CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Filgotinib in Subjects with Impaired Hepatic Function	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND No.: **EudraCT No.:**	IND 115510 2017-000156-25	
Indication:	Rheumatoid Arthritis	
Protocol ID:	GS-US-417-4048	
Gilead Medical Monitor	Name: Telephone: Fax: Cell:	PPD PPD PPD PPD
Protocol Version/Date:	Original:	19 December 2017

CONFIDENTIALITY STATEMENT

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

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

Study Title:	A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Filgotinib in Subjects with Impaired Hepatic Function
IND Number: **EudraCT Number:**	IND 115510 2017-000156-25
Study Centers Planned:	Multiple centers in the United States, Germany, and New Zealand
Objectives:	The primary objective of this study is as follows: • To evaluate the pharmacokinetics (PK) of filgotinib and its metabolite, GS-829845, in subjects with impaired hepatic function relative to matched, healthy controls The secondary objective of this study is as follows: • To evaluate the safety and tolerability of filgotinib in subjects with normal and impaired hepatic function
Study Design:	Phase 1, open-label, adaptive, single-dose study
Number of Subjects Planned:	Up to 60 subjects enrolled for up to 48 evaluable: • **Cohort 1 (Moderate Hepatic Impairment):** 20 subjects (10 subjects with moderate hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group). • **Adaptive Cohort 2 (Severe Hepatic Impairment):** 20 subjects (10 subjects with severe hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group). • **Adaptive Cohort 3 (Mild Hepatic Impairment):** 20 subjects (10 with mild hepatic impairment and 10 matched healthy controls for 8 evaluable subjects per group). A subject with normal hepatic function may serve as a matched control across cohorts but may only serve as a matched control to one hepatically impaired subject within a cohort. Subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and Cohort 3 (Mild Hepatic Impairment) may be enrolled after the review by Sponsor of safety and PK data from subjects in Cohort 1 (Moderate Hepatic Impairment).

Target Population:	Male and nonpregnant, nonlactating female subjects, aged 18 to 70 years (inclusive), with varying degrees of hepatic impairment and matched healthy controls. Subjects with hepatic impairment will be enrolled based upon the Child-Pugh-Turcotte (CPT) classification system indicating moderate hepatic impairment (CPT Class B; Cohort 1), severe hepatic impairment (CPT Class C; Cohort 2), or mild hepatic impairment (CPT Class A; Cohort 3). The control group will consist of matched healthy subjects with normal hepatic function.
Duration of Dosing:	1 day
Study Duration:	Up to 15 days (not including screening window)
Diagnosis and Main Eligibility Criteria:	Eligible subjects will be male and nonpregnant, nonlactating female subjects, aged 18 to 70 years (inclusive), body mass index (BMI) between 18 and 36 kg/m^2 (inclusive), with either impaired hepatic function or normal hepatic function. Subjects will be current nonsmokers (no use of tobacco, nicotine-containing, or tetrahydrocannabinol (THC)-containing products within the last 14 days). Subjects with hepatic impairment will be categorized by the CPT classification system indicating hepatic impairment as follows: • Class A (mild): CPT score 5-6 • Class B (moderate): CPT score 7-9 • Class C (severe): CPT score 10-15 Hepatic impairment must have been stable during the 3 months (90 days) prior to study drug. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 15%).
Study Procedures/ Frequency:	Following completion of Screening and Day -1 assessments, eligible subjects will receive a single oral dose of 100 mg filgotinib (1 x 100 mg tablet) on Day 1, in fasting state. Dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments. **Study Visits and Confinement** Following Screening and admission assessments, eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 6. Subjects will return for an in-clinic follow-up (FU) visit on Day 15 (± 1 day).

Study Drug Administration

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour blood sample, relative to study drug dosing. Additionally, subjects will be restricted from water consumption 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment. A standardized meal may be provided to subjects after collection of the 4-hour blood draw.

Pharmacokinetic Assessments

Intensive PK sampling will occur relative to dosing of filgotinib at the following time points:

Day 1: 0 (predose, ≤ 5 minutes prior to dosing), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours postdose

A blood sample for PK analysis will be collected at the Early Termination (ET) visit (if applicable) and may be analyzed.

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be measured and PK parameters determined. Plasma concentrations of other metabolites may be determined and PK explored.

Protein binding of filgotinib and its major metabolite (GS-829845) will be assessed at their T_{max} time point(s) as well as at another later time point.

Safety Assessments

Complete Physical Exam: Screening and the FU visit or the ET visit (if applicable)

Symptom-driven Physical Exam: Days -1, 1, and every day during confinement (as needed based on reported signs and symptoms)

Vital Signs (blood pressure, pulse, respiration rate, and temperature): Screening, Days -1, 1, 3, 6, and the FU or the ET visit (if applicable)

Height: Screening

Weight: Screening and Day -1

Clinical Laboratory Tests (hematology, blood chemistry including coagulation, and urinalysis): Screening, Days -1, 1, 6, and the FU or the ET visit (if applicable)

Urine Drug, Cotinine, and Alcohol Assessments: Screening, Day -1 and the FU or the ET visit (if applicable)

