CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Study to Evaluate OATP Transporter-Mediated Drug-Drug Interactions Between Filgotinib and Statins as Probe Drugs in Healthy Participants
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	115510
EudraCT Number:	Not Applicable
Clinical Trials.gov Identifier:	Not Available
Indication:	Rheumatoid Arthritis
Protocol ID:	GS-US-417-5937
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 25 Septemeber 2020

This study will be conducted under United States Food and Drug Administration investigational new drug (IND) regulations (21 Code of Federal Regulations Part 312).

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.

333 Lakeside Drive
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USA

Study Title:	A Phase 1 Study to Evaluate OATP Transporter-Mediated Drug-Drug Interactions Between Filgotinib and Statins as Probe Drugs in Healthy Participants
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	115510 Not Applicable Not Available
Study Centers Planned:	Single Phase 1 center in the United States (US)
Objectives:	The primary objective of this study is as follows: • To evaluate the effect of filgotinib on a mixed organic anion transporting polypeptide/cytochrome P450 3A (OATP/CYP3A), OATP/breast cancer resistance protein (BCRP), and OATP substrates using phenotypic probes The secondary objective of this study is as follows: • To evaluate the safety and tolerability of multiple filgotinib doses administered alone or in combination with probe drugs
Study Design:	Phase 1, randomized, two-way cross-over, open-label, single and multiple dose, single center study
Number of Participants Planned:	30 participants (for 26 evaluable)
Target Population:	Healthy nonpregnant, nonlactating female and surgically sterile male participants, aged 18-55, inclusive
Duration of Dosing:	13 days
Study Duration:	Up to 27 days (not including screening window) for Sequence AB Up to 30 days (not including screening window) for Sequence BA

Diagnosis and Main Eligibility Criteria:

Eligible participants will be surgically sterile male and nonpregnant, nonlactating female participants, with body mass index (BMI) of ≥ 19 and ≤ 30 kg/m^2, normal 12-lead electrocardiogram (ECG), normal renal function, and no significant medical history. Participants will also be in good general health as determined by the investigator at the screening evaluation performed no more than 28 days prior to the scheduled first dose.

Study Procedures/ Frequency:

Following completion of screening and admission assessments (Day 1), eligible participants will be randomized the evening of Day 1 to receive 1 of 2 treatment sequences starting on Day 1:

The study treatments are as follows:

OATP/CYP3A substrate: Atorvastatin (ATV) 40 mg

OATP substrate: Pravastatin (PRA) 40 mg

OATP/BCRP substrate: Rosuvastatin (ROS) 10 mg

Pravastatin/Rosuvastatin (PRA/ROS) will be coadministered as a probe cocktail

Treatment A: Single dose of ATV 40 mg, followed by a washout period of one day or a single dose of the PRA 40 mg/ROS 10 mg cocktail

Treatment B: Filgotinib 200 mg administered once daily for 11 days, with a single dose of ATV 40 mg administered on the sixth day followed by a single dose of PRA 40 mg/ROS 10 mg cocktail administered on the eighth day

Sequence	**Days**								
AB	**Period 1**				**Period 2**				
	1	**2**	**3**	**4-6**	**7-11**	**12**	**13**	**14**	**15-17**
	ATV	WO	PRA + ROS	WO	FIL	FIL + ATV	FIL	FIL + PRA + ROS	FIL
BA	**Period 1**						**Period 2**		
	1-5	**6**	**7**	**8**	**9-11**	**12-17**	**18**	**19**	**20**
	FIL	FIL + ATV	FIL	FIL + PRA + ROS	FIL	WO	ATV	WO	PRA + ROS

FIL filgotinib; ATV atorvastatin; PRA pravastatin; ROS rosuvastatin; WO washout

Study Visits and Confinement

Following screening and admission assessments, eligible participants will be confined to the study center beginning Day 1 until the completion of assessments on Day 17 (Sequence AB) or Day 23 (Sequence BA). All participants will be contacted by telephone 7 (± 2) days after last dose for follow up (ie, on Day 24 [± 2] for Sequence AB or Day 27 [± 2] for Sequence BA).

Study Drug Administration

All study treatments will be administered at approximately the same time each day with 240 mL of water following an overnight fast (no food or drinks except water) for at least 10 hours. On non-intensive Pharmacokinetic (PK) days, participants will continue to fast for 2 hours after dosing postdose relative to study drug dosing.

On the days of intensive PK sampling, study treatments will be administered in the morning following an overnight fast (no food or drinks except water for at least 10 hours). Participants will continue to fast until after collection of the 4-hour PK sample, relative to study drug dosing. Additionally, participants will be restricted from water consumption 1 hour before and until 2 hours after dosing, except for the 240 mL given with the study treatment. After collection of the 4-hour PK sample, participants will be provided with a standardized meal.

Pharmacokinetic Assessments

Intensive plasma PK sampling will occur relative to dosing of study drug at the following time points for each study day as specified below:

Sequence AB:

- Days 1 and 12: 0 (pre-dose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 3 and 14: 0 (pre-dose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

Sequence BA:

- Days 6 and 18: 0 (pre-dose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 8 and 20: 0 (pre-dose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

Plasma concentrations of ATV, PRA, and ROS will be determined and PK evaluated. Plasma concentrations of filgotinib and its metabolite (GS-829845) may be analyzed. Plasma concentrations of metabolites of probe drugs or filgotinib may be analyzed, if applicable.

Safety Assessments

Assessment of adverse events (AEs) and concomitant medications will continue throughout the study. All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in protocol Appendix 4.

The schedules of assessments are as follows:

Sequence AB

Complete physical exam: screening, admission (Day 1), Day 9, 17, and at the early termination (ET) visit, if applicable.

Symptom-driven physical exam: Daily during confinement as needed based on reported signs and symptoms

Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Admission (Day 1), Days 1, 3, 6, 7, 10, 12, 14, 15, 17, and at the ET visit, if applicable

Height: Screening

Weight: Screening, Admission (Day 1), Days 7, 14, 17, and at the ET visit, if applicable

12-lead ECG: Screening

Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus type 1 testing (HIV-1): Screening

Follicle Stimulating Hormone (FSH): Screening

Urine drug and alcohol assessments: Screening and Admission (Day 1)

Thyroid-stimulating hormone (TSH): Screening

Serum pregnancy test (female of childbearing potential only): Screening, Admission (Day 1), (Day 17), and at the ET visit, if applicable

Urine pregnancy test: Admission (Day 1), Day 7

Clinical laboratory tests (hematology, chemistry, creatine phosphokinase [CPK], and urinalysi): Screening, Admission (Day 1), Days 1, 3, 6, 7, 12, 13, 14, 15, 17, and at the ET visit, if applicable

Calculated Creatinine Clearance (CL_{cr}): Screening, Admission (Day 1), Days 7, 14, 17, and at the ET visit, if applicable

Sequence BA

Complete physical exam: Screening, Admission (Day 1), Days 9, 23, and at the ET visit, if applicable

Symptom-driven physical exam: Daily during confinement as needed based on reported signs and symptoms

Vital signs (blood pressure, heart rate, respiration rate, and body temperature): Screening, Admission (Day 1), Days 1, 3, 6, 7, 8, 9, 11, 18, 20, 23 and at the ET visit, if applicable

Height: Screening

Weight: Screening, Admission (Day 1), Days 7, 11, 18, 23, and at the ET visit, if applicable

12-lead ECG: Screening

Hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus type 1 testing (HIV-1): Screening

Follicle Stimulating Hormone (FSH): Screening

Urine drug and alcohol assessments: Screening and Admission (Day 1)

Thyroid-stimulating hormone (TSH): Screening

Serum pregnancy test (female of childbearing potential only): Screening, Admission (Day 1), Days 7 and 20 and at the ET visit, if applicable

Urine pregnancy test: Admission (Day 1), Day 7

Clinical laboratory tests (hematology, chemistry, CPK, and urinalysis): Screening, Admission (Day 1), Days 1, 5, 6, 7, 8, 9, 11, 18, 20, 23 and at the ET visit, if applicable

Calculated Creatinine Clearance (CL_{cr}): Screening, Admission (Day 1), Days 7, 11, 18, and 23, and at the ET visit, if applicable

All Sequences

Coronavirus Disease 2019 (COVID-19) Real-Time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) Test: RT-PCR testing will be conducted and reviewed per site specific policy at Screening, Admission, and as needed during the study. Alternatively, a comparable test may be used after consultation with the Sponsor.

	Genomic Sample Collection A single blood sample for genomic testing and genotyping to identify polymorphisms of drug transporters (eg, OATP1B1) will be obtained for all participants and may be analyzed, as applicable. This sample should be collected on Day 1, but may be collected at any time during the study, if necessary.
Test Product, Dose, and Mode of Administration:	**Treatment B:** Filgotinib 200 mg administered once daily with a single dose of ATV 40 mg or a single dose of PRA 40 mg/ROS 10 mg cocktail. All agents should be administered in the morning under fasted conditions.
Reference Therapy, Dose, and Mode of Administration:	**Treatment A:** Single dose of ATV 40 mg or a single dose of the PRA 40 mg/ROS 10 mg cocktail administered in the morning under fasted conditions.
Criteria for Evaluation:	
Safety:	Safety will be assessed during the study through the documentation of AEs, and by clinical laboratory tests, physical examinations, vital signs, and 12-lead safety ECGs at various time points during the study.
Efficacy:	Not applicable
Pharmacokinetics:	The following plasma PK parameters will be calculated for ATV, PRA, and ROS, as applicable: $AUC_{last,}$ AUC_{inf}, $\%AUC_{exp}$, C_{max}, C_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/F, λz, and V_z/F. PK parameters for other analytes may be determined.
Statistical Methods:	**Pharmacokinetics**: Plasma concentrations and PK parameters will be listed and summarized using descriptive statistics by treatment. An analysis of variance (ANOVA) using a mixed-effects model with treatment, and sequence as fixed effects and participant as a random effect will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for each analyte. Two-sided 90% CIs will be calculated for the ratios of geometric least-squares means (GLSMs) of primary PK parameters between test (Treatment B) versus reference (Treatment A) treatments. Lack of PK interaction between the test and reference treatments will be concluded if the 90% CIs for the GLSM ratios are contained within the 0.70 and 1.43 range for ATV, PRA, and ROS AUC and C_{max}. Additional analyses may be performed if useful and appropriate.

