the modified Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the 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 adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 3 and Appendix 4.

Table 3. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death related AE

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol-mandated procedures.

7.3.1. Adverse Events

Following initiation of study medication until 30 days after the last administration of IMP, all AEs must be collected, regardless of cause or relationship, and reported to the eCRF database as instructed.

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, 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 protocol-required post treatment follow-up period, must be reported to the eCRF database and Gilead DSPH as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post-treatment follow-up visit but within 30 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 study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event to Gilead DSPH.

Electronic Serious Adverse Event (eSAE) Reporting Process

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead DSPH: **Fax:** PPD
E-mail: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail 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 event description section of the SAE form.

7.4. 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, serious adverse drug reactions (SADRs), or 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 IBs.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study investigational medicinal product (IMP). 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.

To minimize the possibility of exposing study subjects to unusual risk, the safety information from this study will also be reviewed periodically by an independent Data Monitoring Committee (DMC; as described in Section 8.10). The DMC may have access to partially blinded or unblinded data and will make recommendations regarding the study according to the DMC charter

7.5. Clinical Laboratory Abnormalities

Asymptomatic laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, or urinalysis) that require medical or surgical intervention or lead to study drug interruption or discontinuation must be recorded as an AE or SAE, as 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 (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE (Appendix 4). 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.

7.6. Toxicity Management

All clinical toxicities and clinically significant laboratory toxicities will be managed according to the following uniform guidelines, which are detailed in Appendix 3.

For study-specific interruption and discontinuation criteria, refer to Section 3.5. The specific toxicity discontinuation criteria in Section 3.5 supercede the general toxicity guidelines. In general, if discrepancy is present, the more conservative criteria apply.

The Gilead Medical Monitor should be consulted prior to study drug discontinuation ifmedically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

For Grades 1 and 2 laboratory abnormalities or clinical events not specified in Section 3.5, continue study drug at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

For Grade 3 laboratory abnormalities or clinical events not specified in Section 3.5, the following toxicity management guidelines apply:

- For Grade 3 clinical event, or clinically significant (confirmed) laboratory abnormality, study drug may be continued if the event is considered to be unrelated to study drug.
- For a Grade 3 clinical event, or clinically significant (confirmed) laboratory abnormality, considered to be **related** to study drug, study drug should be interrupted until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with study drug and is considered related to study drug, then study drug should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to study drug may not require permanent discontinuation, and study drug may be continued at the discretion of the investigator.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

For Grade 4 laboratory abnormalities or clinical events not specified in Section 3.5, the following toxicity management guidelines apply:

- For a Grade 4 clinical event, or clinically significant (confirmed) laboratory abnormality, study drug should be permanently discontinued and the subject managed according to local clinical practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.
- Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase after strenuous exercise or nonfasting triglyceride elevation that can be medically managed) or a clinical event considered unrelated to the study drug(s).

Grade 4 treatment-emergent toxicities should be noted by the investigator and brought to the attention of the Gilead Sciences Medical Monitor, who will discuss with the investigator and determine the appropriate course of action. All subjects experiencing AEs, regardless of if the AEs are treatment-related, must be monitored periodically until symptoms subside, any

abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Histologic hemorrhage and thrombosis have been observed in cynomolgus monkeys that received GS-9876 at doses ≥ 20 mg/kg/day. The clinical relevance of these findings to humans is unknown; these adverse events have not been reported in clinical studies of GS-9876. Any treatment-emergent adverse event involving significant bleeding or thrombosis is to be reported to the investigator and brought to the attention of the Gilead Sciences medical monitor or designee, to discuss the appropriate course of action.

Any questions regarding toxicity management should be directed to the Gilead Sciences Medical Monitor.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, pregnancy reports regardless of an associated AE, an AE in an infant following exposure from breastfeeding, and an occupational exposure with an AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product 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 medicinal product 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 with an AE is defined as exposure to medicinal product as result of one's professional or non-professional occupation.

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study drug and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination 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. 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 7.1.1 and Section 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows:
Email: PPD and Fax: PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report 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.