	12-lead electrocardiogram (ECG): Screening, Days -1, 1 (2 hours post dose), 6, and the FU or ET visit (if applicable) *Serum Pregnancy Test (women of childbearing potential only)*: Screening, Days -1, 6 and the FU or the ET visit (if applicable) *Serology Test (HBV, HCV, HIV):* Screening *α-fetoprotein Test:* Screening Assessment of adverse events (AE) and concomitant medications will continue throughout the study. All clinical AEs and clinically significant laboratory abnormalities will be managed according to uniform guidelines detailed in protocol Appendix 3 **Protocol-Specific Stopping Rules** If ≥ 2 subjects in any cohort experience the same or similar Grade 3 or Grade 4 treatment-emergent AE or confirmed laboratory abnormality that is not attributable to obvious alternative explanation (hematuria occurring in a menstruating female, creatine kinase [CK] elevation after strenuous exercise, or triglyceride elevation that is non-fasting, etc), a review of all safety data generated in subjects dosed to date will be initiated. The decision as to whether and how to proceed with further enrollment will be determined based on the safety review.
Test Product, Dose, and Mode of Administration:	A single dose of 100 mg filgotinib (1 x 100 mg tablet), in a fasted state.
Reference Therapy, Dose, and Mode of Administration:	Not applicable
Criteria for Evaluation:	
Safety:	Safety will be assessed during the study through the reporting of AEs, and by clinical laboratory tests, physical examinations, vital signs, and ECGs at various time points during the study.
Efficacy:	Not applicable.
Pharmacokinetics:	The following plasma PK parameters of filgotinib and its metabolite (GS-829845) will be calculated, as appropriate: C_{max}, T_{max}, C_{last}, T_{last}, λ_z, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, $t_{½}$, CL/F, and V_z/F.

Statistical Methods:

Pharmacokinetics:

Plasma PK parameters for filgotinib and GS-829845 will be listed and summarized by hepatic function group (normal or CPT Class A, B, or C) using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation [CV], standard deviation [SD], median, minimum, and maximum).

An analysis of variance appropriate for a parallel design will be fit to the natural logarithm-transformed PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for filgotinib and GS-829845. The 90% confidence intervals (CIs) will be constructed for the geometric least-squares mean (GLSM) ratio of PK parameters for filgotinib and GS-829845 in groups of subjects with hepatic impairment versus matched controls.

Protein binding of filgotinib and GS-829845 at their T_{max} and another later time point will be summarized by hepatic function group using descriptive statistics.

Safety:

Safety data will be listed by subject and summarized by hepatic function group (normal or CPT Class A, B, or C) and frequency of event/abnormality or descriptive statistical summaries, as appropriate.

Sample Size:

With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the geometric least-square mean (GLSM) ratio of test vs reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability, if the estimated GLSM ratio were 1.0. This is assuming the SDs for PK parameters between subjects within each group is no more than 0.347 (or 0.203) for the natural logarithm-transformed PK parameters for filgotinib (or GS-829845). Such assumptions are supported by PK data from a prior Gilead study of filgotinib (GS-US-417-3900) with 100 mg dose in healthy volunteers.

An overage of 2 subjects per group will be enrolled in order to accommodate subject drop-outs, so a total sample size of 20 subjects (10 per group) for each cohort will be required.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log concentration versus time curve of the drug
$\%AUC_{exp}$	percentage of AUC extrapolated between AUC_{last} and AUC_{inf}
°C	degrees Celsius
°F	degrees Fahrenheit
AE	adverse event
ALT	alanine aminotransferase (previously serum glutamic pyruvic transaminase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
BMI	body mass index
BUN	blood urea nitrogen
CBC	complete blood count
CD	Crohn's disease
CES	carboxylesterases
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CL/F	apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug
C_{last}	last observed quantifiable concentration of the drug
CL_{cr}	creatinine clearance
C_{max}	maximum observed concentration of drug
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form
CV	coefficient of variation
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EudraCT	European Clinical Trials Database
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
FU	follow-up

GCP	Good Clinical Practice
GI	gastrointestinal
Gilead	Gilead Sciences, Inc.
GLP	Galapagos
GLSM	geometric least-squares mean
HBV	hepatitis B virus
HBcAb	hepatitis B virus core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV, HIV-1, HIV-2	human immunodeficiency virus, type 1, type 2
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IEC	independent ethics committee
IND	investigational new drug (application)
IRB	institutional review board
IUD	intrauterine device
JAK	janus kinases
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NDA	new drug application
PK	pharmacokinetic(s)
PT	prothrombin time
PTT	partial thromboplastin time
PVE	Pharmacovigilance & Epidemiology
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur
RA	rheumatoid arthritis
RBC	red blood cell
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
STAT	signal transduction and activator of transcription

SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{last}	time (observed time point) of C_{last}
T_{max}	the time (observed time point) of C_{max}
TYK	tyrosine kinases
UC	ulcerative colitis
UGT	uridine disphosphate glucuronosyltransferases
ULN	upper limit of normal
US, USA	United States, United States of America
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 subjects with RA. Despite these developments, therapeutic challenges remain. The current conventional and biological disease-modifying anti-rheumatic drugs are ineffective or produce only partial responses in some subjects 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 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 transduction and activator of transcription (STAT) signaling pathways are evolutionarily conserved and ubiquitous in animals and are activated by a variety of cytokines, growth factors, and other chemical messengers. Dysregulation of the JAK/STAT functionality is implicated in the pathogenesis of multiple diseases, including immuno-inflammatory diseases. Janus kinase inhibitors block the signaling of various cytokines, growth factors and hormones, including the pro-inflammatory cytokine interleukin (IL)-6. Four different types of JAKs are known which (co-)interact with different sets of membrane receptors: JAK1, JAK2, JAK3 and TYK2. Janus kinase plays a critical role in innate and adaptive immunity and hematopoiesis. The etiology of multiple inflammatory and autoimmune conditions may involve a combination of genetic predisposition, environmental factors, and ultimately a pathogenic inflammatory state. This culminates in a loss of self-tolerance and expansion of T-cells that ultimately secrete pro-inflammatory cytokines, which activate and signal other cells of the immune system (eg, macrophages, natural killer cells, and neutrophils) that infiltrate targeted tissue {Clark 2014}. Inhibition of JAK/STAT signaling is a therapeutic option for a range of inflammatory conditions including RA and inflammatory bowel disease (IBD), two conditions with high and rising prevalence and significant unmet medical needs.

