CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Randomized, Double-Blind, Multicenter Study Evaluating the Safety and Efficacy of Filgotinib and GS-9876 in Subjects with Lupus Membranous Nephropathy (LMN)	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	123903	
EudraCT Number:	Not Applicable	
Clinical Trials.gov Identifier:	NCT03285711	
Indication:	Lupus Membranous Nephropathy	
Protocol ID:	GS-US-437-4093	
Gilead Clinical Program Manager:	Name: Telephone: Fax: Email:	PPD PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile: Email:	PPD PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1: Amendment 2:	09 March 2017 05 July 2017 21 March 2018

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 2, Randomized, Double-Blind, Multicenter Study Evaluating the Safety and Efficacy of Filgotinib and GS-9876 in Subjects with Lupus Membranous Nephropathy (LMN)
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	123903 Not Applicable NCT03285711
Study Centers Planned:	Approximately 20 centers in North America
Objectives:	The primary objective of this study is: • To evaluate the efficacy of filgotinib and GS-9876 in subjects with LMN The secondary objectives of this study are: • To evaluate the safety and tolerability of filgotinib and GS-9876 in subjects with LMN • To evaluate the pharmacokinetics (PK) of filgotinib and GS-9876 in subjects with LMN The exploratory objectives of this study are: [redacted]

Study Design:

This is a Phase 2, randomized, double-blind, multicenter study in subjects with LMN. Subjects will be randomized in a 1:1 ratio to receive once daily oral doses of the following study drugs for 16 weeks:

Arm	Study Drugs
Filgotinib (n=16)	Filgotinib 200 mg + PTM GS-9876
GS-9876 (n=16)	GS-9876 30 mg + PTM Filgotinib

PTM = Placebo to match

Randomization will be stratified by prior treatment with cyclophosphamide.

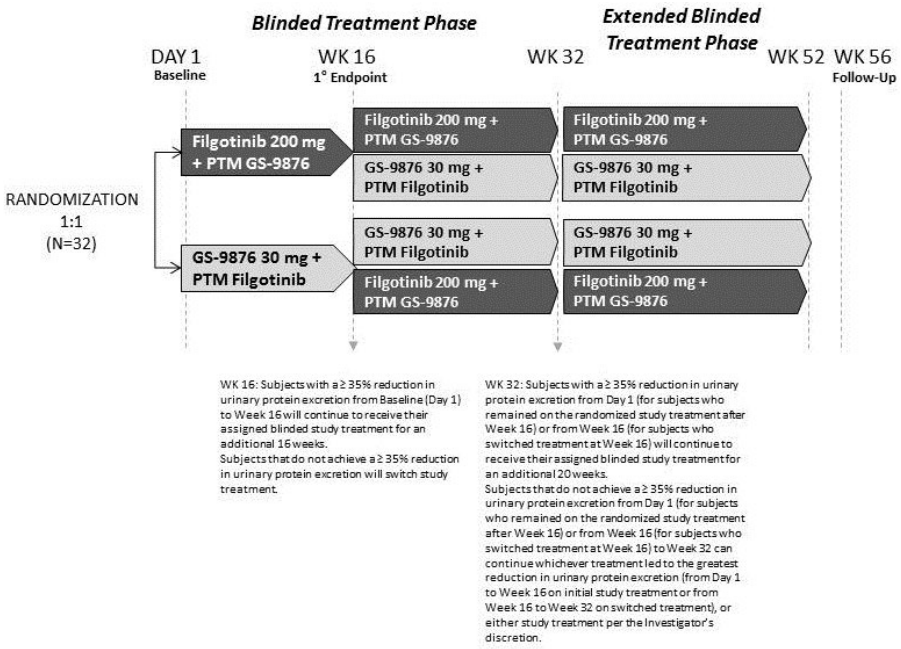
Urinary protein excretion will be determined using 2 methods – two consecutive morning voids as well as a 24-hour urine collection. For the Baseline (Day 1) assessment, all 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible. At Week 16, the primary study endpoint will be assessed by urine protein excretion during a 24-hour urine collection. Two consecutive morning voids prior to the Week 16 visit will be used to determine response for subsequent study treatment. All subjects who achieve a ≥ 35% reduction in urinary protein excretion (using an average of the urine protein creatinine ratio [UPCR] from 2 morning voids) from Baseline (Day 1) will continue to receive their assigned blinded study treatment (filgotinib 200 mg + PTM GS-9876, or GS-9876 30 mg + PTM filgotinib) for an additional 16 weeks. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

Subjects who do not achieve a ≥ 35% reduction in urinary protein excretion from Baseline (Day 1) to Week 16 will switch study treatment for 16 weeks in a blinded fashion (ie, those on filgotinib will switch to GS-9876 + PTM filgotinib, while those on GS-9876 will switch to filgotinib + PTM GS-9876).

After 32 weeks of blinded treatment, those who have a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) will continue their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase.

Subjects that do not achieve a ≥ 35% reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever study treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator's discretion (eg, differences in tolerability or other non-renal benefits that support overriding the treatment assignment according to reduction in urinary protein excretion) during the Extended Blinded Treatment Phase.

All subjects, including those who terminate early from the study, will be required to complete a Final Follow-Up (FU) visit 4 weeks (± 5 days) after the last dose of study drug.



Substudies:	CCI [redacted]
Number of Subjects Planned:	Approximately 32 subjects
Target Population:	Male or female subjects between 18 and 75 years of age, inclusive, with active lupus membranous nephropathy who are not in partial or complete remission in response to treatment with one or more anti-inflammatory or immunosuppressive agents.
Duration of Treatment:	Subjects will receive a maximum of 52 weeks of study drug(s).
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Section 4. **Key Inclusion Criteria** 1) Male or female between 18 and 75 years of age, inclusive, at the time of initial informed consent 2) Kidney biopsy within the 36 months prior to Screening with a histologic diagnosis of LMN (International Society of Nephrology [ISN] and the Renal Pathology Society [RPS] 2003 classification of lupus nephritis), either Class V alone, or Class V in combination with Class II. If the biopsy indicates segmental glomerular scarring indicative of prior Class III or IV lesions but there is limited or no evidence of current Class III or IV activity, the subject would be eligible if the Class V findings are active. A copy of the kidney biopsy pathology report will be obtained from each subject and forwarded to the Gilead Medical Monitor for review and confirmation of eligibility prior to randomization on Day 1.

3) Urine protein excretion $\geq$ 1.5 grams per day based on 24-hour urine sample collected during Screening
4) Estimated glomerular filtration rate ($eGFR_{MDRD}$) $\geq$ 40 mL/min/1.73 m^2 based on the MDRD formulation at Screening
5) Prior treatment for LMN with at least one immunosuppressive therapy for a sufficient duration before Screening, including but not limited to:
   a) Calcineurin inhibitors (cyclosporin A, tacrolimus),
   b) Alkylating agents (chlorambucil, cyclophosphamide), or
   c) Antimetabolite drugs (azathioprine, mycophenolate mofetil)
   d) Other (eg, methotrexate, leflunomide, moderate- to high-dose steroids, etc.)

   Prior therapy should be specified on the Prior and Concomitant Medication – LMN and SLE eCRF (ie, therapy name, dose, and start/stop dates).
6) Treatment with an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) at a dose deemed appropriate for the subject per the Investigator for at least 6 weeks prior to and during Screening, with a stably prescribed dose for at least 14 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of ACEi or ARB treatment throughout the study.

   Subjects who are not taking any ACEi or ARB may be screened if there is documented intolerance to ACEi and/or ARB.
7) If a subject is taking oral glucocorticoids, the dose must be $\leq$ 20 mg/day prednisone (or equivalent) and must have been on a stably prescribed dose for at least 28 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of prednisone treatment through Week 16 of the study (after assessment of the primary outcome).
8) If a subject is taking the following agents, they must have been on a stably prescribed dose for at least 28 days prior to Day 1:
   a) Hydroxychloroquine ($\leq$ 400 mg/day),
   b) Chloroquine ($\leq$ 250 mg/day), or
   c) Quinacrine ($\leq$ 100 mg/day)

   Enrolled subjects should remain on the stably prescribed dose of the above treatments throughout the study.

9) Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is permitted if the dose has been stably prescribed for at least 14 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of NSAID treatment throughout the study. Intermittent use (pro re nata [PRN]) for non-LMN indications should be minimized.

10) All disease modifying anti-rheumatic drugs (DMARDs) or immunosuppressive agents other than glucocorticoids, hydroxychloroquine (as specified above), azathioprine (up to a maximum of 2 mg/kg body weight/day or 200 mg/day, whichever is lower), and methotrexate (≤ 20 mg per week) should be withdrawn at least 28 days prior to Day 1.

11) Systolic blood pressure (SBP) below 160 mmHg AND diastolic blood pressure (DBP) below 90 mmHg will be measured at Screening. The Screening blood pressure may be repeated (a maximum of 2 times) as an unscheduled visit prior to Day 1.

12) Meet the following tuberculosis (TB) Screening criteria:

    a) No evidence of active or latent TB as assessed during Screening by:

        - A negative QuantiFERON® TB-Gold In-Tube test at Screening AND
        - A chest radiograph (if consistent with local guidelines) taken at Screening or within 90 days prior to Screening (with the report or films available for Investigator review) without evidence of active or latent TB infection

    b) Subjects previously treated for latent TB: subject who has previously received an adequate course of therapy as per local standard of care for latent TB (eg, 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are <5% or an acceptable alternative regimen). In these cases, no QuantiFERON® TB-Gold In-Tube test (or equivalent assay) need be obtained, but a chest radiograph must be obtained if not done so within 90 days prior to Screening (with the report or films available for Investigator review). It is the responsibility of the Investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation. Subjects with a history of untreated or inadequately treated latent TB are excluded from the study

    c) Subjects with newly identified latent TB during Screening are excluded from the study.

Cases falling under category "b" need to be approved by the Sponsor prior to enrollment in the study. Subjects with any history of or current active TB (regardless of past or present anti-TB treatment) are excluded.

Key Exclusion Criteria

1) Prior treatments as follows:
   a) Previous treatment with a JAK inhibitor within 3 months of Day 1
   b) Use of rituximab or other selective B lymphocyte depleting agents (including experimental agents) within 6 months of Day 1. Enrollment is permitted if the last dose was given > 6 months and CD19-positive B cells are detectable at Screening.
   c) Anticipated use of disallowed medications in Section 5.3.2
2) Known hypersensitivity or allergy to the study drugs (filgotinib, GS-9876), their metabolites, or formulation excipients
3) History of, or current, inflammatory or autoimmune disease other than SLE (e.g., scleroderma, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease) that will interfere with clinical evaluation during the study, per judgment of the Investigator. Secondary Sjogren's syndrome or controlled thyroiditis is acceptable, per judgment of the Investigator.
4) Administration of a live/attenuated vaccine within 30 days prior to Day 1, or planned during the study or through 12 weeks after subject's last dose of study drug

Study Procedures/ Frequency:

After the screening period and randomization on Day 1, eligible subjects will enter the Blinded Treatment Phase and return to the study center at specified visits.

Blinded Treatment Phase

- Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24, 28, and 32

Following completion of 16 weeks of dosing, the primary endpoint of the study will be evaluated in all subjects. To test their change in urinary protein excretion, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 16 visit. These results will inform their treatment assignment for the additional 16 weeks. Subjects who achieve a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Baseline (Day 1) to Week 16 will continue to receive their assigned blinded study treatment (filgotinib

200 mg + PTM GS-9876 once daily; or GS-9876 30 mg + PTM filgotinib once daily) for an additional 16 weeks. Those subjects who do not achieve a ≥ 35% reduction in urinary protein excretion from Baseline (Day 1) to Week 16 will switch study treatment for 16 weeks in a blinded fashion (ie, those on filgotinib 200 mg + PTM GS-9876 once daily will switch to GS-9876 30 mg + PTM filgotinib once daily, while those on GS-9876 30 mg + PTM filgotinib 200 mg once daily will switch to filgotinib 200 mg + PTM GS-9876 once daily). The primary outcome for urinary protein excretion will be determined using a 24-hour urine collection that is collected immediately prior to the Week 16 visit, or as close to the Week 16 visit as possible. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

After 32 weeks of blinded treatment, those who have received some benefit (a ≥ 35 % reduction in urinary protein excretion using an average of the UPCR from 2 morning voids from Day 1 [for subjects who remained on the randomized study treatment after Week 16] or from Week 16 [for subjects who switched treatment at Week 16]) will continue on their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase. To test their change in urinary protein excretion, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 32 visit. These results will inform their treatment assignment for the additional 20 weeks in the Extended Blinded Treatment Phase. Subjects will also submit a 24-hour urine collection that is collected immediately prior to the Week 32 visit, or as close to the Week 32 visit as possible. Subjects who do not achieve a ≥ 35% reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever study treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator's discretion (eg, differences in tolerability or other non-renal benefits that support overriding the treatment assignment according to reduction in urinary protein excretion) during the Extended Blinded Treatment Phase.

Extended Blinded Treatment Phase

- Weeks 36, 40, 44, 48, and 52

All subjects who received at least one dose of study drug and discontinue the study early will complete an Early Termination (ET) visit at the time of study discontinuation.

All subjects, including those who terminate early from the study, will be required to complete a Final Follow-Up (FU) visit 4 weeks (± 5 days) after the last dose of study drug. For subjects that complete the entire study, the Final FU visit will be conducted at Week 56.

Screening Study Assessments:

Complete medical history, complete physical exam (PE) (including height and weight), morning urine voids and 24-hour urine collection for protein, urinalysis (with urine microscopy and spot protein-to-creatinine ratio), vital signs (ie, blood pressure, respiratory rate, heart rate, and body temperature), clinical laboratory tests (hematology, serum chemistry, and coagulation), hemoglobin A1c (HbA_{1c}), thyroid stimulating hormone (TSH) test, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), autoantibody panel and complement levels, serum pregnancy test for females of childbearing potential or follicle stimulating hormone (FSH) test for females of nonchildbearing potential (as defined in Appendix 5), human immunodeficiency virus type 1 and 2 (HIV-1, HIV-2) test, hepatitis B virus (HBV) tests, hepatitis C virus (HCV) test, HCV RNA monitoring (if subject is HCV Ab positive), QuantiFERON® TB-Gold In-Tube Test (if applicable) and chest x-ray (if one has not already been obtained within 3 months prior to screening), and standard 12-lead electrocardiogram (ECG).

Subjects will be screened up to 35 days prior to randomization (Day 1) to determine eligibility for participation in the study. The Screening visit will take two separate days to complete. In addition, Screening Day 2 cannot occur earlier than 3 days after Screening Day 1 due to the timing of the morning urine voids and the 24 hour urine collection. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

Day 1 (Baseline) through Final Follow-Up Visit Assessments:

At a minimum, the following safety assessments will be performed at every study visit (refer to Appendix 2 for a complete list of required study assessments for each study visit):

Urinalysis (with urine microscopy and spot protein-to-creatinine ratio) (except Final FU visit), vital signs (ie, blood pressure, respiratory rate, heart rate, and body temperature), clinical laboratory tests (hematology, serum chemistry, and coagulation), CRP, ESR, HCV RNA monitoring (if applicable) and urine pregnancy test for females of childbearing potential.

