CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA	
IND Number:	123903	
EudraCT Number:	2016-003558-34	
Clinical Trials.gov Identifier:	NCT03100942	
Indication:	Sjogren's Syndrome	
Protocol ID:	GS-US-445-4189	
Gilead Clinical Program Manager:	Name: Telephone:	PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile:	PPD PPD PPD PPD
Protocol Version/Date:	Original: Amendment 1:	09 November 2016 12 July 2018

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

Study Title:	A Randomized, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome
IND Number:	123903
EudraCT Number:	2016-003558-34
Clinical Trials.gov Identifier:	NCT03100942
Study Centers Planned:	Approximately 60-80 centers globally
Objectives:	The primary objective of this study is: • To assess the efficacy of filgotinib, GS-9876, and GS-4059 in adult subjects with active Sjogren's Syndrome (SjS) The secondary objectives of this study are: • To assess the safety and tolerability of filgotinib, GS-9876, and GS-4059 in active SjS • To assess the effect of filgotinib, GS-9876 and GS-4059 on patient reported outcomes in active SjS The exploratory objectives of this study are: CCI

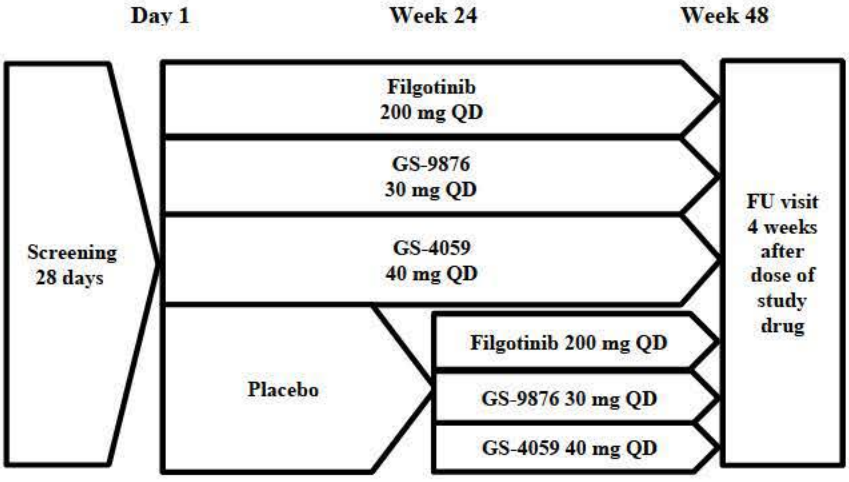
Study Design:

This will be a multicenter, randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of filgotinib, GS-9876, and GS-4059 in adult male and female subjects with active SjS. Eligible subjects will be randomized 1:1:1:1 to daily oral filgotinib (200 mg), or GS-9876 (30 mg), or GS-4059 (40 mg) or placebo to match (PTM). Randomization will be stratified by: use of concurrent immunomodulatory drugs at baseline (Y/N: conventional synthetic disease modifying antirheumatic drugs (csDMARD[s]) or corticosteroids), and the hematologic + biological component scores of the EULAR Sjogren's syndrome disease activity index (ESSDAI) obtained at screening (combined score of <2 or ≥ 2). Stable medications at Day 1 should be continued during the study dosing period. Dose adjustments for toxicities and dose adjustment of corticosteroids after Week 12 are outlined in Section 5.8.

At the Week 24 visit, subjects on placebo will be re-randomized 1:1:1, in a blinded fashion, to daily oral filgotinib (200 mg), GS-9876 (30 mg), or GS-4059 (40 mg) without further stratification. Dosing and assessments for all subjects will continue through Week 48.

CCI [redacted]

Subjects who interrupt or permanently discontinue study drug dosing will continue the study visits, procedures, and assessments, if deemed medically a'ppropriate by the investigator.



Number of Subjects Planned:

Approximately 140 adult subjects with active SjS

Target Population:	Male and female subjects with active SjS between 18 and 75 years of age (inclusive) at the time of consent
Duration of Treatment:	Up to 48 weeks of dosing
Diagnosis and Main Eligibility Criteria:	Subjects must meet the all eligibility criteria participate in this study. For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3, respectively. • Male or female subjects between 18 and 75 years of age (inclusive) • Diagnosed with SjS according to American European Consensus Group (AECG) classification • Active SjS as defined by an ESSDAI ≥5 • Seropositivity for antibodies to SjS-associated antigens A and B (anti-SSA or anti-SSB) • No concurrent treatment with any bDMARD (washout as per protocol Section 5.8)
Study Procedures/ Frequency:	Participating subjects will visit the clinical study center at Screening, Day 1, Weeks 2, 4, 8, 12, 18, 24, 26, 28, 32, 36, 42 and 48 or early termination (ET) plus follow up visit. At Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive filgotinib (200 mg), GS-9876 (30 mg), GS-4059 (40 mg), or PTM. Screening and on-treatment assessments will include: Vital Signs, Physical Examination (PE), 28 Swollen and Tender Joint count, Investigator's Assessment of SjS disease activity, Investigator's global assessment of concomitant Rheumatoid Arthritis (RA) or Systemic Lupus Erythematosus (SLE) disease activity (as applicable), ESSDAI, urine drug screen, pregnancy test (as applicable), CCI [redacted], TB testing, chest X-ray (CXR as applicable), CD19+ B cell count (as applicable), HbA1c, Thyroid-Stimulating Hormone (TSH), hematology, Erythrocyte Sedimentation Rate (ESR) as available, chemistry and hsCRP, viral serology and viral monitoring (as applicable), autoantibodies, complement, immunoglobulins, fasting lipid profile, CCI [redacted], Patient Reported Outcome (PRO) questionnaires and Visual Analogue Scales (VAS), Pulmonary Function Test (PFT as available), CCI [redacted] s test, concomitant medications, Adverse Events (AEs), and at available sites: mCCI [redacted]

	A resting 12-lead ECG should be performed at Screening, Day 1, Weeks 2, 8, 12, 24, 26, 32, 36 and 48 or ET. ECGs should be interpreted by the investigator (or qualified designee) for clinical significance. CCI [redacted] CCI [redacted] CCI [redacted] Post treatment follow-up assessments include AEs, concomitant medications, physical examination, 12-lead ECG, vital signs, blood and urine sampling for safety laboratory tests, and urine pregnancy tests (if applicable).
Test Product, Dose, and Mode of Administration:	Filgotinib 200 mg (1 x 200 mg tablet), administered orally once daily GS-9876 30 mg (1 x 30 mg tablet), administered orally once daily GS-4059 40 mg (1 x 40 mg tablet), administered orally once daily
Reference Therapy, Dose, and Mode of Administration:	PTM filgotinib (1 x placebo tablet), administered orally once daily PTM GS-9876 (1 x placebo tablet), administered orally once daily PTM GS-4059 (1 x placebo tablet), administered orally once daily
Criteria for Evaluation:	
Safety:	Safety will be assessed through the reporting of AEs, clinical laboratory tests, PEs, vital sign assessments, and ECGs at various time points during the study.
Efficacy:	The primary endpoint is the proportion of subjects fulfilling protocol-specified response criteria at Week 12, as compared to baseline. Response is defined as follows:

	• For subjects with elevated hsCRP (defined as ≥ 1.5 upper limit of normal (ULN) of hsCRP) at Day 1, subjects are considered to be a responder if they achieve all of the following : - ≥ 20% improvement in hsCRP - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related visual analog scales (VAS; subject's assessment of global disease, pain, oral dryness, ocular dryness and fatigue) - no worsening (defined as > 30 mm increase from baseline) in any of the above VAS • For subjects without elevated hsCRP (< 1.5 ULN of hsCRP) at Day 1, subjects are considered to be a responder if achieve all of the following: - no increase ≥ 1.5 ULN of hsCRP - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related VAS (subject's assessment of global disease, pain, oral dryness, ocular dryness and fatigue) - no worsening (defined as > 30 mm increase from baseline) in any of the above VAS Secondary endpoints include: the change in ESSDAI and in ESSPRI from baseline to Week 12 and 24
Pharmacokinetics:	Plasma concentrations of filgotinib (and its metabolite GS-829845), GS-9876, and GS-4059 will be listed and summarized using descriptive statistics.
Statistical Methods:	The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug. The primary endpoint is the proportion of subjects fulfilling response criteria as outlined above. The primary analysis will consist of a superiority test of each of filgotinib, GS-9876 or GS-4059 compared to placebo, respectively. Cochran Mantel Haenszel (CMH) approach adjusted for the randomization stratification factors will be used for the hypothesis testing at the 2-sided 0.05-level. Based on results of prior SjS studies, assuming a response rate of 70% for the active arm and 30% for the placebo arm at Week 12, at least 35 evaluable subjects will be needed in each arm to achieve 85% power to detect a significant difference at a 2-sided, 0.05-level. Therefore, a total of approximately 140 subjects are planned to be enrolled in the study.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group and by study part. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by treatment group and by study part.

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

ADL	Activities of Daily Living
AE(s)	Adverse Event(s)
AECG	American European Consensus Group
ALT	Alanine Aminotransferase
Anti-SSA	Anti-Sjogren's-syndrome-related antigen A
Anti-SSB	Anti-Sjogren's-syndrome-related antigen B
ATP	adenosine triphosphate
AST	Aspartate Aminotransferase
$AUC_{0-\tau}$	Area under the plasma drug concentration-time curve of a dosing interval
AUROC	Area Under Receiver Operating Characteristic
BCR	B-cell receptor
bDMARD(s)	Biologic Disease Modifying Antirheumatic Drug(s)
BLQ	Below the Limit of Quantitation
BTK	Bruton's tyrosine kinase
C_{τ}	Trough plasma concentration (just before the next dosing ie pre-dose sample)
C_{ave}	Average observed concentration
CCP	Cyclic citrullinated peptide
csDMARD(s)	Conventional synthetic disease modifying antirheumatic drugs
CFR	Code of Federal Regulations
CIA	Collagen-Induced Arthritis
C_{max}	Maximum observed plasma concentration
CLE	cutaneous lupus erythematosus
CMH	Cochran Mantel Haenszel
CNS	central nervous system
CRO	Contract Research Organization
hsCRP	High sensitivity C-Reactive Protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DAS28	Disease Activity Score based on 28 joints
DMARD(s)	Disease-Modifying Antirheumatic Drugs
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
ESSDAI	EULAR Sjogren's syndrome disease activity index
ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
ET	Early Termination
EU	European Union

EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
FEF	Forced expiratory flow
FEV	Forced expiratory volume
FSH	Follicle Stimulating Hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma Glutamyl Transferase
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HCV	hepatitis C virus
hCG	Human chorionic gonadotropin
HCQ	Hydroxychloroquine
HDL	High Density Lipoprotein
hERG	Human ether-a-gogo related gene
HIV	Human immunodeficiency virus
HLGT	High Level Group Term
HLT	High Level Term
HR	Heart Rate
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDEEL	Impact of Dry Eye on Everyday Life
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Independent Review Board
IWRS	Interactive Web Response System
JAK	Janus kinase
LDL	Low Density Lipoprotein
LLOQ	Lower Limit Of Quantitation
LLT	Lower-Level Term
LMN	Lupus Membranous Nephropathy
MAD	Multiple Ascending Dose
MATE1	Multidrug and toxin extrusion protein 1
MCV	Mean Corpuscular Volume
MTX	Methotrexate
NOAEL	No-observed-adverse-effect-level

NOEL	No-observed-effect-level
NSAIDs	Nonsteroidal anti-inflammatory drugs
OATP	Organic anion transporter polypeptide
OCT1	Organic cation transporter 1
OHIP- 14	Oral Health Impact Profile-14
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PE	Physical examination
PFT	Pulmonary Function Test
P-gp	P-glycoprotein
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PROFAD-SSI- SF	Profile of Fatigue and Discomfort-Sicca Symptoms Inventory
PT	Preferred Term
PTM	Placebo To Match
PVE	Pharmacovigilance and Epidemiology
QD	*quaque die*; once daily
QTc interval	Corrected QT interval
RA	Rheumatoid Arthritis
ROC	Receiver Operating Characteristic
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SF-36	Short-form health survey
SI	International system of units
SjS	Sjogren's Syndrome
SLE	Systemic Lupus Erythematosus
SOC	System Organ Class
STAT	Signal Transducer and Activator of Transcription
SYK	Spleen tyrosine kinase
TB	Tuberculosis
TBNK	T-cells, B-cells and NK cells
TEAEs	Treatment emergent adverse events
T_{FH}	Follicular B T helper cells
t_{max}	Time of occurrence of maximum observed plasma concentration
TSH	Thyroid-Stimulating Hormone
TSQM	Treatment Satisfaction Questionnaire for Medication
UGT	Uridine 5'-disphosphate glucuronosyltransferase
ULN	Upper Limit of Normal
U/S	Ultrasound
VAS	Visual analog scale

VC	Vital Capacity
VL	Viral Load
vs.	Versus
WBC	White Blood Cell

1. INTRODUCTION

1.1. Background

Sjogren's Syndrome (SjS) is estimated to affect approximately 1% of the population worldwide {Patel 2014}; it is a systemic autoimmune disease that is primarily diagnosed in women 40 to 60 years of age, but can occur at any age. About half of all patients with SjS also have another concurrent autoimmune disease, most often, RA or SLE. Although prior convention was to label these patients as "secondary" SjS, the distinction is arbitrary and the designations of "primary" and "secondary" have fallen out of favor {The Sjogren's Syndrome Foundation 2016}.