1.2. Filgotinib

1.2.1. General Information

Filgotinib (GS-6034, formerly GLPG0634) is a potent and selective oral inhibitor of JAK1 being developed by Gilead Sciences, Inc. (Gilead) and Galapagos (GLP) NV. Janus kinase 1 is believed to play an integral part in the pathogenesis of various autoimmune diseases, due its role in inflammatory cytokine signaling.

For further information on filgotinib refer to the Investigator's Brochure (IB), including information on the following:

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

1.2.2. Preclinical Pharmacology, Pharmacokinetics and Toxicology

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

Filgotinib demonstrates good oral bioavailability in all nonclinical species and plasma protein binding is low (< 70%). The PK of filgotinib is generally dose proportional without gender differences. The mean terminal half-life after oral administration is 4 and 5 hours in rats and dogs, respectively. In the rat, filgotinib showed a rapid and even distribution in most tissues throughout the body. High concentrations were observed only in the gastrointestinal (GI) tract and urinary bladder. Filgotinib does not penetrate into central nervous system (CNS) tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues. Excretion occurs primarily via the urine and feces in rat and dog and is nearly complete within 24 hours (rat) and 48 hours (dog) post-dosing. The formation of the major metabolite, GS-829845, is mediated by carboxylesterases (CES) and is not dependent on cytochrome P450 (CYP); in vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine disphosphate glucuronosyltransferases (UGTs), and no relevant inhibition of key drug transporters, by filgotinib or GS-829845.

In rats, filgotinib and GS-829845 had no effects on the respiratory system and CNS and no relevant effects on cardiovascular parameters (human ether-a-gogo related gene and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845, at exposures 14-fold that of the C_{max} in human subjects dosed with filgotinib 100 mg once daily. Administration of filgotinib did not affect female fertility but impaired male fertility was observed in rats at exposures approximately 30-fold the human exposure at 100 mg of filgotinib. The metabolite, GS-829845, did not have any effects on fertility parameters.

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility, however sperm counts remained

low. A dose of 100 mg once daily of filgotinib results in an estimated mean clinical area under the curve (AUC) of 1.38 µg·h/mL in subjects with RA, which represents an exposure margin of 4.8, 3.7, and 6.9-fold when considering the mean AUC in male dogs at the no-observed-effect-levels in the 26-week and 39-week chronic toxicity studies, and the 39-week targeted exposure toxicity study, respectively. GS-829845-related findings in general repeat dose toxicity studies were similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 are non-genotoxic. In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits at exposures similar to the human exposure at 200 mg once daily of filgotinib in subjects with RA. Exposures comparable to the human exposure at 100 mg once daily have not been evaluated in rats or rabbits.

1.2.3. Additional Clinical Studies of Filgotinib

As of April 2017, filgotinib has been taken by more than 348 healthy volunteers or special populations (15 subjects with renal impairment), 959 subjects with RA, 153 subjects with Crohn's disease (CD) and 2 subjects with ulcerative colitis (UC), and has been generally safe and well tolerated. A detailed description of all clinical studies can be found in the IB.

In eleven Phase 1 studies conducted in healthy subjects (Studies GPLG0634-CL-101, -102, -103, -104, -105, -106, -107, -110, GS-US-417-3900, GS-US-417-3911, and GS-US-417-3916), filgotinib administered at doses of up to 450 mg once daily for up to 10 days was safe and well tolerated.

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

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

Currently, Phase 3 studies are ongoing in subjects with RA, UC (Phase 2b/3), and CD, and Phase 2 Proof of Concept studies are ongoing in Uveitis, Sjogren's, Lupus, psoriatic arthritis and ankylosing spondylitis, small bowel CD and fistulizing CD.

1.3. Rationale for This Study

Hepatic disease may alter absorption, disposition, and elimination of drugs resulting in PK and subsequent pharmacodynamic changes. Hence, the objective of this study is to investigate potential changes in the pharmacokinetics of a single-dose of filgotinib in subjects with hepatic impairment. Since both filgotinib and its major metabolite GS-829845 exhibit time-independent

PK, the administration of filgotinib as a single-dose is expected to predict steady-state PK and therefore is deemed satisfactory for this study. This is consistent with recommendations included in the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".

This study will be conducted in an adaptive manner. Specifically, initial subjects to be enrolled will have moderate (CPT Class B) hepatic impairment (Cohort 1). Pharmacokinetic and safety data from these subjects will be compared to matched subjects with normal hepatic function. Review of Sponsor Safety and PK results obtained from Cohort 1 will indicate whether further evaluation in subjects with mild or severe hepatic impairment is needed. Dosing of subjects with mild or severe hepatic impairment will occur only after the review of safety and PK from subjects with moderate impairment in Cohort 1 (moderate hepatic impairment).

Based on PK properties of filgotinib, the "reduced PK study design" is considered appropriate following the FDA Guidance. In humans, filgotinib is highly metabolized to its active metabolite GS-829845, primarily by carboxylesterase isoform 2 (CES2) in the intestine and to a lesser extent by CES1 in the liver. Following a single dose of [^{14}C]-filgotinib, a majority of the dose (86.9%) was recovered in urine, suggesting that renal clearance is the main pathway of elimination for filgotinib and its metabolites. GS-829845 (54.0% of the dose) and its *N*-glucuronide derivative (14.6% of the dose) were the major species excreted in urine, followed by the parent filgotinib (9.37% of the dose). Among the 15.4% radioactivity recovered in feces, GS-829845 and filgotinib accounted for 8.88% and 4.47% of dose, respectively. Based on these data, significant changes in plasma exposures of filgotinib or GS-829845 are not expected with impairment in hepatic function. Therefore, it is considered safe to evaluate a single dose of 100 mg filgotinib in subjects with moderate hepatic impairment first, followed by subjects with mild or severe hepatic impairment in an adaptive manner, if indicated.