Refer to Section 7.3 and the eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports 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.

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 efficacy of filgotinib and GS-9876 in female subjects with moderately-to-severely active CLE

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of filgotinib and GS-9876 in moderately-to-severely active CLE

The exploratory objectives of this study are as follows:

[redacted]

8.1.2. Primary Endpoint

The primary endpoint is change from baseline in CLASI activity score from baseline to Week 12.

8.1.3. Secondary Endpoints

The secondary endpoints of this study are:

- Proportion of subjects at Week 12 with decrease of ≥ 5 points in CLASI activity score from baseline

- Proportion of subjects at Week 12 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)

- Proportion of subjects at Week 24 with decrease of ≥ 5 points in CLASI activity score from baseline

- Proportion of subjects at Week 24 with no worsening in CLASI activity score from baseline (worsening defined as ≥ 3 point increase)

8.1.4. Exploratory Endpoints

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

The all randomized analysis set includes all subjects who are randomized in the study. This is the primary analysis set for by subject 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 one dose of study drug.

8.2.1.3. Safety

The primary analysis set for safety analyses will be the Safety Analysis Set, which includes all subjects who received at least one dose of study drug.

8.2.1.4. Pharmacokinetics

The primary analysis set for PK analyses will be the PK analysis set, which includes all subjects in the Safety Analysis Set who have at least 1 nonmissing concentration data for the analyte of interest.

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 one dose of study drug and have at least one baseline measurement available for the specific parameter of interest.

8.3. Data Handling Conventions

Pharmacokinetic concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. Below the limit of quantitation values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation (LLOQ).

Laboratory data that are continuous in nature but are less than the lower limit of quantitation or above the upper limit of quantitation will be imputed to the value of the lower or upper limit minus or plus one 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).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm using standard descriptive statistics including sample size, mean, standard deviation (SD), median, 1st quartile (Q1), 3rd quartile (Q3), minimum, and maximum for continuous variables and number and percentages of subjects for categorical variables.

Demographic data will include race, ethnicity, and age.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is the change in CLASI activity score from baseline to Week 12. The primary analysis will consist of superiority test of filgotinib 200 mg versus placebo and GS-9876 30 mg versus placebo, respectively. The primary endpoint will be analyzed using a mixed-effect repeated measures (MMRM) model. The model may include terms for baseline CLASI value, treatment, visit, and treatment-by-visit interaction. Subjects will be included as a random effect.

8.5.2. Secondary and Exploratory Analyses

For categorical endpoints, Cochran-Mantel-Haenszel approach adjusting for the randomization stratification factors will be used. For continuous endpoints, a similar MMRM approach will be used to evaluate treatment effect on change from baseline (Day 1).

The summary statistics will be provided by treatment arm. Differences across treatment arms will be summarized and treatment comparisons may be performed. Details on efficacy analyses will be described in the statistical analysis plan (SAP).

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set.

Safety will be evaluated by assessment of clinical laboratory tests, physical examinations, vital signs measurements at various time points during the study, and by the documentation of AEs.

All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study plus 30 days will be summarized by treatment arm (according to the study drug received).

8.6.1. 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 arm.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment arm.

8.6.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Treatment-Emergent Adverse Events (TEAEs) are defined as one or both of the following:

- Any AEs with an onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided by treatment arm. Treatment-emergent adverse events will also be summarized by relationship to study drug and severity. In addition, TEAEs leading to premature discontinuation of study drug will be summarized and listed.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment arm. Absolute values and change from baseline at all scheduled timepoints will be summarized.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least one toxicity grade from baseline at any time post baseline up to the date of last dose of study drug plus 30 days, will be summarized by treatment.

8.6.4. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided.

8.7. Pharmacokinetic Analysis

Plasma concentrations of filgotinib, its metabolite (GS-829845), and GS-9876 will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations of each analyte over time may be plotted in semi logarithmic and linear formats as mean ± standard deviation.