Complete PE, symptom-driven PE, weight, morning urine voids and 24-hour urine collection for protein, fasting lipids, quantitative serum immunoglobulin test, autoantibody panel and complement levels, Safety of Estrogens in Lupus Erythematosus National Assessment trial-based SLE Disease Activity Index (SELENA-SLEDAI), British Isles Lupus Activity Group (BILAG) Index, Patient Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, 36-Item Short Form Health Survey, standard 12-lead ECG, in-clinic study drug administration, study drug accountability, and study drug dispensation will be performed at selected study visits (refer to Appendix 2).

Early Termination Study Assessments:

Complete PE, weight, vital signs (ie, blood pressure, respiratory rate, heart rate, and body temperature), clinical laboratory tests (hematology, serum chemistry, and coagulation), CRP, ESR, HCV RNA monitoring (if applicable), urine pregnancy test for females of childbearing potential, standard 12-lead ECG, and study drug accountability.

Assessment of adverse events (AEs) and concomitant medications will continue throughout the duration of the study.

Pharmacokinetic (PK) Assessments:

Blood samples will be collected for plasma PK analysis of filgotinib and its active metabolite GS-829845, and GS-9876 post dose at Weeks 2, 4 and 20 (at least 30 minutes and up to 3 hours after dosing), anytime at Weeks 8 and 24, and within 2 hours prior to dosing at Weeks 16 and 32.

Urine PK analyses may be performed for filgotinib and its active metabolite GS-829845, and GS-9876, using the 24-hour urine collection at Week 16.

Biomarker Assessments:

Urine samples will be collected for biomarker assessments at Screening, Day 1 (predose), Weeks 2, 16, 32, 52, ET, and at the Final FU.

Blood samples for biomarker assessments (whole blood TBNK biomarker, serum and plasma biomarkers, vfPBMC, and PAXgene RNA) will be collected at Screening, Day 1 (predose), Weeks 2, 16, 32, 52, ET, and at the Final FU.

Concomitant Medication Management:

Stable medications at Day 1 (per Section 5.3.1) are to be continued during the study. Refer to Table 5-1 for a list of prohibited medications.

Test Product, Dose, and Mode of Administration:	Filgotinib 200 mg (1 × 200 mg tablet) administered orally once daily in the AM GS-9876 30 mg (1 × 30 mg tablet) administered orally once daily in the AM
Reference Therapy, Dose, and Mode of Administration:	PTM Filgotinib (1 tablet) administered orally once daily in the AM PTM GS-9876 (1 tablet) administered orally once daily in the AM

Criteria for Evaluation:

Safety:

Safety will be assessed during the study through the reporting of AEs, clinical laboratory tests, vital sign assessments, physical examinations findings, and ECGs. Treatment emergent AEs including infection, worsening of proteinuria, or decrease in eGFR will be of particular interest.

Efficacy:

Primary Endpoint

- The percent change in urine protein from Baseline (Day 1) to Week 16 (assessed by urine protein excretion during a 24-hour urine collection).

Secondary Endpoints

- Change from Baseline (Day 1) in urine protein (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Change from Baseline (Day 1) in eGFR at Week 16
- Change from Baseline (Day 1) in UPCR (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Proportion of subjects with partial remission (defined as urine protein excretion below < 3 g/d and urine protein excretion decrease by ≥ 50% among subjects with Baseline (Day 1) nephrotic range proteinuria [urine protein excretion ≥ 3 g/d]; or urine protein excretion decrease by ≥ 50% among subjects with subnephrotic range proteinuria [urine protein excretion < 3 g/d]) at Week 16
- Proportion of subjects with complete remission (defined as urine protein excretion below 0.5 g/day, with no hematuria) at Week 16

Biomarker Endpoints

- Change in JAK-STAT-, SYK-, and disease-related biomarkers in peripheral blood and urine

- Association of changes in peripheral blood and urine biomarkers with clinical outcomes
- Association of Baseline markers with disease severity and response to filgotinib and GS-9876

Pharmacokinetics: Plasma concentrations of GS-9876, filgotinib and an active filgotinib metabolite, GS-829845, will be analyzed. Urine concentrations of GS-9876, filgotinib, and GS-829845 may be analyzed.

Statistical Methods:

Analysis Methods:

The primary endpoint, the percent change from Baseline (Day 1) in 24-hour proteinuria at Week 16, will be calculated for each treatment group and the 95% confidence interval will be constructed. 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.

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). 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.

Efficacy and safety data collected up to Week 16 will be summarized by treatment group for all subjects. Data from subjects who do not switch treatment will be summarized for the duration of the study by treatment group. Summaries by the combinations of treatment groups may be provided, if applicable.

The sample size was chosen based on the practical considerations and to ensure that a clinically meaningful reduction in proteinuria from Baseline (Day 1) could be detected in any of the treatment groups (filgotinib or GS-9876). With 16 subjects per treatment group (32 subjects total), there is a 80% power to detect a 35% reduction from Baseline (Day 1) in proteinuria at Week 16 with a standard deviation of 50% and a 2-sided 0.05 significance level.

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

ACEi	angiotensin-converting enzyme inhibitor
ACR20	American College of Rheumatology 20% improvement
AE	adverse event
AhR	aryl hydrocarbon receptor
ALT	alanine aminotransferase
ANA	antinuclear antibody
Anti-dsDNA	anti-double stranded DNA
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
BCR	b-cell receptor
BCRP	breast cancer resistance protein
bDMARDs	biologic disease-modifying antirheumatic drugs
BILAG	British Isles Lupus Activity Group Index
BLQ	Below the limit of quantitation
BMI	body mass index
C_{ave}	average concentration
CD	cluster of differentiation
Cis	Confidence intervals
CIA	collagen-induced arthritis
CLE	cutaneous lupus erythematosus
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRO	Contract Research Organization
CYP	Cytochrome
DKD	Diabetic kidney disease
DMARDs	disease-modifying antirheumatic drugs
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSS	Dextran sulphate sodium
EC_{50}	geometric mean half-maximal effective concentration
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
ET	early termination
EU	European Union

FACS	Fluorescence-activated cell sorting
FAS	Full Analysis Set
FceRl	Fc epsilon Receptor I alpha
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle stimulating hormone
FU	Follow-Up
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	Gastrointestinal
GLPG	Galapagos
HBV	Hepatitis B virus
HCV	hepatitis C virus
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 Harmonization
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
INR	international normalized ratio
IP	interferon gamma-induced protein
IRB	Independent Review Board
IWRS	interactive web response system
JAK	janus kinase
LLOQ	lower limit of quantitation
LMN	lupus membranous nephropathy
MCV	mean corpuscular volume
MDRD	The Modification of Diet in Renal Disease Study
MTX	Methotrexate
NDA	New Drug Application
NOAEL	no-observed-adverse-effect level
NOELs	no observed effect levels
NSAID	nonsteroidal anti-inflammatory drugs

NZB/NZW	New Zealand Black / New Zealand White (mouse strain)
OAT	organic ion transporter
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PE	Physical exam
P-gp	P-glycoprotein
PK	Pharmacokinetics
PT	preferred term
PTM	Placebo to match
PVE	Pharmacovigilance and Epidemiology (formally Drug Safety and Public Health –DSPH)
PXR	Pregnane x receptor
QTcF	QT interval corrected for heart rate according to Fridericia
RA	rheumatoid arthritis
RNA	ribonucleic acid
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SELENA-SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment Trial-Based SLE Disease Activity Index
SLE	Systemic lupus erythematosus
SOC	system organ class
STAT	signal transduction and activation of transcription
sTNFR2	soluble tumor necrosis factor receptor-2
SYK	spleen tyrosine kinase
TB	Tuberculosis
TEAEs	Treatment emergent adverse events
t_{max}	the time of occurrence of maximum observed plasma concentration
TNFα	tumor necrosis factor alpha
TYK	tyrosine kinase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
US	United States
vfPBMCs	Viably frozen peripheral blood mononuclear cells
VL	Viral load
WBC	white blood cell

1. INTRODUCTION

1.1. Background

Systemic lupus erythematosus (SLE) is a chronic systemic inflammatory disease that affects approximately 1.5 million adults in the United States (US) {Sarpel 2016}. SLE manifests principally as an autoimmune disease characterized by autoantibodies to nuclear and cytoplasmic antigens that leads to protean manifestations that follows a relapsing and remitting course with considerable mortality, morbidity, and impact on quality of life. Although SLE has a variety of signs and symptoms, it often affects the joints, skin, brain, lungs, kidneys, and blood vessels. Patients with SLE may experience fatigue, pain or swelling in joints, skin rashes, and fevers. Although people of any age can be affected, the onset of SLE is most frequent between the ages of 15 and 44 years, and women are affected 4-12 times more often than men {Dall'Era 2013}. While the cause of SLE is still not completely understood, genetic, environmental, and hormonal factors may lead to autoreactive B-cells and T-cells, activation of the adaptive immune system, and perpetuation of inflammatory responses that have all been implicated in its pathogenesis.

Kidney involvement in SLE continues to be a major contributor to morbidity and mortality {Danila 2009}. Up to 50% of SLE patients will have clinically evident kidney disease at presentation, and during follow-up, kidney involvement may occur in over 60% of patients, with an even greater representation among children and young adults {Waldman 2006}. The type of renal disease can vary quite widely from asymptomatic hematuria and/or proteinuria to nephrotic syndrome and rapidly progressive glomerulonephritis. One subtype of kidney disease is membranous nephropathy, which is a common cause of nephrotic syndrome in non-diabetic adults. When it occurs in SLE patients it is considered to be a secondary cause of membranous nephropathy (class V lupus membranous nephropathy [LMN]) and occurs in 10-20% of patients with lupus nephritis {Danila 2009}. Patients with LMN are at risk for developing end-stage renal disease (ESRD) due to protracted nephrotic syndrome. In addition they are predisposed to hypercholesterolemia and hypertension, which contribute to accelerated atherosclerosis, as well as hypercoagulability and an increased risk of infection {Kolasinski 2002}.

There are limited studies investigating the benefit of disease-modifying antirheumatic drugs (DMARDs) or biologic disease-modifying antirheumatic drugs (bDMARDs) in the treatment of LMN {Austin 2009, Ginzler 2005, Hallegua 2000, Karim 2005, Kasitanon 2008, Mok 2004, Mok 2009, Yap 2012}. In particular, randomized, controlled trials are lacking. Prior studies support the use of prednisone and azathioprine {Mok 2004} mycophenolate mofetil {Ginzler 2005, Karim 2005, Kasitanon 2008}cyclophosphamide {Austin 2009} sequential use of prednisone, cyclophosphamide, and azathioprine {Chan 1999} cyclosporine {Austin 2009, Hallegua 2000}, chlorambucil {Moroni 1998}, and plasmapheresis {Sloan 1996}. However, these studies have been small, have used variable outcome measures, and have not always reported dose and duration of therapy. There are no trials directly comparing immunosuppression versus non-immunosuppressive medications, and thus a consensus regarding optimal treatment does not exist. Standard of care for LMN is controversial, but generally includes immunosuppression when high-grade proteinuria exists (> 3.5 g/day despite

non-immunosuppressive therapy) or serum creatinine progressively rises. Given the toxicity and variable efficacy of current immunosuppressive medications used in the treatment of LMN, there is an unmet need for a safer, more effective therapy.

Recent human studies reveal critical roles of Janus kinase (JAK) inhibition in the treatment of rheumatoid arthritis {Fleischmann 2012, Genovese 2016, Keystone 2015, Lee 2014, van Vollenhoven 2012}and psoriasis {Bachelez 2015}.

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective oral inhibitor of JAK1 being developed by Gilead Sciences, Inc. (Gilead) and Galapagos (GLPG) NV. Filgotinib is effective in treating collagen-induced arthritis in rodents {Van Rompaey 2013}, and has demonstrated efficacy in two large Phase 2b clinical studies in subjects with RA. Upon activation, receptor-associated JAKs phosphorylate the intracellular portion of their receptors and provide a docking site for transcription factors known as signal transducers and activators of transcription (STATs) {O'Shea 2015}. Activated STATs dimerize, enter the nucleus, bind DNA, and directly regulate gene expression. A number of cytokines, growth factors, and hormones selectively act as ligands for one of four JAKs, leading to the preferential activation of 1 of 7 STATs. Notably, JAK1 is responsible for signaling by inflammatory cytokines that are involved in autoimmune diseases, such as IFN- α, IFN-β, IFN-γ, IL-2, IL-6, IL-10, IL-15, and IL-21, amongst others {O'Shea 2015}.

A study for the treatment of diabetic kidney disease (DKD) with baricitinib, a JAK1-2 selective inhibitor, indicated a dose-related reduction in albuminuria and inflammatory biomarkers involved in DKD progression, such as urinary interferon gamma-induced protein-10 (IP-10) and plasma soluble tumor necrosis factor receptor-2 (sTNFR2) {Brosius 2015, Tuttle 2015}. Although the exact pathogenesis of lupus, and more specifically lupus membranous nephropathy, are incompletely understood, it is believed that IFN-α {Feng 2006}, IL-10 {Houssiau 1995, Rahman 2008}, IL-21 {Bubier 2009, Sawalha 2008, Wang 2014}, and IL-6 {Maier-Moore 2014, Mao 2014, Sato 2014} play a role in SLE given their elevation and association with disease activity in lupus patients. Signaling of these cytokines function through JAK 1 in SLE, and thus inhibition of this pathway with filgotinib may offer a rational therapeutic target.

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 {Woroniecka 2011}. Signaling of these immune complex through SYK in various kidney diseases, and accumulating evidence from pre-clinical and clinical studies suggest a pathogenic role of SYK in proliferative glomerulonephritis, including anti-glomerular basement membrane disease, anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, immunoglobulin A nephropathy, and lupus nephritis {Crispin 2010, Ma 2016}. 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 {Ryan 2016, Smith 2010}. Thus, inhibition of the SYK pathway with GS-9876 may offer a rational therapeutic target in lupus nephritis.

1.2. Filgotinib

1.2.1. General Information

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

1.2.2. Preclinical 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 Central Nervous System (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 were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility, however sperm counts remained low. A dose of 200 mg once daily of filgotinib results in an estimated mean clinical area under the curve (AUC) of 2.80 µg·h/mL in rheumatoid arthritis (RA) subjects, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26-week and 39-week chronic toxicity studies and the 39-week targeted exposure toxicity study, respectively. GS-829845-related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

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

As of April 2017, filgotinib has been taken by more than 1400 subjects, including more than 950 with RA and more than 150 subjects with Crohn's disease, and has been generally safe and well tolerated. Clinical trials of filgotinib have not been previously undertaken in subjects with LMN. A detailed description of all clinical studies can be found in the IB.

In 9 Phase 1 studies conducted in healthy subjects (Studies GPLG0634-CL-101, -102, -103, -104, -105, -106, -107, -110, and GS-US-417-3900), filgotinib administered at doses of up to 450 mg once daily for up to 10 days was safe and well tolerated.

In 2 Phase 2a studies in subjects with RA (Study GLPG0634-CL-201 and -202), dosing with filgotinib was well tolerated and achieved maximal efficacy at a 200 mg daily dose (American College of Rheumatology 20% improvement [ACR20] response of 75-92% at Week 4).