Finally, the data from this study will inform dosing recommendations for subjects with chronic inflammatory disease including RA, UC, or CD who have hepatic dysfunction.

1.4. Rationale for the Dose Selection

A single-dose of 100 mg filgotinib will be tested in this study. This dose is expected to be well tolerated based on safety data from single and multiple dose studies in healthy volunteers and patients with RA or CD. As of April 2017, 1462 subjects (348 healthy subjects or special populations [15 subjects with renal impairment]), 153 subjects with CD, 2 subjects with UC, and more than 959 subjects with RA) have received single or multiple doses of filgotinib up to 450mg for up to 60 weeks in duration in clinical studies. Filgotinib is considered well tolerated across these dosing regimens in these subjects.

Evaluating the 100 mg filgotinib dose in subjects with hepatic impairment is clinically relevant. Filgotinib is being tested at 100 mg and 200 mg once daily in Phase 3 programs in subjects with RA, UC, or CD. The 100 mg single dose is also chosen to ensure clinically safe filgotinib / GS-829845 exposures in study subjects in case of unexpected alteration in filgotinib PK by hepatic impairment. Further, since filgotinib exhibits approximately dose-proportional PK, PK results from this study (ie, 100 mg single dose) can be extrapolated to other doses (ie, 200 mg) of filgotinib.

1.5. Risk/Benefit Assessment for the Study

Potential risks of a participant's study involvement include unknown AEs, general risks associated with frequent clinic visits and laboratory blood draws, and the associated pain and discomfort of phlebotomy. Strategies to mitigate these risks include close monitoring of lab values as well as AEs. For this study, frequent assessments of hepatic function will also be performed from the collection of both blood and urine samples. Parameters for discontinuation of the study drug due to AEs will be well defined and closely followed.

There is no direct benefit to subjects participating in this study; however, data from this study will support the development of filgotinib for the treatment of RA and other chronic inflammatory conditions. Potential benefits may include the participant's contribution to the sponsor's understanding of the PK, safety, and tolerability of filgotinib in subjects with hepatic insufficiency.

Considering the above, the benefit-risk balance for this study is considered positive.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is as follows:

- To evaluate the PK of filgotinib and its metabolite, GS-829845 , in subjects with impaired hepatic function relative to matched, healthy controls

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of filgotinib in subjects with normal and impaired hepatic function

3. STUDY DESIGN

3.1. Study Design

This protocol describes a Phase 1, open-label, adaptive, single-dose study to evaluate the PK of filgotinib and its metabolite, GS-829845, in subjects with impaired hepatic function relative to matched, healthy controls. Up to 60 subjects will be enrolled (for up to 48 evaluable).

Cohort 1 (Moderate Hepatic Impairment): 20 subjects (10 with moderate hepatic impairment and 10 matched healthy controls for 8 evaluable subjects per group).

Adaptive Cohort 2 (Severe Hepatic Impairment): 20 subjects (10 subjects with severe hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group).

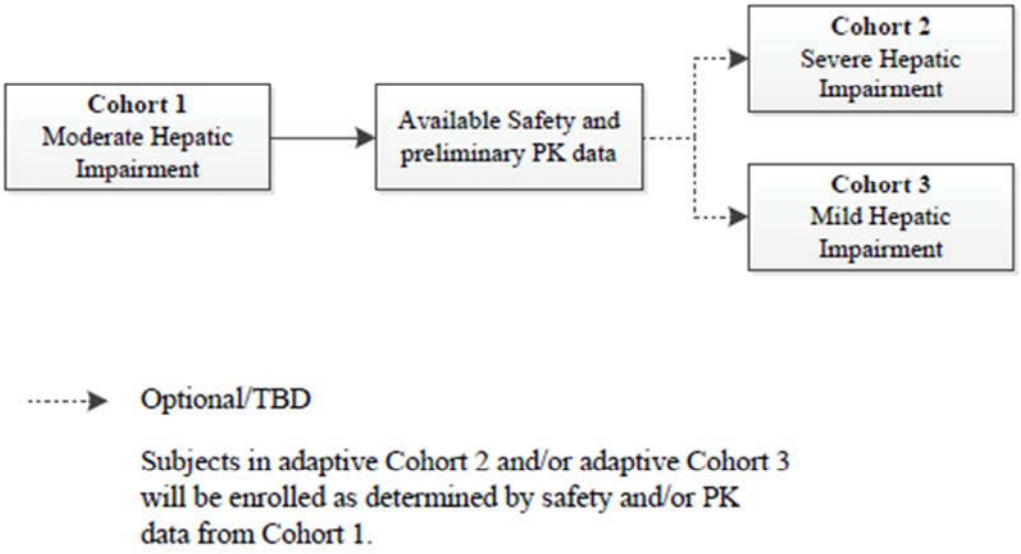
Adaptive Cohort 3 (Mild Hepatic Impairment): 20 subjects (10 subjects with mild hepatic impairment and 10 healthy matched controls for 8 evaluable subjects per group).

Male and nonpregnant, nonlactating female subjects aged 18 through 70 years, inclusive, with severely impaired, moderately impaired, mildly impaired, and normal hepatic function will be enrolled into the study. Subjects will be current nonsmokers (no use of tobacco, nicotine-containing or THC-containing products within the last 14 days). Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 15%). A subject with normal hepatic function may serve as a matched control across cohorts but may only serve as a matched control to one hepatic impaired subject within a cohort.

Subjects in adaptive Cohort 2 (Severe Hepatic Impairment) and Cohort 3 (Mild Hepatic Impairment) may be enrolled after the review by Sponsor of safety and PK data from subjects in Cohort 1 (Moderate Hepatic Impairment).