8.8. Biomarker Analysis

For analysis of the pharmacodynamics markers, the baseline level and the modulation pattern upon treatment, including change over time from baseline level, will be evaluated by treatment arm. Descriptive statistics will be provided at each sampling time, by treatment arm. 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 change from baseline, as appropriate.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.9. Sample Size

With a sample size of 50 subjects (20 in each active treatment arm and 10 in the placebo arm), there is a 79% power to detect a 2-point difference between each active arm and the placebo arm in the primary endpoint using a 2-sided 0.1-level test, assuming a common standard deviation of 2 and a 10% drop-out rate per arm.

8.10. Data Monitoring Committee

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data and provide recommendations to Gilead on whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or whether the study should continue with modifications.

The first DMC meeting will be conducted after approximately 50% of the subjects have completed their Week 12 study visit. The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

8.11. Analysis Schedule

The primary analysis will be conducted when all enrolled subjects either complete their Week 12 visit or prematurely discontinue from the study. The final analysis will be performed when all subjects complete the study or prematurely discontinue from the study.

Additionally, to assess the safety and efficacy of GS-9876 and filgotinib for further planning and development of these products, a Gilead internal unblinded team independent of the blinded study team will be assembled. This group will consist of at least one representative from Clinical Research, Biostatistics, and Pharmacovigilance/Epidemiology, and may include other personnel as necessary. The Gilead internal unblinded team will be granted access to unblinded clinical

data including treatment assignments to closely monitor study progress and drug safety. The membership, responsibilities, conduct, specific activities and meeting schedule of the unblinded internal team will be documented in a Gilead Internal Unblinded Team Charter.

To mitigate the risks of inadvertently releasing the treatment information to the sites and subjects, the internal team will keep the unblinded information confidential and will not communicate the information to the blinded study team, site staff or subjects. Data unblinding due to medical emergency will follow standard Gilead procedures.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

The investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, and 21 CFR, part 56.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under 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.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, 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 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.

9.1.3. 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 and before undertaking any study-related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent will be appropriately signed and dated by the subject

and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC local requirements. CCI [redacted]

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or 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 showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. 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 investigator brochure, this protocol, eCRF, the IMP, 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.

9.1.5. 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 two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, 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 (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, 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 IMP, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including 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 until 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, United States, 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, until 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.

9.1.6. 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 EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal

Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator 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. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in 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 trial, Gilead will provide the site 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 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead, the site may destroy used (empty or partially empty) and unused IMP supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMP destroyed. Records must show the identification and quantity of each unit destroyed, the method of destruction, and the person who disposed of the IMP. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRB/IEC, 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 (CSR) will be prepared and provided to the regulatory agency(ies). 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 9.1.4).

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's 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 trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the 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 on the 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 of 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.

9.3.4. Study Discontinuation

Both the sponsor 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 appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Filgotinib and GS-9876 in Female Subjects with Moderately-To-Severely Active Cutaneous Lupus Erythematosus (CLE)

GS-US-436-4092, Amendment 4, 15 October 2018

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

PPD

Name (Printed)
Author

PPD

Signature

October 16, 2018

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. Study Procedures Table

		Study Dosing Period									24-week Extension Period					
			Week 2	Week 4	Week 8	Week 12	Week 14	Week 16	Week 20	Week 24	Week 30	Week 36	Week 42	Week 48	ET[c]	F/U[d]
Study Procedures	**Screen[a]**	**Day 1[b]**	**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 5 days**	**± 5 days**
Written Informed Consent	X															
Review of Inclusion/ Exclusion Criteria	X															
Medical History[e]	X	X														
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Examination	X															
Symptom-driven Physical Examination[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician's Global Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Detailed Target Lesion Assessment[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Photography of Areas with Skin Involvement[w]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Detailed Mucous Membrane Assessment[x]		X	X			X	X			X		X		X		
Subject's Global Assessment and other subject-reported measures[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]