In 2 Phase 2b studies, filgotinib at total daily doses of 50 mg, 100 mg, or 200 mg, administered in addition to background therapy with methotrexate (MTX) (GLPG0634-CL-203) or as monotherapy (GLPG0634-CL-204) was safe and effective in subjects with moderately to severely active RA who had an inadequate response to MTX alone.

Safety data collected across Phase 2 clinical studies in RA and Crohn's Disease showed no dose-dependent trends in the incidence of adverse events (AEs) or serious adverse events (SAEs), including infections, or laboratory abnormalities with the exception of a numerical increase in select gastrointestinal AEs (eg, nausea, vomiting, abdominal pain, and upper abdominal pain). This numerical increase was observed in the 200 mg compared to the 100 mg dose. However, the overall frequency was low and clinical relevance is unknown. The safety profile of filgotinib was consistent with that observed for an immunomodulatory compound administered to subjects with RA.

1.3. GS-9876

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

1.3.1. Nonclinical Pharmacology and Toxicology

1.3.1.1. 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 of differentiation (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 with GS-492429, a compound with similar selectively as GS-9876, showed a dose-responsive decrease in anti-dsDNA antibody titers and inhibition of proteinuria 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. This confirmed previously published data from the study of the SYK inhibitor, fostamitinib, in a NZB/NZW murine model and in a MRL/lpr murine model that demonstrated delayed onset of proteinuria and azotemia, reduced renal pathology and kidney infiltrates in lupus-prone mice {Bahjat 2008, Deng 2010}

In 2 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.

1.3.1.2. 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 at the high dose of 15 mg/kg/day, 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-437-4093, 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-437-4093, 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 1-1. 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)	$AUC_{0\text{-}24}$ (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

1.3.1.3. 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 (OATP1B1 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.

1.3.2. Clinical Trials of GS-9876

As of February 2016, 62 healthy volunteers have been dosed with GS-9876 in two clinical studies.

1.3.2.1. Completed Clinical Trial

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.

1.3.2.2. Ongoing Clinical Trials

GS-US-379-1582: This is a 12 week proof of concept trial of GS-9876 in patients with RA to evaluate efficacy, safety, tolerability, and PK of GS-9876.

GS-US-379-1932: This is a Phase 1, open-label, parallel-group, adaptive, single-dose, multi-center, PK study in subjects with renal impairment and matched healthy controls. Preliminary PK results showed no change in GS-9876 PK by moderate renal impairment.

GS-US-445-4189: This is a 48 week proof of concept trial of GS-9876 in patients with Sjogren's syndrome to evaluate efficacy, safety, tolerability, and PK of GS-9876.

1.4. Rationale for This Study

Although patients with LMN are at increased risk for end-stage renal disease, thromboembolic events and transition to proliferative lupus nephritis, therapeutic options for LMN are limited {Swan 2011}. There are very limited clinical trial data in LMN for the various newer biologic and synthetic DMARDs that have been approved for other indications. Prior studies support the use of prednisone and azathioprine {Mok 2004, Mok 2009}, mycophenolate mofetil {Ginzler 2005, Karim 2005, Kasitanon 2008}, cyclophosphamide {Austin 2009} sequential use of prednisone, cyclophosphamide, and azathioprine {Chan 1999}, cyclosporine {Austin 2009, Hallegua 2000}, chlorambucil {Moroni 1998}, and plasmapheresis {Sloan 1996}. However, these investigations have been small, have used variable outcome measures, and have not always reported dose and duration of therapy. In addition, some individuals with LMN have an inadequate response or intolerance to available therapies. Thus, 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. JAK1 activation is required for type I interferon (IFN) signaling, which is thought to be central to both systemic lupus and lupus nephritis. Although in vivo studies using a JAK inhibitor attenuated the progression of renal inflammation in the MRL/lpr mouse model of lupus using AG490 (JAK 2 inhibitor) {Wang 2010}, as well as the NZB/WF1 mouse model of lupus using CP-690,550 (JAK3 inhibitor) {Ripoll 2016}, there are no published data regarding JAK1 inhibition. However, preclinical studies at Gilead in MRL/lpr mice suggest mild reduction in proteinuria with JAK1/3 inhibition, and even greater effectiveness when combined with a SYK inhibitor.

Given its central role in immune cell signaling, inhibition of SYK is expected to have pleiotropic anti-inflammatory effects and affect multiple steps in lupus nephritis pathogenesis. Compared with normal T cells, T cells obtained from lupus patients demonstrated substantially higher SYK expression and activity {Krishnan 2008}In addition, B cells have been implicated in the pathogenesis of lupus nephritis, and B cell depletion demonstrates an effect in individuals with certain types of LMN {Ulinski 2014}. As a critical mediator of BCR signaling, SYK inhibition suppresses BCR-stimulated proliferation, co-stimulatory molecule expression, and autoantibody production {Braselmann 2006, Coffey 2012}. Further, inhibiting SYK in vitro delays the onset of proteinuria and azotemia, reduced renal pathology and kidney infiltrates and significantly prolonged survival in lupus prone NZB/NZW mice {Bahjat 2008}. In MRL/lpr mice, inhibiting SYK prevented the development of renal disease and reduced proteinuria in established disease {Deng 2010}

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

1.4.1. Rationale for Endpoint and Timing

Change in proteinuria will be the primary measure of efficacy. Proteinuria has long been used as a surrogate endpoint because it correlates well with kidney function, and it has been implicated in the pathogenesis of chronic kidney disease. In LMN it is associated with thromboembolic events, as well as cardiovascular events. Proteinuria is a standardized outcome measure of lupus nephritis, and an attractive choice because following an intervention, the change in proteinuria is often earlier and larger than the observed change in kidney function. It might be useful therefore in slowly progressive or early stages of disease. A magnitude of 35% or greater reduction in proteinuria was selected based on response rates observed during other trials of lupus nephritis {Borchers 2012}, including LMN {Swan 2011}.

Secondary measures will include additional measures of kidney structure and function (eg, proteinuria and glomerular filtration rate) at various time points, as well as measures of lupus activity. Validated scales will be used for lupus, including the Safety of Estrogens in Lupus Erythematosus National Assessment trial-based SLE Disease Activity Index (SELENA-SLEDAI) and the British Isles Lupus Activity Group (BILAG).

The selection of the 16-week time point is based on prior studies of LMN and lupus nephritis more broadly, as well as 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 lupus nephritis {Borchers 2012} including LMN {Swan 2011}, demonstrates a range of drug administration duration between 10 weeks for cyclophosphamide and 6 months for azathioprine and mycophenolic acid, supporting the idea that a 16-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) or GS-9876 (30 mg) with matched placebo tablets. The planned treatment of filgotinib and GS-9876 is based on safety data from clinical studies and supported by non-clinical safety data. Clinical efficacy data in RA further support the filgotinib dose.

Results from Phase 2a studies (GLPG0634-CL-201 and GLPG0634-CL-202) and Phase 2b studies (GLPG0634-CL-203 and GLPG0634-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 some clinical similarities of RA and systemic lupus erythematosus, 200 mg once daily filgotinib is expected to be a safe dose to evaluate efficacy in subjects with LMN.

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 systemic lupus erythematosus, a 30 mg once daily dose is expected to have an acceptable safety profile and have the potential to be efficacious in LMN.

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. It is proposed to study filgotinib in LMN at a dose of 200 mg once daily, a dose at which maximal clinical benefit has been observed for subjects with active RA.

Filgotinib has been administered in large Phase 2b studies of subjects with RA and Crohn's Disease 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 was observed in Phase 1 and 2 trials of filgotinib.

In the Phase 2b studies in RA, the most common AEs were in the infections and infestations system organ class (SOC), and infections were reported more commonly in the filgotinib groups. Pneumonia is an identified risk and serious infection is considered an important potential risk for filgotinib. Reference is made to the IB for further information about clinical infection findings.

As filgotinib is an immunomodulating agent, malignancy is closely monitored in clinical studies with filgotinib. 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 for filgotinib. Reference is made to the IB for further information about clinical malignancy findings, carcinoma, and nonmelanoma skin cancers. All reported malignancies occurred in subjects with RA.

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. The clinical relevance of nonclinical testicular findings in rats and dogs is unknown. A male safety study is planned to assess the effects, if any, of filgotinib on semen parameters in males with inflammatory diseases. Until the definitive results of this study are available, all males will be informed about this potential toxicity in the informed consent form and only men understanding and accepting the potential risk for loss of fertility will be enrolled. In addition, SLE is a disease of female predominance and although this may vary across some study populations, the ratio of those affected is approximately 9 fold higher in females than males. 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. Based on available non-clinical findings, GS-9876 is not contraindicated in pregnancy, although pregnancy in GS-9876 trials should be avoided. Measures to minimize other potential risks to subjects will include site/investigator training regarding monitoring for infection.

Preclinical and clinical data support the further clinical development of GS-9876 and filgotinib due to their potential benefit as novel therapies in lupus nephritis, 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 lupus nephritis and related diseases.

1.6. Compliance

This study will be conducted in compliance with this protocol, GCP, and all applicable regulatory requirements.

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of filgotinib and GS-9876 in subjects with LMN

The secondary objectives of this study are:

- To evaluate the safety and tolerability of filgotinib and GS-9876 in subjects with LMN
- To evaluate the PK of filgotinib and GS-9876 in subjects with LMN

The exploratory objectives of this study are:

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Endpoints

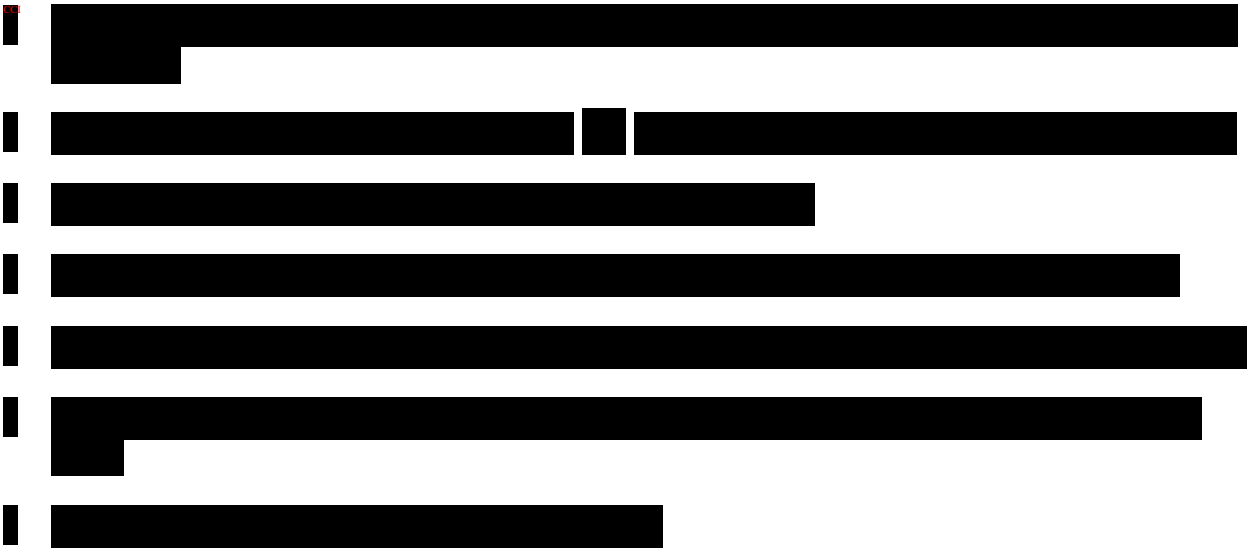
The primary endpoint of this study is:

- The percent change in urine protein from Baseline (Day 1) to Week 16 (assessed by urine protein excretion during a 24-hour urine collection)

The secondary endpoints of this study are:

- Change from Baseline (Day 1) in urine protein (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Change from Baseline (Day 1) in eGFR at Week 16
- Change from Baseline (Day 1) in UPCR (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Proportion of subjects with partial remission (defined as urine protein excretion below < 3 g/d and urine protein excretion decrease by ≥ 50% among subjects with Baseline (Day 1) nephrotic range proteinuria [urine protein excretion ≥ 3 g/d]; or urine protein excretion decrease by ≥ 50% among subjects with subnephrotic range proteinuria [urine protein excretion < 3 g/d]) at Week 16
- Proportion of subjects with complete remission (defined as urine protein excretion below 0.5 g/day, with no hematuria) at Week 16

The exploratory endpoints of this study are:



The biomarker endpoints of this study are:

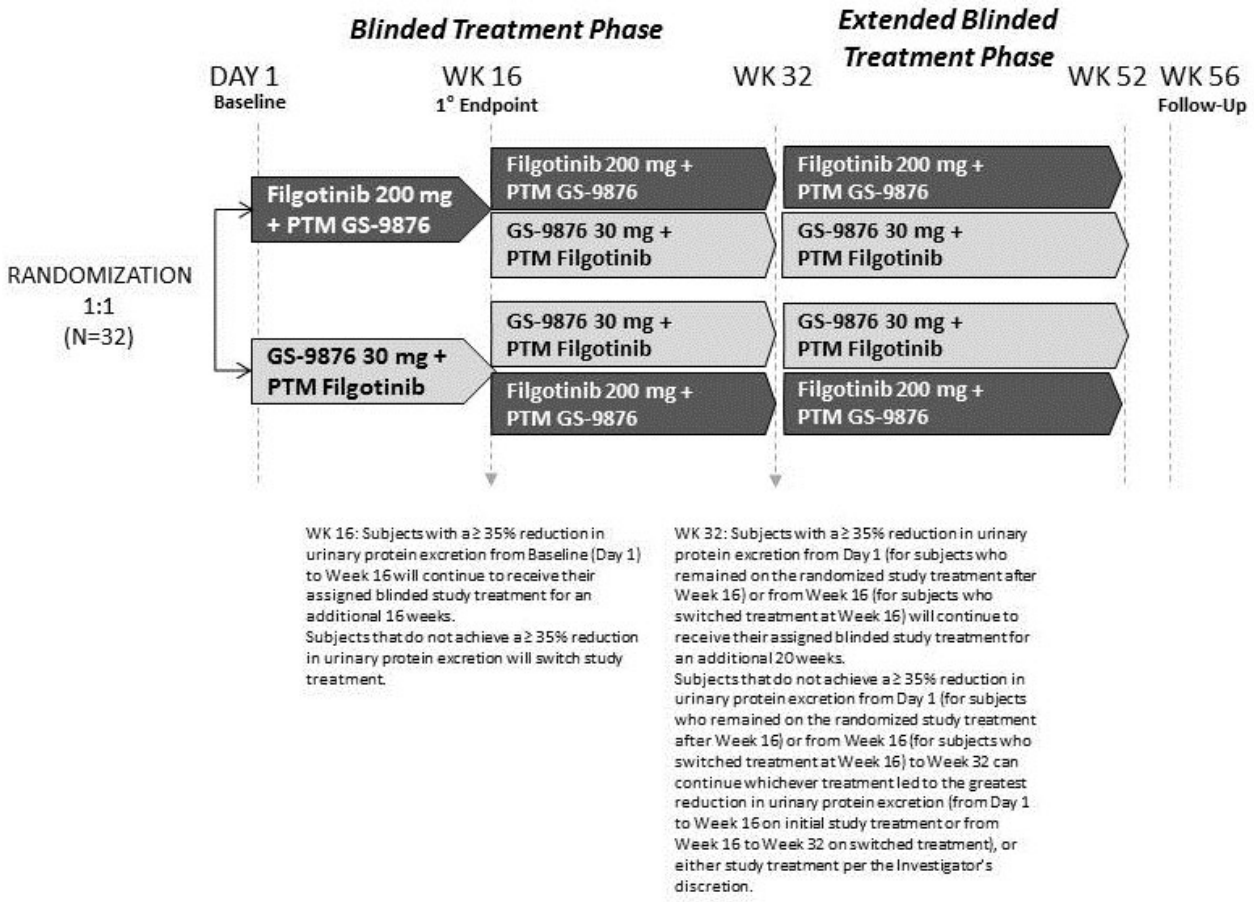
- Change in JAK-STAT-, SYK-, and disease-related biomarkers in peripheral blood and urine
- Association of changes in peripheral blood and urine biomarkers with clinical outcomes
- Association of Baseline markers with disease severity and response to filgotinib and GS-9876

3.2. Study Design

This is a Phase 2, randomized, double-blind, multicenter study to evaluate the safety and efficacy of filgotinib and GS-9876 in subjects with active LMN who are not in partial or complete remission in response to treatment with one or more anti-inflammatory or immunosuppressive agents.