Safety:

The AE data will be listed by participant. Treatment-emergent AEs, serious adverse events (SAEs), and AEs leading to permanent study drug discontinuation will be summarized by treatment, system organ class, and preferred term using the current version of the Medical Dictionary for Regulatory Activities (MedDRA).

Listings of individual participant laboratory results will be provided. Laboratory results and change from predose values for selected lab tests will be summarized by treatment sequence at scheduled visits. The incidence of treatment-emergent laboratory abnormalities will be summarized by treatment.

Vital signs and ECG data will be summarized by treatment/treatment sequence.

Sample Size:

With 26 evaluable participants the estimated two-sided 90% CI of the GLSM ratio of test versus reference treatments, with regards to AUC_{inf}, $AUC_{last,}$ and C_{max}, will be within [70%, 143%] with ≥ 85% probability, if the true GLSM ratio is 1.0. This is assuming a standard deviation (SD) of differences of no more than 0.569 on a natural logarithm scale, supported by PK data from Study GS-US-402-2102. With 4 participants for overage, a total sample size of 30 participants will be required.

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

$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
AE	adverse event
AE	adverse events
eCRF	electronic case report form
ALT	alanine aminotransferase
ANOVA	analysis of variance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
ATV	atorvastatin
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
BCRP	breast cancer resistance protein
BMI	body mass index
CD	Crohn's Disease
CI	confidence interval
CK	creatine kinase
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
COVID-19 RT-PCR	a real-time reverse transcription polymerase chain reaction (rTT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2
CPK	creatine phosphokinase
CTCAE	Common Terminology Criteria for Adverse Events
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
Gilead	Gilead Sciences
GLPS	Global Patient Safety
GLSM	geometric least-squares mean

HBV	hepatitis B virus
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
IB	investigator's brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IC50	half maximal inhibitory concentration
IND	investigational new drug
IRB	institutional review board
JAK	Janus kinase
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration of drug versus time curve of the drug
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
Macrogol/PEG 3350	based oral osmotic laxative promotes the retention of water in the bowel
MedDRA	Medical Dictionary for Regulatory Activities
OATP	organic anion transporting polypeptide
OATP/CYP3A	organic anion transporting polypeptide/cytochrome P450 3A
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PRA	Pravastatin
PRA/ROS	Pravastatin/Rosuvastatin
PsA	psoriatic arthritis
PT	preferred term
QT syndrome	a disorder of the heart's electrocial activity
RA	rheumatoid arthritis
ROS	Rosuvastatin
SAE	serious adverse event
SD	standard deviation
SDV	source data verification
SOC	system organ class
SOP	standard operating procedure
SSRs	Special situation reports
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
TEAE	treatment-emergent adverse event

TSH	thyroid-stimulating hormone
TYKs	tyrosine kinases
UC	ulcerative colitis
US	United States
V_z/F	apparent volume of distribution of the drug

1. INTRODUCTION

1.1. Background

Over the last decade changes in rheumatoid arthritis (RA) treatment strategies, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for patients with RA. Despite these developments, therapeutic challenges remain. The current conventional and biological disease-modifying anti-rheumatic drugs (DMARDs) may be ineffective or produce only partial responses in some patients and are associated with significant safety and tolerability concerns. There is an unmet medical need for simple, orally administered therapies with novel mechanisms of action that can effectively improve the disease course while being safe and well tolerated.

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors to the nucleus of cells. JAK/signal transducer and activator of transcription (STAT) signaling pathways are evolutionarily conserved and ubiquitous in humans and animals and are activated by a variety of cytokines, growth factors, and other chemical messengers.

Filgotinib is a potent JAK inhibitor that is highly selective for JAK1. The main metabolite of filgotinib, GS-829845, is pharmacologically active and is also a selective inhibitor of JAK1. It is expected that targeted inhibition of JAK1 will retain the clinical efficacy, while improving upon the safety profile of the less selective JAK family inhibitors. To date, JAK inhibitors approved for the treatment of RA include tofacitinib, baricitinib, and upadacitinib. Filgotinib is currently in development for the treatment of multiple inflammatory conditions including RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC), Crohn's disease (CD), and uveitis.

1.1.1. Filgotinib General Information

Filgotinib (GS-6034, formerly GLPG0634) is an orally administered potent and selective inhibitor of JAK1. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine IL-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which co-interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA, UC, and CD. The compound has shown good preliminary efficacy in participants with PsA {Mease 2018}, AS {van der Heijde 2018} and CD in Phase 2 studies (filgotinib Investigator's Brochure [IB] Edition 15, dated 03 September 2020). In Phase 3 RA studies, filgotinib was generally well tolerated for the duration of the studies (24 weeks in GS-US-417-0302 and 52 weeks in GS-US-417-0301 and GS-US-417-0303) (filgotinib IB). Filgotinib is currently under assessment in ongoing Phase 3 PsA, UC, CD studies (clinicaltrials.gov). Additionally, filgotinib is currently under review by regulatory agencies for the treatment of adults who are living with moderate-to-severe RA.

For further information on filgotinib, refer to the IB, including information on the following:

- Nonclinical pharmacokinetic (PK) and in vitro metabolism
- Nonclinical pharmacology and toxicology
- Clinical experience

1.1.2. Preclinical Pharmacology, Pharmacokinetics, and Toxicology

For detailed information on all supporting preclinical data for filgotinib, please refer to the IB.

1.1.3. Additional Clinical Studies of Filgotinib

An overview of clinical studies conducted with filgotinib is available in the IB.

As of 30 June 2020, 41 Phase 1, 2, and 3 clinical studies have been conducted/are ongoing in which 394 healthy volunteers or special populations (15 subjects with renal impairment and 10 subjects with hepatic impairment), 4126 subjects with RA, an estimated 1121 subjects with CD, an estimated 1334 subjects with UC, 94 subjects with AS, an estimated 178 subjects with PsA, and an estimated 111 subjects with other inflammatory diseases have been dosed with filgotinib. Subjects in long-term extension (LTE) studies (Studies GLPG0634-CL-205, GS-US-417-0304, GS-US-419-3896, and GLPG0634-CL-225) were not included in subject numbers in order to eliminate double-counting. Information About Atorvastatin, Pravastatin, and Rosuvastatin

1.1.4. Atorvastatin

Atorvastatin (ATV) is a synthetic lipid-lowering agent that works via inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. Atorvastatin 40 mg is representative of the middle of the recommended ATV dose range used in clinical practice (10 mg to 80 mg). Drug interactions resulting in significant changes in ATV exposure generally involve inhibition of cytochrome P450 (CYP) 3A4 (eg, cyclosporine) (Elsby et al 2012), and filgotinib has been show to not inhibit CYP34A4 in vivo GLPG0634-CL-103; accordingly, large increases in ATV exposure are not expected when administered with filgotinib, which does not inhibit CYP enzymes.

Atorvastatin, as well as some of its metabolites, are pharmacologically active in humans. The liver is the primary site of action and the principal site of cholesterol synthesis and low-density lipoprotein (LDL) clearance. Atorvastatin has 14% bioavailability via oral administration and is rapidly absorbed after oral administration in the fasted state; maximum plasma concentrations occur within 1 to 2 hours. Food slows the rate of absorption. Hepatic CYP3A4 is the major metabolic pathway. Elimination is mostly through the biliary route, with 1-2% also being excreted renally. Mean plasma elimination half-life of ATV in humans is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to

the contribution of active metabolites. Atorvastatin 10 to 80 mg once daily is the recommended dose range used in clinical practice to treat hyperlipidemia or to prevent cardiovascular disease.

Further information regarding ATV is available in the prescribing information.

1.1.5. Pravastatin

Pravastatin (PRA) is a HMG-CoA reductase inhibitor used in patients with elevated cholesterol and with a risk of cardiovascular disease. In this study, PRA 40 mg (1 × 40 mg tablet), will be administered as a single dose to healthy participants to assess organic anion transporting polypeptide (OATP) activity in the presence and absence of filgotinib. The sensitivity of PRA as an in vivo probe for assessing OATP activity at this dose has been previously established {Giacomini 2010}.

After oral administration, peak plasma PRA concentrations were observed 1 to 1.5 hours postdose. Based on urinary recovery of total radiolabeled drug, the average oral absorption of PRA is 34% and absolute bioavailability is 17%. Food in the gastrointestinal tract reduces systemic bioavailability of PRA. Pravastatin is not extensively protein bound (50%). The major biotransformation pathways of PRA are 1) isomerization to 6-epi PRA and the 3α-hydroxyisomer of PRA and 2) enzymatic ring hydroxylation. Approximately 20% of a radiolabeled oral dose is excreted in urine and 70% in the feces. After intravenous administration of radiolabeled PRA to healthy participants, approximately 47% of total body clearance was via renal excretion and 53% by non-renal routes (eg, biliary excretion and biotransformation). Following single dose oral administration of 14C-PRA, the radioactive elimination $t_{1/2}$ for PRA is 1.8 hours in humans. Pravastatin is indicated for hyperlipidemia and for cardiovascular disease prevention, the recommended starting dose is 40 mg once daily, and to use 80 mg dose only for patients not reaching LDL-Cholesterole goal with 40 mg.

Further information regarding PRA is available in the prescribing information.