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

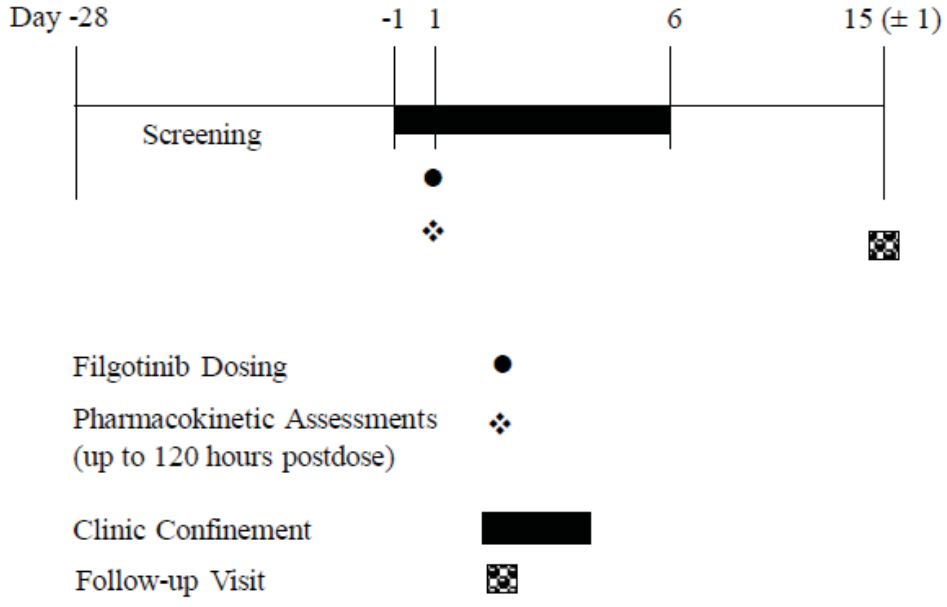
Figure 3-1. High-Level Study Schema



3.1.1. Cohorts 1 – 3

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

Figure 3-2. Study Schema



3.2. Study Drug Administration

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour blood sample, relative to study drug dosing. Additionally, subjects will be restricted from water consumption 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment. A standardized meal may be provided to subjects after collection of the 4-hour blood draw.

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

3.3. Clinic Confinement

Following Screening and admission assessments, eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 6. Subjects will return for an in-clinic follow-up (FU) visit on Day 15 (± 1 day).

3.4. Pharmacokinetic Assessments

Pharmacokinetic assessments will occur on assigned study days as outlined in Table 6-1 and Section 6.8.

3.4.1. Plasma Pharmacokinetic Collection

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be measured and PK parameters determined. Plasma concentrations of other metabolites may be determined and PK explored.

Protein binding of filgotinib and its major metabolite (GS-829845) will be assessed at their T_{max} time point(s) as well as at another later time point.

3.5. Samples for Optional Future Research

PPD

3.6. Safety Assessments

Safety assessments will be performed through the study as outlined in Table 6-1 and in Section 6.9.

3.7. End of Study

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

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 60 unique subjects will be enrolled in the study. Eligible subjects include male and nonpregnant, nonlactating female subjects of 18 through 70 years of age, inclusive, with varying degrees of hepatic impairment and matched healthy controls. If necessary, replacement subjects may be enrolled if subjects do not complete all intensive PK procedures with sponsor approval. Replacement subjects will not be enrolled for subjects who discontinue the study due to study drug-related AEs.

Those subjects with hepatic impairment will be categorized based upon the CPT classification system indicating hepatic impairment as recommended by the United States FDA and European Medicines Agency(EMA) and international guidance documents {U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER) 2003}. Within the CPT system, subjects will be assigned to Class A, B, or C (CPT Class A, B, or C) based on a cumulative score evaluating the presence and severity of hyperbilirubinemia, hypoalbuminemia, prolongation of INR for coagulation time, ascites, and hepatic encephalopathy. Classification of hepatic impairment will be assigned as follows:

- Mild: Class A, CPT score of 5-6
- Moderate: Class B, CPT score of 7-9
- Severe: Class C, CPT score of 10-15

Based on CPT classification, subjects with hepatic impairment and healthy matched controls will be enrolled as described in Section 5.1. The control group will consist of matched healthy subjects with normal hepatic function. Each subject in the control group will be matched to a subject with impaired hepatic function by age (± 10 years), gender, and body mass index (± 15%).

4.2. Inclusion Criteria

4.2.1. All Subjects

Subjects 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 70 years of age, inclusive at screening
3) Be a nonsmoker. No use of tobacco, nicotine or nicotine-containing or THC-containing products within the last 14 days of Day 1

4) Have a calculated body mass index (BMI) of ≥ 18.0 and ≤ 36.0 kg/m^2 at screening

5) Have a creatinine clearance (CL_{cr}) ≥ 60 mL/min (using the Cockcroft-Gault method {Cockcroft 1976}) based on serum creatinine and actual body weight as measured at screening, ie,

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

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

6) Females of childbearing potential (as defined in Appendix 3) must have a negative serum pregnancy test at screening and Day -1

7) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 3

8) Female subjects must refrain from egg donation or harvest from clinic admission (eg, Day -1), through the study period, and continuing for at least 35 days after the last dose of study drug

9) Male subjects must refrain from sperm donation from clinic admission (eg, Day -1), throughout the study period, and continuing for at least 90 days following the last dose of study drug

10) Subjects have not 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.