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

Figure 3-1. Study Schema



3.3. Study Treatments

Eligible subjects will be randomized in a 1:1 ratio to receive once daily oral doses of the following study drugs for 16 weeks:

Arm	Study Drugs
Filgotinib (n=16)	Filgotinib 200 mg + PTM GS-9876
GS-9876 (n=16)	GS-9876 30 mg + PTM Filgotinib

PTM = Placebo to match

Randomization will be stratified by prior treatment with cyclophosphamide.

Urinary protein excretion will be determined using 2 methods – two consecutive morning voids as well as a 24-hour urine collection. For the Day 1 assessment, all 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible. At Week 16, the primary study endpoint will be assessed by urine protein excretion during a

24-hour urine collection. Two consecutive morning voids prior to the Week 16 visit will be used to determine response for subsequent study treatment. All subjects who achieve a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Day 1 will continue to receive their assigned blinded study treatment (filgotinib 200 mg + PTM GS-9876, or GS-9876 30 mg + PTM filgotinib) for an additional 16 weeks. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

Subjects who do not achieve a ≥ 35% reduction in urinary protein excretion from Day 1 to Week 16 will switch study treatment for 16 weeks in a blinded fashion (ie, those on filgotinib will switch to GS-9876 + PTM filgotinib, while those on GS-9876 will switch to filgotinib + PTM GS-9876).

After 32 weeks of blinded treatment, those who have a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) will continue their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase. Subjects that do not achieve a ≥ 35% reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator's discretion (eg, differences in tolerability or other non-renal benefits that support overriding the treatment assignment according to reduction in urinary protein excretion) during the Extended Blinded Treatment Phase.

3.4. Duration of Treatment

Eligible subjects will receive a maximum of 52 weeks of study drug.

3.5. Discontinuation Criteria

3.5.1. Study Drug Interruption Considerations

The Gilead Sciences, Inc. (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 when medically 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 Serious Adverse Event (SAE) reporting criteria
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active HCV during the study, as evidenced by HCV ribonucleic acid (RNA) positivity
- Evidence of active HBV during the study, as evidenced by HBV deoxyribonucleic acid (DNA) positivity or HBV core antibody 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
- Pregnancy 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)

- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the Gilead Medical Monitor.

- 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 for lack of efficacy but may continue with study visits per investigator judgment; refer to Section 5.3.1.1

- Laboratory Criteria: After becoming aware of any of the following abnormal laboratory values, 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 discontinued and further care of the subject should be directed per the investigator.

  a) Neutrophils < 1.0×10^3 cells/mm^3 (SI: < 1.0×10^9 cells/L)

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

  c) Platelets < 75.0×10^3 cells/mm^3 (SI: < 75.0×10^9 cells/L)

  d) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal range (ULN) AND total bilirubin > 2 × ULN or accompanied by symptoms consistent with hepatic injury[1]

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

  f) AST or ALT > 5 × ULN[1]

  g) Estimated glomerular filtration rate ($eGFR_{MDRD}$) < 40 mL/min/1.73 m^2 based on the MDRD 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 20-week Extended Blinded Treatment Phase. Subjects who permanently discontinue study medication for any reason will not be replaced. Subjects withdrawing from the study should complete the early termination (ET) and Final 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).

[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.

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 52 weeks of dosing plus the follow-up visit 4 weeks (± 5 days) after the last dose of study drug (ie, Week 56).

3.7. Post Study Care

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

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 events and to help inform the mechanism of action and mechanisms of resistance to filgotinib and GS-9876 in lupus nephritis. The specific analyses may include, but will not be limited to, the assays listed below.

The biomarker analyses may include the following:

- Measuring the expression and phosphorylation state of STAT and SYK proteins
- Characterization of tissue lymphocyte subsets
- Plasma and serum samples for analysis of circulating factors including but not limited to cytokines, microRNA, and metabolites.
- Urine samples for analysis of excreted biomarkers associated with nephritis.
- PBMC samples to assess cell phenotype.
- PAXgene blood samples for leukocyte gene expression analysis.

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 Laboratory Manual.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

A sufficient number of subjects will be screened to enroll approximately 32 subjects with LMN.

4.2. Inclusion Criteria

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

1) Able and willing to sign the informed consent as approved by the Institutional Review Board (IRB). Written consent must be provided before initiating any screening evaluations. Subjects must have read and understood the informed consent form (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 or any other individual
2) Male or female between 18 and 75 years of age, inclusive, at the time of initial informed consent
3) Kidney biopsy within the 36 months prior to Screening with a histologic diagnosis of LMN (International Society of Nephrology [ISN] and the Renal Pathology Society [RPS] 2003 classification of lupus nephritis), either Class V alone, or Class V in combination with Class II. If the biopsy indicates segmental glomerular scarring indicative of prior Class III or IV lesions but there is limited or no evidence of current Class III or IV activity, the subject would be eligible if the Class V findings are active.

   A copy of the kidney biopsy pathology report will be obtained from each subject and forwarded to the Gilead Medical Monitor for review and confirmation of eligibility prior to randomization on Day 1.
4) Urine protein excretion $\geq$ 1.5 grams per day based on 24-hour urine sample collected during Screening
5) Estimated glomerular filtration rate ($eGFR_{MDRD}$) $\geq$ 40 mL/min/1.73 m^2 based on the MDRD formulation at Screening
6) Prior treatment for LMN with at least one immunosuppressive therapy for a sufficient duration before Screening, including but not limited to:
   a) Calcineurin inhibitors (cyclosporin A, tacrolimus),
   b) Alkylating agents (chlorambucil, cyclophosphamide), or
   c) Antimetabolite drugs (azathioprine, mycophenolate mofetil)
   d) Other (eg, methotrexate, leflunomide, moderate- to high-dose steroids, etc.)

   A brief Investigator summary of prior therapy should be provided (ie, therapy name, duration/dates, and response).

7) Treatment with an ACEi or ARB at a dose deemed appropriate for the subject per the Investigator for at least 6 weeks prior to and during Screening, with a stably prescribed dose for at least 14 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of ACEi or ARB treatment throughout the study.

   Subjects who are not taking any ACEi or ARB may be screened if there is documented intolerance to ACEi and/or ARB

8) If a subject is taking oral glucocorticoids, the dose must be ≤ 20 mg/day prednisone (or equivalent) and must have been on a stably prescribed dose for at least 28 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of prednisone treatment through Week 16 of the study (after assessment of the primary outcome).

9) If a subject is taking the following agents, they must have been on a stably prescribed dose for at least 28 days prior to Day 1:

   a) Hydroxychloroquine (≤ 400 mg/day),

   b) Chloroquine (≤ 250 mg/day), or

   c) Quinacrine (≤ 100 mg/day)

   Enrolled subjects should remain on the stably prescribed dose of the above treatments throughout the study.

10) Use of NSAIDs is permitted if the dose has been stably prescribed for at least 14 days prior to Day 1. Enrolled subjects should remain on the stably prescribed dose of NSAID treatment throughout the study. Intermittent use (PRN) for non-LMN indications should be minimized.

11) All DMARDs or immunosuppressive agents other than glucocorticoids, hydroxychloroquine (as specified above), azathioprine (up to a maximum of 2 mg/kg body weight/day or 200 mg/day, whichever is lower), and methotrexate (≤ 20 mg per week) should be withdrawn at least 28 days prior to Day 1.

12) Systolic blood pressure (SBP) below 160 mmHg AND diastolic blood pressure (DBP) below 90 mmHg will be measured at Screening. The Screening blood pressure may be repeated (a maximum of 2 times) as an unscheduled visit prior to Day 1.

13) Females of childbearing potential (as defined in Appendix 5) must have a negative pregnancy test at Screening, Day 1 and throughout the study at each study visit.

14) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5. Specifically, female subjects must agree to refrain from attempting conception, egg donation or harvest from the time of signing consent through 36 days following the last dose of study drug. Male subjects must agree to refrain from attempting conception, or sperm donation from the time of signing consent through 90 days following the last dose of study drug.

15) Subjects must agree to refrain from blood donation from Screening through at least 30 days following the last dose of study drug.

16) Lactating female subjects must agree to discontinue nursing from Screening through at least 36 days following the last dose of study drug.

17) Meet the following TB Screening criteria:

    a) No evidence of active or latent TB as assessed during Screening by:

        - A negative QuantiFERON® TB-Gold In-Tube test at Screening AND

        - A chest radiograph (if consistent with local guidelines) taken at Screening or within the 90 days prior to Screening (with the report or films available for investigator review) without evidence of active or latent TB infection

    b) Subjects previously treated for latent TB: subject who has previously received an adequate course of therapy as per local standard of care for latent TB (eg, 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are <5% or an acceptable alternative regimen). In these cases, no QuantiFERON® TB-Gold In-Tube test (or equivalent assay) need be obtained, but a chest radiograph must be obtained if not done so within 90 days prior to Screening (with the report or films available for Investigator review). It is the responsibility of the Investigator to verify the adequacy of previous anti-tuberculosis treatment and provide appropriate documentation. Subjects with a history of untreated or inadequately treated latent TB are excluded from the study.

    c) Subjects with newly identified latent TB during Screening are excluded from the study.

    Cases falling under category "b" need to be approved by the Sponsor prior to enrollment in the study. Subjects with any history of or current active TB (regardless of past or present anti-TB treatment) are excluded.

18) In the judgment of the investigator, participation in the study offers an acceptable benefit/risk ratio when considering current lupus membranous nephropathy disease status, medical condition, and the potential benefits and risks of alternative treatments for lupus membranous nephropathy

4.3. Exclusion Criteria

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

1) Prior treatments as follows:

    a) Previous treatment with a JAK inhibitor within 3 months of Day 1

b) Use of rituximab or other selective B lymphocyte depleting agents (including experimental agents) within 6 months of Day 1. Enrollment is permitted if the last dose was given > 6 months and CD19-positive B cells are detectable at Screening.

c) Anticipated use of disallowed medications in Section 5.3.2

2) Known hypersensitivity or allergy to the study drugs (filgotinib, GS-9876), their metabolites, or formulation excipients

3) History of, or current, inflammatory or autoimmune disease other than SLE (e.g., scleroderma, reactive arthritis, rheumatoid arthritis, ankylosing spondylitis, Lyme disease) that will interfere with clinical evaluation during the study, per judgment of the Investigator. Secondary Sjogren's Syndrome or controlled thyroiditis is acceptable, per judgment of Investigator

4) Administration of a live/attenuated vaccine within 30 days prior to Day 1, or planned during the study or through 12 weeks after subject's last dose of study drug

5) Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives prior to Screening, whichever is longer. Exposure to investigational biologics should be discussed with the Sponsor

6) End stage renal disease (ESRD; peritoneal dialysis, hemodialysis, or status post-renal transplantation)

7) History of lymphoproliferative disease or current lymphoproliferative disease

8) History of organ or bone marrow transplant

9) Positive serology for human immunodeficiency virus (HIV) 1 or 2 at Screening

10) Evidence of active HCV infection. Subjects with positive HCV Ab at Screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA viral load (VL) at Screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require ongoing monitoring as outlined in the schedule of assessments. Subjects with active HCV during the study, as evidenced by RNA positivity, will be discontinued from study drug as outlined in the protocol.

11) Evidence of active or prior HBV infection. Subjects with positive HBV surface antigen (HBsAg) at Screening are excluded from the study. Subjects with positive HBV DNA or HBV core Ab are excluded from the study.

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

13) Active infection that is clinically significant, as per judgment of the investigator, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 60 days of Day 1; or any infection requiring oral anti‑infective therapy within 30 days of Day 1.

14) Currently on any treatment or prophylaxis for chronic infection (such as pneumocystis, cytomegalovirus, herpes zoster, and atypical mycobacteria). Past history of disseminated Staphylococcus aureus or disseminated Herpes simplex infection.

15) History of symptomatic herpes zoster infection within 12 weeks prior to Screening or history of disseminated/complicated herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, central nervous system involvement or postherpetic neuralgia)

16) 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 5.3.2 (NOTE: stably prescribed chronic aspirin therapy ≤ 325 mg/day for cardiovascular prophylaxis is allowed).

17) History of an infected joint prosthesis or other implanted device with retention of the prosthesis or device in situ

18) Current drug or alcohol abuse, per investigator judgment

19) History of or current moderate to severe congestive heart failure (New York Heart Association [NYHA] class III or IV), OR within the last 6 months, a cerebrovascular accident, myocardial infarction, unstable angina, unstable arrhythmia, OR new or significant ECG finding at Screening, or any other cardiovascular condition which, in the opinion of the investigator, would put the subject at risk by participation in the study.

20) History of malignancy within the past 5 years prior to Screening (except for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin or cervical carcinoma in situ, with no evidence of recurrence).

21) Significant blood loss (> 450 mL) or transfusion of any blood product within 12 weeks prior to Day 1.

22) Tests performed at the central laboratory at Screening that meet any of the criteria below (out of range lab values that are believed to be in error may be rechecked one time, after consultation with the sponsor or its designee, before subject is considered a screen failure):

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

    b) Neutrophils < 1.5×10^3 cells/mm^3 (SI: < 1.5×10^9 cells/L);

    c) Platelets < 100×10^3 cells/mm^3 (SI: < 100×10^9 cells/L);

d) Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5 × ULN;

e) Total bilirubin level ≥ 2 × ULN unless the subject has been diagnosed with Gilbert's disease and this is clearly documented;

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 tests/procedures 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 emergency medical care for the subject. The rationale for unblinding must be clearly explained in source documentation and on the case report form/ electronic case report form (eCRF), along with the date on which the treatment assignment was unblinded. 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.

Gilead Pharmacovigilance and Epidemiology (PVE) may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.2. Description and Handling of GS-9876, PTM GS-9876, Filgotinib and PTM Filgotinib

5.2.1. 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.