The features of SjS include the classic symptoms of dry eyes and dry mouth, but also generalized fatigue with myalgias and arthralgias. Many patients with SjS also suffer from cognitive difficulties, and find it increasingly difficult to perform their occupation. Due to the nonspecific nature of the disease, it is often undiagnosed or misdiagnosed. Therefore, patients remain generally untreated, unless they have another autoimmune syndrome (eg, RA or SLE) for which they are receiving care. Immune dysfunction and autoimmunity are evident by the presence of antibodies to SjS-associated antigens A and B (SSA and SSB), and the abnormal histology of exocrine glands, with ectopic germinal center formation {Fox 2005}. Although the perception is that this disease is generally benign, there may be serious multiorgan consequences, including early cerebro-cardiovascular disease, pulmonary and renal disease {Fox 2005}. An increased risk of lymphoma has also been demonstrated for patients with SjS {Fox 2005}.

Therapeutic options for SjS are few. There are no approved disease-modifying, anti-rheumatic drugs (DMARDs) for SjS, and only limited clinical trial data in SjS for the various newer biologic and synthetic DMARDs approved for other indications. Milder SjS is often treated with oral and ocular hydration, non-steroidal anti-inflammatory drugs (NSAIDs), hydroxychloroquine (HCQ) and/or low dose oral steroids. Although treatment with methotrexate (MTX) and other conventional synthetic immunomodulators has been attempted, there are no strong data demonstrating amelioration of disease or its long-term effects. Thus, a need exists for new therapies with proven benefit in this disease.

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective oral inhibitor of JAK1 being developed by Gilead Sciences, Inc. (Gilead) and Galapagos NV for the treatment of inflammatory diseases. JAK1 is believed to play an integral part in the pathogenesis of various autoimmune diseases, due to its role in inflammatory cytokine signaling.

GS-9876 is a potent and selective oral inhibitor of SYK being developed by Gilead for the treatment of inflammatory diseases. SYK is a cytoplasmic tyrosine kinase primarily expressed in cells of hematopoietic lineage, where it functions as a key signaling molecule mediating immunoreceptor signaling in a range of cells involved in inflammatory diseases.

GS-4059, also named tirabrutinib, is a potent and selective oral inhibitor of BTK being developed by Gilead and Ono Pharmaceutical Co, Ltd. (Ono) for the treatment of B-cell malignancies and inflammatory diseases. BTK is an intracellular tyrosine kinase primarily expressed in hematopoietic cell lineages {Genevier 1994}, {de Weers 1993}, {Smith 1994}, and mediates immunoreceptor signaling in B lymphocytes, antigen-presenting cells , and mast cells, basophils, and osteoclasts. In addition, BTK is involved in integrin receptor and adaptor protein signaling, through which it plays a role in cell adhesion {de Rooij 2012} and osteoclast differentiation {Lee 2008}, {Shinohara 2008}, {Tai 2012}.

Given the important roles of these proteins (JAK1, SYK, and BTK) in immune cell signaling, inhibition of these targets is expected to ameliorate autoimmune disease, via pleiotropic anti-inflammatory effects.

1.2. Filgotinib

CCI [redacted]

1.2.1. Nonclinical Pharmacology and Toxicology

CCI [redacted]

CCI [redacted]

[redacted]

1.2.2. Clinical Trials of Filgotinib

CCI [redacted]

1.3. GS-9876

CCI [redacted]

1.3.1. Nonclinical Pharmacology and Toxicology

1.3.1.1. Nonclinical Pharmacology and Safety Pharmacology

CCI [redacted]

[redacted]

CCI

[redacted]

[redacted]

1.3.1.2. Nonclinical Toxicology

CCI

[redacted]

[redacted]

[redacted]

[redacted]

1.3.2. Clinical Trials of GS-9876

[redacted]

1.4. GS-4059

CCI [redacted]

1.4.1. Nonclinical Pharmacology and Toxicology

CCI [redacted]


CCI

CCI

1.4.2. Clinical Trials of GS-4059

CCI

1.5. Rationale for Current Study

Therapeutic options for SjS are few. There are no approved DMARDs for the treatment of SjS, and there are only limited clinical trial data in SjS using newer biologic and synthetic DMARDs approved for other indications. Milder SjS is often treated with oral and ocular hydration, NSAIDS, HCQ and/or low dose oral steroids; highly active disease is treated off-label with significant immunosuppression. Although treatment with MTX and other conventional synthetic immunomodulators has been attempted in SjS, there are no strong data showing amelioration of the disease or its sequelae.{Kruszka 2009}, {Ramos-Casals 2005}, {Mariette 2015}. For the dry eyes and dry mouth associated with SjS (keratoconjunctivitis sicca and xerostomia), topical artificial tear solutions or muscarinic agonists such as pilocarpine and cevimeline {Rising Pharmaceuticals Inc }, {Pfizer 2014} are used for symptomatic control {Kruszka 2009}, {Wu

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[redacted]

1.6. Rationale for Dose Selection

Filgotinib: 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}. Filgotinib 200 mg is one of the doses currently investigated in a phase 3 program for RA. Based on the overall risk-benefit ratio observed in Phase 2b studies, as well as the clinical overlap of RA and SjS, 200 mg once daily filgotinib is expected to be safe and to have the potential to be efficacious in SjS.

GS-9876: In the multiple ascending dose (MAD) study (GS-US-379-1900), doses of up to 50 mg once daily GS-9876 for 7 days were well tolerated in healthy volunteers. The 30-mg once daily dose of GS-9876 was the highest dose administered in Study GS-US-379-1582 in subjects with RA and was well-tolerated. Based on the similarity for risk-benefit between RA and SjS, 30 mg once daily GS-9876 is expected to be safe and to have the potential to show clinical activity in SjS.

GS-4059: A dose of 40 mg once daily GS-4059 was selected for this study based on available PK, PD, and safety data, guided by the goal of maximizing target occupancy. Based on a PK/PD analysis from two Phase 1 studies in healthy volunteers and subjects with RA (GS-US-401-1765 and GS-US-407-1833), a dose of 40 mg once daily GS-4059 is expected to provide near maximal BTK occupancy over the dosing interval (median >90% occupancy). In addition, the selection of 40 mg once daily GS-4059 for this study is supported by the current overall safety and tolerability profile of GS-4059. Preliminary results from Study GS-US-407-1833 demonstrate that a total daily dose of 20 mg GS-4059 was well tolerated during a 4-week treatment period in subjects with RA (N=21). The maximum tolerated dose (MTD) of GS-4059 was 480 mg once daily in subjects with non-Hodgkin's lymphoma, with dose limiting toxicity events of rash and non-immune reaction at the 600 mg once daily dose; no MTD was identified in subjects with chronic lymphocytic leukemia at doses up to 600 mg once daily. Therefore, 40 mg once daily GS-4059 is expected to be well tolerated and to have the potential to show clinical activity in subjects with SjS.

1.7. Risk/Benefit Assessment for the Study

Sjogren's Syndrome is a chronic, systemic inflammatory disease that affects approximately 1% of the population. Currently, there are no DMARDs approved for the treatment of SjS. The need for new, therapeutic options with a favorable efficacy and safety profile has prompted efforts to evaluate orally administered, small molecules in this disease setting.

Please refer to respective Investigator's Brochures (IB) for updated safety information and risk/benefit assessment.

Filgotinib, a once-daily, oral, and potent JAK-1 inhibitor, is being developed for the treatment of RA and other autoimmune diseases.In the ongoing and concluded studies, filgotinib has been generally safe and well tolerated The primary endpoint was achieved in two large dose ranging studies (GLPG-CL-203 and GLPG-CL-204) evaluating the effect of filgotinib on RA disease activity. However, a potential increased risk of infection may be considered consistent with the mechanism of JAK inhibition. In the filgotinib RA program, deaths were reported due to infectious etiologies.

Nonclinical studies in rats and dogs identified lymphoid tissues and testes as target organs for filgotinib; microscopic findings in the testes included germ cell depletion and degeneration in both species, with reduced sperm content and reduced fertility in male rats. The clinical relevance of nonclinical testicular findings in rats and dogs is unknown. A male safety study is ongoing to assess the effects, if any, of filgotinib on semen parameters in males with inflammatory diseases. Until the definite 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 SjS is a disease of female predominance and depending on the study population the incidence of SjS in females is reported to be 10 to 20 fold higher in females than males{Patel 2014}.

GS-9876 is a highly selective SYK inhibitor. SYK is a key signaling molecule involved in innate and adaptive immune system responses and is important in various cell types, including platelets, phagocytes, fibroblasts, and osteoclasts, and in the generation of the inflammasome. Nonclinical studies show that SYK inhibition may have therapeutic value in the treatment of allergic and autoimmune diseases. Clinical trials with fostamatinib (an experimental SYK inhibitor) have demonstrated responses in RA and in idiopathic thrombocytopenic purpura.

In non-clinical studies of GS-9876 in rats and in cynomolgus monkeys, the primary observed effects were reversible, dose-dependent decreases in circulating lymphocytes and 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 the ongoing and concluded clinical studies, GS-9876 generally has been well tolerated.

GS-4059 is a highly selective BTK inhibitor. BTK is primarily expressed in cells of the hematopoietic lineage. It is a key mediator in coupling activated immunoreceptors to downstream signaling events that affect diverse biological functions, from cellular proliferation, differentiation and adhesion to innate and adaptive immune responses. As such, pharmacological inhibitors of BTK are being actively pursued as potential immunomodulatory agents for the treatment of autoimmune and inflammatory disorders.

In non-clinical studies of GS-4059 in rats and in monkeys, the primary effects were generally minor, reversible, dose-dependent decreases in lymphocytes in various tissues (spleen, lymph nodes, and/or thymus) consistent with expected pharmacologic effects of BTK inhibition. Additionally, minor, reversible effects on erythrocytes were seen in rats and monkeys. Effects on the pancreas, adrenal and thyroid glands, liver and kidney in rats were considered to be species-specific and of limited to no relevance to humans. In clinical studies of GS-4059 in healthy volunteers and subjects with RA, a 20 mg daily dose of GS-4059 was generally well tolerated. Further, doses up to 600 mg of GS-4059 have been administered to patients with hematologic malignancies with an acceptable safety profile for the population studied.