11) Have either a normal 12-lead electrocardiogram (ECG) or one with abnormalities that are considered clinically insignificant by the investigator

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

4.2.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment must also meet the following additional inclusion criteria to be eligible for participation in the study:

13) Aside from hepatic insufficiency, the subject must, in the opinion of the investigator, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, and screening laboratory evaluations

14) Must have diagnosis of chronic (> 6 months), stable hepatic impairment with no clinically significant changes within 3 months (or 90 days) prior to study drug administration (Day 1)

15) Must meet all of the following laboratory parameters at Screening:

- ALT value ≤ 10 × ULN
- AST value ≤ 10 × ULN
- Total bilirubin ≤ 10 x ULN
- Albumin ≥ 2.0 g/dL
- Absolute neutrophil count ≥ 1,000/mm^3
- Platelets ≥ 25,000/mm^3
- Hemoglobin ≥ 8 g/dL
- INR ≤ 2.3 (without the use of anticoagulants)
- α-fetoprotein < 50 ng/mL

16) Subjects with ***mild*** hepatic impairment must have a score on the CPT scale of 5-6 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification

17) Subjects with ***moderate*** hepatic impairment must have a score on the CPT scale of 7-9 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification

18) Subjects with ***severe*** hepatic impairment must have a score on the CPT scale of 10-15 at Screening. If a subject's score changes during the course of the study, the score at Screening will be used for classification.

19) Subjects with hepatic impairment with comorbid diseases not associated with hepatic impairment requiring medication(s) must be taking the medication(s) without a change in dose for at least 2 weeks (or 5 half-lives, whichever is longer) prior to dosing. Any change in the dosage during this timeframe should be reviewed and approved by the Sponsor.

4.2.3. Healthy Matched Control Subjects

Healthy matched control subjects must also meet the following additional inclusion criteria to be eligible for participation in this study:

20) Must meet all of the following laboratory parameters at Screening:

- INR ≤ 1 × ULN
- Albumin ≥ 1 × LLN

- Total bilirubin ≤ 1 × ULN
- AST value ≤ 1 × ULN
- ALT value ≤ 1 × ULN
- Alkaline phosphatase ≤ 1 × ULN
- α-fetoprotein ≤ 1 × ULN

21) Must match in age (± 10 years), gender, and BMI (± 15%) with the respective subject in the hepatic impairment group.

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

4.3. Exclusion Criteria

4.3.1. All Subjects

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

1) Pregnant or lactating subjects

2) Participation in any clinical study of an investigational drug/device within 4 weeks or 5 half-lives (whichever is longer) of the drug prior to Day -1. Exposure to investigational biologics should be discussed with the sponsor.

3) Have current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance or subject safety

4) Have a positive test result for human immunodeficiency virus type 1 or type 2 (HIV-1/2) antibody or antigen

5) Have poor venous access that limits phlebotomy

6) Receipt of a live attenuated vaccine within 4 weeks prior to Day 1, or planned administration of a live attenuated vaccine in the 6 weeks following Day 1

7) Have been treated with systemic (parenteral or oral) corticosteroids, immunosuppressant therapies, or chemotherapeutic agents within 3 months prior to screening or is expected to receive these agents during the study (eg, corticosteroids, immunoglobulins, and other immune- or cytokine-based therapies). Specific exception will be made for orally administered systemic corticosteroids, which are allowed until 28 days prior to Day 1. Beginning 28 days prior to Day 1, subjects with any systemic corticosteroid treatment (parenteral or oral) will be excluded.

8) 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 hepatotoxicity)

   c) Known hypersensitivity to filgotinib, its 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%), or a family history of long QT syndrome or unexplained death in an otherwise healthy individual between the ages of 1 and 30 years

   e) Primary varicella zoster virus (VZV) infection in the 4 weeks prior to Day 1; or history of herpes zoster (HZ) within the 4 weeks prior to Day 1; or any prior history of disseminated herpes zoster infection, herpes zoster ophthalmicus, or complication of varicella virus infection involving the central nervous system (CNS)

   f) History of syncope, recurrent palpitations, or unexplained dizziness

   g) Severe peptic ulcer disease, severe gastroesophageal reflux disease, or other gastric acid hypersecretory conditions

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

   i) Implanted defibrillator or pacemaker

   j) Prior allogeneic bone marrow progenitor cell or solid organ transplantation or currently registered on an organ transplantation list

   k) Prior placement of a portosystemic shunt (such as TIPS), unless vascular imaging indicates the shunt has no current blood flow.

9) Are unable to comply with study requirements or are otherwise believed, by the study investigator, to be inappropriate for study participation for any reason.

4.3.2. Subjects with Impaired Hepatic Function

Subjects with mild, moderate, or severe hepatic impairment meeting *any* of the following additional exclusion criteria are not to be enrolled in this study:

10) Aside from hepatic insufficiency, any serious or active medical or psychiatric illness that, in the opinion of the Investigator, would interfere with subject treatment, assessment, or compliance with the protocol. This would include any renal, cardiac, hematological, unstable hepatic, pulmonary (including chronic asthma), endocrine (eg, diabetes), central nervous,

gastrointestinal (including an ulcer), vascular, metabolic (eg, thyroid, or adrenal), or infectious disorders, as well as any immunodeficiency, malignancy, or spontaneous/unprovoked bleeding, that are clinically significant.

11) Positivity for serum hepatitis B virus surface antigen (HBsAg) at Screening or positivity for serum hepatitis B virus core antibody (HBcAb) at Screening

12) Positivity for serum hepatitis C virus (HCV) antibody (Ab) at Screening if accompanied by detectable HCV viremia. Subjects with positive serum HCV Ab at screening will undergo reflex plasma HCV RNA testing, and subjects with HCV RNA positivity will be excluded. Eligibility of those subjects with positive HCV Ab and negative HCV RNA at Screening will be allowed based on the investigator's judgment

13) Positive test for drugs of abuse, including alcohol at Screening or admission, with the exception of opioids and tetrahydrocannabinol (THC, marijuana) under prescription and Investigator verification for pain management. Subjects who screen positive for benzodiazepines may be allowed if prescribed under the care of a physician and after review by Investigator and Sponsor.