Matching placebo tablets will be supplied that are identical in physical appearance to the 30 mg GS-9876 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.

5.2.2. Formulation of Filgotinib and PTM Filgotinib

Filgotinib will be provided as 200 mg tablets that are capsule-shaped, and film-coated beige debossed with "GSI" on one side and "200" on the other. 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.

PTM filgotinib tablets are identical in appearance to the active filgotinib tablets. PTM filgotinib tablets contain 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.

5.2.3. Packaging and Labeling of Study Drugs

GS-9876 tablets, 30 mg, filgotinib tablets, 200 mg, and PTM 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 with an induction-sealed and aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA) and/or other local regulations.

5.2.4. Storage and Handling of Study Drugs

GS-9876 tablets, filgotinib tablets, and PTM tablets should be stored at a 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 bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

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

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

5.2.5. Dosage and Administration of GS-9876

GS-9876 30 mg (1 × 30 mg tablet), or GS-9876 PTM (1 tablet) will be provided by Gilead Sciences, Inc. and are to be administered orally once daily with water. The study drug should be swallowed whole. GS-9876 or GS-9876 PTM may be taken with or without food. Each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses. Subjects will be instructed to take study drug at approximately the same time each morning. At Weeks 2, 4 and 20, subjects will be instructed to take their study drug in clinic as the first study procedure prior to any others scheduled for that visit. At Weeks 16 and 32 subjects will be instructed to take their study drug after predose assessments have been completed (eg, PK sample collection).

For missed dose(s) of study medication, subject should be instructed to take the missed dose(s) of study medication, as soon as possible, during the same day. If more than 8 hours has elapsed since the scheduled time of the missed dose, the subject should be instructed to wait and take the next dose at the regularly scheduled time. Subjects should be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

5.2.6. Dosage and Administration of Filgotinib

Filgotinib 200 mg tablets and PTM filgotinib 200 mg tablets 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. At Weeks 2, 4 and 20, subjects will be instructed to take their study drug in clinic as the first study procedure prior to any others scheduled for that visit. At Weeks 16 and 32 subjects will be instructed to take their study drug after predose assessments have been completed (eg, PK sample collection).

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 more than 8 hours has elapsed since the scheduled time of the missed dose, the subject should be instructed to wait and take the next dose at the regularly scheduled time. 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.

5.3. Prior and Concomitant Medications

All medications taken for the treatment of lupus and lupus nephritis will be recorded in the source documents and on the eCRF. All other medications (for non-SLE 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, and instruct subjects to hold study drug administration while taking an excluded medication.

5.3.1. Allowed Concomitant Medications

5.3.1.1. Concomitant Medications for LMN

The allowed concomitant medication(s) for LMN should be maintained, as much as possible, at stable doses (defined as no change in prescription) 28 days prior to Day 1 through Week 16:

- Oral corticosteroids for SLE ≤ 20 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 SLE (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 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

- Oral azathioprine (≤ 2 mg/kg bodyweight/day or 200 mg/day, whichever is lower) for SLE or lupus nephritis (administered per investigator judgment). Subjects who are not planning to continue oral azathioprine during the study must have discontinued them at least 28 days prior to Day 1

After completion of the Week 16 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 for lack of efficacy 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.

5.3.1.2. Other Concomitant Medications

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

- Vitamins, minerals, and herbal supplements
- Hormonal contraceptives or male 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

5.3.2. Prohibited Concomitant Medications

Examples of prohibited medications are provided below. This list does not include medications such as anti-HIV agents that would be contraindicated based on other exclusion criteria.

Table 5-1. Prohibited Medications

Drug Class	Agents Disallowed	Prohibited Period
Biologic Immunomodulator	Anti-tumor necrosis factor drugs infliximab, adalimumab, belimumab, golimumab, certolizumab, rituximab, dupilumab, or biosimilar agent (if applicable)	90 days prior to screening through the end of study participation (6 months for rituximab and demonstration of CD19+ B cell presence)
	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 SLE Medications		
Corticosteroids	Oral corticosteroids > 20 mg prednisone equivalent/day	28 days prior to Day 1 through the end of study participation
	Injectable corticosteroids	14 days prior to Day 1 through the end of study participation
Non-biologic Immunomodulator	Azathioprine (> 2 mg/kg bodyweight/day or 200 mg/day, whichever is lower), colchicine, cyclosporine, cyclophosphamide, tacrolimus (oral or topical), gold salts, leflunomide, minocycline, MTX > 20 mg/week (subcutaneous or oral), mycophenolate, penicillamine, sirolimus, everolimus, temsirolimus, or other immunomodulatory/immunosuppressive therapies (with the exception of oral antimalarials as permitted in Section 5.3.1.1)	28 days prior to Day 1 through the end of study participation

Drug Class	Agents Disallowed	Prohibited Period
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)	
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, entospletinib, or other 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

5.4. 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 30 days 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.

5.5. Accountability for 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 drug returned, along with the initials of the person recording the information. Dispensing records will include the initials of the person dispensing the study drug or supplies

5.5.1. Investigational Medicinal Product 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 details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

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

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 35 days prior to randomization (Day 1) to determine eligibility for participation in the study. The Screening visit will take two separate days to complete. In addition, Screening Day 2 cannot occur earlier than 3 days after Screening Day 1 due to the timing of the morning urine voids and the 24 hour urine collection. Additional details regarding urine collection procedures will be specified in the Laboratory Manual and Subject Procedures Manual.

The following will be performed and documented at Screening:

- Obtain written informed consent
- [redacted]
- Obtain medical history, including a copy of the kidney biopsy pathology report with a histologic diagnosis of LMN performed within the 36 months prior to Screening. The report will be forwarded to the Gilead Medical Monitor for review and confirmation of eligibility prior to randomization on Day 1.

- Review inclusion and exclusion criteria
- Height and weight
- Complete PE
- Obtain urine samples for:
  - Urinary protein excretion will be determined using 2 consecutive morning voids as well as a 24-hour urine collection.
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes). In such circumstances, investigators may ask patients to return for another screening visit.
  - Urine biomarker sample
- Vital signs
- Standard 12-lead ECG
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - HbA_{1c} and TSH
  - CRP and ESR
  - Autoantibody panel and complement levels
  - 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)
  - HCV RNA VL (if subject is HCV Ab positive)
  - QuantiFERON® TB Gold in Tube Test (if applicable)
  - Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)

- Chest x-ray (if one has not already been obtained within 3 months prior to screening)
- Record any serious adverse events and all adverse events related to protocol mandated procedures occurring after signing of the consent form
- Record any concomitant medication in the medical history

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 35 days after screening 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.

A single retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters, or if the initial value was either due to a sample processing error or an extenuating circumstance.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all concomitant medication, serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (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 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Baseline Assessments

The following will be performed and documented prior to dosing:

- Updates to medical history (if applicable)
- Review inclusion and exclusion criteria
- Weight
- Symptom-driven PE
- Obtain urine samples for:
  - Urinary protein excretion will be determined using 2 consecutive morning voids as well as a 24-hour urine collection. All 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible.
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).

  - Urine pregnancy test (for females of childbearing potential)
  - Urine biomarker sample
- SELENA-SLEDAI
- BILAG
- Patient Global Assessment of Disease activity
- Physician Global Assessment of Disease activity
- 36-Item Short Form Health Survey
- Vital signs
- Standard 12-lead ECG
- Obtain predose blood samples for:
  - Fasting Clinical Laboratory Tests (hematology, serum chemistry with lipid assessments, and coagulation)
  - CRP and ESR
  - Quantitative serum immunoglobulin test
  - Autoantibody panel and complement levels
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
  - CCI [redacted]
  - Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)
- Study drug dispensing
- Review and record all AEs and concomitant medications

Following the completion of the above assessments, the subject will be randomized and administered study drug.

CCI [redacted]

6.3. Randomization

Subjects may not be randomized until the Gilead Medical Monitor has reviewed the kidney biopsy pathology report and has confirmed that a subject is eligible. Upon qualification for the study, subjects will be randomized in a 1:1 ratio using a computerized IWRS system.

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

Refer to Sections 3.3 and 6.1 for additional details.

6.4. Week 1 Assessments

- Weight
- Symptom-driven PE
- Obtain urine samples for:
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
- Vital signs
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
- Study drug accountability
- Review and record all AEs and concomitant medications

6.5. Weeks 2 through Week 28 Assessments (excluding Week 16)

At Weeks 2, 4, and 20, subjects will be instructed to take their study drug in the clinic as the first study procedure prior to any others scheduled for those visits.

- Weight
- Symptom-driven PE

- Obtain urine samples for:
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
  - Urine biomarker sample (Week 2 only)
- SELENA-SLEDAI
- Vital signs
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR
  - Quantitative serum immunoglobulin test (Weeks 8 and 24 only)
  - Autoantibody panel and complement levels (Weeks 2, 4, and 8 only)
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
  - Plasma PK samples (Weeks 2, 4, and 20 [at least 30 minutes and up to 3 hours after dosing] and anytime at Weeks 8 and 24)
  - Biomarker Samples (Week 2 only [whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample])
- Study drug accountability
- Study drug dispensing (Weeks 4, 8, 12, 20, 24, and 28 only)
- Review and record all AE and concomitant medications

6.6. Week 16 and Week 32 Assessments

At Weeks 16 and 32 subjects will be instructed to take their study drug after predose assessments have been completed (eg, up to 2 hours after PK sample collection). The following will be performed and documented prior to dosing:

- Weight
- Symptom-driven PE

- Obtain urine samples for:
  - For Week 16, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 16 visit to test their change in urinary protein excretion. Subjects will also submit a 24-hour urine collection that is collected immediately prior to the Week 16 visit, or as close to the Week 16 visit as possible. These results will inform their treatment assignment for the additional 16 weeks.
  - For Week 32, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 32 visit to test their change in urinary protein excretion. Subjects will also submit a 24-hour urine collection that is collected immediately prior to the Week 32 visit, or as close to the Week 32 visit as possible. These results will inform their treatment assignment for the additional 20 weeks in the Extended Blinded Treatment Phase.
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
  - Urine PK sample (Week 16 only)
  - Urine biomarker sample
- SELENA-SLEDAI
- BILAG
- Patient Global Assessment of Disease activity
- Physician Global Assessment of Disease activity
- 36-Item Short Form Health Survey
- Vital signs
- Standard 12-lead ECG
- Obtain predose blood samples for:
  - Fasting Clinical Laboratory Tests (hematology, serum chemistry with lipid assessments, and coagulation)
  - CRP and ESR

- Autoantibody panel and complement levels
- HCV RNA VL (if subject was HCV Ab positive at Screening)
- Plasma PK sample (within 2 hours prior to dosing)
- Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)

- Study drug accountability
- Study drug dispensing
- Review and record all AEs and concomitant medications

6.7. Week 36 through Week 48 Assessments

- Weight
- Symptom-driven PE
- Obtain urine samples for:
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
- SELENA-SLEDAI
- Vital signs
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR
  - Quantitative serum immunoglobulin test (Week 48 only)
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
- Study drug accountability

- Study drug dispensing
- Review and record all AEs and concomitant medications

6.8. Week 52 Assessments

- Weight
- Symptom-driven PE
- Obtain urine samples for:
  - Morning voids and 24-hour Urine Collection for Urine Protein. Urine samples from 3 consecutive days will be collected to evaluate urine protein, including morning voids during 2 consecutive days prior to each 24-hour urine collection (on the 3rd consecutive day).
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
  - Urine biomarker sample
- SELENA-SLEDAI
- BILAG
- Patient Global Assessment of Disease activity
- Physician Global Assessment of Disease activity
- 36-Item Short Form Health Survey
- Vital signs
- Standard 12-lead ECG
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR

- Autoantibody panel and complement levels
- HCV RNA VL (if subject was HCV Ab positive at Screening)
- Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)

- Study drug accountability
- Review and record all AEs and concomitant medications

6.9. Early Termination Assessments

All subjects who received at least one dose of study drug and discontinue the study early will have the below assessments completed at the time of study discontinuation:

- Weight
- Complete PE
- Obtain urine samples for:
  - Urine pregnancy test (for females of childbearing potential)
  - Urine biomarker sample
- Vital signs
- Standard 12-lead ECG
- Obtain blood samples for:
  - Clinical Laboratory Tests (hematology, serum chemistry, and coagulation)
  - CRP and ESR
  - Autoantibody panel and complement levels
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
  - Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)
- Study drug accountability
- Review and record all AEs and concomitant medications

6.10. Final Follow-Up Assessments (4 Weeks Post Treatment)

The following procedures will be completed 4 weeks (± 5 days) after the subject's last dose of study drug. Subjects that discontinue early from the study will be required to complete the FU visit.

- Weight
- Complete PE
- Obtain urine samples for:
  - Morning voids and 24-hour Urine Collection for Urine Protein. Urine samples from 3 consecutive days will be collected to evaluate urine protein, including morning voids during 2 consecutive days prior to each 24-hour urine collection (on the 3rd consecutive day).
  - Urine pregnancy test (for females of childbearing potential)
  - Urine biomarker sample
- SELENA-SLEDAI
- BILAG
- Patient Global Assessment of Disease activity
- Physician Global Assessment of Disease activity
- 36-Item Short Form Health Survey
- Vital signs
- Obtain blood samples for:
  - Fasting Clinical Laboratory Tests (hematology, serum chemistry with lipid assessments, and coagulation)
  - CRP and ESR
  - Autoantibody panel and complement levels
  - HCV RNA VL (if subject was HCV Ab positive at Screening)
  - Biomarker Samples (whole blood TBNK biomarker sample, serum and plasma biomarker samples, vfPBMC sample, and PAXgene RNA sample)
- Review and record all AEs and concomitant medications

6.11. Unscheduled Visit (exacerbation of LMN)

The following procedures will be completed at an unscheduled visit for exacerbation of LMN (worsening of proteinuria, and/or decrease in eGFR):

- Symptom-driven PE
- Obtain urine samples for:
  - Urinalysis (with urine microscopy and spot protein-to-creatinine ratio). As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes).
  - Urine pregnancy test (for females of childbearing potential)
- Vital signs
- Review and record all AEs and concomitant medications

6.12. Study Assessments

6.12.1. Priority of Assessments

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

6.12.2. Efficacy

Efficacy assessments will be performed at the time points indicated in the study procedures table (Appendix 2).

6.12.2.1. Urine Protein Excretion

Several methods exist to assess urine protein excretion. Measurement of protein excretion in a 24-hour collection period has been the longstanding “gold standard” for the quantitative evaluation of proteinuria, and will be used to assess the primary outcome. An alternative method for quantitative evaluation of proteinuria is measurement of the ratio of protein to creatinine in an untimed “spot” urine specimen (UPCR). These ratios correct for variations in urinary concentration due to hydration and provide a more convenient method of assessing protein and albumin excretion than those requiring timed urine collections, and will be used to provide a preliminary assessment of response prior to the Week 16 and Week 32 visits.

6.12.2.2. Safety of Estrogens in Lupus Erythematosus National Assessment -Systemic Lupus Erythematosus Activity Index (SELENA-SLEDAI)

The SELENA-SLEDAI is an index of SLE flares commonly used in clinical trials as an assessment tool of SLE activity with scores that range from 0 to 105, with higher scores indicating more severe disease activity.