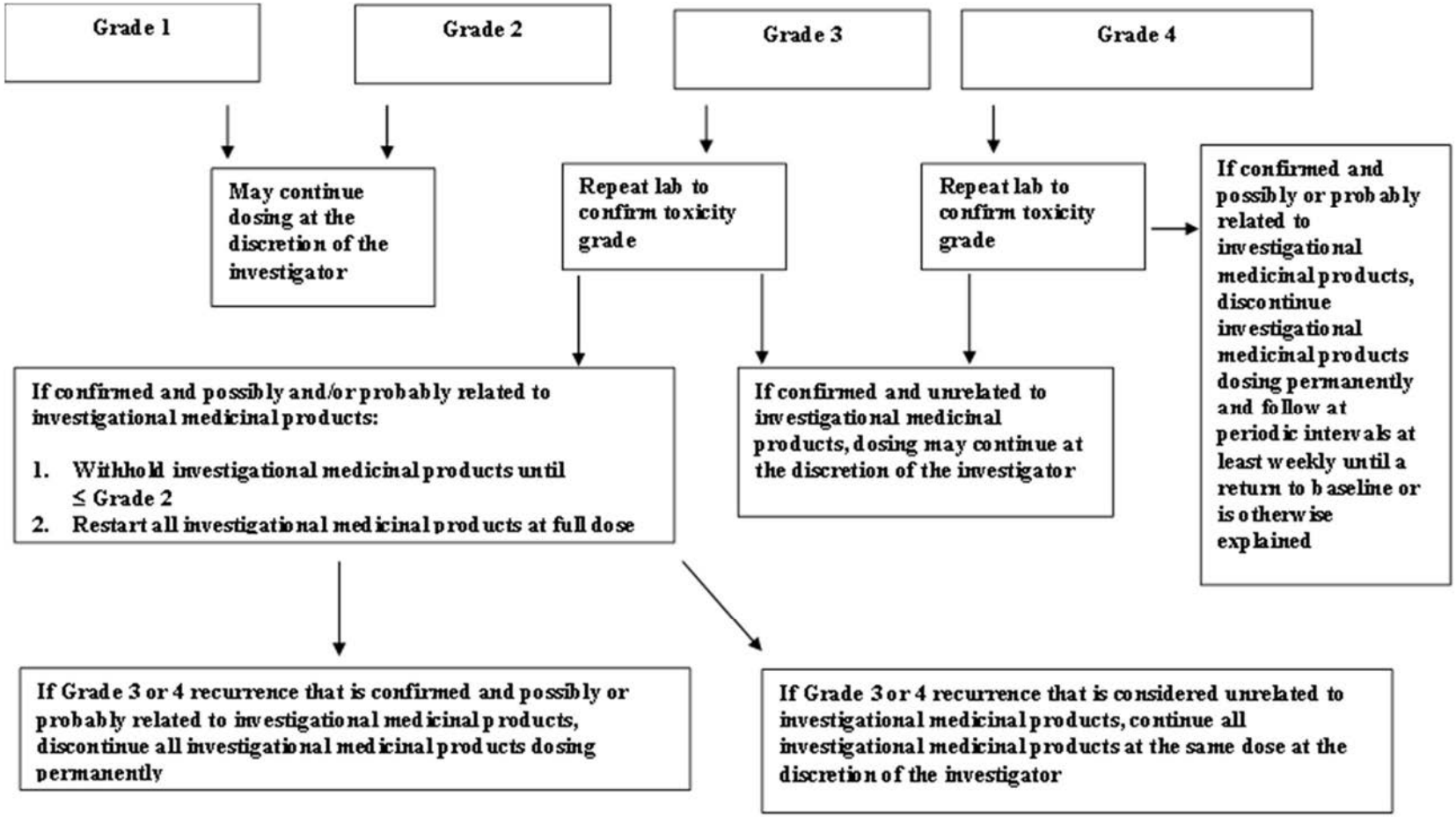
		Study Dosing Period									24-week Extension Period					
			Week 2	Week 4	Week 8	Week 12	Week 14	Week 16	Week 20	Week 24	Week 30	Week 36	Week 42	Week 48	ET[c]	F/U[d]
Study Procedures	**Screen[a]**	**Day 1[b]**	**± 2 days**	**± 3 days**	**± 3 days**	**± 3 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 5 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 7 days**	**± 5 days**	**± 5 days**
12-lead ECG	X									X		X		X	X[y]	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting Lipids[j]		X				X				X			X			
CRP and ESR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HbA_{1c} and TSH	X															
Urinalysis and Urine protein to creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine Drug and Alcohol Screen	X															
Serum Pregnancy Test[k]	X															
Urine Pregnancy Test[k, l]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH Test[m]	X															
HIV-1, HIV-2, HBV, HCV Serology	X															
HCV Monitoring[n]						X				X		X		X	X[y]	
Quantiferon Test[o]	X															
Chest X-ray[o]	X															
Quantitative Serum Immunoglobulin Test		X			X				X				X			
Autoantibody Panel		X				X				X			X			