Based on available non-clinical findings, GS-9876 is not contraindicated in pregnancy, although pregnancy in GS-9876 trials should be avoided. However, filgotinib and GS-4059 are contraindicated in pregnancy; highly effective contraception is to be used across all clinical studies to mitigate this risk. Measures to minimize other potential risks to subjects will include site/investigator training regarding monitoring for infection, and collection of AEs of special interest, including major adverse cardiac events, malignancies, infections, and specific laboratory abnormalities.

Preclinical and clinical data for filgotinib, GS-9876, and GS-4059 indicate that these novel agents have potential to offer therapeutic benefit in autoimmune and inflammatory diseases including SjS. These drugs have an acceptable level of risk that is consistent with that of other immunomodulatory agents in patient populations with autoimmune diseases. Given the clinical and nonclinical data available to date for these 3 drugs, and their overall safety, tolerability, and PK characteristics, there is a favorable benefit: risk profile for development of these agents in SjS. This study will help to determine the potential of filgotinib, GS-9876, or GS-4059 as much needed alternatives to existing treatment options for SjS and related diseases.

1.8. Compliance

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

2. OBJECTIVES AND ENDPOINTS

Study Objectives	Study Endpoints
Primary objective: • To assess the efficacy of filgotinib, GS-9876, and GS-4059 in adult subjects with active SjS	Primary endpoint: The primary endpoint is the proportion of subjects fulfilling protocol-specified response criteria at Week 12, as compared to baseline. Response is defined as follows: • For subjects with elevated hsCRP (defined as ≥ 1.5 upper limit of normal (ULN) of hsCRP) at Day 1, subjects are considered to be a responder if they achieve all of the following : - ≥ 20% improvement in hsCRP - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related visual analog scales (VAS; subject's assessment of global disease, pain, oral dryness, ocular dryness and fatigue) - no worsening (defined as > 30 mm increase from baseline) in any of the above VAS • For subjects without elevated hsCRP (< 1.5 ULN of hsCRP) at Day 1, subjects are considered to be a responder if achieve all of the following: - no increase ≥ 1.5 ULN of hsCRP - ≥ 20% improvement in at least 3 out of 5 subject reported, SjS related VAS (subject's assessment of global disease, pain, oral dryness, ocular dryness and fatigue) - no worsening (defined as > 30 mm increase from baseline) in any of the above VAS
Secondary objectives: • To assess the safety and tolerability of filgotinib, GS-9876, and GS-4059 in adult subjects with active SjS • To assess the effect of filgotinib, GS-9876, and GS-4059 on patient reported outcomes in active SjS, including fatigue, disability, and quality of life	Secondary endpoints: • Change from baseline in ESSDAI and ESSPRI at Weeks 12 and 24.

Study Objectives	Study Endpoints
The exploratory objectives of this study are: CCI	The exploratory endpoints of this study are: CCI

3. STUDY DESIGN

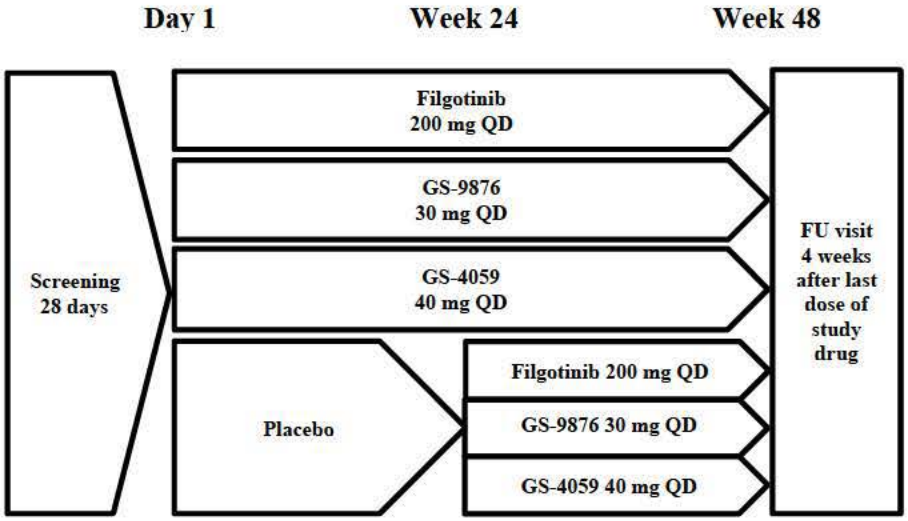
3.1. Study Design

Adult male and female subjects who provide written, informed consent will enter a Screening period (28 days) during which they will be evaluated for eligibility, based on the Inclusion/Exclusion criteria.

At Day 1, eligible subjects will be randomized to study drug (see Section 3.2). Subjects will return to the study site for scheduled study visits at Weeks 2, 4, 8, 12, 18, 24, 26, 28, 32, 36, 42 and 48. After completion of the Week 24 assessments and procedures, subjects on placebo will be re-randomized 1:1:1 to filgotinib, or GS-9876, or GS-4059, in a blinded fashion. Dosing will continue through Week 48.

Subjects who discontinue study drug for any reason (other than noncompliance) may continue to participate in scheduled study visits and procedures, as long as deemed medically appropriate by the investigator. Subjects who discontinue all study participation will have an early termination (ET) visit; these subjects, and those who complete the study, should return to the study site for a follow-up visit, 4 weeks after the last dose of study drug (subjects who have discontinued study drug ≥ 4 weeks prior to the ET/Week 48 visit, do not need a follow up visit).

Figure 3-1. Study Design Schematic



For details regarding dosing and blinding, see Section 5.7.

For details regarding concomitant and excluded medications, see Section 5.8.

For study visit schedule and procedures, including clinical laboratory tests and [redacted], see Schedule of Activities in Section 6 and Appendix 2.

3.2. Study Treatments

Following completion of screening assessments, eligible subjects will be randomized 1:1:1:1 in a blinded fashion to active investigational product or PTM:

- **Filgotinib 200 mg arm (n=35): filgotinib (1 x 200 mg tablet** once daily) + PTM GS-9876 (1 x tablet once daily) + PTM GS-4059 (1 x tablet once daily)
- **GS-9876 30 mg arm (n=35):** PTM filgotinib (1 x tablet once daily) + **GS-9876 (1 x 30 mg tablet** once daily **)** + PTM GS-4059 (1 x tablets once daily)
- **GS-4059 40 mg arm (n=35):** PTM filgotinib (1 x tablet once daily) + PTM GS-9876 (1 x tablet once daily) + GS-4059 **(1 x 40 mg tablet** once daily)
- **Placebo arm (n=35):** PTM filgotinib (1 x tablet once daily) + PTM GS-9876 (1 x tablet once daily) + PTM GS-4059 (1 x tablet once daily)

Randomization will be stratified by use of concurrent immunomodulatory drugs at baseline (Y/N: csDMARDs or corticosteroids), and the hematologic + biological component scores of the ESSDAI obtained at screening (combined score of <2 or ≥ 2).

3.3. Duration of Treatment

Subjects will be dosed for up to 48 weeks and will return for a Follow-Up Visit, 4 weeks after their last visit (Week 48 or ET); the Follow-Up Visit will not be performed if the subject has discontinued study drug ≥ 4 weeks prior to their final study visit.

3.4. Criteria for Interruption and Discontinuation Criteria

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. In these cases, an Early Termination visit should be performed as soon as possible.

CCI [redacted]

3.4.1. Study Drug Interruption Considerations

The 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 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 treatment should not be resumed until the subject's event has resolved, per judgment of the investigator.

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.

3.4.2. Study Drug Discontinuation Considerations

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

Study medication should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is not considered to be in the subject's best interest
- Need for prohibited concomitant medication (see Section 5.8)

- Subject request to discontinue for any reason
- Subject noncompliance, as per judgment of investigator
- Request from Gilead, a regulatory agency or an IRB or IEC
- Female subject becomes pregnant during the study; refer to Section 7.7.2.1
- Positive HCV VL
- Investigator discretion
- Laboratory criteria:
  After becoming aware of any of the below described abnormal laboratory values at any time, an unscheduled visit should occur within 3 to 7 days, with the exception of creatinine clearance which should be retested within 7 to 14 days. Retest may be obtained sooner if medically indicated per investigator judgment. If the laboratory abnormality is confirmed by the retest, then study medication should be discontinued and further care of the subject should be directed per the investigator.

  — total white blood cell (WBC) count < 2000 cells/mm^3 (SI: < $2.0x10^9$ cells/L)

  — neutrophil count < 1000 neutrophils/mm^3 (SI: < $1.0x10^9$ cells/L)

  — hemoglobin < 8.0 g/dL (SI: < 80 g/L)

  — platelet count < 75,000 platelets/mm^3 (SI: < $75.0x10^9$ cells/L)

  — AST or ALT elevation:

    ■ > 3xULN with at least 1 total bilirubin value >2xULN

    ■ > 3xULN with elevated international normalized ratio (INR)

    ■ > 5xULN, regardless of total bilirubin or accompanying symptoms

    Note: For the above described AST or ALT elevations, additional investigations (such as: review of ethanol, recreational drug use, dietary supplement consumption; testing for acute hepatitis A, B or C infection and biliary tract imaging) should be promptly considered by the investigator; these subjects should be discussed with the study Medical Monitor.

  — estimated creatinine clearance < 40 mL/min based on the Cockroft-Gault formula

Subjects who stop study drugs for any reason will not be replaced. Subjects withdrawing from the study should complete the ET and 4 week Follow Up visits, as applicable. Subjects may 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 source documents and in the electronic case report form (eCRF).

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

3.5. End of Study

The end of study is defined as when the last subject has completed their final study visit (Week 48 or ET) plus the 4 week post treatment visit (Follow-Up Visit – if applicable).

3.6. Post Study Care

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

3.7. Biomarker Testing

CCI [redacted]

Table 3-1. List of Exploratory Biomarker Samples

3.7.1. Biomarker Samples to Address the Study Objectives:

The following biologic specimens will be collected in this study in order to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or adverse events, and to increase knowledge and understanding of SjS and related diseases, the development of a companion diagnostic, and/or to help inform how inhibition of JAK1, SYK, or BTK affect downstream markers. Because biomarker science is a rapidly evolving area of investigation, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing proposed in Table 3-1 based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests and/or to add new tests based upon the growing state of knowledge. The biomarker sample collection schedule is described in the Schedule of Assessments Table (Appendix 2).

3.7.2. Biomarker Samples for Optional Future Research

CCI [redacted]

[redacted]

3.7.3. Biomarker Samples for Optional Genomic Research

CCI [redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 140 subjects will be enrolled in this study.

4.2. Inclusion Criteria

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

1) Male or female 18 to 75 years of age (inclusive) at the time of signing initial consent, with all of the following at Screening:

    a. Diagnosis of SjS based on AECG classification (Appendix 7)

    b. Active SjS, with ESSDAI ≥5

    c. Seropositivity for anti-SSA or anti-SSB, per central laboratory

2) A negative serum pregnancy test at Screening and a negative urine pregnancy test at Day 1 are required for female subjects of child-bearing potential (as defined in Appendix 5)

3) Starting at the time of written consent, through the study, and for 90 days (male) and 36 days (female) following their last dose of study drug:

    a. Male 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,

    b. Male subjects must agree to refrain from sperm donation

    c. Female subjects must agree not to breastfeed or to donate/harvest eggs for the purpose of fertilization,

4) Subjects with prior exposure to a B-cell depleting bDMARD (at any time) must have a documented return of CD19+ B cells at Screening.

5) Stable dose (defined as no change in prescription for at least 4 weeks prior to Day 1) of NSAIDs, HCQ, MTX and/or oral corticosteroids is permitted during the study, but not required (see protocol Section 5.8 for definitions, full list of allowed prior and concomitant medications and permitted doses).