14) Requires paracentesis > 1 time per month during the past 3 months.

15) Changes in concomitant medications or dosage used to treat symptoms of hepatic impairment or associated comorbid conditions within 28 days prior to Day 1. This could lead to clinically significant changes in medical conditions during the course of the study that would affect the ability to interpret potential drug-drug interactions.

16) Any current signs or symptoms of severe hepatic encephalopathy, that in the opinion of the Investigator may affect the ability of the subject to provide initial and continuing informed consent to participate

17) History of gastric or esophageal variceal bleeding in which varices have not been adequately medically or surgically treated, or any history of variceal bleeding in the last 6 months unless banded

18) History of hepatorenal or hepatopulmonary syndrome

19) Current signs or symptoms consistent with spontaneous bacterial peritonitis, known active spontaneous bacterial peritonitis, or a history of spontaneous bacterial peritonitis within the last 6 months

20) Recent hospitalization (within the last 2 months) related to cirrhosis or its complications

21) Confirmed hypotension (defined as < 80 mmHg systolic and/or <50 mmHg diastolic) at screening, as measured in the supine position after resting for at least 5 minutes

22) Suspicion of hepatocellular carcinoma, ie, if α-fetoprotein > 50 ng/mL at Screening, enrollment is only allowed if results of appropriate diagnostic studies (eg CT scan or hepatic ultrasound) are inconsistent with a diagnosis of hepatocellular carcinoma

All concomitant medications including over-the-counter and herbal products must be approved by the Investigator and Medical Monitor prior to study enrollment and study drug administration.

4.3.3. Healthy Matched Control Subjects

Healthy matched controlled subjects meeting *any* of the following additional exclusion criteria are not to be enrolled in this study:

23) A positive test result for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody

24) Positive test for drugs of abuse, including alcohol at Screening or admission.

25) Have any serious or active medical or psychiatric illness (including depression) that, in the opinion of the investigator, would interfere with subject 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.

26) History of liver disease

27) 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.

5. STUDY DRUGS

5.1. Enrollment

It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a screening number at the time of consent.

At screening, study participants will be assigned to a cohort. Once eligibility has been confirmed following completion of the admission study procedures, eligible subjects will be assigned a subject number on Day 1 and will receive the study treatments as described in Section 5.3.

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. Once a subject number has been assigned to a subject, it will not be reassigned to another subject. If necessary, replacement subjects may be enrolled after discussion and approval from sponsor. A new unique subject number will be assigned to the replacement subject.

A subject number list will be provided to the study center by the sponsor.

5.2. Description and Handling of Filgotinib

5.2.1. Formulation

Filgotinib tablets, 100 mg, are beige, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "100" on the other. Each tablet contains the equivalent of 100 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, 100 mg, are packaged in white, high density polyethylene bottles (HDPE). Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap fitted with an induction-sealed, aluminum-faced liner.

Study drugs to be distributed to participating centers shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products) and/or other local regulations, as applicable.

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 subjects, all drug products should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study 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. Dosage and Administration of Study Drug

Following completion of Screening and Day -1 assessments, eligible subjects will receive a single oral dose of 100 mg filgotinib (1 × 100 mg tablet) on Day 1, in fasting state. Dosing in subjects with normal hepatic function will begin after a matched subject with hepatic impairment has completed all Day 1 PK assessments.

5.4. Fasting and Meals

Study drug will be administered on Day 1 with 240 mL of water following an overnight fast (no food or drinks except for water) for at least 10 hours. Subjects will continue to fast until after collection of the 4-hour blood sample, relative to study drug dosing. Additionally, subjects will be restricted from water consumption 1 hour before until 2 hours after dosing, except for the 240 mL given with the study treatment. A standardized meal may be provided to subjects after collection of the 4-hour blood draw.

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

5.5. 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 subjects 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 subjects.

5.5.1. Study Drug Return or Disposal

Please refer to Section 9.1.7.

5.6. Concomitant Medications and Other Protocol Restrictions

5.6.1. Concomitant Medications

5.6.1.1. Hepatic Impairment Groups

Concomitant use of certain medications or herbal/natural supplements with study drug may result in PK interactions resulting in increases or decreases in exposure of study drug or these medications.

Concomitant medications taken within 30 days of Screening through the FU visit need to be recorded in the source documents and Case Report Form (CRF)/electronic Case Report Forms (eCRFs).

Subjects with hepatic impairment with comorbid diseases not associated with hepatic impairment requiring medication(s) must be taking the medication(s) without a change in dose for at least 2 weeks (or 5 half-lives, whichever is longer) prior to dosing. Any change in the dosage during this timeframe should be reviewed and approved by the Sponsor.

Subjects with hepatic impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a change in dose within 28 days of Day 1.

All concomitant medications including over-the-counter and herbal products must be approved by the Investigator and Medical Monitor prior to study enrollment and study drug administration.

The following medications are prohibited from 28 days prior to Day 1 through discharge:

- Any and all illegal or illicit drug use, including use of prescription drugs outside the care of the prescribing physician.
- Hematologic stimulating agents (eg, erythropoiesis-stimulating agents [ESAs]; granulocyte colony stimulating factor [GCSF]; thrombopoietin [TPO] mimetics)
- Chronic systemic immunosuppressants including, but not limited to, corticosteroids azathioprine, or monoclonal antibodies (eg, infliximab).
- Investigational agents or devices for any indication

- Filgotinib is a P-gp substrate. Concomitant use of P-gp inducers or inhibitors with filgotinib may result in changes in exposure of filgotinib or its metabolite GS-829845 and are prohibited from 21 days prior to Day 1 through discharge. Example P-gp inducers and inhibitors are listed below:

  — P-gp inducers: phenobarbital, phenytoin, carbamazepine, rifabutin, rifapentine, rifampin, St. John's wort, and danshen (salvia miltiorrhiza)

  — P-gp inhibitors: amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, and verapamil.