1.1.6. Rosuvastatin

Rosuvastatin (ROS), is a HMG-CoA reductase inhibitor used in patients with elevated cholesterol and with a risk of cardiovascular disease. In this study, ROS 10 mg (1 × 10 mg tablet) will be administered as a single dose to healthy participants to collectively assess OATP1B1/1B3 and breast cancer resistance protein (BCRP) activity in the presence and absence of filgotinib {Chu 2018, Giacomini 2010}.

The relative contribution of OATP and BCRP in determining in vivo ROS disposition is not known. However, emerging data on the significance of SLCO1B1 polymorphisms and associated statin-induced myopathy provides compelling evidence on the importance of OATP in ROS PK {Elsby 2012, Meyer zu Schwabedissen 2009, Neuvonen 2010, Pasanen 2007}. Collectively, use of both PRA and ROS as probes in this study will allow for a better understanding and/or discrimination of the effects of filgotinib on OATP and BCRP.

Rosuvastatin can be taken with or without food, any time of the day, over a dose range of 5 to 40 mg once daily. Rosuvastatin peak plasma concentrations are reached in 3 to 5 hours after oral dosing, and administration with food does not affect the AUC of ROS. Rosuvastatin is not extensively metabolized and the major metabolite, N-desmethyl rosuvastatin, is formed principally by CYP2C9; this metabolite displays one-sixth to one-half of the HMG-CoA-reductase inhibitory activity of the parent. Overall, greater than 90% of active plasma HMG-CoA-reductase inhibitory activity is accounted for by the parent compound. The elimination half-life of ROS is approximately 19 hours. Rosuvastatin clearance is not dependent on metabolism by CYP3A4 to a clinically significant extent.

Further information regarding ROS is available in the package insert.

1.2. Rationale for This Study

The objective of this study is to evaluate filgotinib as a perpetrator of drug-drug interactions (DDIs) with OATPs. Filgotinib and its metabolite, GS-829845, are determined to be in vitro inhibitors of OATP1B1 and OATP1B3. Filgotinib inhibits OATP1B1 and OATP1B3 at a half-maximal inhibitory concentration (IC_{50}) of 98 µM and > 285 µM, respectively. GS-829845 inhibits OATP1B1 and OATP1B3 at an IC_{50} of 260 µM and > 473 µM, respectively (AD-417-2024). Based on in vitro data, filgotinib and GS-829845 are unlikely to have in vivo DDIs mediated by OATP1B1 and OATP1B3. Data generated from this study will be used to further support the use of filgotinib with OATP substrates such as statins. This study will evaluate the potential effect of filgotinib and GS-829845 on OATP1B1 and OATP1B3 transporters using probe substrates of ATV (probe for CYP3A and OATP), ROS (probe for BCRP and OATP), and PRA (probe for OATP). The probe drugs selected for this study are based on the recommendations from the International Transporter Consortium on “Membrane Transporters in Drug Development” and “Transporters in Drug Development: Advancing on the Critical Path”{Giacomini 2010, Huang 2010}.

The design of this study is based on the results of a comprehensive panel of nonclinical studies, and in accordance with the Food and Drug Administration (FDA) guidance entitled “Drug Interaction Studies Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” (Jan 2020) and the European Medicines Agency (EMA) guidance entitled “Guideline on the Investigation of Drug Interactions” (June 2012).

Data from this DDI study will inform the suitability of filgotinib co-administration with concomitant medications and the need for dose adjustment, as applicable.

Healthy participants will be selected for this study to remove any potential confounding effects of background medications and other therapies, and to avoid the need to make multiple, short-term changes in treatment regimens in patients for the purpose of examining the PK of the different agents and their combinations. For safety and adherence monitoring, all participants will be confined within a Phase 1 unit for the duration of the study.

1.3. Rationale for the Dose Selection

Filgotinib will be administered at 200 mg once daily for 11 days. The 200 mg once daily dose of filgotinib is the highest therapeutic dose under evaluation for multiple inflammatory diseases including RA, UC, PsA, and AS. This dose has been selected based on efficacy, tolerability, and safety data derived across Phase 1, Phase 2, and Phase 3 clinical studies. In Phase 2 and Phase 3 studies in participants with RA, treatment with filgotinib was well tolerated and achieved a high level of efficacy (ACR20/50/70) at a 200 mg daily dose. Exposure-efficacy analysis based on data from all Phase 2 and Phase 3 studies indicated an increase in efficacy (ACR50/70) with increasing filgotinib exposure, with a plateau in response corresponding to filgotinib exposures at the 200 mg daily dose. No trend in adverse events (AEs) or laboratory abnormalities have been observed in exposure-safety analysis of filgotinib up to 300 mg administered as once daily doses. Therefore, the 200 mg dose of filgotinib is selected as the clinically relevant dose for evaluation. Multiple doses of filgotinib at 200 mg once daily is selected to achieve steady state exposure of filgotinib and its metabolite, GS-829845, in order to assess the potential impact of the highest clinically relevant exposure of filgotinib (as an inhibitor) on the PK of the OATP transporter probes (ATV, ROS, and PRA).

Atorvastatin 40 mg (1 × 40 mg tablet) will be administered as a single dose to healthy participants in a crossover design to assess OATP activity in the presence and absence of filgotinib. Atorvastatin 40 mg is representative of the middle of the recommended ATV dose range used in clinical practice (10 mg to 80 mg). Drug interactions resulting in significant changes in ATV exposure generally involve inhibition of CYP3A4 (eg, cyclosporine) {Elsby 2012}. Additionally, filgotinib is not expected to be a strong inhibitor of OATPs. Accordingly, large increases in ATV exposure are not expected when administered with filgotinib, which does not inhibit CYP enzymes.

Pravastatin 40 mg (1 × 40 mg tablet) will be administered as a single dose to healthy participants in a crossover design to assess OATP activity in the presence and absence of filgotinib. Pravastatin 40 mg is representative of the middle of the PRA dose range used in clinical practice (10 mg to 80 mg). The sensitivity of PRA as an in vivo probe for assessing OATP activity at this dose has been previously established {Giacomini 2010}.

Rosuvastatin 10 mg (1 × 10 mg tablet) will be administered as a single dose to healthy participants in a crossover design to collectively assess OATP1B1/1B3 and BCRP activity in the presence and absence of filgotinib {Chu 2018, Giacomini 2010}. Rosuvastatin 10 mg is representative of the recommended dose range used in clinical practice (5 mg to 40 mg). Collectively, use of both PRA and ROS as probes in this study will allow for a better understanding and/or discrimination of the effects of filgotinib and its primary metabolite on OATP and BCRP.

Rosuvastatin and PRA will be administered as a cocktail of drug transport probe substrates. The use of this cocktail as a measure of OATP and BCRP activity has been confirmed in a previous study (GS-US-334-2130), in which these probe drugs were administered simultaneously with no effect on their respective exposure as compared with administration alone and thus are sensitive to measure changes in OATP and BCRP activity when administered as a cocktail.

1.4. Risk/Benefit Assessment for the Study

Potential risks of a participant's involvement in this study include AEs related to short-term use of filgotinib, ATV, PRA and/or ROS, in addition to the general risks associated with frequent laboratory blood draws.

An infectious disease pandemic may pose additional risks to study drug availability, study visit schedule, and adherence to protocol-specified safety monitoring or laboratory assessments.

There is no anticipated benefit to healthy participants. However, data from this study will support the development of filgotinib for the treatment of chronic inflammatory diseases (eg, RA, PsA, IBD). All participants will be monitored for AEs and laboratory parameters, and eligibility criteria will ensure a healthy participant population. Individual participant and study stopping criteria are outlined as an added measure of safety. Finally, safety data will be evaluated on an ongoing basis. Taken together with the totality of the nonclinical toxicology and clinical safety data outlined in the filgotinib IB, the risks to healthy participants are considered acceptable.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the effect of filgotinib on a mixed OATP/CYP3A, OATP/BCRP, and OATP substrates using phenotypic probes

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of multiple filgotinib doses administered alone or in combination with probe drugs

3. STUDY DESIGN

3.1. Study Design

This protocol describes a Phase 1, randomized, two-way crossover, open-label, single and multiple dose, single center study to evaluate the effect of filgotinib on a mixed OATP/CYP3A, OATP/BCRP, and OATP substrates using phenotypic probes in healthy normal participants. Up to 30 participants will be enrolled.

Healthy surgically sterile male and nonpregnant, nonlactating female participants aged 18 through 55 years will be enrolled into the study.

An overview of the study design is described below and shown in Figure 3-1 and Figure 3-2.

Treatment A: Single dose of ATV 40 mg, followed by a washout period of 1 day and a single dose of the PRA 40 mg/ROS 10 mg cocktail

Treatment B: Filgotinib 200 mg administered once daily for 11 days, with a single dose of ATV 40 mg administered on the sixth day or a single dose of PRA 40 mg/ROS 10 mg cocktail administered on the eighth day