6.12.2.3. British Isles Lupus Activity Group (BILAG) Index

The BILAG is an index of SLE flares commonly used in clinical trials as an organ-specific assessment tool of SLE activity that includes a 97-question assessment based upon the evaluating physician's intent to treat, which requires an assessment of improved (1), the same (2), worse (3), or new (4) over the last month. Within each of 8 organ systems, multiple manifestations and laboratory tests are combined into a single score for that organ that range from A through E, with A representing very active disease and E indicating that the organ was never involved.

6.12.2.4. Physician's Global Assessments of Disease Activity

The Physician's Global Assessment of Disease Activity will be recorded on a 0 to 100 mm visual analogue scale (VAS; Appendix 9), with 0 indicating "no LMN disease activity" and 100 indicating "maximum LMN disease activity". It represents the average assessment of a patient's disease activity based on physical examination and laboratory data according to the evaluating physician.

6.12.2.5. Patient's Global Assessments of Disease Activity

The Patient Global Assessment reflects the patient's perceived overall health and disease activity, with disease activity estimated on a 0 to 100 mm visual analog scale.

6.12.2.6. 36-Item Short Form (SF) Healthy Survey (SF-36)

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.

6.12.3. Safety

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

6.12.4. Clinical Laboratory Evaluations

All 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. Subjects only need to be fasted on days were lipid profiling is scheduled.

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

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator as indicated.

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) after the investigator has consulted with the medical monitor. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section 3.5 for additional information).

The details of sample handling and shipment instructions will be provided in a separate Laboratory Manual.

6.12.5. 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.

6.12.6. Physical Examination

A physical examination should be performed at the time points indicated in the study procedures table Appendix 2. Any changes from baseline will be recorded. 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 should 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.

6.12.7. Other Safety Assessments

6.12.7.1. 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.

6.13. Pharmacokinetics Assessments

Blood samples will be collected for plasma PK analysis of filgotinib and its active metabolite GS-829845, and GS-9876 post dose at Weeks 2, 4, and 20 (at least 30 minutes and up to 3 hours after dosing), anytime at Weeks 8 and 24, and within 2 hours prior to dosing at Weeks 16 and 32.

Urine PK analyses may be performed for filgotinib and its active metabolite GS-829845, and GS-9876, using the 24-hour urine collection at Week 16.

6.14. Biomarker Assessments

Urine samples will be collected for biomarker assessments at Screening, Day 1 (predose), Weeks 2, 16, 32, 52, ET, and at the Final FU.

Blood samples for biomarker assessments (whole blood TBNK biomarker, serum and plasma biomarkers, vfPBMC, and PAXgene RNA) will be collected at Screening, Day 1 (predose), Weeks 2, 16, 32, 52, ET, and at the Final FU.

CCI [redacted]

CCI [redacted]

[redacted]

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)
- 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 CRF.

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 IMP treatment 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 investigational medicinal product.

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) 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 CTCAE, version 4.03. For each episode, the highest grade attained should be reported. 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.

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 7-1 and Appendix 4.

Table 7-1. 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 case report form (CRF/eCRF): all SAEs and adverse events related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, all AEs, regardless of cause or relationship, until 30-days after last administration of study drug(s) must be reported to the CRF/eCRF database as instructed.

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

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 CRF/eCRF database and Gilead Pharmacovigilance and Epidemiology (PVE) 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(s), 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(s), he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the CRF/eCRF database within the timelines outlined in the CRF/eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE 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 PVE: **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 CRF/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 suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study 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.

7.5. Clinical Laboratory Abnormalities

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, coagulation, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, 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 Common Terminology Criteria for Adverse Events (CTCAE) and Laboratory Abnormalities. 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 and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

For study-specific interruption and discontinuation criteria, refer to Section 3.5. Specific toxicity discontinuation criteria in Section 3.5 supersede below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply.

The Gilead Medical Monitor should be consulted prior to study drug discontinuation when medically 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. Grades 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 a Grade 3 clinically significant laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to IMP, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local clinical practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation and study drug may be continued at the discretion of the investigator.

7.6.3. Grades 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 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 will 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 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 AEs associated with product complaints, occupational exposure with an AE, pregnancy reports (regardless of an associated AE), and an AE in an infant following potential exposure from breastfeeding.

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).

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

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

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 medication and throughout the study, including the post study drug follow-up period, to Gilead PVE the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to Section 7.3 and the CRF/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 Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead 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 PVE. Gilead PVE contact information is as follows:
Email: PPD and Fax: PPD

Pregnancies of female partners of male study subjects exposed to study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the pregnancy should continue until its conclusion. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE, fax number PPD or email 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 PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP 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 CRF/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 CRF/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

Efficacy and safety data collected up to Week 16 will be summarized by treatment group for all subjects. Data from subjects who do not switch treatment will be summarized for the duration of the study by treatment group. Summaries by the combinations of treatment groups may be provided, if applicable.

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective is:

- To evaluate the efficacy of filgotinib and GS-9876 in subjects with LMN

The secondary objectives are:

- To evaluate the safety and tolerability of filgotinib and GS-9876 in subjects with LMN
- To evaluate the PK of filgotinib and GS-9876 in subjects with LMN

The exploratory objectives are:

[redacted]

8.1.2. Primary Endpoint

The primary endpoint is the percent change in urine protein from Baseline (Day 1) to Week 16. Urine protein is assessed by urinary protein excretion during a 24-hour urine collection.

8.1.3. Secondary Endpoints

- Change from Baseline (Day 1) in urine protein (assessed by urine protein excretion during a 24-hour urine collection) at Week 16
- Change from Baseline (Day 1) in eGFR at Week 16
- Change from Baseline (Day 1) in UPCR (assessed by urine protein excretion during a 24-hour urine collection) at Week 16

- Proportion of subjects with partial remission (defined as urine protein excretion below < 3 g/d and urine protein excretion decrease by ≥ 50% among subjects with Baseline (Day 1) nephrotic range proteinuria [urine protein excretion ≥ 3 g/d]; or urine protein excretion decrease by ≥ 50% among subjects with subnephrotic range proteinuria [urine protein excretion < 3 g/d]) at Week 16

- Proportion of subjects with complete remission (defined as urine protein excretion below 0.5 g/day, with no hematuria) at Week 16

8.1.4. Exploratory Endpoints

[redacted]

[redacted] protein excretion below 0.5 g/day, with no hematuria) at each visit other than Week 16

8.1.5. Biomarker Endpoints

- Change in JAK-STAT-, SYK-, and disease-related biomarkers in peripheral blood and urine
- Association of changes in peripheral blood and urine biomarkers with clinical outcomes
- Association of Baseline markers with disease severity and response to filgotinib and GS-9876

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. All data collected during treatment plus 30 days after the last dose of study drug will be included in the safety summaries**.**

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 non-missing PK concentration data for GS-9876, filgotinib or their metabolites.

8.2.1.5. Biomarkers

The primary analysis set for biomarker analyses will be the Biomarker Analysis Set, which includes all subjects in the Safety Analysis Set who have at least one evaluable measurement available at any time point for a given biomarker 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. BLQ 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 measurements will be summarized using standard descriptive statistics including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and number and percentages of subjects for categorical variables.

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

Baseline characteristics will include and not limited to a range of proteinuria (< 3g/d, >= 3g/d), histologic diagnosis, prior and current treatment for lupus membranous nephropathy, and patient-reported and physician-reported outcome assessments.

8.5. Efficacy Analysis

Details of the efficacy analyses will be described in the Statistical Analysis Plan (SAP).

8.5.1. Primary Analysis

The primary endpoint, the percent change from Baseline (Day 1) in 24-hour proteinuria at Week 16, will be calculated and the 95% confidence interval will be constructed for each treatment group.

8.5.2. Secondary Analyses

All continuous secondary 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 group. All categorical secondary endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition. The 95% CI will be provided, as appropriate.

8.5.3. Exploratory Analyses

CCI [redacted]

8.6. Safety Analysis

All safety analyses will be performed using the safety analysis set. Safety will be evaluated by the 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 drug + 30 days will be included in the safety analysis.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF.

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

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (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 on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug.

Summaries (number and percentage of subjects) of treatment-emergent adverse events (by SOC, and PT) will be provided. TEAEs will also be summarized by relationship to study drug and severity.

All observed AEs will be presented in by-subject listings.

8.6.3. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) along with corresponding changes. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale in Appendix 4.

Laboratory abnormalities that occur before the first dose of study drug or after the subject has been discontinued from treatment for at least 30 days will be included in a data listing.

8.6.4. Other Safety Evaluations

Individual data for physical examination findings, prior and concomitant medications and medical history will be provided. Vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

8.7. Pharmacokinetic Analysis

Plasma concentrations and other PK parameters of filgotinib, the active metabolite of filgotinib (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 other filgotinib or GS-9876 metabolite(s) may also be determined and analyzed.

Urine PK analyses may be performed for GS-9876, filgotinib and its active metabolite, GS-829845, using the 24h urine collection at Week 16.

8.8. Biomarker Analysis

CCI [redacted]

For biomarker analysis, 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 changes, as appropriate.

CCI [redacted]

Biomarker objectives may be further described and updated based on evolving scientific knowledge of filgotinib and GS-9876. CCI [redacted]

8.9. Sample Size

The sample size was chosen based on the practical considerations and to ensure that a clinically meaningful reduction in proteinuria from Baseline (Day 1) could be detected in any of the treatment groups, filgotinib or GS-9876. With 16 subjects per treatment group (32 subjects total), there is a 80% power to detect a 35% reduction from Baseline (Day 1) in proteinuria at Week 16 with a standard deviation of 50% and a 2-sided 0.05 significance level.

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 recommendation to Gilead 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 the study should continue with modifications.

The first DMC data review meeting will be conducted after approximately 50% of planned subjects enroll and complete through 16 weeks of study treatment. 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 and secondary analyses will be conducted after all subjects either complete their Week 16 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.

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. The investigator will not begin any study subject activities until approval from the IRB 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 any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB 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-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person

conducting the consent discussion, and also by an impartial witness if required by IRB 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, 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, CRF/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, CRF and query forms, IRB 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 will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF 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. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points

as described in the clinical data management plan), 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. The eCRF capture the data required per the protocol schedule of events and procedures. 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 (e.g. data entry error). 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 Sciences, 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 IRBs 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 in accordance with local requirements and receive documented IRB 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, e.g. 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 CRF/eCRF.

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

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or 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

Austin HA, 3rd, Illei GG, Braun MJ, Balow JE. Randomized, controlled trial of prednisone, cyclophosphamide, and cyclosporine in lupus membranous nephropathy. J Am Soc Nephrol 2009;20 (4):901-11.

Bachelez H, van de Kerkhof PC, Strohal R, Kubanov A, Valenzuela F, Lee JH, et al. Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial. Lancet 2015;386 (9993):552-61.

Bahjat FR, Pine PR, Reitsma A, Cassafer G, Baluom M, Grillo S, et al. An orally bioavailable spleen tyrosine kinase inhibitor delays disease progression and prolongs survival in murine lupus. Arthritis Rheum 2008;58 (5):1433-44.

Barr PM, Wei C, Roger J, Schaefer-Cutillo J, Kelly JL, Rosenberg AF, et al. Syk inhibition with fostamatinib leads to transitional B lymphocyte depletion. Clin Immunol 2012;142 (3):237-42.

Borchers AT, Leibushor N, Naguwa SM, Cheema GS, Shoenfeld Y, Gershwin ME. Lupus nephritis: a critical review. Autoimmunity reviews 2012;12 (2):174-94.

Braselmann S, Taylor V, Zhao H, Wang S, Sylvain C, Baluom M, et al. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. J Pharmacol Exp Ther 2006;319 (3):998-1008.

Brosius FC, Tuttle KR, Adler SG, Kretzler M, Mehta RL, Tumlin JA, et al. Baricitinib in Diabetic Kidney Disease: Biomarker Analysis from a Phase 2, Randomized, Double-Blind, Placebo-Controlled Study [Abstract TH-OR034]. American Society of Nephrology Kidney Week; 2015 03-08 November; San Diego, CA.

Bubier JA, Sproule TJ, Foreman O, Spolski R, Shaffer DJ, Morse HC, 3rd, et al. A critical role for IL-21 receptor signaling in the pathogenesis of systemic lupus erythematosus in BXSB-Yaa mice. Proc Natl Acad Sci U S A 2009;106 (5):1518-23.

Chan TM, Li FK, Hao WK, Chan KW, Lui SL, Tang S, et al. Treatment of membranous lupus nephritis with nephrotic syndrome by sequential immunosuppression. Lupus 1999;8 (7):545-51.

Coffey G, DeGuzman F, Inagaki M, Pak Y, Delaney SM, Ives D, et al. Specific inhibition of spleen tyrosine kinase suppresses leukocyte immune function and inflammation in animal models of rheumatoid arthritis. J Pharmacol Exp Ther 2012;340 (2):350-9.

Crispin JC, Kyttaris VC, Terhorst C, Tsokos GC. T cells as therapeutic targets in SLE. Nature reviews. Rheumatology 2010;6 (6):317-25.

Dall'Era M. Current Diagnosis & Treatment: Rheumatology, Third Edition. Section 111. Lupus & Related Autoimmune Disorders. Chapter 21. Systemic Lupus Erythematosus. 2013:

Danila MI, Pons-Estel GJ, Zhang J, Vila LM, Reveille JD, Alarcon GS. Renal damage is the most important predictor of mortality within the damage index: data from LUMINA LXIV, a multiethnic US cohort. Rheumatology (Oxford) 2009;48 (5):542-5.

Deng GM, Liu L, Bahjat FR, Pine PR, Tsokos GC. Suppression of skin and kidney disease by inhibition of spleen tyrosine kinase in lupus-prone mice. Arthritis Rheum 2010;62 (7):2086-92.

Feng X, Wu H, Grossman JM, Hanvivadhanakul P, FitzGerald JD, Park GS, et al. Association of increased interferon-inducible gene expression with disease activity and lupus nephritis in patients with systemic lupus erythematosus. Arthritis Rheum 2006;54 (9):2951-62.

Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD, et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med 2012;367 (6):495-507.

Genovese MC, Kremer J, Zamani O, Ludivico C, Krogulec M, Xie L, et al. Baricitinib in Patients with Refractory Rheumatoid Arthritis. N Engl J Med 2016;374 (13):1243-52.

Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. N Engl J Med 2005;353 (21):2219-28.

Hallegua D, Wallace DJ, Metzger AL, Rinaldi RZ, Klinenberg JR. Cyclosporine for lupus membranous nephritis: experience with ten patients and review of the literature. Lupus 2000;9 (4):241-51.

Houssiau FA, Lefebvre C, Vanden Berghe M, Lambert M, Devogelaer JP, Renauld JC. Serum interleukin 10 titers in systemic lupus erythematosus reflect disease activity. Lupus 1995;4 (5):393-5.

Karim MY, Pisoni CN, Ferro L, Tungekar MF, Abbs IC, D'Cruz DP, et al. Reduction of proteinuria with mycophenolate mofetil in predominantly membranous lupus nephropathy. Rheumatology (Oxford) 2005;44 (10):1317-21.