		Study Dosing Period									24-week Extension Period					
Study Procedures	**Screen[a]**	**Day 1[b]**	**Week 2** ± 2 days	**Week 4** ± 3 days	**Week 8** ± 3 days	**Week 12** ± 3 days	**Week 14** ± 5 days	**Week 16** ± 5 days	**Week 20** ± 5 days	**Week 24** ± 5 days	**Week 30** ± 7 days	**Week 36** ± 7 days	**Week 42** ± 7 days	**Week 48** ± 7 days	**ET[c]** ± 5 days	**F/U[d]** ± 5 days
Complement Levels		X				X				X			X		X	X
Pharmacokinetics[p]			X	X		X				X						
CCI																
Whole Blood, Cytochex	X	X[s]	X	X		X				X					X	
Whole Blood, Heparin	X	X[s]	X	X		X				X					X	
Serum biomarker sample	X	X[s]	X	X		X				X				X	X	X
Plasma biomarker sample	X	X[s]	X	X		X				X				X	X	X
vfPBMC	X	X[s]	X	X		X				X					X	
PAXgene RNA sample	X	X[s]	X	X		X				X				X	X	X
Randomization		X				X[t]										
Study Drug Dispensing		X		X	X	X		X	X	X[u]	X	X	X			
Study Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 28 days prior to randomization and administration of the first dose of study drugs.
b Day 1 procedures, including study drug administration, will be performed at the study center. All assessments will be performed prior to dosing unless otherwise indicated.
c Subjects who discontinue from the study prior to Week 24 (or prior to Week 48 for subjects entering the 24-week extension period), will return to the study center for ET assessments.
d Subjects will return to the study center for a FU visit 4 weeks (± 5 days) after their last dose of study drug. Subjects who discontinue study drug ≥ 4 weeks prior to their last visit will not be asked to return for the FU visit.
e At screening, medical history will include collection of demographics and a review of surgical history and CLE history (including documentation of prior skin biopsy results, if available). Medical history will be updated, as needed, on Day 1.
f Symptom-driven physical examinations will be performed, as needed, based on signs and symptoms.
g Vital signs include resting blood pressure, heart rate, respiratory rate, and temperature.