Figure 3-1. Study Schema – Sequence AB

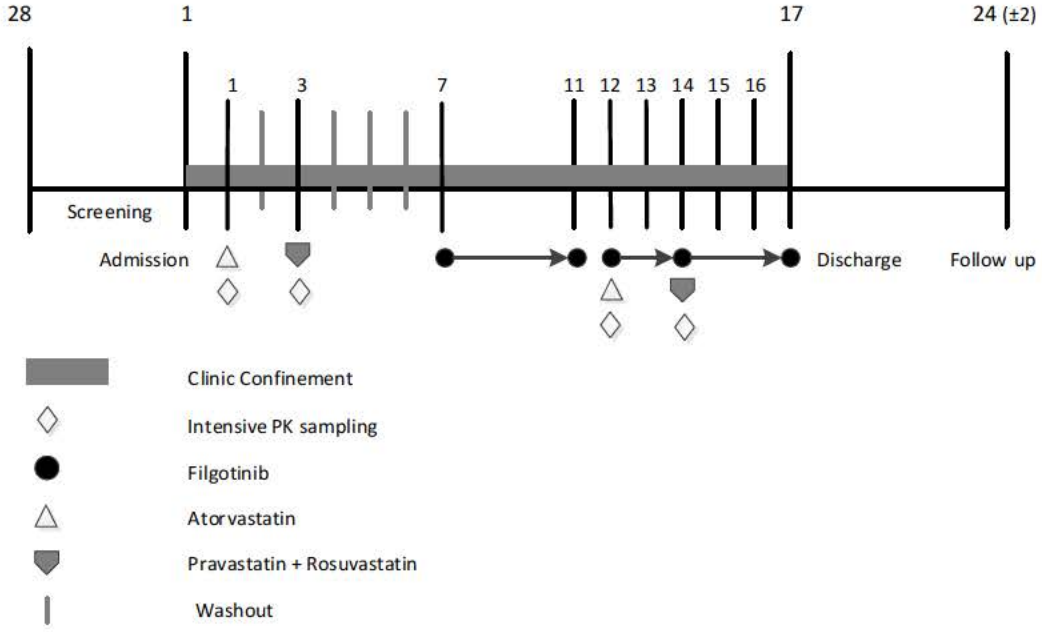
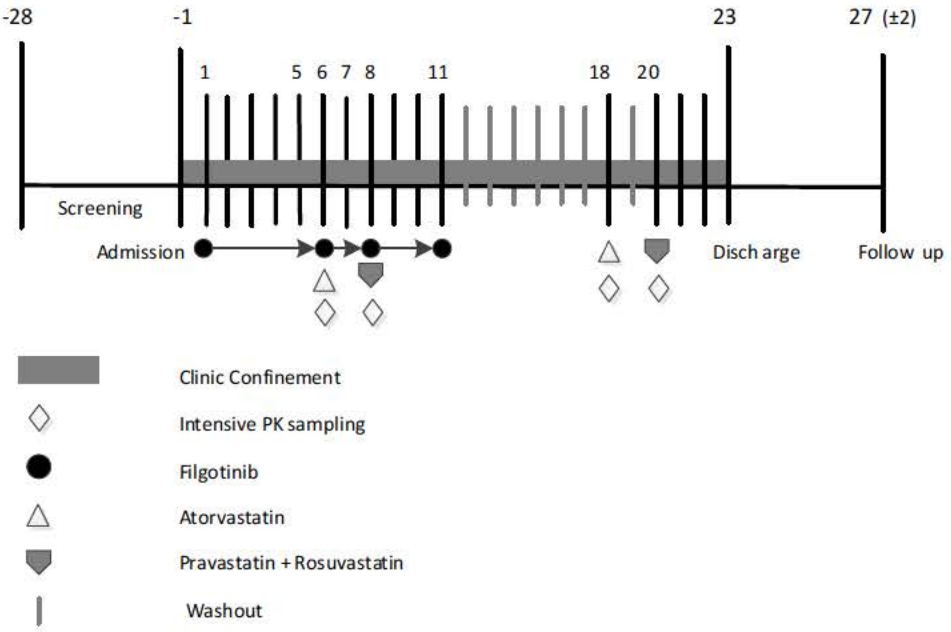


Figure 3-2. Study Schema – Sequence BA



3.2. Study Drug Administration

Please refer to Section 5.3 for additional information for study drug dosage and administration.

3.3. Duration of Dosing

Participants will dose for 13 days, all of which occur during the clinic confinement.

3.4. Clinic Confinement

Following screening and admission procedures, eligible participants will be confined to the study center beginning at admission on Day 1 until the completion of assessments on Day 17 (Sequence AB) or Day 23 (Sequence BA). All participants will be contacted by telephone 7 (± 2) days after last dose for follow up (ie, on Day 24 [± 2] for Sequence AB or on Day 27 [± 2] for Sequence BA).

3.5. Pharmacokinetic Assessments

Pharmacokinetic assessments will occur on assigned study days as outlined in Table 6-1 through Table 6-2 and in Section 6.5.

3.5.1. Plasma Pharmacokinetic Collection

Plasma concentrations of ATV, PRA, and ROS will be determined and PK parameters estimated as outlined in Section 6.5.1. Plasma concentrations of filgotinib and its metabolite (GS-829845) may be analyzed. Plasma concentrations of metabolites of probe drugs or filgotinib may be analyzed, if applicable.

3.5.2. Genomic Sample Collection

A mandatory blood sample will be collected from all participants who have provided consent to participate in this study. This sample will be collected for the extraction of DNA for genomic testing and genotyping to identify polymorphisms of drug transporters (eg, OATP1B1) . This sample should be collected on Day 1, before administration of the first dose of study drug, but may be collected at any time during the study, if neccessary.

CCI [redacted]

3.6. Safety Assessments

Safety assessments will be performed through the study as outlined in Table 6-1 through Table 6-2 and in Section 6.6.

3.7. End of Study

The end of this study will be the last participant's last observation (or visit).

3.8. Discontinuation Criteria

Study treatment and/or study procedures may be discontinued in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered not to be in the participant's best interest
- Participant requests to discontinue for any reason
- Participant noncompliance
- Pregnancy during the study (refer to **Appendix 2**)
- Investigator discretion
- Discontinuation of the study at the request of Gilead, regulatory agency, or an institutional review board (IRB)

3.9. Source Data

The source data for this study will be obtained from electronic data capture (EDC), a local laboratory, and specialty laboratory (for PK and/or pharmacodynamics data) .

3.9.1. Discontinuation

3.9.1.1. Study Stopping Criteria

- If 3 or more participants in any group experience the same or similar Grade 3 treatment-emergent AE or confirmed laboratory abnormality, unless there is a clear and obvious physiologic explanation for the events (eg, blood in urine occurring in a menstruating female or creatine phosphokinase (CPK) elevation after strenuous exercise, etc.), then a review of all safety data generated in participants dosed to date will be initiated.

- If 2 or more participants in any group experience the same or similar Grade 4 treatment-emergent AE or confirmed laboratory abnormality, then a review of all safety data generated in participants dosed to date will be initiated. Dosing will be on hold until the review of all the safety data is completed. If the safety review determines that it is safe and tolerable to continue dosing, study drug administration will continue. If the safety review determines that dosing should not continue, the study will be stopped. The decision whether or not to complete the full course of study medication will be made by the sponsor, in consultation with the principal investigator, with disclosure of new information to the study participant(s).

4. PARTICIPANT POPULATION

4.1. Number of Participants and Participant Selection

Approximately 30 unique participants will be enrolled in the study, which include healthy nonpregnant, nonlactating female and surgically sterile male participants 18 through 55 years of age, inclusive

4.1.1. Participant Replacement

If necessary, replacement participants may be enrolled after discussion and approval from the sponsor if participants do not complete all intensive PK procedures or the participant is considered nonevaluable. Replacement participants will not be enrolled for participants who discontinue the study due to study drug-related AEs.

4.2. Inclusion Criteria

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

1) Have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures

2) Be aged 18 through 55 years, inclusive, at screening

3) Be a nonsmoker. The use of nicotine or nicotine-containing products must be discontinued 90 days prior to the first dose of study drug

4) Have a calculated body mass index (BMI) of ≥ 19.0 and ≤ 30.0 kg/m^2 at screening

5) Have a creatinine clearance (CL_{cr}) ≥ 90 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured at screening and upon admission:

   Male: $\dfrac{(140 - \text{Age [years]}) \times (\text{Weight [kg]})}{72 \times (\text{Serum Creatinine [mg/dL]})}$ CL_{cr} (mL/min)

   Female: $\dfrac{(140 - \text{Age [years]}) \times (\text{Weight [kg]}) \times 0.85}{72 \times (\text{Serum Creatinine [mg/dL]})}$ CL_{cr} (mL/min)

6) Female participants of childbearing potential (as defined in Appendix 2) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at clinic admission.

7) Male participants must be surgically sterile

8) Male participants and female participants of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in **Appendix 2**.

9) Screening laboratory evaluations and 12-lead electrocardiogram (ECG) evaluations must be without clinically significant abnormalities as assessed by the investigator.

10) Have liver biometric tests such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin below the upper limit of normal at screening

11) Must be willing and able to comply with all study requirements

12) Must, in the opinion of the investigator, be in good health based upon medical history and physical examination, including vital signs

13) Participants must not have donated blood within 56 days of study entry or plasma within 7 days of study entry and must refrain from blood donation from clinic admission, throughout the study period, and continuing for at least 30 days following the last dose of study drug.

4.3. Exclusion Criteria

Participants who meet *any* of the following exclusion criteria will not be enrolled in this study:

1) Positive serum pregnancy test (Female participant) (**Appendix 2**)

2) Lactating female

3) Have received any investigational drug/device within 30 days prior to study dosing (or within 5 half-lives of the drug, whichever is longer)

4) Have current alcohol or substance abuse judged by the investigator to potentially interfere with participant compliance or participant safety, or a positive drug or alcohol test at screening or admission.

5) Have a positive test result for human immunodeficiency virus type 1 (HIV-1) antibody, hepatitis B virus (HBV) surface antigen (HBsAg), or hepatitis C virus (HCV) antibody at screening

6) Have positive Coronavirus Disease 2019 (COVID-19) Real-Time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) testing on screening and admission.