Kasitanon N, Petri M, Haas M, Magder LS, Fine DM. Mycophenolate mofetil as the primary treatment of membranous lupus nephritis with and without concurrent proliferative disease: a retrospective study of 29 cases. Lupus 2008;17 (1):40-5.

Keystone EC, Taylor PC, Drescher E, Schlichting DE, Beattie SD, Berclaz PY, et al. Safety and efficacy of baricitinib at 24 weeks in patients with rheumatoid arthritis who have had an inadequate response to methotrexate. Annals of the rheumatic diseases 2015;74 (2):333-40.

Kolasinski SL, Chung JB, Albert DA. What do we know about lupus membranous nephropathy? An analytic review. Arthritis Rheum 2002;47 (4):450-5.

Krishnan S, Juang YT, Chowdhury B, Magilavy A, Fisher CU, Nguyen H, et al. Differential expression and molecular associations of Syk in systemic lupus erythematosus T cells. J Immunol 2008;181 (11):8145-52.

Lee EB, Fleischmann R, Hall S, Wilkinson B, Bradley JD, Gruben D, et al. Tofacitinib versus methotrexate in rheumatoid arthritis. N Engl J Med 2014;370 (25):2377-86.

Ma TK, McAdoo SP, Tam FW. Spleen Tyrosine Kinase: A Crucial Player and Potential Therapeutic Target in Renal Disease. Nephron 2016;133 (4):261-9.

Maier-Moore JS, Horton CG, Mathews SA, Confer AW, Lawrence C, Pan Z, et al. IL-6 Deficiency Corrects Nephritis, Lymphocyte Abnormalities, and Secondary Sjogren's Features Sle1.Yaa lupus-prone mice. Arthritis Rheumatol 2014;66 (9):2521-31.

Mao X, Wu Y, Diao H, Hao J, Tian G, Jia Z, et al. Interleukin-6 promotes systemic lupus erythematosus progression with Treg suppression approach in a murine systemic lupus erythematosus model. Clinical rheumatology 2014;33 (11):1585-93.

Mok CC, Ying KY, Lau CS, Yim CW, Ng WL, Wong WS, et al. Treatment of pure membranous lupus nephropathy with prednisone and azathioprine: an open-label trial. Am J Kidney Dis 2004;43 (2):269-76.

Mok CC, Ying KY, Yim CW, Ng WL, Wong WS. Very long-term outcome of pure lupus membranous nephropathy treated with glucocorticoid and azathioprine. Lupus 2009;18 (12):1091-5.

Moroni G, Maccario M, Banfi G, Quaglini S, Ponticelli C. Treatment of membranous lupus nephritis. Am J Kidney Dis 1998;31 (4):681-6.

Namour F, Diderichsen PM, Cox E, Vayssiere B, Van der Aa A, Tasset C, et al. Pharmacokinetics and Pharmacokinetic/Pharmacodynamic Modeling of Filgotinib (GLPG0634), a Selective JAK1 Inhibitor, in Support of Phase IIB Dose Selection. Clin Pharmacokinet 2015;54 (8):859-74.

O'Shea JJ, Schwartz DM, Villarino AV, Gadina M, McInnes IB, Laurence A. The JAK-STAT pathway: impact on human disease and therapeutic intervention. Annu Rev Med 2015;66:311-28.

Rahman A, Isenberg DA. Systemic lupus erythematosus. N Engl J Med 2008;358 (9):929-39.

Ripoll E, de Ramon L, Draibe Bordignon J, Merino A, Bolanos N, Goma M, et al. JAK3-STAT pathway blocking benefits in experimental lupus nephritis. Arthritis research & therapy 2016;18 (1):134.

Ryan J, Ma FY, Han Y, Ozols E, Kanellis J, Tesch GH, et al. Myeloid cell-mediated renal injury in rapidly progressive glomerulonephritis depends upon spleen tyrosine kinase. The Journal of pathology 2016;238 (1):10-20.

Sarpel D, Wasserman I, Trochtenberg A, Bichoupan K, DelBello D, Perumalswami PV, et al. Non-adherence is the most important risk factor for ledipasvir/sofosbuvir HCV treatment failure in the real world [Poster P1978]. American Association for the Study of Liver Diseases (AASLD); 2016 11-15 November; Boston, MA.

Sato S, Lennard Richard M, Brandon D, Jones Buie JN, Oates JC, Gilkeson GS, et al. A critical role of the transcription factor fli-1 in murine lupus development by regulation of interleukin-6 expression. Arthritis Rheumatol 2014;66 (12):3436-44.

Sawalha AH, Kaufman KM, Kelly JA, Adler AJ, Aberle T, Kilpatrick J, et al. Genetic association of interleukin-21 polymorphisms with systemic lupus erythematosus. Annals of the rheumatic diseases 2008;67 (4):458-61.

Sloan RP, Schwartz MM, Korbet SM, Borok RZ. Long-term outcome in systemic lupus erythematosus membranous glomerulonephritis. Lupus Nephritis Collaborative Study Group. J Am Soc Nephrol 1996;7 (2):299-305.

Smith J, McDaid JP, Bhangal G, Chawanasuntorapoj R, Masuda ES, Cook HT, et al. A spleen tyrosine kinase inhibitor reduces the severity of established glomerulonephritis. J Am Soc Nephrol 2010;21 (2):231-6.

Swan JT, Riche DM, Riche KD, Majithia V. Systematic review and meta-analysis of immunosuppressant therapy clinical trials in membranous lupus nephritis. J Investig Med 2011;59 (2):246-58.

Tuttle KR. Baricitinib in Diabetic Kidney Disease: Results from a Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study [Abstract 114-LB]. American Diabetes Association (ADA); 2015 05-08 July; Boston, MA.

Ulinski T, Davourie-Salandre A, Brocheriou I, Aoun B. Immunoadsorption: a new strategy to induce remission in membranous lupus nephritis. Case Rep Nephrol Urol 2014;4 (1):37-41.

Van Rompaey L, Galien R, van der Aar EM, Clement-Lacroix P, Nelles L, Smets B, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. J Immunol 2013;191 (7):3568-77.

van Vollenhoven RF, Fleischmann R, Cohen S, Lee EB, Garcia Meijide JA, Wagner S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. N Engl J Med 2012;367 (6):508-19.

Waldman M, Appel GB. Update on the treatment of lupus nephritis. Kidney Int 2006;70 (8):1403-12.

Wang L, Zhao P, Ma L, Shan Y, Jiang Z, Wang J, et al. Increased interleukin 21 and follicular helper T-like cells and reduced interleukin 10+ B cells in patients with new-onset systemic lupus erythematosus. The Journal of rheumatology 2014;41 (9):1781-92.

Wang S, Yang N, Zhang L, Huang B, Tan H, Liang Y, et al. Jak/STAT signaling is involved in the inflammatory infiltration of the kidneys in MRL/lpr mice. Lupus 2010;19 (10):1171-80.

Woroniecka KI, Park AS, Mohtat D, Thomas DB, Pullman JM, Susztak K. Transcriptome analysis of human diabetic kidney disease. Diabetes 2011;60 (9):2354-69.

Yap DY, Yu X, Chen XM, Lu F, Chen N, Li XW, et al. Pilot 24 month study to compare mycophenolate mofetil and tacrolimus in the treatment of membranous lupus nephritis with nephrotic syndrome. Nephrology (Carlton) 2012;17 (4):352-7.

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, Multicenter Study Evaluating the Safety and Efficacy of Filgotinib and GS-9876 in Subjects with Lupus Membranous Nephropathy (LMN)

GS-US-437-4093, AMENDMENT 2, 21 MARCH 2018

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

PPD

PPD (Printed)
Study Director and Medical Monitor

PPD

Signature

March 26, 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

	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		
	Screen[a]	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16[b]	Week 32[c]	Weeks 36, 40, 44, 48	Week 52	F/U[d]	ET[e]	Unscheduled Visit (exacerbation of LMN)[f]
Visit Window (Days)	**-35**	**0**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	
Written Informed Consent	X										
Medical History, including kidney biopsy report	X										
Review Inclusion/Exclusion Criteria	X	X									
Randomization		X									
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	
Complete Physical Examination	X								X	X	
Symptom-driven Physical Examination[g]		X	X	X	X	X	X	X			X
2 Morning voids & 24-hour Urine Collection[h]	X[h]	X[h]			X[h]	X[h]		X[h]	X[h]		
Urinalysis[i]	X	X	X	X	X	X	X	X			X
SELENA-SLEDAI[j, bb]		X		X	X	X	X	X	X		
BILAG[k, bb]		X			X	X		X	X		

	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN)[f]
	Screen[a]	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16[b]	Week 32[c]	Weeks 36, 40, 44, 48	Week 52	F/U[d]	ET[e]	
Visit Window (Days)	**-35**	**0**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	
Patient Global Assessment of disease activity[l, bb]		X			X	X		X	X		
Physician Global Assessment of disease activity[m, bb]		X			X	X		X	X		
36-Item Short Form Health Survey [bb]		X			X	X		X	X		
Vital Signs[n]	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X			X	X		X		X	
Hematology	X	X	X	X	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	X	X	X	X	
Fasting Lipids		X			X	X			X		
Coagulation	X	X	X	X	X	X	X	X	X	X	
HbA_{1c} and TSH	X										
CRP and ESR	X	X	X	X	X	X	X	X	X	X	
Quantitative Serum Immunoglobulin Test		X		X[cc]			X[dd]				
Autoantibody Panel & Complement Levels	X	X		X[z]	X	X		X	X	X	
Serum Pregnancy Test[o]	X										
Urine Pregnancy Test[o, p]		X	X	X	X	X	X	X	X	X	X

	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN)[f]
	Screen[a]	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16[b]	Week 32[c]	Weeks 36, 40, 44, 48	Week 52	F/U[d]	ET[e]	
Visit Window (Days)	**-35**	**0**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	
FSH Test[q]	X										
HIV-1/2, HBV, HCV Serology	X										
HCV RNA VL[r]	X	X	X	X	X	X	X	X	X	X	
QuantiFERON® TB Gold in Tube Test[s]	X										
Chest X-Ray[s]	X										
Plasma PK Sample[t]				X	X	X					
Urine PK Samples[u]					X						
CCI											
Whole Blood TBNK Biomarker Sample	X	X		X[x]	X	X		X	X	X	
Serum Biomarker Sample	X	X		X[x]	X	X		X	X	X	
Plasma Biomarker Sample	X	X		X[x]	X	X		X	X	X	
vfPBMC Sample	X	X		X[x]	X	X		X	X	X	
PAXgene RNA Sample	X	X		X[x]	X	X		X	X	X	

	Blinded Treatment Phase						Extended Blinded Treatment Phase		End of Study		Unscheduled Visit (exacerbation of LMN)[f]
	Screen[a]	D1/ Baseline	Week 1	Weeks 2, 4, 8, 12, 18, 20, 24, 28	Week 16[b]	Week 32[c]	Weeks 36, 40, 44, 48	Week 52	F/U[d]	ET[e]	
Visit Window (Days)	**-35**	**0**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±5**	**±5**	
Urine Biomarker Sample	X	X		X[x]	X	X		X	X	X	
In-Clinic Study Drug Administration[y]		X		X	X	X					
Study Drug Accountability			X	X	X	X	X	X		X	
Study Drug Dispensing		X		X[aa]	X	X	X				
Review AEs & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X

a Prospective subjects should be screened no more than 35 days prior to the administration of the first dose of study treatment. The Screening visit will take two separate days to complete. In addition, Screening Day 2 cannot occur earlier than 3 days after Screening Day 1 due to the timing of the morning urine voids and the 24 hour urine collection.

b Urinary protein excretion will be determined using 2 methods – 2 consecutive morning voids as well as a 24-hour urine collection. For the Baseline assessment, all 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible. At Week 16, the primary study endpoint will be assessed by urine protein excretion during a 24-hour urine collection. Two consecutive morning voids prior to the Week 16 visit will be used to determine response for subsequent study treatment. All subjects who achieve a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from the morning voids) from Baseline (Day 1) will continue to receive their assigned blinded study treatment (filgotinib 200 mg + PTM GS-9876, or GS-9876 30 mg + PTM filgotinib) for an additional 16 weeks. Subjects who do not achieve a ≥ 35% reduction in urinary protein excretion from Baseline (Day 1) to Week 16 will switch study treatment for 16 weeks in a blinded fashion (ie, those on filgotinib will switch to GS-9876 + PTM filgotinib, while those on GS-9876 will switch to filgotinib + PTM GS-9876)

c After 32 weeks of blinded treatment, those who have a ≥ 35% reduction in urinary protein excretion (using an average of the UPCR from 2 morning voids) from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) will continue their assigned blinded treatment for an additional 20 weeks in the Extended Blinded Treatment Phase. Subjects that do not achieve a ≥ 35% reduction in urinary protein excretion from Day 1 (for subjects who remained on the randomized study treatment after Week 16) or from Week 16 (for subjects who switched treatment at Week 16) to Week 32 will be allowed to continue whichever treatment led to the greatest reduction in urinary protein excretion (from Day 1 to Week 16 on initial study treatment or from Week 16 to Week 32 on switched treatment), or either study treatment per the Investigator's discretion during the Extended Blinded Treatment Phase.

d The Follow-up (FU) Visit as detailed in the End of Study section of the Study Procedures Table will be completed 4 weeks after the last dose of study treatment. For subjects that complete the entire study, the FU visit will be conducted at Week 56.

e Subjects who discontinue from the study for any reason will complete the Early Termination (ET) Visit at the time of study discontinuation.

f Subjects seen at an unscheduled visit for disease exacerbation (worsening of proteinuria, and/or decrease in eGFR) will complete the Unscheduled Visit assessments.

g Symptom-driven physical examinations will be performed, as needed, based on reported signs and symptoms.

h Urinary protein excretion will be determined using 2 consecutive morning voids as well as a 24-hour urine collection.
-For the Day 1 assessment, all 3 urine samples will be collected prior to Day 1, with the 24-hour urine collection as close to the Day 1 visit as possible.
-For Week 16, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 16 visit to test their change in urinary protein excretion. Subjects will also submit a 24-hour urine collection that is collected immediately prior to the Week 16 visit, or as close to the Week 16 visit as possible. These results will inform their treatment assignment for the additional 16 weeks.
-For Week 32, subjects will submit 2 consecutive morning urine void samples to the study center approximately 7 days prior to the Week 32 visit to test their change in urinary protein excretion. Subjects will also submit a 24-hour urine collection that is collected immediately prior to the Week 32 visit, or as close to the Week 32 visit as possible. These results will inform their treatment assignment for the additional 20 weeks in the Extended Blinded Treatment Phase.

i The urinalysis will include urine microscopy and spot protein-to-creatinine ratio. As contamination by menstrual blood may interfere with the primary endpoint, whether or not the patient is menstruating will be recorded on the CRF; microscopic urine examination will evaluate for active urine sediment (any of: > 5 WBC/hpf [pyuria], > 5 RBC/hpf [hematuria], or red cell casts in the absence of infection or other causes). In such circumstances, investigators may ask patients to return for another screening visit.

j Safety of Estrogens in Lupus Erythematosus National Assessment trial-based SLE Disease Activity Index (SELENA-SLEDAI)

k British Isles Lupus Activity Group (BILAG)

l Patient global assessment of disease activity

m Physician global assessment of SLE disease activity

n Vital signs include resting blood pressure, respiratory rate, heart rate, and body temperature.

o Females of childbearing potential only.

p If a urine pregnancy test is positive, study drug should be immediately interrupted and the subject should return to the site for a serum pregnancy test to confirm result.

q Females of nonchildbearing potential only.

r Subjects with positive HCV Ab, but negative HCV RNA VL at Screening are eligible per investigator judgment, but require ongoing monitoring during the study.

s Subjects previously treated for latent TB or active TB described in Inclusion # 17 do not need to have the QuantiFERON® TB-Gold In-Tube test (or equivalent assay) obtained, but a chest radiograph must be obtained if not done so 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) obtained at screening AND a chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review).

t Blood samples will be collected for plasma PK analysis of filgotinib and its active metabolite GS-829845, and GS-9876 post dose at Weeks 2, 4 and 20 (at least 30 minutes and up to 3 hours after dosing), anytime at Weeks 8 and 24, and within 2 hours prior to dosing at Weeks 16 and 32.

u Urine PK analyses will be collected for GS-9876, filgotinib and its active metabolite, GS-829845, using the 24h urine collection at Week 16.