6) Meet one of the following (a or b) tuberculosis (TB) Screening criteria:

   a. No evidence of active or latent TB:

      - Negative history of TB infection and
      - Negative QuantiFERON® TB-Gold In-Tube test and

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

      - Negative chest X-ray results (radiographs taken at Screening or within 90 days prior to Screening with films or report available for investigator review).

   b. Subjects with prior latent TB who have been treated with a full course of prophylaxis as per local guidelines.

      Note: Appropriate documentation of previous treatment is required.
      In these cases, a QuantiFERON® TB-Gold In-Tube test is not needed, but a chest radiograph must be obtained within 3 months prior to Screening (report or films must be available).
      In addition, these cases must be approved by the Medical Monitor prior to enrollment.
      Subjects with a new diagnosis of latent TB or prior untreated/partially treated latent TB are NOT allowed (ie, subjects who require prophylactic therapy for TB during the study). Subjects with any prior active TB are excluded regardless of treatment.

7) Are willing and able to sign the informed consent form and comply with study requirements, procedures, and scheduled visits.

Note: Subjects who cannot read or understand the ICF may not be enrolled by a guardian, representative, or any other individual

4.3. Exclusion Criteria

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

1) Concurrent treatment at Screening with any bDMARD (prior bDMARD treatment allowed with appropriate washout as defined in Section 5.8)

2) Any prior use of cyclophosphamide

3) Use of cyclosporine within 4 weeks prior to the first dose of study drug (Day 1) or anticipated chronic use while on study (other than ophthalmic cyclosporine as described as per Section 5.8)

4) Clinically significant abnormalities on 12-lead ECG as judged by the investigator.

5) Treatment with moderate or strong CYP3A inducers or inhibitors within 2 weeks, or strong P-gp inducers within 3 weeks prior to the first dose of study drug (Day 1) or anticipated chronic use while on study (see Section 5.8)

6) Participation in any clinical study of an investigational drug within 4 weeks or 5 drug half-lives prior to Screening, whichever is longer. Washout duration for exposure to investigational biologics should be discussed with the sponsor

7) Treatment with any commercially available or investigational drug listed below within 3 months of Screening:

    a. BTK inhibitor, such as ibrutinib, or

    b. SYK inhibitor, such as fostamatinib, or

    c. JAK inhibitor, such as tofacitinib or baricitinib

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

9) History of symptomatic Herpes zoster or Herpes simplex infection within 12 weeks prior to Screening or history of disseminated/complicated Herpes zoster infection (multi-dermatomal involvement, ophthalmic zoster, CNS involvement or postherpetic neuralgia) at any time

10) Known hypersensitivity to the study drug, its metabolites, or any of the excipients, or previous clinically significant allergic reaction to any drug, per judgment of the investigator

11) Another highly active inflammatory/autoimmune/rheumatic disease (such as highly active RA, highly active SLE, highly active nephritis or CNS inflammation) which would compromise subject safety or interfere with the conduct of the study.

Note: Subjects with stable autoimmune disease, (eg, RA, SLE, or thyroiditis) not requiring prohibited medications are permitted

12) History of head/neck irradiation, sarcoidosis, graft v host disease, or IgG4 related disease {Stone 2012}, {Umehara 2012}

13) Female subjects who are pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study up to 36 days after the last dose of study drug or males who are planning to father a child during the study up to 90 days after the last dose of study drug (as per Appendix 5)

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

15) History of live or attenuated vaccines within 30 days of Day 1, or planned during the study period or for 12 weeks after the subject's last dose of study drug. Refer to Section 5.9

16) 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).

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

18) Hepatitis B virus (HBV) surface antigen (HBsAg) or positive HBV core antibodies at Screening

19) Hepatitis C virus (HCV) antibodies and positive HCV RNA viral load (VL).

Note: Subjects with positive HCV Ab, but negative HCV RNA VL are eligible per investigator judgment, but require monitoring as outlined in Appendix 2. Subject with active HCV during the study as evidenced by RNA positivity will be discontinued from study drug as outlined in Section 3.4.

20) Serious active infection of any kind at Screening or Day 1

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

22) Known bleeding disorder or hypercoagulable state; antiphospholipid antibody syndrome with prior clinically significant event (per judgment of investigator); or on chronic anticoagulation or anti-platelet therapy

Note: Aspirin therapy ≤325 mg/day for cardiovascular prophylaxis is permitted

23) Current drug or alcohol abuse, or heavy tobacco use, as per judgment of investigator

24) Clinically significant laboratory values at Screening, including the following:

a. Hemoglobin <9 g/dL (International System of Units [SI]: <90 g/L)

b. Neutrophil count <1.5 x 10^9/L (SI: <1.5 x 10^9 cells/L)

c. Platelets <100 x 10^3 cells/mm3 (SI: <100 x 10^9 cells/L);

d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥1.5x upper limit of normal (ULN)

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

f. Estimated creatinine clearance <60 mL/min per Cockcroft-Gault equation

Note: Abnormal values may be rechecked one time, at discretion of the investigator if an error is suspected

4.4. Screen Failure

Subjects who do not meet the Inclusion/Exclusion criteria for entry into the study ("screen failures") may be rescreened one time in selected cases with written permission from the Sponsor; for example, to meet a drug washout period.

Subjects who do not enter the study due to administrative reasons (for example, exceeding the screening window due to issues with appointment scheduling or obtaining results of laboratory data) may be rescreened one time with written permission from the Sponsor; this rescreening option is in addition to the rescreening permitted above.

Neither of the rescreening options is to be used to recheck a subject who is likely unsuitable for the study, for example, to check whether their 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 consent form; they will receive a new subject number. In these cases, lab screening tests do not need to be repeated if they were performed within 28 days of randomization, and within 90 days for Quantiferon and/or Chest X-ray, if needed.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web and Mobile 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 the individual subject treatment assignment directly from the IWRS system. Gilead recommends, but does not require, that the investigator contact the Gilead Medical Monitor before breaking the blind. Treatment assignments 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 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 Phase 2 clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will be discontinued from the trial.

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

5.2. Description of Filgotinib and PTM Filgotinib

CCI [redacted]

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

CCI [redacted]

5.4. Description of GS-4059 and PTM GS-4059

CCI [redacted]

5.5. Packaging and Labeling of All Study Drugs for this Protocol

Filgotinib 200 mg tablets, PTM filgotinib 200 mg tablets, GS-9876 30 mg tablets, PTM GS-9876 30 mg tablets, GS-4059 40 mg tablets, and PTM GS-4059 40 mg tablets for each drug 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.

All 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), the European Union (EU) Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations, as applicable.

5.6. Storage and Handling of Study Drugs

Study drugs (filgotinib, GS-9876, GS-4059, and PTM tablets for each) should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drug(s) should not be stored in a container other than the container in which they were supplied.

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

5.7. Dosage and Administration of Investigational Medicinal Products

Subjects will receive study drugs according to their randomization arm as described in Section 3.2.

The study drugs should be administered orally once daily with water, with or without food. The study drugs should be swallowed whole and all 3 tablets administered at the same time. Subjects should be instructed to take study drugs at approximately the same time each morning.

On study visit days, subjects should not take their study drugs at home, but should bring them to the clinic and take them as instructed by site staff (in order to enable timing of PK blood draws and/or other procedures).

On Day 1, subjects will be instructed to take their dose in clinic as the last in-clinic study procedure (after all other procedures for that visit have been completed).

At Weeks 4, 8, 12, 24, 36 and 48/ET, subjects will be instructed to take their dose after PK assessments have been completed.

At Week 18, subjects will be instructed to take their dose in clinic in order to have a pre-dose biomarker blood draw, and a post-dose PK and biomarker blood draw approximately 2 hours after study drug administration.

For a missed dose of study medication, subjects should be instructed to take the missed dose of study medication as soon as possible during the same day. If more than 12 hours have elapsed since the scheduled time of the missed dose, the subject should be instructed to return the missed unused tablets to the study drug bottles and take the next dose at the regularly scheduled time. Subjects should be reminded never to double the missed dose of study drug with their next dose, under any circumstances.

5.8. Prior and Concomitant Medications

- Prior medications that are allowed in this study:

  See I/E criteria

- Prior medications that are prohibited in this study:

  See I/E criteria

- Concomitant medications allowed in this study:

  Doses of concomitant chronic medications should be stable (defined as no change in prescription for at least 28 days prior to Day 1) and should be continued at the stable dose throughout at least the first 12 weeks of the study. However, dose adjustments for toxicities are allowed, and should be recorded in the eCRF, along with documentation of the AE requiring the dose change.

  — Cevilimine or pilocarpine, as prescribed by investigator.

  — Ophthalmic cyclosporine, as prescribed by investigator.

  — Oral NSAIDs, as prescribed by investigator.

  — Oral or injectable MTX ≤ 20 mg per week (subjects on MTX should also be on chronic folic acid supplementation [or equivalent], as 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, leflunomide, or other folate antagonists) should be avoided, as much as possible, in accordance with clinical practice.

  — Chloroquine ≤ 250 mg/day or HCQ ≤ 400 mg/day.

  — Oral leflunomide ≤ 20 mg/day (Leflunomide in combination with MTX is not allowed)

  — Azathioprine up to maximum of 2 mg/kg or 300 mg, whichever is lower

  — Vitamins, minerals, or herbal supplements, as per judgment of the investigator.

  Note: after completion of the Week 12 visit, the dose of any of the above medications may be reduced, and subsequently increased, as often as needed, per judgment of the investigator; however, the highest dose prescribed should not exceed the subject's Baseline dose. Subjects requiring a dose higher than their Baseline dose for more than 14 consecutive days should be withdrawn from study drug, but may continue with study visits.

— Oral corticosteroids ≤ 10 mg prednisone (or equivalent) per day.

Note: after completion of the Week 12 visit, the dose of corticosteroids may be reduced, and subsequently increased, as often as needed, per investigator judgment; however, the dose should not exceed the subject's Baseline dose. Subjects requiring oral corticosteroids > 10 mg prednisone/day should be withdrawn from study drug, but may continue with study visits.

— Other chronic therapies at stable doses (eg, antihypertensives, female hormone replacement therapy, thyroid replacement therapy, anti-depressants), as per judgment of the investigator.

- Concomitant medications that are not allowed in this study:

— Cyclophosphamide

— Cyclosporine (other than ophthalmic cyclosporine, as described above)

— Moderate or strong CYP3A inhibitors or inducers are prohibited within 2 weeks prior to the first dose of study drug and throughout the study. Strong P-gp inducers are prohibited within 3 weeks prior to the first dose of study drug and throughout the study.

Examples of these medicines are provided below.

This list does not include medications such as anti-HIV agents that would be contraindicated based on other exclusion criteria (questions regarding these medications should be discussed with the Medical Monitor):

Drug Class	Agents Disallowed
Strong CYP3A Inhibitors[a]	clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole, telaprevir, boceprevir, grapefruit juice, idelalisib, Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir), troleandomycin, mibefradil
Strong CYP3A Inducers[a, b]	Carbamazepine, phenytoin, rifampin, fosphenytoin, pentobarbital, primidone, rifabutin, rifapentine, phenobarbital, mitotane, avasimibe, St. John's Wort, enzalutamide
Strong P-gp inducers[c]	Phenobarbital, phenytoin, carbamazepine, rifabutin, rifapentine, rifampin, St. John's wort, danshen (salvia miltiorrhiza)
Moderate CYP3A Inhibitors[a,]	fluconazole, erythromycin, diltiazem, dronedarone, aprepitant, casopitant, imatinib, verapamil, tofisopam, ciprofloxacin, cimetidine, cyclosporine, Schisandra sphenanthera, crizotinib, netupitant, nilotinib, isavuconazole
Moderate CYP3A Inducers[a]	bosentan, thioridazine, nafcillin, modafinil, semagacestat, genistein

[a] In vitro data indicated GS-9876 is a substrate of CYP3A4. Co-administration of CYP3A inhibitors may increase GS-9876 exposure and coadministration of CYP3A inducers may decrease GS-9876 exposure.
[b] GS-4059 is a substrate of CYP3A and P-gp. Coadministration of strong CYP3A/P-gp inducers may decrease GS-4059 exposure.
[c] Filgotinib is a P-gp substrate. Coadministration of strong P-gp inducers may decrease filgotinib exposure.