7) Have poor venous access that limits phlebotomy

8) Have taken any prescription medications or over-the-counter medications, including herbal products, within 28 days prior to start of study drug dosing, with the exception of vitamins and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications

9) Have been treated with systemic steroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, other immune- or cytokine-based therapies)

10) Have a history of any of the following:

    a. Significant serious skin disease, such as but not limited to rash, food allergy, eczema, psoriasis, or urticaria

    b. Significant drug sensitivity or drug allergy (such as anaphylaxis or hepatoxicity)

    c. Known hypersensitivity to the study drugs, their metabolites, or to formulation excipients (see Section 5)

    d. Significant cardiac disease (including history of myocardial infarction based on ECG and/or clinical history, any history of ventricular tachycardia, congestive heart failure, or dilated cardiomyopathy with left ventricular ejection fraction < 40%), a family history of long QT syndrome, or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years

    e. Recurrent syncope, palpitations, or unexplained dizziness

    f. Implanted defibrillator or pacemaker

    g. Liver disease, including Gilbert syndrome

    h. Severe peptic ulcer disease, gastroesophageal reflux disease, or other gastric acid hypersecretory conditions requiring prolonged (> 6 months) medical treatment

    i. Medical or surgical treatment that permanently altered gastric absorption (eg, gastric or intestinal surgery). A history of cholecystectomy is not exclusionary

11) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with participant treatment, assessment, or compliance with the protocol. This would include renal, cardiac, hematological, hepatic, pulmonary (including chronic asthma), endocrine (including diabetes), central nervous, gastrointestinal (including an ulcer), vascular, metabolic (thyroid disorders, adrenal disease), immunodeficiency disorders, active infection, or malignancy that are clinically significant or requiring treatment.

5. STUDY DRUGS

5.1. Randomization, Blinding, and Treatment Codes Access

5.1.1. Randomization

Following screening and admission assessments, eligible participants will be confined to the study center. Once eligibility has been confirmed and following completion of the admission study procedures, eligible participants will be randomized at 1:1 ratio on the evening of Day 1 to receive 1 of 2 treatment sequences starting on Day 1.

All screening and admission (Day 1) tests and procedures must be completed and reviewed by the investigator prior to the administration of the first dose of study drug on Day 1. It is the responsibility of the investigator to ensure that the participant is eligible for the study prior to enrollment. Once a participant number has been assigned to a participant, it will not be reassigned to another participant. If necessary, replacement participants may be enrolled after discussion and approval from the sponsor.

5.1.2. Blinding

Blinding of treatment assignments or data will not be performed in this study.

5.2. Description and Handling of Filgotinib

5.2.1. Formulation

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

5.2.2. Packaging and Labeling

Filgotinib tablets, 200 mg, are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed and aluminum-faced liner.

Sufficient quantities of filgotinib tablets, 200 mg to complete the entire study will be shipped to the investigator or qualified designee from the Gilead Supply Management Team.

Study drugs to be distributed to the participating site shall be labeled to meet applicable requirements of the United States FDA.

5.2.3. Storage and Handling

Filgotinib tablets should be stored at controlled room temperature of 25 °C (77 °F); excursions are permitted between 15 °C and 30 °C (59 °F to 86 °F).

Storage conditions are specified on the label. Until dispensed to the participants, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product should not be stored in a container other than the container in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Description and Handling of Commercially Available Drugs

Commercial product of ATV, PRA, and ROS will be used for the study. Further information regarding storage and handling are available in the Prescribing Information for these commercial products.

5.4. Dosage and Administration of Study Drug

Following completion of screening and admission assessments (Day 1), eligible participants will be randomized the evening of Day 1 to receive 1 of 2 treatment sequences starting on Day 1:

OATP/CYP3A substrate: ATV 40 mg

OATP substrate: PRA 40 mg

OATP/BCRP substrate: ROS 10 mg

Pravastatin/Rosuvastatin (PRA/ROS) will be coadministered as a probe cocktail.

Treatment A: Single dose of ATV 40 mg, followed by a washout period of one day followed by a single dose of the PRA 40 mg/ROS 10 mg cocktail

Treatment B: Filgotinib 200 mg administered once daily for 11 days, with a single dose of ATV 40 mg administered on the sixth day followed by a single dose of PRA 40 mg/ROS 10 mg cocktail administered on the eighth day

Sequence	Days								
AB	Period 1				Period 2				
	1	**2**	**3**	**4-6**	**7-11**	**12**	**13**	**14**	**15-17**
	ATV	WO	PRA + ROS	WO	FIL	FIL + ATV	FIL	FIL + PRA + ROS	FIL
BA	Period 1						Period 2		
	1-5	**6**	**7**	**8**	**9-11**	**12-17**	**18**	**19**	**20**
	FIL	FIL + ATV	FIL	FIL + PRA + ROS	FIL	WO	ATV	WO	PRA + ROS

FIL filgotinib; ATV atorvastatin; PRA pravastatin; ROS rosuvastatin; WO Washout

5.5. Fasting and Meals

All study treatments will be administered orally at the study center in the morning at approximately the same time on each day with 240 mL of water following an overnight fast (no food or drink, except water, for at least 10 hours). On non-intensive PK days, participants will continue to fast for 2 hours postdose relative to study drug dosing.

On the days of intensive PK sampling (Days 1, 3, 12, and 14 for Sequence AB and Days 6, 8, 18, and 20 for Sequence BA), the study drug will be administered in the morning following an overnight fast (no food or drink, except water, for at least 10 hours). On intensive PK days, participants will be restricted from food intake until after collection of the 4-hour blood draw. Participants will continue to fast until after collection of the 4-hour PK sample, relative to study drug dosing. Additionally, participants will be restricted from water consumption 1 hour before and until 2 hours after dosing, except for the 240 mL given with the study treatment(s). After collection of the 4-hour PK sample, participants will be provided with a standardized meal.

All meals and/or snacks given to participants during their stay in the clinical study facility will be standardized for all participants and should be similar in calorie and fat content and taken at approximately the same time each day. All meals provided must be approved by the sponsor. Components of meals (eg, margarine, jelly, bread) should be given to participants in individual portions (eg, 1 tablespoon) per the approved meal schedule. The provision of meal components in bulk (eg, a jar of jelly for participants to share) should not be practiced. All meals should be given at approximately the same time each day (eg, 07:30, 12:00, 18:00).

5.6. Dispensing, Accountability, and Disposal or Return of Study Drug

The investigator (or designee, eg, study center pharmacist) will acknowledge receipt of the study drug (after reviewing the shipment's content and condition) from Gilead (or designee). The investigator will maintain an accurate inventory of all study drug(s). Each dose of the study drug(s) administered at the study center will be administered by qualified study center staff. The dose of study drug(s) administered to participants in the clinic under the supervision of staff will be accurately recorded on the Study Drug Accountability form provided by Gilead (or on equivalent documentation maintained by the study center), which indicates the date and quantity of each dosage formulation dispensed to individual participants.

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

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

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

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

5.7. Concomitant Medications and Other Protocol Restrictions

5.7.1. Concomitant Medications

The following medications are excluded while participants are participating in the study (from screening until discharge):

- Any prescription medications and over-the-counter medications, including herbal products and antacids, with the exception of vitamins, and/or acetaminophen and/or ibuprofen and/or hormonal contraceptive medications. However, the short-term use of topical hydrocortisone cream or A&D ointment to treat minor skin irritation due to ECG leads will be allowed. If a participant requires use of a disallowed medication, a request for such use must be reviewed by the sponsor and if approved, participants may continue to participate in the study.

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.

5.7.2. Other Protocol Restrictions

- Participants will be required to refrain from the consumption of food and beverages containing alcohol 72 hours prior to the first dose of study drug and during the course of the study through discharge.

- Participants will be required to refrain from the use of nicotine or nicotine-containing products 90 days prior to first dose of study drug and during the course of the study through discharge.

- Participants will be required to refrain from consumption of grapefruit juice, grapefruits, and Seville orange juice 72 hours prior to the first dose of study drug and during the course of the study through discharge.

- While confined at the study center, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methyl xanthines will be prohibited on each dosing day. At all other times, caffeine-containing beverages and foodstuffs may be served or withheld in accordance with normal study center practice. Caffeine-containing beverages and foodstuffs will not be restricted while participants are outside of the clinic.

- Participants will be encouraged to avoid strenuous or prolonged exercise, as well as saunas, steambaths, and sunbathing or other prolonged ultraviolet exposure (eg, in a tanning salon) from the screening evaluation and during the course of the study through discharge, as these activities are known to affect certain clinical laboratory test parameters (eg, creatine kinase) and will provide false indicators of a potentially treatment-related toxicity.

Upon every admission to the clinic, each participant will be questioned as to their compliance with the above protocol restrictions. If a participant is unable to comply with any of the restrictions described above, the participant's continued participation in the study will be reevaluated by the investigator in consultation with the sponsor.

6. STUDY ASSESSMENTS

The study procedures to be conducted for each participant enrolled in the study are detailed below.

Any deviation from protocol procedures should be noted in the participant's clinical chart and appropriate electronic case report forms (eCRFs). In addition, the sponsor should be promptly notified of any protocol deviations.

The study center will not initiate dosing until the following have all been met:

- The IRB has reviewed and approved the study and the informed consent document.
- All requested regulatory documents have been submitted to and approved by Gilead.
- A master services agreement and/or study agreement is executed.
- The study initiation meeting has been conducted by the Gilead (or designee).

The initiation meeting will include but is not limited to a review of the protocol, the IB, study drugs, and investigator responsibilities.

Documentation of the personally signed and dated ICF for each participant, using the study-specific, IRB approved ICF, is required before initiating the screening process.

6.1. Participant Enrollment and Treatment Assignment

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

It is the responsibility of the investigator to ensure that participants are eligible to participate in the study prior to enrollment and continue to remain eligible throughout the study.

Once the ICF has been obtained, all screening and admission tests and assessments have been assessed, and study eligibility has been confirmed, participants will be enrolled to receive study drug on Day 1.

Participants will receive the study treatments as described in Section 5.3.