[redacted]

x Biomarker assessments will be collected at Week 2 only.

y At Weeks 2, 4, and 20, subjects will be instructed to take their study drug in clinic as the first study procedure prior to any others scheduled for that visit. At Day 1, and Weeks 16 and 32, subjects will be instructed to take their study drug after predose assessments have been completed (eg, 2 hours after PK sample collection at Weeks 16 and 32).

z Autoantibody panel and complement levels will be collected at Weeks 2, 4, and 8 only.

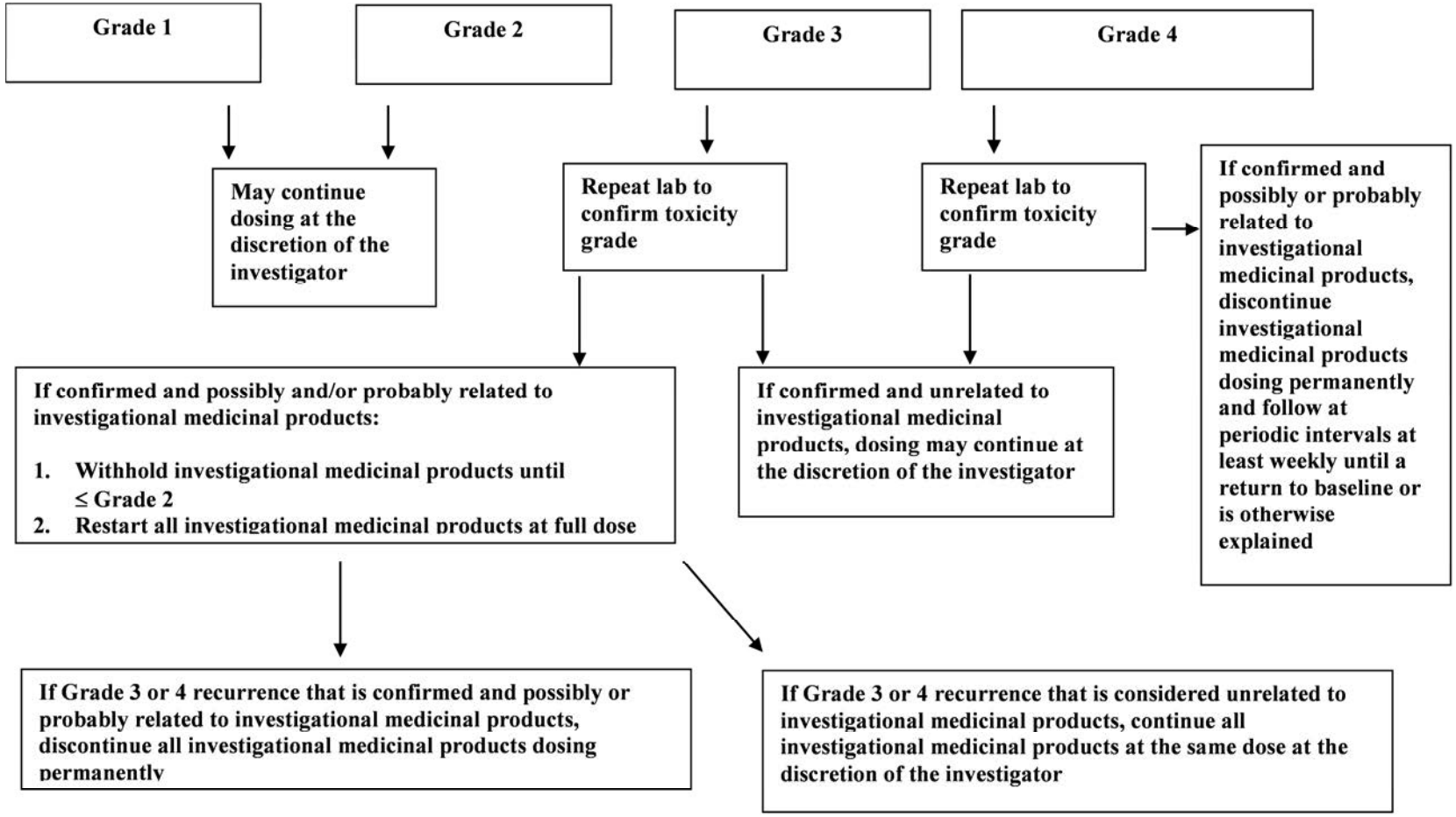
aa Study drug will be not be dispensed at Weeks 2 and 18.

bb Questionnaires will be administered where available.

cc Quantitative serum immunoglobulin testing will be performed at Week 8 and 24 only.

dd Quantitative serum immunoglobulin testing will be performed at Week 48 only.

Appendix 3. Management of Clinical and Laboratory Adverse Events



* Refer to Sections 3.5 and 7.6 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 v4.03 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, Definition for Female 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. Relevant non-clinical reproductive toxicity studies of GS-9876 did not have findings that raise a strong suspicion for human teratogenicity/fetotoxicity. There is no data from pregnant women who have taken GS-9876.

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 below criteria for being post-menopausal, are not permanently sterile, or do not have medically documented ovarian failure must have pregnancy testing as outlined by 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 permanent sterilization.

b) Definition of Male Fertility

For the purposes of this study, a male-born subject is considered fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or has medical documentation of permanent male infertility. Vasectomy is not considered 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 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. Relevant non-clinical reproductive toxicity studies of GS-9876 did not have findings that raise a strong suspicion for human teratogenicity/fetotoxicity. In vitro drug interaction assessment of GS-9876 and hormonal contraceptives suggests that there is no clinically relevant effects that would decrease contraception efficacy.

For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

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

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. 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 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)

Or

- Female subjects who wish to use a hormonally based method must 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. Hormonally-based 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 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 refrain from egg donation and in vitro fertilization during the study and until 36 days after the last study drug dose.

3) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant concentration of study drug may be achieved in a female partner from exposure to the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during study participation and for 90 days after the last study drug dose. Female partners of male study subjects should consider using one of the above methods of contraception as well. Male subjects must also refrain from sperm donation during the study and until 90 days after the last dose of study drug.

4) 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.

5) 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. Male subjects whose partner has become pregnant or suspects she is pregnant during the study or up to 90 days after the last dose of study drug are to report the information to the investigator immediately.

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

6) Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks during the study. If a positive urine pregnancy test is reported, the female subject should stop all study drugs and return to the clinic for a serum pregnancy test.

Appendix 6. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urine	Other
White blood cell (WBC) count Hematocrit Hemoglobin Red blood cell (RBC) count Red blood cell indices Platelet count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count	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[1] Glucose Phosphorus Magnesium Potassium Sodium Creatine Phosphokinase (CPK) Amylase Lipase Uric acid (at screening only)	Appearance Blood Color Dipstick Glucose Specific gravity Nitrites Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal. Spot urine protein and creatinine (for UPCR) 24-hour urine for protein and creatinine	QuantiFERON® TB – Gold In-Tube Analysis (if required per inclusion criteria; at screening only) FSH (as applicable; at screening only) 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[2] with reflex ENA[3] [dsDNA[4], Sm[5], RNP[6], SSA, and SSB]) Complement levels (C3, C4, and CH50)
		Virology	
		Hepatitis B surface antigen (HBsAg) Hepatitis B virus (HBV) core antibody HBV DNA (reflex) Hepatitis C Virus (HCV) Ab (if positive, then reflex HCV RNA) HCV Viral Load (if applicable) Human immunodeficiency virus 1 and 2 Ab	
Coagulation	**Fasting Lipids**	**Pregnancy**	
Activated partial thromboplastin time (aPTT) Prothrombin time International normalized ratio (INR)	Total cholesterol Low-density lipoprotein (LDL) High-density lipoprotein (HDL) Triglycerides	*In females of childbearing potential:* Serum pregnancy test Urine pregnancy test	

Estimated glomerular filtration rate based on the MDRD formulation ($eGFR_{MDRD}$)
ANA = antinuclear antibody
ENA = extractable nuclear antigen
dsDNA = double stranded DNA
Sm = Smith antigen
RNP = ribonucleoprotein

Appendix 7. Safety of Estrogens in Lupus Erythematosus National Assessment trial-based Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)

Hybrid SELENA SLEDAI with SELENA SLEDAI FLARE INDEX and PGA

(Circle in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 4 weeks)

Item no.	Check if active	Score	Descriptor	Definition
1		8	**Seizure**	Recent onset, exclude metabolic, infectious or drug causes
2		8	**Psychosis**	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
3		8	**Organic brain syndrome**	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes
4		8	**Visual disturbance**	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis, scleritis or episcleritis. Exclude hypertension, infection, or drug causes
5		8	**Cranial nerve disorder**	New onset of sensory or motor neuropathy involving cranial nerves
6		8	**Lupus headache**	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia THIS WOULD RARELY BE ATTRIBUTED TO SLE...ALMOST NEVER SCORED
7		8	**CVA**	New onset Cerebrovascular accident(s). Exclude arteriosclerosis
8		8	**Vasculitis**	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages or biopsy or angiogram proof of vasculitis
9		4	**Arthritis**	> 2 joints with pain and signs of inflammation (i.e. tenderness with swelling or effusion)
10		4	**Myositis**	Proximal muscle aching/weakness, associated with elevated creatinine phosphokinase (CK)/aldolase, or EMG changes or a biopsy showing myositis
11		4	**Urinary casts**	Heme-granular or RBC casts
12		4	**Hematuria**	> 5 RBC/high power field. Exclude stone, infection or other cause
13		4	**Proteinuria**	More than 0.5 gm/24 hours.
14		4	**Pyuria**	> 5 WBC/high power field. Exclude infection
15		2	**Rash**	Inflammatory type rash
16		2	**Alopecia**	Abnormal, patchy or diffuse loss of hair
17		2	**Mucosal ulcers**	Oral or nasal ulcerations
18		2	**Pleurisy**	Pleuritic chest pain or pleural rub or effusion, or pleural thickening (does not require an objective component if medically convincing)
19		2	**Pericarditis**	Classic pericardial pain and/or rub, effusion or ECG or echocardiogram confirmation (does not require an objective component if medically convincing)
20		2	**Low complement**	Decrease in CH50, C3 or C4 < lower limit of nl for testing laboratory
21		2	**Increased DNA binding**	Increased DNA binding above normal range for testing laboratory
22		1	**Fever**	> 38°C. Exclude infectious cause
23		1	**Thrombocytopenia**	< 100 x 10^9 platelets/L, exclude drug causes
24		1	**Leukopenia**	< 3 x 10^9 WBC/L, exclude drug causes

_____ **Total SCORE**

Appendix 8. British Isles Lupus Activity Group (BILAG) Index

BILAG2004 INDEX

Only record items due to SLE Disease Activity & assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)

Scoring: **ND** Not Done
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
☐ indicate if not due to SLE activity
(default is 0 = not present)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

Revision: 12/Jan/2007

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) ☐
79. Diastolic blood pressure (mm Hg) value ( ) ☐
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) ☐
82. Urine albumin-creatinine ratio mg/mmol ( ) ☐
83. Urine protein-creatinine ratio mg/mmol ( ) ☐
84. 24 hour urine protein (g) value ( ) ☐
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) ☐
87. GFR (calculated) ml/min/1.73 m^2 ( ) ☐
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) ☐
91. Total white cell count (x 10^9/l) value ( ) ☐
92. Neutrophils (x 10^9/l) value ( ) ☐
93. Lymphocytes (x 10^9/l) value ( ) ☐
94. Platelets (x 10^9/l) value ( ) ☐
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Appendix 9. Physician's Global Assessment of Disease Activity

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

Instructions:

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

No LMN disease activity **Maximum LMN disease activity**

Appendix 10. Patient Global Assessment of Disease Activity

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

Instructions:

Place a mark on the line below to indicate how active your lupus has been over the last week:

I have no lupus **I have the worst lupus**

Appendix 11. 36-Item Short Form Health Survey

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

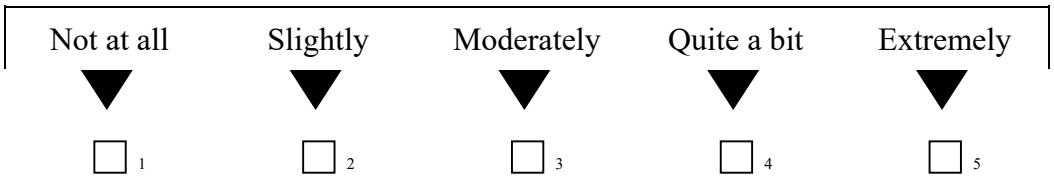
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

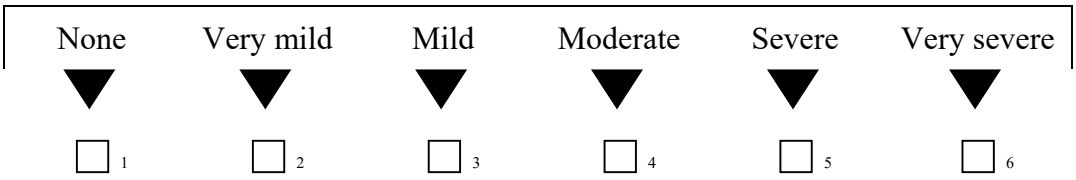
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

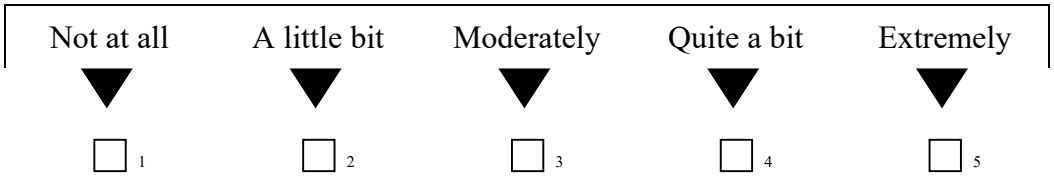
6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?



8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!