- GS-4059 has the potential to inhibit P-gp, which may affect the plasma concentrations of its substrates. Caution should be exercised when co-administering medicines that are P-gp substrates with narrow therapeutic windows, such as digoxin, dabigatran etexilate, ranolazine and aliskiren

- The following medications are prohibited within 4 weeks prior to the first dose of study drug and throughout the study: gold salts, minocycline, penicilamine, sulfasalazine, tacrolimus, sirolimus, everolimus, mycophenolate mofetil, etanercept, adalimumab, anakinra, or biosimilar versions of these drugs, where applicable

- The following medications are prohibited within 10 weeks prior to the first dose of study drug and throughout the study: infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, or biosimilar versions of these drugs, where applicable

- Parenteral corticosteroids are prohibited during the first 24 weeks of the study (except for one joint injection, at a maximum dose of 40 mg triamcinolone, or equivalent; the injected joint should be marked as "non-assessible" for the remainder of the study

- Concurrent therapy with any anti-coagulant (eg, coumadin [warfarin], any Vitamin K antagonist, any novel oral anticoagulant, heparins or low molecular heparins, any inhibitors of factor Xa) or any anti-platelet therapy (eg, adenosine diphosphate [ADP] receptor inhibitors, phosphodiesterase inhibitors, Protease-activated receptor 1 (PAR-1) antagonists, Glycoprotein 2b/3a inhibitors). NOTE: aspirin therapy ≤ 325 mg/day for cardiac prophylaxis is allowed.

5.9. Vaccine Guidelines

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

- 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 with vaccinated person for 4 weeks following vaccination

  - Oral polio vaccination – avoid contact with vaccinated person for 6 weeks following vaccination

  - Attenuated rotavirus vaccine – avoid contact with vaccinated person for 10 days following vaccination

- Inhaled flu vaccine – avoid contact with vaccinated person for 1 week following vaccination

- Inactivated vaccines (such as non-live flu vaccines) should be administered according to local vaccination standards whenever deemed medically appropriate by the investigator; however, there are no available data on the concurrent use of filgotinib, GS-9876, or GS-4059 and their respective impacts (if any) on immune responses following vaccination.

5.10. Investigational Medicinal Product Accountability and Disposal or Return

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All partially used or unused study drugs 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 drugs

- Record the date, subject number, subject initials, the study drug numbers dispensed

- Record the date, quantity of used and unused study drugs returned, along with the initials of the person recording the information.

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

6. STUDY PROCEDURES

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

The investigator should document any deviation from protocol procedures and notify the sponsor or its designee.

6.1. Subject Enrollment and Treatment Assignment

It is the responsibility of the Investigator to ensure that subjects are eligible to participate in the study prior to randomization/enrollment and throughout the study.

Once consent has been obtained, all screening tests and procedures have been assessed, and study eligibility has been confirmed, eligible subjects will be randomized to study treatment as described in Section 3.2.

The study center will not be activated and allowed to screen patients until:

- The IRB or IEC have reviewed and approved the study and the informed consent document
- All required regulatory documents have been submitted to and approved by Gilead or its designee
- A master services agreement and/or study agreement is executed
- The site initiation meeting has been conducted by Gilead or its designee. The initiation meeting will include, but is not limited to, a review of the protocol, the IB, and the Investigator's responsibilities.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened before randomization to determine eligibility for participation in the study. The screening window may be extended to up to 28 days prior to the Day 1 visit. Subject-reported outcomes, including Global Assessment, VAS assessments 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, as much as possible. The following will be performed and documented at screening:

- Obtain written Informed Consent
- Obtain non-SjS and SjS medical/surgical history, including diagnosis and prior treatments

- Vital Signs, including weight and height
- Complete Physical Examination
- ESSDAI
- PE for domains of ESSDAI, (including glandular exam, lymph nodes, general skin, neurologic exam for peripheral neuropathy, pulmonary exam)
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urine drug screen (amphetamines cocaine, methadone opiates)
  - Urinalysis with spot protein/microalbumin/creatinine
- Obtain blood samples for:
  - Serum Pregnancy Test (female subjects of child bearing potential) or follicle stimulating hormone (FSH, as applicable)
  - TB testing (Quantiferon gold)
  - CD19+ B cell count (as applicable)
  - HbA1c, TSH
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Viral Screening and Reflex PCR
  - Autoantibodies: anti-SSA or anti-SSB
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - Biomarker samples
- Chest X-ray (for subject who had no previous chest X-ray available for review by the investigator within the last 3 months)

- VAS
- 12‑Lead ECG
- PFTs (as applicable at selected sites)
- CCI [redacted]
- CCI [redacted]
- Adverse Events
- Concomitant medications (All non‑SjS medication used within 30 days of consent (including any changes) are to be documented in the eCRF. All prior medication(s) used in the treatment for SjS or any other autoimmune disease, are to be documented in the eCRF)

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after screening for randomization into the study.

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.

From the time of obtaining informed consent through the first administration of investigational medicinal product, the investigative site is to record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (CRF/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 CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Day 1 Assessments

At Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive one of four study dosing regimens.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to D1 visit to ensure an approximate 8-hour fast prior to the blood sample collection under fasting condition the next morning.

VAS and subject reported QOLs assessments 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. The following will be performed and documented at Day 1 prior to dosing:

- Randomization
- Vital Signs, including weight

- Symptom-directed PE
- ESSDAI (lab results and PFTs as applicable from screening will be used)
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
  - Fasting urine for biomarker
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Fasting lipid profile, as outlined in Appendix 6
  - Biomarker samples
  - Autoantibodies: deamidated gliadin peptide antibodies (anti DGP IgA or IgG); Anti endomysial antibodies (EMA), RF, CCP (cyclic citrullinated peptide), dsDNA, ANA, IgA anti tTA (tissue transglutaminase antibodies)
  - CCI [redacted]
- VAS
- Subject reported QOLs
- Other questionnaires addressing disease, activity and fatigue may be provided when and where available.
- Treatment Satisfaction Questionnaire for Medication (TSQM)

- CCI [redacted]
- 12-Lead ECG
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Adverse Events
- Concomitant medications

6.3. Randomization

Subjects will be randomly allocated to a dosing group according to a pre-specified randomization scheme prepared by an independent statistician. Upon qualification for the study, subjects will be randomized using a computerized IWRS system.

The clinic will contact the IWRS system and for the appropriate kit number to be dispensed as directed by the IWRS. The kit will contain the relevant study drugs for the period until the next dispensation visit.

At Week 24 subjects originally randomized to placebo will be re-randomized to either filgotinib, GS-9876 or GS-4059. Sites and subjects will continue to remain blinded throughout the study.

6.4. Week 2 and Week 26

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOLs assessments 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.

- Vital Signs, including weight
- Symptom-directed PE
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Biomarker samples
  - CCI [redacted]
- VAS
- 12-Lead ECG
- CCI [redacted]
- CCI [redacted]
- Drug accountability
- Adverse Events
- Concomitant medications

6.5. Week 4

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic after the pre-dose PK assessment is completed.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOLs assessments 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.

- Vital Signs, including weight
- Symptom-directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - PK samples, collected prior to study drug administration (pre-dose)
  - CCI [redacted]
  - Biomarker samples
- VAS
- Subject reported QOLs

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.6. Week 8

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic after the pre-dose PK assessment is completed.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOLs assessments 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.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)

- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - PK samples, collected prior to study drug administration (pre-dose)
  - CCI [redacted]
  - Biomarker samples
- VAS
- Subject reported QOLs
- CCI [redacted]
- 12-Lead ECG
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.7. Week 12

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic after the pre-dose PK assessment is completed.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to Week 12 visit to ensure an approximate 8-hour fast prior to the blood sample collection under fasting condition the next morning.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOL assessments 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.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
  - Fasting urine for biomarker
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Viral Monitoring for HCV as applicable (see Exclusion criteria, Section 4.3)
  - Autoantibodies: deamidated gliadin peptide antibodies (anti DGP IgA or IgG); Anti endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, SSA, SSB, IgA anti tTA (tissue transglutaminase antibodies)
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - Fasting lipid profile
  - PK samples, collected prior to study drug administration (pre‑dose)
  - Biomarker samples

- VAS
- Subject reported QOLs
- TSQM
- CCI [redacted]
- 12-Lead ECG
- PFTs (at selected sites)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.8. Week 18

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic as soon as possible after the pre-dose biomarker blood draw is completed, so PK samples and post-dose biomarker samples can be drawn approximately 2 hours after dose.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and outcomes assessments are recommended to be completed before any other study procedures. Invasive study procedures such as blood draws should be done after VAS and outcome assessments.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - PK samples will be collected approximately 2 hours post dose
  - Biomarker samples
- VAS
- Subject reported QOLs
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.9. Week 24

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic after the pre-dose PK assessment is completed.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to Week 24 visit to ensure an approximate 8-hour fast prior to the blood sample collection under fasting condition the next morning.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and outcomes assessments 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.

- Randomization, subjects on placebo will be re‑randomized 1:1:1 to either filgotinib, or GS−9876 or GS-4059
- Vital Signs, including weight
- Complete Physical Examination
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
  - Fasting urine for biomarker
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Viral Monitoring

  - Autoantibodies: deamidated gliadin peptide antibodies (anti DGP IgA or IgG); Anti endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, SSA, SSB, IgA anti tTA (tissue transglutaminase antibodies)
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - Fasting lipid profile
  - PK samples, collected prior to study drug administration (pre−dose)
  - Biomarker samples
- VAS
- Subject reported QOLs
- TSQM
- CCI [redacted]
- 12‑Lead ECG
- PFTs (if available, at selected sites)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.10. Week 28

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and outcomes assessments 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.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM,serum and urine immunofixation
  - Biomarker samples
- VAS
- Subject reported QOLs

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.11. Week 32

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOL assessments 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.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)

- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Biomarker samples
- VAS
- Subject reported QOLs
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications
- 12-Lead ECG

6.12. Week 36

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic after the pre-dose PK assessment is completed.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and outcomes assessments 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.

- Vital Signs, including weight
- Symptom-directed PE
- ESSDAI

- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Viral Monitoring
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - CCI [redacted]
  - CCI [redacted]
- VAS
- Subject reported QOLs
- TSQM
- CCI [redacted]
- 12‑Lead ECG
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Drug dispensing

- Drug accountability
- Adverse Events
- Concomitant medications

6.13. Week 42

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOL assessments 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.

- Vital Signs, including weight
- Symptom‑directed PE
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Complement (C3, C4, CH50), and CK
  - Biomarker samples

- VAS
- Subject reported QOLs
- CCI
- Drug dispensing
- Drug accountability
- Adverse Events
- Concomitant medications

6.14. Week 48/Early Termination (ET)

If a subject discontinues study, every attempt should be made to perform the required study-related ET visit and Follow-up visit procedures.

Subject should be instructed **to hold their dose of study drugs** in the morning of the visit. The dose should be taken at the clinic.

Subjects should be instructed to fast (no food or drink, except water [including for study drug intake]), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to Week 48/ET visit to ensure an approximate 8-hour fast prior to the blood sample collection under fasting condition the next morning.

The following assessments will be completed at each visit or as specified in the Schedule of Assessments in Appendix 2.

Note: VAS and Subject reported QOL assessments 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.