h Includes VAS (subject assessment of CLE on sexual activity; autoimmune disease-related dry eyes/mouth, body pain, joint pain/stiffness, and fatigue), SF-36, DLQI, and TSQM. Subject reported outcomes are recommended to be performed at the beginning of each visit prior to any other visit-related procedures (other than signing of informed consent).
i The TSQM will not be administered at the FU visit.
j An overnight fast (no food or drinks, except water) of at least 8 hours is required prior to collection of blood samples for lipid testing.
k Females of childbearing potential only (see Appendix 5).
l When visits are greater than 4 weeks apart, women should continue to have urine pregnancy tests every 4 weeks using at home pregnancy test kits that will be provided to them. The site will call the subject every 4 weeks to obtain results of these pregnancy tests and will record the information in the source documents and eCRF. If any urine pregnancy test is positive, study drug should be immediately interrupted and the subject should return to the study center for a serum pregnancy test.
m Females of non-childbearing potential only (see Appendix 5).
n Viral monitoring for HCV every 12 weeks, as applicable (see exclusion criteria, Section 4.3).
o Subjects previously treated for latent TB (see Inclusion # 9) do not need to have the QuantiFERON® TB-Gold In-Tube test (or equivalent assay), but a chest radiograph must be obtained if one is not available within 3 months prior to screening (with the report or films available for investigator review). All other subjects must have the QuantiFERON® TB-Gold In-Tube test (or equivalent assay) at screening and a chest radiograph (views as per local guidelines) at screening or within 3 months prior to screening (with the report or films available for investigator review).
p Pharmacokinetic samples will be collected on Week 2 (at least 30 minutes and up to 3 hours after dosing), Week 4 (anytime), Week 12 (within 2 hours prior to study drug administration), and Week 24 (within 2 hours prior to study drug administration).
[redacted]
s On Day 1, biomarker samples will be collected prior to study drug administration.
t At the end of the Week 12 visit, subjects on placebo will be re-randomized 1:1 in a blinded fashion to receive filgotinib 200 mg + PTM GS-9876 30 mg once daily or GS-9876 30 mg + PTM filgotinib 200 mg once daily for the remainder of the study.
u For subjects who enter the 24-week extension period only.
v See Section 6.9.2.3 for details.
w A separate manual will be provided for instructions on photography of areas with skin involvement.
x See Section 6.9.2.4 for details.
y To be performed at ET visit if not completed within the prior 12 weeks.

Appendix 3. Management of Clinical and Laboratory Adverse Events



* Refer to Sections 3.5 and 7.5 for details

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, which can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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.

The only modification to the CTCAE criteria is the addition of a Grade 1 upper respiratory infection as follows:

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

Appendix 5. Pregnancy Precautions, Definitions of Females of Childbearing Potential, and Contraceptive Requirements

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Therefore, filgotinib is contraindicated during pregnancy. Non-clinical reproductive toxicity studies of GS-9876 do not indicate a strong suspicion of human teratogenicity/fetotoxicity. There are no data for GS-9876 in pregnant women.

For participation in this study, the use of *highly effective* contraception is required as outlined below for all subjects of childbearing potential. In addition, women of childbearing potential should have a urine pregnancy test every 4 weeks during the study.

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 post-menopausal, permanently sterile or with medically documented ovarian failure. Women who do not meet the protocol definitions of post-menopausal, or permanently sterile, or do not have medically documented ovarian failure, must have pregnancy testing as outlined in the protocol.

Women are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of $\geq$ 12 months may also be considered postmenopausal if their 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. Bilateral tubal ligation is not considered to be permanent sterilization.

2) Contraception for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Data from a clinical drug-drug interaction study of filgotinib and hormonal contraceptives demonstrated that filgotinib does not alter the pharmacokinetics of representative hormonal contraceptives levonorgestrel/ethinyl estradiol.

GS-9876 has not been studied in pregnant women. There is no evidence of human teratogenicity based on class effects or genotoxic potential. In vitro drug interaction assessment of GS-9876 and hormonal contraceptives suggests that there is no clinically relevant effects that would decrease contraceptive efficacy.

Please refer to the latest version of the IBs for filgotinib and GS-9876 for additional information.

b. Contraception for Female Subjects of Childbearing Potential

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the Day 1 visit prior to randomization. Pregnancy tests will be performed at monthly intervals thereafter. In the event of a delayed menstrual period (> one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for women with infrequent or irregular periods.

Female subjects of childbearing potential must agree to use highly effective contraception. Subjects must agree to use one of the following methods from screening until 36 days following the last dose of study drug.