Table 6-1. Schedule of Assessments (Sequence AB)

Study Procedure	Screening[a]	Admission Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Discharge Day 17[b]	Follow Up[c] Day 24 ± 2	ET[d]
Written Informed Consent	X																				
Medical History	X																				
Complete Physical Examination	X	X									X								X		X
Symptom Driven Physical Examination[e]			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X			
Height	X																				
Weight	X	X							X							X			X		X
Vital Signs[f]	X	X	X		X			X	X			X		X		X	X		X		X
HIV 1, HBV, and HCV Testing[g]	X																				
Hematology[g]	X	X	X		X			X	X					X	X	X	X		X		X
Chemistry[g]	X	X	X		X			X	X					X	X	X	X		X		X
Creatine phosphokinase (CPK)	X	X	X		X			X	X					X	X	X	X		X		X
Calculated Creatinine Clearance	X	X							X							X			X		X
Urinalysis[g]	X	X	X		X			X	X					X	X	X	X		X		X
Serum Pregnancy Test[g,h]	X	X																	X		X
Urine Pregnancy Test[h]		X							X												

Study Procedure	Screening[a]	Admission Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Discharge Day 17[b]	FollowUp[c] Day 24 ± 2	ET[d]
Follicle Stimulating Hormone (FSH)[gh]	X																				
Thyroid Stimulating Hormone (TSH)[gh]	X																				
Urine Drug and Alcohol Screen[g]	X	X																			
12 Lead ECG	X																				
COVID 19 RT PCR	X	X																			
Randomization/ Enrollment[i]		X																			
Study Drug Administration[j]			X		X				X	X	X	X	X	X	X	X	X	X	X		
Intensive Plasma PK[k]			X		X									X		X					
Genotype Testing[l]			X																		
Review Study Restrictions	X	X																	X	**X**	
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review AEs & Concomitant Medications[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE adverse event; ECG electrocardiogram; COVID 19 RT PCR a real time reverse transcription polymerase chain reaction (rTT PCR) test for the qualitative detection of nucleic acid from SARS CoV 2
eCRF electronic case report form; ET early termination; HBV hepatitis B virus; HCV hepatitis C virus; HIV 1 human immunodeficiency virus type 1 and type 2; PE physical examination; PG pharmacogenomic; PK pharmacokinetic(s

a. Prospective participant should be screened no more than 28 days prior to administration of the first dose of study drug.

b. Participants will be discharged from the clinic on Day 17 (Sequence AB) following all assessments.
c. 7 (± 2) days after the last administration of study drug, all participants will be contacted via telephone to review and document AEs and concomitant medications
d. Early termination (ET) assessments will be performed within 72 hours of prematurely discontinuing from the study.
e. Symptom driven PEs will be performed during confinement as needed, based on reported signs and symptoms.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. See Section 6.6.5 for specifics.
h. Females of childbearing potential only.
i. On Day 1, participants will be randomized the evening to receive 1 of 2 treatment sequences starting on Day 1.
j. See Section 5.4 for specifics.
k. Intensive PK sampling will occur relative to the morning dosing of study drug at the time points as outlined in Section 6.5.1.
l. Blood sample should be collected on Day 1, but may be collected at any time during the study, if necessary
m. From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.

Table 6-2. Schedule of Assessments (Sequence BA)

Study Procedure	Screening[g]	Admission Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Discharge Day 23[h]	Follow-Up[f] Day 27 ± 2	ET[l]
Written Informed Consent	X																										
Medical History	X																										
Complete Physical Examination	X	X									X														X		X
Symptom Driven Physical Examination[e]	X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X			
Height	X																										
Weight	X	X							X				X							X					X		X
Vital Signs[f]	X	X	X		X			X	X	X	X		X							X		X			X		X
HIV 1, HBV, and HCV Testing[g]	X																										
Hematology[g]	X	X	X				X	X	X	X	X		X							X		X			X		X

Study Procedure	Screening[a]	Admission Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Discharge Day 23[b]	Follow Up[c] Day 27 ± 2	ET[d]
Chemistry[g]	X	X	X				X	X	X	X	X		X							X		X			X		X
Creatine phosphokinase (CPK)	X	X	X				X	X	X	X	X		X							X		X			X		X
Calculated Creatinine Clearance	X	X							X				X							X					X		X
Urinalysis[g]	X	X	X				X	X	X	X	X		X							X		X			X		X
Urine Pregnancy Test		X							X																		
Follicle Stimulating Hormone (FSH) [g,h]	X																										
Thyroid Stimulating Hormone (TSH)[g,h]	X																										
Serum Pregnancy Testg, [h]	X	X							**X**													X					X
Urine Drug and Alcohol Screen[g]	X	X																									
12 Lead ECG	X																										
COVID 19 RT PCR	X	X																									
Randomization /Enrollment[i]		X																									
Study Drug Administration[j]			X	**X**	X	X	X	X	X	X	X	X	X							X		X					
Intensive Plasma PK[k]								X		X										X		X					
Genotype Testing[l]			X																								

Study Procedure	Screening[a]	Admission Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Discharge Day 23[b]	Follow Up[c] Day 27 ± 2	ET[d]
Review Study Restrictions	X	X																							X	X	
Clinic Confinement		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Review AEs & Concomitant Medications[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE adverse event; ECG electrocardiogram; COVID 19 RT PCR a real time reverse transcription polymerase chain reaction (rTT PCR) test for the qualitative detection of nucleic acid from SARS CoV 2
eCRF electronic case report form; ET early termination; HBV hepatitis B virus; HCV hepatitis C virus; HIV 1 human immunodeficiency virus type 1 and type 2; PE physical examination; PG pharmacogenomic; PK pharmacokinetic(s); COVID 19 RT PCR a real time reverse transcription polymerase chain reaction (rTT PCR) test for the qualitative detection of nucleic acid from SARS CoV 2

a. Prospective participants should be screened no more than 28 days prior to administration of the first dose of study drug.
b. Participants will be discharged from the clinic on Day 23 (Sequence BA) following all assessments.
c. 7 (± 2) days after the last administration of study drug, all participants will be contacted via telephone to review and document AEs and concomitant medications.
d. Early termination (ET) assessments will be performed within 72 hours of prematurely discontinuing from the study.
e. Symptom driven PEs will be performed during confinement as needed, based on reported signs and symptoms.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. See Section 6.6.5 for specifics.
h. Females of childbearing potential only.
i. On Day 1, participants will be randomized the evening to receive 1 of 2 treatment sequences starting on Day 1.
j. See Section 5.4 for specifics.
k. Intensive PK sampling will occur relative to the morning dosing of study drug at the time points as outlined in Section 6.5.1.
l. Blood samples should be collected on Day 1, but may be collected at any time during the study, if necessary
m. From the time of obtaining informed consent through the first administration of study drug, record all SAEs, as well as any nonserious AEs related to protocol mandated procedures, on the AE eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.2. Pretreatment Assessments

6.2.1. Screening Assessments

Prospective participants should be screened no more than 28 days prior to administration of the first dose of study drug. If a participant does not begin the treatment phase within this 28-day window, all screening evaluation procedures must be repeated. Screening laboratory assessments may be repeated once within 28 days prior to administration of study drug to rule out laboratory error.

A sufficient number of participants will be screened to identify planned number of participants for randomization.

Participants 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 the screening visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection the next morning.

Written informed consent must be obtained from each participant before initiation of any screening procedure. After a participant has provided informed consent, the investigator and other study personnel will determine if the participant is eligible for participation in the study. This assessment will include a review of the inclusion/exclusion criteria and completion of all screening procedures as outlined in Table 6-1 through Table 6-2 and described in the following text.

Eligible participants meeting all of the inclusion criteria and none of the exclusion criteria will be instructed on all protocol requirements, including the restrictions on concomitant medication usage and other substances as well as consumption of food or beverages containing alcohol, caffeine, or xanthine. Participants will be asked to arrive at the study center on Day 1 for admission assessments.

From the time of obtaining informed consent through the first administration of study drug, record all serious adverse events (SAEs), as well as any adverse events related to protocol-mandated procedures on the adverse events case report form (AE eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7, Adverse Events and Toxicity Management, for additional details.

6.2.2. Admission Assessments

6.2.2.1. Admission

Participants 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 the admission visit to ensure an approximate 8-hour fast prior to the fasted blood sample collection.

Participants meeting all eligibility criteria following the screening evaluation will return to the clinic for admission assessments on Day 1. The admission evaluations and/or procedures are outlined in Table 6-1 through Table 6-2.

Prior to dosing on Day 1, the results of the clinical and laboratory evaluations (as described in Table 6-1 through Table 6-2) must be reviewed by the investigator to confirm the continued eligibility of each participant to participate in the study. At the time of randomization, participants will be assigned a participant number as described in Section 5.1. Participants will remain confined to the study clinic for the duration as described in Section 6.2.2.2 and Table 6-1 through Table 6-2.

Prior to study drug administration, record any SAEs and all AEs related to protocol-mandated procedures. After drug administration, report all AEs and SAEs.

6.2.2.2. Clinic Confinement

Participants will be confined to the study clinic starting at on Day 1 until completion of assessments on Day 17 (Sequence AB) or Day 23 (Sequence BA).

6.3. Check-in Assessments

Following completion of screening and Day 1 assessments, eligible participants will be randomized the evening of Day 1 to receive 1 of 2 treatment sequences starting on Day 1 in Section 5.4.

6.4. Treatment Assessments

Study treatment assessments are outlined in Table 6-1 through Table 6-2.

6.5. Pharmacokinetic Assessments

6.5.1. Plasma PK Collection

Plasma concentrations of ATV, PRA, and ROS will be determined and PK parameters evaluated. Plasma concentrations of filgotinib and its metabolite (GS-829845) may be analyzed. Plasma concentrations of metabolites of probe drugs or filgotinib may be analyzed, if applicable. Intensive PK sampling will occur relative to dosing of study drug at the following time points:

Sequence AB:

- Days 1 and 12: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 3 and 14: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

Sequence BA:

- Days 6 and 18: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours postdose
- Days 8 and 20: 0 (predose, ≤ 5 minutes), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, and 72 hours postdose

6.6. Safety Assessments

Safety will be evaluated throughout the study. Refer to Table 6-1 through Table 6-2 for the schedule of assessments.

6.6.1. Electrocardiogram Assessment

Participants should rest quietly in the supine position for a minimum of 10 minutes prior to each scheduled ECG acquisition and should remain in that position until the recording is complete.