- Vital Signs, including weight
- Complete Physical Examination
- ESSDAI
- PE for domains of ESSDAI
- 28 Swollen and Tender Joint count
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable

- Obtain urine sample for:
  - Urinalysis with spot protein/ microalbumin/creatinine
  - Urine Pregnancy Test (female subjects of child bearing potential only)
  - Fasting urine for biomarker
- Obtain blood samples for:
  - Hematology, ESR as applicable, chemistry and hsCRP
  - Viral Monitoring
  - Autoantibodies: deamidated gliadin peptide antibodies (anti DGP IgA or IgG); Anti endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, SSA, SSB, IgA anti tTA (tissue transglutaminase antibodies)
  - Complement (C3, C4, CH50), and CK
  - Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation
  - Fasting lipid profile
  - CCI [redacted]
  - CCI [redacted]
- VAS
- Subject reported QOLs
- TSQM
- CCI [redacted]
- 12‑Lead ECG
- PFTs (if available, at selected sites)
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- Drug accountability
- Adverse Events
- Concomitant medications

6.15. Follow-up Visit

The following procedures will be completed 4 weeks after the subject's last dose of study treatment.

- Vital Signs, including weight
- Symptom‑directed PE
- Urine Pregnancy Test (female subjects of child bearing potential only)
- Physician's Global Assessment of SjS disease activity
- Physician's Global Assessment of concomitant RA or SLE disease activity as applicable
- Obtain blood sample for:
  - hematology, ESR as applicable, chemistry and hsCRP
  - Biomarker samples
- VAS
- 12‑Lead ECG
- Adverse Events
- Concomitant medications

6.16. Study Assessments

This study consists of 14 scheduled visits plus a follow up visit 4 weeks after study drug is stopped, with total study duration of 48 weeks (+4 weeks).

The study procedures to be conducted for each subject enrolled in the study are described in the following sections. In addition, Appendix 2 presents the study procedures in tabular form.

6.16.1. Patient Reported Outcomes: Visual Analogue Scales and Questionnaires

PROs, including Visual Analogue Scales (VAS) and questionnaires, are to be completed by the subject (where local language questionnaires are available) and should be recommended to be completed before any other study procedures. Please refer to schedule of assessments in Appendix 2 for the time points for which all PRO assessments are to be completed.

6.16.1.1. Global Assessment of Disease Activity

The subject will complete a Global Assessment of Disease Activity, recorded on a 0-100 mm VAS, with 0 indicating "no Sjogren's Syndrome activity" and 100 indicating "most severe Sjogren's Syndrome activity".

For subjects who have concomitant RA or SLE, a second global disease activity VAS will be completed by the subject.

For subjects with concomitant RA: The Global Assessment of Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "no Rheumatoid arthritis activity" and 100 indicating "most severe Rheumatoid arthritis activity".

For subjects with concomitant SLE: The Global Assessment of Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "no SLE activity" and 100 indicating "most severe SLE activity".

6.16.1.2. Assessment of Vaginal Dryness, Ocular Dryness and Oral Dryness

Subjects will complete an assessment of vaginal dryness, ocular dryness and of oral dryness. These assessments will be recorded on 0-100 mm VAS's, with 0 indicating "no dryness" and 100 indicating "most severe dryness".

6.16.1.3. Assessment of Pain and Fatigue

Subjects will complete an assessment of overall pain and fatigue related to the underlying disease. These assessments will be recorded on 0-100 mm VAS's, with 0 indicating "no pain"/"no fatigue" and 100 indicating "most intense pain"/"most severe fatigue".

6.16.1.4. FACIT-Fatigue Scale

Fatigue will be assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) scale. The FACIT-fatigue scale measures an individual's level of fatigue during their usual daily activities over the past week. It consists of 13 questions with a 7-day recall period on a 5-point Likert scale, with 0 indicating "not at all" and 4 indicating "very much". The total score ranges from 0 to 52. Higher scores indicate a better the quality of life.

6.16.1.5. 36-Item Short-form Health Survey

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

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

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

6.16.1.6. Exploratory Patient Reported Outcomes

CCI [redacted]

6.16.1.7. EULAR Sjogren's Syndrome Patient Reported Index

EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) is completed by the patient and it contains just three items to be given an activity level score between 0-10: pain, fatigue and dryness, the final ESSPRI score is the mean of all three scores and therefore also between 0-10.

6.16.1.8. Treatment Satisfaction Questionnaire for Medication

The TSQM is a composite measure based on the subject's rating of medication effectiveness, side effects, and convenience. At Day 1, this questionnaire will be used to assess prior medications used to treat the subject's SjS. At all other time points, specified in the schedule of assessments in Appendix 2, the TSQM will be used to assess the subject's opinion of the study drugs. Site staff should remind the subject of which SjS drugs they should be evaluating at each visit.

6.16.1.9. Oral Health Impact Profile

The Oral Health Impact Profile (OHIP- 14) has been endorsed as a disease specific QOL and measures aspects directly related to oral health and function independent of other problems associated with SjS in 14 questions.

6.16.1.10. Impact of Dry Eye on Everyday Life

Impact of Dry Eye on Everyday Life (IDEEL) is a dry eye questionnaires, that evaluates QOL in subjects with dry eye disease. It covers 57 items organized into 3 modules, Dry Eye Symptom-Bother, Dry Eye Impact on Daily Life, and Dry Eye Treatment Satisfaction, that allow a comprehensive evaluation of the burden of the dry eye condition on patients with SjS.

6.16.1.11. Profile of Fatigue and Discomfort-Sicca Symptoms Inventory

Profile of Fatigue and Discomfort-Sicca Symptoms Inventory (PROFAD-SSI- SF) is questionnaire developed specifically to assess fatigue in SjS patients with 19 questions.

6.16.2. Physician Reported Outcomes: Visual Analogue Scales, Joint Exam and Disease Activity Index

Physician reported outcomes, including VAS, joint exam and disease activity index, are to be completed by the physician, independently of the subject's responses to any PRO assessments. Please refer to schedule of assessments in Appendix 2 for the time points for which all assessments are to be completed.

6.16.2.1. Physician Assessment of Disease Activity

The evaluating physician should complete the global assessment independently of the subject's assessments. The Global Assessment of Disease Activity will be recorded on a 0-100 mm VAS, with 0 indicating "no Sjogren's Syndrome activity" and 100 indicating "most severe Sjogren's Syndrome activity."

For subjects who have concomitant RA or SLE, a second global disease activity VAS will be completed by the provider.

For subjects with concomitant RA: The Global Assessment of Disease Activity will be completed by the provider on a 0-100 mm VAS, with 0 indicating "no Rheumatoid arthritis activity" and 100 indicating "most severe Rheumatoid arthritis activity".

For subjects with concomitant SLE: The Global Assessment of Disease Activity will be completed by the provider on a 0-100 mm VAS, with 0 indicating "no SLE activity" and 100 indicating "most severe SLE activity".

6.16.2.2. Evaluation of Disease Activity: Tender and Swollen Joint Counts

Sites will complete an assessment of tenderness and swelling for 28 of their joints. A list of the 28 joints to be evaluated will be outlined in the site operations manual.

A designated joint assessor with adequate training and experience in performing joint assessments at each study site should perform all joint assessments. The joint assessor should preferably be a rheumatologist; however, if a rheumatologist is not available, he/she should be a health care worker with experience in performing joint assessments. The subject's joint assessor should remain the same throughout the study, as much as possible.

6.16.2.3. EULAR Sjogren's Syndrome Disease Activity Index

EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI) is a disease activity instrument to measure disease activity of primary Sjogren's Syndrome. It consists of 12 domains and each domain is divided into 3–4 levels of activity (Appendix 8). Definition of each activity level is provided by a detailed description of what should be considered in that item. The ESSDAI should be filled out by the health care provider.

6.16.3. Pulmonary Function Testing

6.16.3.1. Spirometry

Spirometry testing will be performed as outlined in the site operations manual (at selected sites). Please refer to schedule of assessments in Appendix 2 for the time points at which spirometry is to be completed. The following measurements are performed at the visits where spirometry is indicated, where available

- Vital capacity (VC)
- Forced vital capacity (FVC)
- Forced expiratory volume (FEV) at timed intervals of 0.5, 1.0 (FEV_1), 2.0, and 3.0 seconds
- Forced expiratory flow 25–75% ($FEF_{25–75}$)

6.16.4. Clinical Laboratory Evaluations

Hematology, chemistry, urinalysis (with spot protein/microalbumin/creatinine), endocrine, serology, drug screen, hsCRP, TB testing and pregnancy assessments will be carried out as per laboratory assessment table in Appendix 6.

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

Plasma concentrations of filgotinib (and its metabolite, GS-829845), GS-9876, and GS-4059 will be measured and PK parameters determined.

PK samples will be collected prior to study drug administration (pre-dose) at Weeks 4, 12, and 24; anytime in relation to last study drug administration at Weeks 8, 36, and 48/ET visit. At Week 18, PK samples will be collected approximately 2 hours after study drug administration (post dose).

The samples will be used to evaluate PK of study drug and may also be used to measure protein binding of filgotinib, GS-9876, or GS-4059. Plasma concentrations of other metabolites may be determined, as applicable.

CCI [redacted]

Refer to the central laboratory instruction manual for information on collection and shipment of required study samples.

6.16.5. Salivary Flow Measurements

CCI [redacted]

6.16.6. Tear Production

CCI [redacted]

6.16.7. Parotid Gland Ultrasound

CCI [redacted]

6.16.8. 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 for 5 min and are to include HR, respiratory rate, systolic blood pressure, diastolic blood pressure, and body temperature.

6.16.9. Cognitive Test

CCI [redacted]

Paper questionnaires will be considered source documents.

6.16.10. 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 should be measured at Screening only (subjects should remove shoes). At Screening, Week 24, and Week 48 (or at ET), a complete physical examination should be performed. Symptom–directed physical examinations should be performed at all other visits. Physical exam evaluating the domains of the ESSDAI should be performed at the time points indicated in the schedule of assessments (Appendix 2).

Weight is measured at all visits.

6.16.11. Other Assessments

12-lead Electrocardiogram

A resting 12-lead ECG should 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 5 min and will include 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. ECGs will be interpreted by the investigator for clinical significance and results will be entered into the eCRF.

CCI [redacted]

[redacted].

Ophthalmologic Exams

CCI [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 (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history 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 therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product rather than by another etiology.

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

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

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

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

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

For purposes of consistency with the CTCAE, these intensity grades are defined in Table 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, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP 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 occur 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 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 IMP, 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 IMP, 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.

<u>Electronic Serious Adverse Event (eSAE) Reporting Process</u>

- 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 as described above.

  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.

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

- 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 IBs.

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 and Other Abnormal Assessments

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, 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, respectively. If the

laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity of laboratory abnormality should be recorded and graded according to the modified CTCAE Grading Scale Version 4.03, which can be found in Appendix 4.

For adverse events 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

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead Sciences Medical Monitor or designee. Whether or not considered treatment -related, all subjects experiencing AEs should be monitored as clinically indicated, until symptoms subside, and until any abnormal laboratory values have resolved or returned to baseline levels or are considered irreversible, or until there is a satisfactory explanation for the changes observed.

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 3 and as outlined below.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 3 calendar days after receipt of the original test results. Grade 3 or 4 clinically significant laboratory abnormalities should be managed as outlined in Appendix 3 and Section 3.4.

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To assess the efficacy of filgotinib, GS-9876 and GS-4059 in adult subjects with active SjS.

The secondary objectives of this study are:

- To assess the safety and tolerability of filgotinib, GS-9876 and GS-4059 in adult subjects with active SjS
- To assess the effect of filgotinib, GS-9876 and GS-4059 on patient reported outcomes in active SjS, including fatigue, disability and quality of life

The exploratory objectives of this study are:

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects at who fulfill response criteria as outlined in Section 2.