- 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:
  - Intrauterine device (IUD) with a failure rate of < 1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)
- Female subjects who wish to use a hormonal contraceptive must agree to use it in conjunction with a barrier method, preferably a male condom. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study drug dosing. Hormonal contraceptives and barrier methods permitted for use in this protocol are as follows:
  - Barrier methods (each method must be used with a hormonal method):
    - Male condom (with or without spermicide)
    - Female condom (with or without spermicide)
    - Diaphragm with spermicide
    - Cervical cap with spermicide
    - Sponge with spermicide

— Hormonal methods (each method must be used with a barrier method, preferably a male condom):

- Oral contraceptives (either combined or progesterone only)
- Injectable progesterone
- Subdermal contraceptive implant
- Transdermal contraceptive patch
- Contraceptive vaginal ring

All female subjects must also agree to refrain from egg donation and in vitro fertilization during the study and until 36 days after the last study drug dose.

3) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 36 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue all study drugs immediately.

Instructions for reporting pregnancy, and pregnancy outcome are outlined in Section 7.7.2.1.

5) Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the study. During the periods where study visits are every 6-8 weeks, women should continue to have pregnancy tests every 4 weeks, using home pregnancy test kits that will be provided to them. The site will call the subject every 4 weeks to obtain the results of these pregnancy tests and will record the information in the source documents and eCRF. If a positive urine pregnancy test is reported, the female subject will be asked to stop all study drugs and return to the clinic for a serum pregnancy test.

Appendix 6. Clinical Laboratory Assessment Table

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Urinalysis</th><th>Other</th></tr>
<tr><td rowspan="2">White blood cell (WBC) count
Hematocrit
Hemoglobin
Red blood cell (RBC) count
Red blood cell indices
Platelet count
Differentials (absolute and percentage), including, but not limited to:
Lymphocytes
Monocytes
Neutrophils
Eosinophils
Basophils
Reticulocyte count</td><td rowspan="2">Alkaline phosphatase
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Gamma-glutamyl transpeptidase (GGT)
Total bilirubin
Direct and indirect bilirubin
Total protein
Albumin
Bicarbonate
Blood urea nitrogen (BUN)
Calcium
Chloride
Creatinine
Creatinine clearance, CL_{cr}*
Glucose
Phosphorus
Magnesium
Potassium
Sodium
Creatine Kinase (CK)
Amylase
Lipase
Uric acid (at screening only)</td><td>Appearance
Blood
Color
Glucose
Specific gravity
Nitrites
Leukocyte esterase
pH
Protein
Ketones
Bilirubin
Urobilinogen
Reflex to microscopic urinalysis if dipstick result is abnormal.
Urine protein to creatinine ratio</td><td rowspan="2">Urine drug screen for:
Amphetamines
Cocaine
Barbiturates
Opiates
Benzodiazepines
QuantiFERON® TB – Gold In-Tube Analysis (if required per inclusion criteria)
FSH (as applicable)
HbA1c (at screening only)
TSH (at screening only)
C-reactive protein (CRP)
Erythrocyte sedimentation rate (ESR)
Quantitative immunoglobulins (IgG, IgM, and IgA)
Autoantibody panel (ANA with reflex ENA (dsDNA, SSA, SSB, Smith, RNP))
Complement levels (C3, C4, and CH50)</td></tr>
<tr><td>Virology
Hepatitis B surface antigen (HBsAg)
Hepatitis B virus (HBV) core antibody
Hepatitis C Virus (HCV) Ab (if positive, then reflex HCV RNA)
Human immunodeficiency virus Ab</td></tr>
<tr><th>Coagulation</th><th>Fasting Lipids</th><th>Pregnancy</th><th></th></tr>
<tr><td>Activated partial thromboplastin time (aPTT)
Prothrombin time (PT)
International normalized ratio (INR)</td><td>Total cholesterol
Low-density lipoprotein (LDL)
High-density lipoprotein (HDL)
Triglycerides</td><td>In females of childbearing potential:
Serum pregnancy test
Urine pregnancy test</td><td></td></tr>
</table>

* Calculation based on actual body weight,
Females: 0.85×(140−Age[years])×Weight[kg]/(Creatinine[mg/dL]×72)

ANA = antinuclear antibody
ENA = extractable nuclear antigen
dsDNA = double stranded DNA
Sm = Smith antigen
P protein = phosphorylated protein
SSA = Sjogren's-syndrome-related antigen A
SSB = Sjogren's-syndrome-related antigen B