There should be no environmental distractions (including TV, radio, video games, and conversation) while the participants are resting prior to and during the recordings. Electrocardiograms will be recorded using the site's standard ECG equipment. All ECGs will be obtained using instruments that analyze data using the same algorithms and produce the same data for interpretation. Electrode placement will be performed according to the method of Wilson, Goldberger, and Einthoven with a check to confirm that the aVR lead is not inverted.

The investigator or other qualified individuals at the study center will review ECGs to assess for changes in ECG intervals and morphology as compared with pretreatment ECGs. The ECG interval measurements output by the machine will be used for bedside safety monitoring.

Collection of additional ECGs for routine safety monitoring at additional time points or days is at the discretion of the investigator based on GCP.

6.6.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-driven physical examination, as outlined in Table 6-1 through Table 6-2. The complete physical examination conducted at screening will also include the following assessments:

- Review medical history, including history of allergies, prior and current use of nicotine or nicotine-containing products, alcohol and illegal drug use, and prior (within 30 days) and current medication use

6.6.3. Vital Signs

Vital sign measurements include blood pressure, heart rate, respiratory rate, and body temperature and should be taken in the supine position. Participant position for measurement should be kept consistent throughout the study. Refer to Table 6-1 through Table 6-2 for vital signs collection time points.

6.6.4. Body Mass Index

Height and weight will be collected at screening for calculation of BMI for inclusion criteria.

6.6.5. Clinical Laboratory Tests/Assessments

Blood and urine samples for safety evaluations will be collected throughout the study as outlined in Table 6-1 through Table 6-2.

6.6.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: Hematocrit, hemoglobin, platelet count, red blood cell count, white blood cell count with differential (absolute and percentage), including lymphocytes, monocytes, neutrophils, eosinophils, basophils, and mean corpuscular volume
- Chemistry (fasting): alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, total protein, albumin, lactic acid dehydrogenase, CPK, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in participants with total amylase > 1.5 × upper limit of normal)
- Serum pregnancy test (females of childbearing potential only)
- Follicle-stimulating hormone testing (screening only): females who have ceased menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure only
- Thyroid stimulating hormone testing (screening only)
- HIV-1, HBV, and HCV testing (*screening only*)
- COVID-19 RT-PCR testing will be conducted and reviewed per site specific policy at screening, admission, and as needed during the study. Alternatively, a comparable test may be used after consultation with the Sponsor.

6.6.5.2. Urine Samples

Urine samples will be collected for urinalysis, urine pregnancy (females only) and alcohol and drug screen assessments.

6.6.6. Creatinine Clearance

Weight will be collected at the times shown in Table 6-1 through Table 6-2 to calculate CL_{cr}.

6.6.7. Adverse Events/Concomitant Medications/Protocol Restrictions

Evaluation for AEs, review of concomitant medications, and review of protocol restrictions will occur at the times shown in Table 6-1 through Table 6-2 . See Section 7 for more information regarding AEs and Sections 4.3 and 5.7.1 for more information about concomitant medications.

6.7. Posttreatment Assessments

All participants will be contacted by telephone 7 days ± 2 days after last dose of study drug for follow up(ie, on Day 24 [± 2] for Sequence AB or Day 27 [± 2] for Sequence BA). Study procedures and assessments are outlined in Table 6-1 and Table 6-2 .

6.8. Assessments for Early Discontinuation from Study

If a participant discontinues study treatment dosing (see Section 3.8), for example as a result of an AE, every attempt should be made to keep the participant and continue to perform procedures for stabilization per the investigator. Evaluations indicating abnormal results believed to be possibly or probably related to study treatment at the early termination visit should be repeated weekly or as often as deemed appropriate by the investigator until the abnormality resolves, returns to baseline visit levels, or is otherwise explained.

If the participant withdraws consent from the study, the ET evaluations and/or procedures outlined in Table 6-1 through Table 6-2 should be performed within 72 hours of permanently discontinuing the study.

CCI [redacted]

[redacted]

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events and Serious Adverse Events

7.1.1. Adverse Events

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

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.1.3)
- 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 preexisting and should be documented medical history.

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

7.1.2. Serious Adverse Events

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

- Death
- A life-threatening situation (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction; such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent 1 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.

7.1.3. Study Drugs and Gilead Concomitant Therapy Special Situations Reports

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

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

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

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

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

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

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

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

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

Counterfeit or falsified medicine is defined as any study drug with a false representation of (a) its identity, (b) its source, or (c) its history.

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, preexisting condition, underlying disease, intercurrent illness, concomitant medication).

- **Yes**: There is reasonable possibility that the AE may have been caused by the study drug.

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

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

- **No:** Evidence exists that the AE has an etiology other than the study procedure.

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

7.2.2. Assessment of Severity

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Toxicity Grading Scale, Version 5. For each episode, the highest grade attained should be reported as defined in the Toxicity Grading Scale (Appendix 4).

7.3. Investigator Reporting Requirements and Instructions

7.3.1. Requirements for Collection Prior to Study Drug Initiation

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

7.3.2. Adverse Events

Following initiation of study treatment, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug and report to the eCRF database as instructed.

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

7.3.3. Serious Adverse Events

All SAE and death, regardless of cause or relationship, that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, until 30 days after last administration of study drug must be reported on the applicable eCRFs and to Global Patient Safety (GLPS) as instructed below in this section. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

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

Instructions for reporting SAEs are described in Section 7.4.1.

7.3.4. Study Drug Special Situations Reports

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

7.3.5. Concomitant Therapy Reports

7.3.5.1. Gilead Concomitant Therapy Special Situations Report

Special situation reports involving a Gilead concomitant therapy (not considered study drug), that occurs after the participant first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the posttreatment follow-up phone call must be reported to GLPS utilizing the paper SSR (Section 7.4.2.3).

7.3.5.2. Non-Gilead Concomitant Therapy Report

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

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

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

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

7.4.1. Serious Adverse Event Reporting Process

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be transmitted by email or fax when requested and applicable. Transmission of such documents should occur without personal participant identification, maintaining the traceability of a document to the participant 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 participant's eCRF and the SAE narrative section of the Safety Report Form eCRF.

7.4.1.1. Paper Serious Adverse Event Reporting Process

- All SAEs will be recorded on the SAE report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from ICF signature throughout the duration of the study, including the protocol-required posttreatment follow-up period.

Gilead GLPS:	Gilead GLPS Email PPD or Fax: PPD

7.4.2. Special Situations Reporting Process

7.4.2.1. Paper Special Situations Reporting Process for Study Drug

- All SSRs will be recorded on the special situations report form and transmitted by emailing or faxing the report form within 24 hours of the investigator's knowledge of the event to the attention of Gilead GLPS from study drug initiation throughout the duration of the study, including the protocol-required post treatment follow-up period.

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

7.4.2.2. Reporting Process for Gilead Concomitant Medications

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

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

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

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

7.4.2.3. Pregnancy Reporting Process

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

Gilead GLPS: Gilead GLPS
Email: PPD
or
Fax: PPD

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

- All other premature terminations of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE, as described in Section 7.4.1. The underlying medical reason for this procedure should be recorded as the AE term.

- A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.4.1. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to the Gilead GLPS.

- The participant should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy/partner pregnancy should be reported to Gilead GLPS using the pregnancy outcome report form. If the end of the pregnancy/partner pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead GLPS. Gilead GLPS contact information is as follows: email: PPD and fax: PPD.

- Refer to **Appendix 2** for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.5. Gilead Reporting Requirements

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

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

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

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

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

Severity should be recorded and graded according to the CTCAE Toxicity Grading Scale, Version 5 in Appendix 4. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.7. Toxicity Management

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 as soon as possible, and preferably within 3 calendar days after receipt of the original test results.

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

7.7.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

- Continue study drug at the discretion of the investigator.

7.7.2. Grades 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinically significant laboratory abnormality or clinical event, the study drug may be continued if the event is considered to be unrelated to the study drug.

- For a Grade 3 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to the study drug, then the study drug should be withheld until the toxicity returns to ≤ Grade 2.

- If a laboratory abnormality recurs to ≥ Grade 3 following rechallenge with the study drug and is considered to be related to the study drug, then the study drug should be permanently discontinued and the participant managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

7.7.3. Grades 4 Laboratory Abnormality or Clinical Event

- For a Grade 4 clinically significant laboratory abnormality or clinical event confirmed by repeat testing, that is considered to be related to the study drug, the study drug should be permanently discontinued and the participant managed according to local practice. The participant should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first. A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

- Study drug may be continued without dose interruption for a clinically nonsignificant Grade 4 laboratory abnormality (eg, Grade 4 CK elevation after strenuous exercise, triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to the study drug.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, and the appropriate course of action will be discussed and decided. Whether or not considered treatment related, all participants experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Gilead medical monitor.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objectives of this study are as follows:

- To evaluate the effect of filgotinib on a mixed OATP/CYP3A, OATP/ BCRP, and OATP substrates using phenotypic probes

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of multiple filgotinib doses administered alone or in combination with probe drugs.

8.1.2. Primary Endpoint

The primary endpoint of this study is as follows:

- PK parameters AUC_{last}, AUC_{inf}, and C_{max} of ATV, PRA, and ROS.

8.1.3. Secondary Endpoint

The secondary endpoints of this study are as follows:

- Incidences of AEs
- Laboratory abnormalities
- Vital signs

8.2. Planned Analyses

8.2.1. Final Analysis

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

8.3. Analysis Conventions

8.3.1. Analysis Sets

8.3.1.1. All Randomized Analysis Set

The All Randomized Analysis Set includes all participants randomized into the study after screening. This is the primary analysis set for safety listings.

8.3.1.2. Safety Analysis Set

The Safety Analysis Set will include all randomized participants who received at least 1 dose of study drug. Participants who received treatment other than that to which they were assigned will be analyzed according to the treatment received.