8.1.3. Secondary Endpoint

Secondary endpoints are:

- Change from baseline in ESSDAI at Week 12
- Change from baseline in ESSPRI at Week 12
- Change from baseline in ESSDAI at Week 24
- Change from baseline in ESSPRI at Week 24

8.1.4. Exploratory Endpoints

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized

The All Randomized Analysis Set includes all subjects who are randomized in the study. This is the primary analysis set for by-subject listings.

8.2.1.2. Efficacy

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

8.2.1.3. Safety

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

8.2.1.4. Pharmacokinetics

8.2.1.4.1. PK Substudy Analysis Set

CCI [redacted]

8.2.1.4.2. PK Analysis Set

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, GS-4059, and/or their metabolite(s).

8.2.1.5. Biomarker

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 a summary of at least PROs, ESSDAI, disease duration (time from diagnosis), CCI [redacted], 28-joint count, current or prior use of DMARD(s), and oral corticosteroids.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The primary endpoint is the proportion of subjects fulfilling response criteria (as outlined in Section 2). The primary analysis will consist of a superiority test of each of filgotinib, GS-9876 or GS-4059 compared to placebo, respectively. CMH approach adjusting for the randomization stratification factors will be used for the hypothesis testing at the 2-sided 0.05-level.

8.5.2. Secondary and Exploratory Analyses

CCI [redacted]

8.6. Safety Analysis

All safety analyses will be performed using the Safety Analysis Set.

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

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

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. Exposure data will be summarized by treatment group.

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

8.6.2. Adverse Events

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

Treatment-emergent adverse events (TEAEs) are defined as one or both of the following:

- Any AEs with an onset date 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 by treatment group.

8.6.3. Laboratory Evaluations

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

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

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

8.7. Pharmacokinetic Analysis

Plasma concentrations of filgotinib, the active metabolite of filgotinib (GS-829845), GS-9876, and GS-4059 will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

CCI [redacted]

Plasma concentrations of GS-9876 metabolite(s), other filgotinib metabolite(s), and/or GS-4059 metabolite(s) may also be determined and analyzed.

8.8. Biomarker Analysis

For analysis of biomarkers (eg, cytokines, chemokines, leukocyte flow cytometry, etc.) collected at baseline and post-baseline visits, the baseline levels and the modulation pattern upon treatment, including change over time from baseline levels, will be evaluated by treatment group. Descriptive statistics will be provided at each sampling time, by treatment group. Additionally graphical summaries, e.g. mean+/-SD, median+/-interquartile range (Q1, Q3), box plots, and scatter plots to explore correlations between different biomarkers may also be generated, as needed. These graphs may be generated for raw values as well as change from baseline, as appropriate.

CCI [redacted]

CCI [redacted]

8.9. Sample Size

Based on results of prior SjS studies, assuming a response rate of 70% for an active arm and 30% for the placebo arm at Week 12, approximately 35 evaluable subjects will be needed in each arm to achieve 85% power to detect a significant difference at a 2-sided, 0.05-level. Enrollment of approximately 35 subjects per am is planned to ensure that a sufficient number of subjects is available analysis of the primary endpoint.

8.10. Analysis Schedule

The primary and secondary analysis will be conducted after all subjects either complete the Week 24 visit or prematurely discontinue from the study. Gilead personnel involved in the study conduct, as well as study investigators and subjects will remain blinded to the individual treatment assignments. The final analysis will be performed when all subjects complete the study (as defined in Section 3.5) or prematurely discontinue from the study.

Additionally, to assess the safety and efficacy of GS-9876, filgotinib and GS-4059 for further planning and development of these products, a Gilead internal unblinded team independent of the blinded study team will be assembled. This group will consist of at least one representative from Clinical Research, Biostatistics, and Pharmacovigilance/Epidemiology, and may include other personnel as necessary. The Gilead internal unblinded team will be granted access to unblinded clinical data including treatment assignments to closely monitor study progress and drug safety.

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

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

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

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The study investigator must ensure that the potential risk of loss of fertility is discussed with all male subjects during the informed consent process. The investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions.
NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. Study Files and Retention of Records

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

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., 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 (i.e., United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF casebook will be completed by an authorized study staff member whose training for this function is completed in EDC. The eCRF casebook will only capture the data required per the protocol schedule of events and procedures.
The Inclusion/Exclusion Criteria and Enrollment eCRFs should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency.
The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to any interim time points or database lock (as instructed by Gilead), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, IMP should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's IMP disposal procedures and provide appropriate instruction for disposal or return of unused IMP supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead 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 / IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRBs / IECs in accordance with local requirements and receive documented IRBs / IECs approval before modifications can be implemented. Substantial modifications (as classified by EU Directive 2001/20/EC) will be submitted and approved by relevant EU competent authorities, and by non-EU competent authorities as required by local regulations, prior to implementation.

9.2.2. Study Report and Publications

A clinical study report 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.

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11. APPENDICES

Appendix 1. **Investigator Signature Page**

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Appendix 8. **EULAR Sjogren's Syndrome Disease Activity Score (ESSDAI)**

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Randomized, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome

GS-US-445-4189, Amendment 1, 12 July 2018

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

PPD

Name (Printed)
Author

PPD

13-July-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. Schedule of Assessments Table

	Screening [a]	Day 1 [b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET [c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Fasting visit		x				X		x						x	
IP to be taken at the clinic		x	x	x	x	X	x	x	x	x	x	x	x	x	
Written Informed Consent	x														
Randomization		x [e]						x [f]							
Physical exam and provider assessments															
SjS medical/surgical history, including diagnosis and prior treatments,	x														
Medical /Surgical History (non-SjS)	x														
Vital Signs, including weight and height [g]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Complete Physical Examination	x							x						x	
Symptom-directed PE		x	x	x	x	X	x		x	x	x	x	x		x
ESSDAI	x	x [y]		x	x	X	x	x		x	x	x	x	x	
PE for domains of ESSDAI [h]	x	x		x	x	X	x	x		x	x	x	x	x	
28 Swollen and Tender Joint count	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Physician's Global Assessment of SjS activity	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x

	Screening [a]	Day 1[b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET[c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Physician's Global Assessment of concomitant RA or SLE disease activity as applicable	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Laboratory assessments															
Urine drug screen[i]	x														
Urinalysis with spot protein/ microalbumin/creatinine	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Urine Pregnancy Test (female subjects of child bearing potential only)		x	x	x	x	X	x	x	x	x	x	x	x	x	x
Urine for biomarker (fasting)		x				X		x						x	
Serum Pregnancy Test (female subjects of child bearing potential) or FSH	x														
TB testing[j]	x														
CD19+ B cell count[k]	x														
HbA1c, TSH	x														
Hematology, ESR as applicable, chemistry and hsCRP	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
Viral Screening and Reflex PCR[l]	x														
Viral Monitoring[m]						X		x				x		x	
Autoantibodies[n]	x	x				X		x						x	

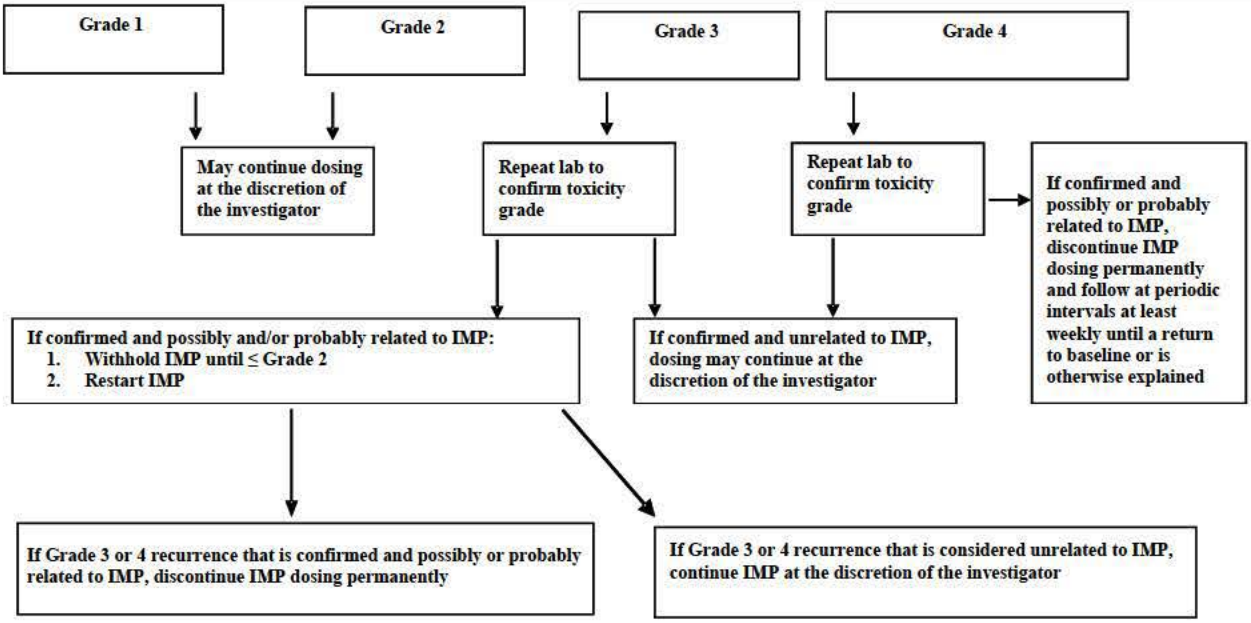
	Screening [a]	Day 1[b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET[c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Complement (C3, C4, CH50), and CK	x	x	x	x	x	X	x	x	x	x	x	x	x	x	
Cryoglobulins, total Ig, quant IgG, IgA, and IgM, serum and urine immunofixation	x			x		X		x		x		x		x	
Lipid profile (fasting)[o]		x				X		x						x	
PK samples[p]				x	x	X	x	x				x		x	
CCI															
Blood for Biomarker samples[r]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
CCI															
PROs and questionnaires															
VAS[t]	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
ESSPRI	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x
FACIT- Fatigue, OHIP-14, PROFAD-SSI-SF [u]		x		x	x	X	x	x		x	x	x	x	x	
SF-36, IDEEL [u]		x				X		x				x		x	
TSQM		x				X		x				x		x	
CCI															