Appendix 7. 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):

No CLE disease activity **Maximum CLE disease activity**

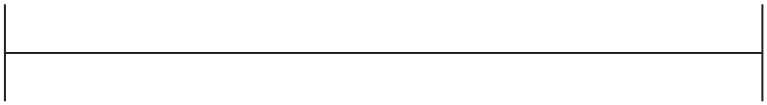
Appendix 8. Subject Global Assessment of CLE Disease Activity and Other Subject Reported Measures

1. Subject 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:

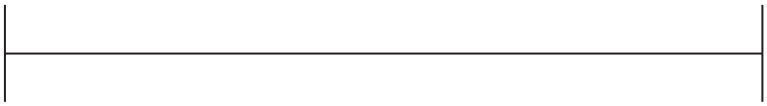


I have no CLE **I have the worst CLE**

2. Subject Assessment of Autoimmune Disease-related Dry Eyes/Mouth

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related dry eyes.

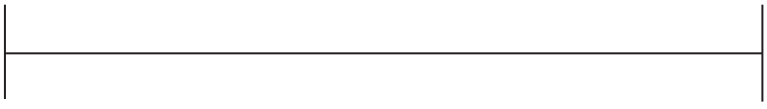
Place a mark on the line below to indicate how much dry eye has been caused by your autoimmune condition over the last week:



I have no dry eye due to my autoimmune condition **I have the worst dry eye due to my autoimmune condition**

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related dry mouth.

Place a mark on the line below to indicate how much dry mouth has been caused by your autoimmune condition over the last week:

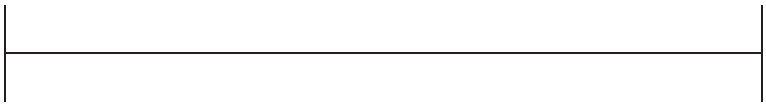


I have no dry mouth due to my autoimmune condition **I have the worst dry mouth due to my autoimmune condition**

3. Subject Assessment of Autoimmune Disease-related Body Pain

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related body pain.

Place a mark on the line below to indicate how much body pain has been caused by your autoimmune condition over the last week:



I have no body pain due to my autoimmune condition **I have the worst body pain due to my autoimmune condition**

4. Subject Assessment of Autoimmune Disease-related Joint Pain/Stiffness

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related joint pain.

Place a mark on the line below to indicate how much joint pain has been caused by your autoimmune condition over the last week:

I have no joint paint due to my autoimmune condition **I have the worst joint pain due to my autoimmune condition**

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related joint stiffness.

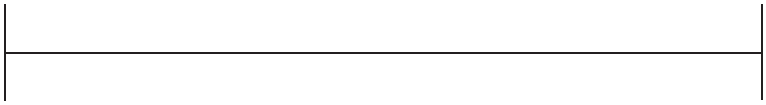
Place a mark on the line below to indicate how much joint stiffness has been caused by your autoimmune condition over the last week:

I have no joint stiffness due to my autoimmune condition **I have the worst joint stiffness due to my autoimmune condition**

5. Subject Assessment of Autoimmune Disease-related Fatigue

A horizontal, visual analog scale will be used to provide the subject's overall assessment of autoimmune disease-related fatigue.

Place a mark on the line below to indicate how much fatigue has been caused by your autoimmune condition over the last week:

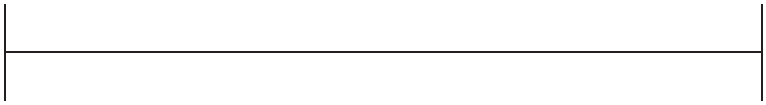


I have no fatigue due to my autoimmune condition **I have the worst fatigue due to my autoimmune condition**

6. Subject Assessment of CLE on Sexual Activity

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

Place a mark on the line below to indicate how much your sexual activity has been affected by your skin condition (CLE) over the last week:



My CLE does not affect my sexual activity **My CLE completely stops my sexual activity**