8.3.1.3. Pharmacokinetics Analysis Set

The PK Analysis Set will include all randomized participants who received at least 1 dose of study drug and had at least 1 nonmissing PK concentration datum reported by PK laboratory for each respective analyte.

8.3.2. Data Handling Conventions

For summary statistics, PK concentration values below the limit of quantitation will be treated as zero at predose and 1-half of the lower limit of quantitation (LLOQ) for postdose time points.

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

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

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized and descriptive statistics will be provided.

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

8.5. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to 30 days after last study drug administration will be summarized by treatment (according to the study drug received) using the Safety Analysis Set.

8.5.1. Extent of Exposure

A participant's extent of exposure to study drug data will be generated from the study drug administration data. Exposure data will be listed.

8.5.2. Adverse Events

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

Treatment-emergent AEs (TEAEs), serious TEAEs, and TEAEs leading to discontinuation of treatment will be summarized by treatment, SOC, and PT using the current version of MedDRA. Adverse event data will be listed by participant.

8.5.3. Laboratory Evaluations

Laboratory results and changes from predose values for selected laboratory tests will be summarized by treatment sequence at scheduled visits. The incidence of treatment-emergent graded laboratory abnormalities will be summarized by treatment. Listings of individual participant laboratory results will be provided.

8.5.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by treatment/treatment sequence..

8.6. Pharmacokinetic Analysis

An analysis of variance (ANOVA) using a mixed-effects model with treatment, period, and sequence as fixed effects and participant as a random effect will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, C_{max}) for each analyte. Two-sided 90% CIs will be calculated for the ratios of geometric least-squares means (GLSMs) of primary PK parameters between test (Treatment B) versus reference (Treatment A) treatments.

Lack of PK interaction between the test and reference treatments will be concluded if the 90% CIs for the GLSM ratios are contained within the 0.70 and 1.43 range for ATV, PRA, and ROS AUC and C_{max}. Additional analyses may be performed if useful and appropriate.

Plasma concentrations and PK parameters $AUC_{last,}$ AUC_{inf}, C_{max}, $\%AUC_{exp}$, C_{last}, T_{max}, T_{last}, $t_{1/2}$, CL/Z, λ_z and V_z/F will be listed and summarized for ATV, PRA, and ROS using descriptive statistics by treatment.

8.7. Sample Size

With 26 evaluable participants, the estimated two-sided 90% CI of the GLSM ratio of test versus reference treatments, with regards to AUC_{inf}, $AUC_{last,}$ and C_{max}, will be within [70%, 143%] with ≥ 85% probability, if the true GLSM ratio is 1.0. This is assuming a standard deviation (SD) of differences of no more than 0.569 on a natural logarithm scale, supported by PK data from Study GS-US-402-2102. With 4 participants for overage, a total sample size of 30 participants will be required.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

9.1.2. Financial Disclosure

The investigator and subinvestigators will provide documentation of their financial interest or arrangements with Gilead or proprietary interests in the study 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 participant completes the protocol-defined activities.

9.1.3. Institutional Review Board Review and Approval

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

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

9.1.4. Informed Consent

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

The ICF will inform participants about genomic testing and/or planned sample retentionConfidentiality

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

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

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

The investigator's study file will contain the protocol/amendments, eCRF, IRB governmental approval with correspondence, ICF, 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 participant:

- Participant identification (name, date of birth, gender)
- Documentation that participant meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- Documentation of the reason(s) a consented participant 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 dates (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end date; causality and severity), and documentation that adequate medical care has been provided for any AE
- Concomitant medication (including start and end dates, dose if relevant, and dose changes)
- Date of study completion and reason for early discontinuation, if it occurs

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

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

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

9.1.6. Case Report Forms

For each participant enrolled, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the participant visit to enable the sponsor to perform central monitoring of safety data, whenever possible. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received and the participant has been enrolled. Subsequent to data entry, a study monitor will perform source data verification SDV within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her login credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and

procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the study, 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. Investigator Inspections

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

9.1.8. 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 participants, may be made only by Gilead. The investigator must submit all protocol modifications to IRB in accordance with local requirements and receive documented IRB approval before modifications may be implemented.

9.2.2. Study Report and Publications

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

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

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

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator'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 study 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 medical monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1 Study to Evaluate OATP Transporter-Mediated Drug-Drug Interactions Between Filgotinib and Stains as Probe Drugs in Healthy Participants

Original Protocol, 25 Septemeber 2020

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

PPD

Name (Printed)
Responsible Person's Title

PPD

Signature

25 September 2020

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

1) Definitions

a. Definition of Childbearing Potential

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

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

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

b. Definition of Male Fertility

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

2) Contraception Requirements for Female Participants

a. Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as a malformative effect has been demonstrated/suspected or is unknown taking into consideration class effect and/or strong suspicion of human teratogenicity/fetotoxicity in early pregnancy based on nonclinical data. Data from clinical PK interaction studies of filgotinib have demonstrated that there is no reduction in the clinical efficacy of hormonal contraception. Refer to the latest version of the IB for additional information.

b. Contraception Requirements for Female Participants of Childbearing Potential

The inclusion of female participants of childbearing potential requires the use of highly effective contraceptive measures with a failure rate of < 1% per year. They must have a negative serum pregnancy test at screening and admission and a urine negative pregnancy test at the Admission (Day 1) prior to randomization. Pregnancy tests will be performed as specified in the protocol.

Female participants of childbearing potential must agree to use one of the contraceptive methods below from Screening until 1 week after 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 participant's preferred and usual lifestyle.

Or

Consistent and correct use of 1 of the following methods of birth control listed below:

- Hormonal or non-hormonal intrauterine device (IUD)
- Subdermal contraceptive implant
- Bilateral tubal occlusion (upon medical assessment of surgical success)
- Vasectomy in the male partner (upon medical assessment of surgical success)

Or

Female participants who wish to use a hormonally-based method must use it in conjunction with a barrier method, preferably a male condom. Hormonal methods are restricted to those associated with the inhibition of ovulation. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

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

    Oral contraceptives (either combined or progesterone only)

    Injectable progesterone

    Transdermal contraceptive patch

    Contraceptive vaginal ring

- Barrier methods (each method must be used with a hormonal method)

    Male condom (with or without spermicide)

    Female condom (with or without spermicide)

    Diaphragm with spermicide

    Cervical cap with spermicide

    Sponge with spermicide

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

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

3) Contraception Requirements for Male Participants

It is theoretically possible that a relevant systemic concentration of study drug may be achieved in a female partner from exposure of the male participant's seminal fluid and poses a potential risk to an embryo/fetus. Therefore, male participants with female partners of childbearing potential must use condoms during treatment until 1 week after last dose of study drug.

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

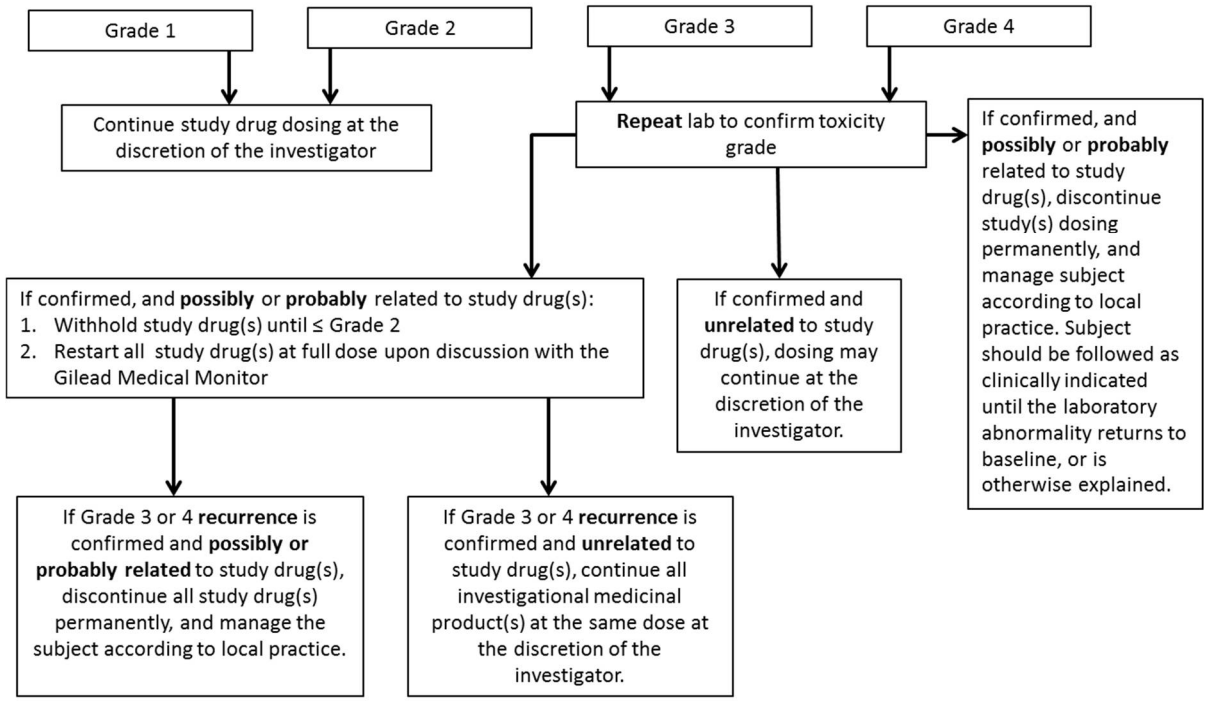
Female participants will be instructed to notify the investigator if they become pregnant or suspect they are pregnant at any time from start of the study to 1 week after the last dose of study drug.

Male subjects whose partner has become pregnant or suspects she is pregnant from start of study through one week after last dose of study drug must also report the information to the investigator.

Study drug must be discontinued immediately upon discussion with the medical monitor.

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

Appendix 3. Management of Clinical and Laboratory Adverse Events



Appendix 4. Common Terminology Criterial for Adverse Events (CTCAE) Grading Scale v5.0

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50