	Screening [a]	Day 1[b]	Week 2	Week 4	Week 8	Week 12	Week 18	Week 24	Week 26	Week 28	Week 32	Week 36	Week 42	Week 48/ET[c]	Follow Up visit 4 weeks after subject's last study visit [d]
Visit window	**None**	**None**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 3 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Procedures and Exams															
12-Lead ECG	x	x	x		x	x		x	x		x	x		x	x
Pulmonary function tests[v]	x					x		x						x	
CCI															
CCI															
Chest X-ray (as applicable)[z]	x														
CCI															
Drug dispensing		x		x	x	x	x	x		x	x	x	x		
Drug accountability			x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications[x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

a Screening window is 28 days prior to Day 1
b Subject will begin study drug on Day 1, following baseline assessments and randomization.
c Early Termination Visit to be performed if subject discontinues before Week 48
d Follow up visit not needed if subject's last dose of study drug was >4 weeks prior to their last study visit
e Subjects will be randomized on Day 1 based on their use of concomitant medications (y/n: csDMARD and/or oral corticosteroid) and ESSDAI hematological plus biological domains score at Day 1, (Y/N: ESSDAI ≥ 2).
f Subjects on placebo will be re-randomized 1:1:1 to either filgotinib, or GS-9876 or GS-4059

g Height is only required at Visit 1 and subjects are to remove shoes during measurement
h Exam should include glandular exam, lymph nodes, general skin, neurologic exam for peripheral neuropathy, pulmonary exam
i Amphetamines Cocaine, Methadone Opiates
j Quantiferon gold
k As applicable
l Hepatitis B surface Ag and core Ab, Hepatitis C Ab, reflex HCV RNA, HIV 1 and 2 at Screening
m Viral monitoring for HCV as applicable (see Exclusion criteria, Section 4.3)
n At screening only: anti SSA and anti SSB
At Day 1: deamidated gliadin peptide antibodies (anti-DGP IgA or IgG); Anti-endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, IgA anti-tTA (tissue transglutaminase antibodies),
At all subsequent time points: deamidated gliadin peptide antibodies (anti-DGP IgA or IgG); Anti-endomysial antibodies (EMA), RF, CCP, dsDNA, ANA, SSA, SSB, IgA anti-tTA (tissue transglutaminase antibodies),
o As outline in Appendix 6
p PK samples will be collected prior to study drug administration (pre-dose) at Weeks 4, 8, 12, 24, 36, and 48/ET visit. At Week 18, PK samples will be collected approximately 2 hours post-dose
q CCI [redacted]
r Inflammation and Pathway Biomarkers, RNA Sample, Whole Blood Sample for MoA Studies. For biomarkers which require specific material for sampling and/or processing, to be done if and when the material is available at site.
s CCI [redacted]
t Visual analog scales include patient global assessment of SJS activity and concomitant RA, concomitant SLE disease activity as applicable, assessment of ocular, oral dryness, vaginal dryness (if applicable) assessment of pain, fatigue, CCI [redacted],
u If available in the primary language of the subject. Questionnaires addressing disease, activity and fatigue may be provided when and where available.
v PFT includes Spirometry. Subjects with the following contraindications to spirometry should not perform the exam: nausea, vomiting, recent stroke, eye surgery, thoracic/abdominal surgery and recent pneumothorax
w CCI [redacted]
x All non-SjS medication used within 30 days of consent (including any changes) is to be documented in the eCRF.
All prior medication(s) used in the treatment for SjS, are to be documented in the eCRF
y For ESSDAI at baseline, lab results and PFT from screening will be used
z For subject who had no previous chest X-ray available for review by the investigator within the last 3 months

Appendix 3. Management of Clinical and Laboratory Adverse Events



See also Sections 3.4 and 7.

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

CTCAE v4.03 can be accessed from the below link:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

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

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

Appendix 5. Pregnancy Precautions, Definition of Female of Childbearing Potential, and Contraceptive Measures

For participation in this study, the use of *highly effective* contraception is required as outlined below for all subjects who are of childbearing potential.

1) Definitions

a. Definition of Female 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, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 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.

Also see I/E Criteria in Section 4.2.

b. Definition of Male Fertility

For the purposes of this study, a male-born subject is considered fertile unless permanently sterile by bilateral orchiectomy or vasectomy with documentation of sperm-free ejaculate at least 3 months after the procedure. Other types of documented permanent infertility may be allowed, after discussion with the Sponsor and approval in writing.

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 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.

GS-4059 is contraindicated in pregnancy as its teratogenicity/fetotoxicity profile is unknown. GS-4059 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy.

In this study, contraceptive steroids are not recommended as a contraceptive method, either solely or as a part of a contraceptive regimen. Subjects may remain on their hormonal contraception if they prefer to do so, but will still be required to choose from additional contraceptive methods delineated below as the efficacy of their hormonal contraception during study dosing is unknown.

Please refer to the latest versions of the filgotinib, GS-9876, and GS-4059 IBs for additional information.

b. Contraceptive Methods Permitted for Female Subjects of Childbearing Potential

The inclusion of female subjects of childbearing potential requires the use of *highly effective* contraceptive measures. Women must not rely on hormone-containing contraceptives as a sole form of birth control during the study, though they may continue hormonal contraception if they prefer to do so. Women must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Day 1 visit prior to first dose of study drug. Pregnancy tests will be performed as defined in Section 6.16.6.

Female subjects of childbearing potential must agree to one of the following 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
  - Ensure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 36 days after the last dose of study drug.

3) Contraception for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the last dose of study drug. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after last dose of study drug.

4) Unacceptable Methods of Birth Control

Birth control methods that are unacceptable include periodic abstinence (including calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), use of spermicides alone, and lactational amenorrhea method (LAM). The female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

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

Male subjects whose partner has become pregnant or suspects she is pregnant, either during the study or for 90 days after his last dose of study drug, are to report the information to the investigator.

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

Appendix 6. Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count WBC count Differentials (absolute and percentage), including: Leucocytes Monocytes Neutrophils Eosinophils Basophils Mean corpuscular volume (MCV) INR	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 Serum creatinine Glucose Phosphorus Magnesium Potassium Sodium Amylase Lipase <u>Lipid profile</u>: Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low-density lipoprotein [LDL]) Leptin LDL particle Homocysteine Apo A1/B	Appearance Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen Reflex to microscopic urinalysis if dipstick result is abnormal.	Urine drug screen for: Amphetamines Cocaine Methadone Opiates C-reactive protein (hsCRP) QuantiFERON- TB GOLD and other test as outlined in Schedule of assessment
Endocrine at screening only		**Serology**	**Pregnancy**
Hemoglobin A1c TSH FSH (see Appendix 5)		Hepatitis BsAg, Hepatitis B surface antibody and core Ab Hepatitis C Ab (if positive reflex HCV RNA) HIV antibodies	*In females of childbearing potential:* Serum β-hCG (at screening and if positive urine β-hCG) Urine β-hCG (all other visits) †

† During the periods where visits are every 6-8 weeks, women should continue to have monthly home pregnancy tests every 4 weeks; the site will contact the subject to obtain the results of the home testing.

Appendix 7. American European Consensus Group (AECG)

Vitali C, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-558.

I. Ocular symptoms: a positive response to at least one of the following questions:

1) Have you had daily, persistent, troublesome dry eyes for more than 3 months?

2) Do you have a recurrent sensation of sand or gravel in the eyes?

3) Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: a positive response to at least one of the following questions:

4) Have you had a daily feeling of dry mouth for more than 3 months?

5) Have you had recurrently or persistently swollen salivary glands as an adult?

6) Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs—that is, objective evidence of ocular involvement defined as a positive result for at least one of the following two tests:

1) Schirmer's I test, performed without anaesthesia (≤ 5 mm in 5 minutes)

2) Rose bengal score or other ocular dye score (≥ 4 according to van Bijsterveld's scoring system)

IV. Histopathology: In minor salivary glands (obtained through normal-appearing mucosa) focal lymphocytic sialoadenitis, evaluated by an expert histopathologist, with a focus score ≥1, defined as a number of lymphocytic foci (which are adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm2 of glandular tissue18

V. Salivary gland involvement: objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1) Unstimulated whole salivary flow (≤ 1.5 ml in 15 minutes)

2) Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary or destructive pattern), without evidence of obstruction in the major ducts19

3) Salivary scintigraphy showing delayed uptake, reduced concentration and/or delayed excretion of tracer20

VI. Autoantibodies: presence in the serum of the following autoantibodies:

1) 1. Antibodies to Ro(SSA) or La(SSB) antigens, or both

For primary SjS:

In patients without any potentially associated disease, primary SjS may be defined as follows:

a) The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive

b) The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, VI)

c) The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in clinical-epidemiological survey

For secondary SjS:

In patients with a potentially associated disease (for instance, another well-defined connective tissue disease), the presence of item I or item II plus any 2 from among items III, IV, and V may be considered as indicative of secondary SjS.

Exclusion criteria:

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency disease (AIDS)
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug).

Appendix 8. EULAR Sjogren's Syndrome Disease Activity Index (ESSDAI)

Seror R, Bowman SJ, Brito-Zeron P,et al. EULAR Sjögren's syndrome disease activity index (ESSDAI): a user guide. RMD Open 2015;1:e000022. doi: 10.1136/rmdopen-2014-000022

Domain	Activity Level	Description
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No = 0	Absence of the following symptoms
	Low = 3	Mild or intermittent fever (37.5°–38.5°C)/night sweats and/or involuntary weight loss of 5 to 10% of body weight
	Moderate = 6	Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy and lymphoma *Exclusion of infection*	No = 0	Absence of the following features
	Low = 4	Lymphadenopathy ≥ 1 cm in any nodal region or ≥ 2 cm in inguinal region
	Moderate = 8	Lymphadenopathy ≥ 2 cm in any nodal region or ≥ 3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 12	Current malignant B-cell proliferative disorder
Glandular *Exclusion of stone or infection*	No = 0	Absence of glandular swelling
	Low = 2	Small glandular swelling with enlarged parotid (≤ 3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate = 4	Major glandular swelling with enlarged parotid (> 3 cm), or important submandibular or lachrymal swelling
Articular *Exclusion of osteoarthritis*	No = 0	Absence of currently active articular involvement
	Low = 2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 4	1 to 5 (of 28 total count) synovitis
	High = 6	≥ 6 (of 28 total count) synovitis
Cutaneous *Rate as "No activity" stable long- lasting features related to damage*	No = 0	Absence of currently active cutaneous involvement
	Low = 3	Erythema multiforma
	Moderate = 6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary *Rate as "No activity" stable long- lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc.)*	No = 0	Absence of currently active pulmonary involvement
	Low = 5	Persistent cough **due to** bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: No breathlessness and normal lung function test.
	Moderate = 10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DLco ≥ 40% or 80% >FVC≥60%
	High = 15	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with

		abnormal lung function tests: DLco < 40% or FVC< 60%
FVC, forced vital capacity: HRCT high- resolution CT; NYHA New York Heart Association.		
Renal *Rate as "No activity" stable long- lasting features related to damage, and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first*	No = 0	Absence of currently active renal involvement with proteinuria< 0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 5	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min)
	Moderate = 10	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 15	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement
GFR, glomerular filtration rate.		
Muscular *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N ≤ CK ≤ 2N)
	Moderate = 12	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N < CK ≤ 4N),
	High = 18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤ 3/5) or elevated creatine kinase (>4N)
*We decided to add this item not included in the initial version since the value of this examination for the diagnosis of myositis was not clear until recently. EMG electromyogram.		
PNS *Rate as "No activity" stable long -lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia **Proven small fibre neuropathy*
	Moderate = 10	Moderately active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 15	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia

*We decided to add this item not included in the initial version since the link between this entity and SS was not clear until recently. CIDP, chronic inflammatory demyelinating polyneuropathy; NCS nerve conduction study.		
CNS *Rate as "No activity" stable long- lasting features related to damage or CNS involvement not related to the disease*	No = 0	Absence of currently active CNS involvement
	Moderate = 10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.
Haematological *For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of auto-immune cytopenia
	Low = 2	Cytopenia of auto-immune origin with neutropenia (1000 < neutrophils < 1500/mm3), and/or anaemia (10 < haemoglobin < 12 g/dL), and/or thrombocytopenia (100,000 < platelets < 150,000/mm3) Or lymphopenia (500 < lymphocytes < 1000/mm3)
	Moderate = 4	Cytopenia of auto-immune origin with neutropenia (500 ≤ neutrophils ≤ 1000/mm3), and/or anaemia (8 ≤ haemoglobin ≤ 10 g/dL), and/or thrombocytopenia (50,000 ≤ platelets ≤ 100,000/mm3) Or lymphopenia (≤500/mm3)
	High = 6	Cytopenia of auto-immune origin with neutropenia (neutrophils < 500/mm3), and/or or anaemia (haemoglobin < 8 g/dL) and/or thrombocytopenia (platelets <50,000/mm3)
Biological	No = 0	Absence of any of the following biological feature
	Low = 1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level > 20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

CIDP= chronic inflammatory demyelinating polyneuropathy; CK= creatine kinase; CNS= central nervous system; DLCO= diffusing CO capacity; EMG= electromyogram; FVC= forced vital capacity; GFR= glomerular filtration rate; Hb= hemoglobin; HRCT= high-resolution computed tomography; IgG= immunoglobulin G; NCS= nerve conduction studies; NHYA= New York heart association classification; Plt= platelet; PNS=peripheral nervous system