Medications for disease conditions **excluded** from the protocol (eg, HIV-1 or HIV-2, HBV, or HCV infection; active cancer; transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

5.6.1.2. Subjects with Normal Hepatic Function

The following medications are excluded while subjects with normal hepatic function are participating in the study:

- Any prescription medications or over-the-counter medications including herbal products and antacids within 28 days of commencing study drug dosing (Day 1) with the exception of vitamins, acetaminophen, ibuprofen and/or hormonal contraceptives. However, the short term use of topical hydrocortisone cream or non-corticosteriod ointment to treat minor skin irritation due to ECG leads will be allowed. If a subject requires use of a disallowed medication, a request for such use must be reviewed by the Sponsor and if approved, subjects 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.

5.6.2. Other Protocol Restrictions

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

- Subjects will be required to refrain from the use of nicotine or nicotine-containing or THC-containing products 14 days prior to first dose of study drug and during the course of the study through the FU visit.

- Subjects 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 the FU visit.

- While confined at the study center, tea, coffee, chocolate, and other foods and beverages containing caffeine and other methylxanthines will be prohibited on 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 subjects are outside of the clinic.

- Subjects 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 until completion of the FU visit, 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 subject will be questioned as to their compliance with the above protocol restrictions**.** If a subject is unable to comply with any of the restrictions described above, the subject'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 subject enrolled in the study are detailed below.

Any deviation from protocol procedures should be noted in the subject's clinical chart and appropriate CRFs/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 institutional review board (IRB)/ethics committee (EC)/other applicable regulatory agencies have 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 subject, using the study-specific, IRB/EC-approved ICF, is required before initiating the screening process.

6.1. Subject Enrollment and Treatment Assignment

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

It is the responsibility of the investigator to ensure that subjects 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, subjects will be enrolled to receive study drug on Day 1.

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

Table 6-1. Schedule of Assessments

Study Procedure	Screen[a]	Day -1	Day 1	Days 2-5	Day 6[b]	Day 15 (± 1 day)[c]	ET[d]
Written Informed Consent	X						
Medical History	X						
Complete Physical Exam	X					X	X
Symptom-Driven Physical Examination[e]		X	X	X	X		
Height	X						
Weight, BMI	X	X					
Vital Signs[f]	X	X	X	X[g]	X	X	X
HIV-1/2, HBV, and HCV Testing	X						
Hematology[h]	X	X[i]	X		X	X	X
Chemistry[h]	X	X[i]	X		X	X	X
Coagulation[h]	X	X[i]	X		X	X	X
α-fetoprotein	X						
Urinalysis	X	X[i]	X		X	X	X
Serum Pregnancy Test[j]	X	X[i]			X	X	X
FSH[k]	X						
Urine Drug, Cotinine, and Alcohol Screen	X	X[i]				X	X
12-Lead ECG	X	X	X[l]		X	X	X
Enrollment[m]			X				
Study Drug Administration			X				
PK Assessments[n]			X				X
Review Study Restrictions	X	X			X	X	X
Clinic Confinement		X					
Review AEs & Concomitant Medications[o]	X						

a Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug.
b Subjects will be discharged from the clinic on Day 6, following all morning assessments.
c Subjects will return for a FU visit on Day 15 (± 1 day).

d Assessments will be performed within 72 hours of early termination (ET) 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 Day 3 only.
h Hematology, Chemistry, Coagulation: See Section 6.9.5.1for specifics.
i Two sets of safety labs will be collected upon clinic admission; one will be sent to the central lab and another will be sent to the sites' local lab to obtain results in time for enrollment on Day 1.
j Females of child-bearing potential only.
k Female subjects < 54 years old with amenorrhea ≥ 12 months as outlined in Appendix 3
l 2 hours postdose.
m On Day 1, subjects will be enrolled immediately prior to dosing.
n Intensive PK sampling will occur relative to dosing of filgotinib on Day 1 at the following time points for each cohort: Day 1: 0 (predose, ≤ 5 min before dose), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours postdose. A blood sample for PK analysis will be collected at the ET visit (if applicable) and may be analyzed.
o 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 Visit

Prospective subjects should be screened no more than 28 days prior to administration of the first dose of study drug. If a subject 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 subjects will be screened to identify up to 60 subjects for enrollment.

Subjects should be instructed to fast (no food or drink, except water), starting from midnight (00:00) or earlier, as appropriate, on the evening prior to 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 subject before initiation of any screening procedure. After a subject has provided informed consent, the investigator and other study personnel will determine if the subject 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 and described in the following text.

Eligible subjects 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. Subjects 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 SAEs, as well as any AE related to protocol-mandated procedures on the AE CRF/eCRF. All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history are to be captured on the medical history CRF/eCRF. See Section 7 Adverse Events and Toxicity Management for additional details.

6.2.2. Admission Assessments

6.2.2.1. Admission

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

Subjects 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.

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

6.2.2.2. Clinic Confinement

Following Screening and admission assessments, eligible subjects will be confined to the study center beginning Day -1 until the completion of assessments on Day 6. Subjects will return for an in-clinic FU visit on Day 15 (± 1 day).

6.3. Check-in Assessments

Following completion of screening and Day -1 assessments, eligible subjects will be assigned a subject number and receive study treatments as shown in Section 5.3.

6.4. Treatment Assessments

Study procedures and assessments are outlined in Table 6-1.

6.5. Posttreatment Assessments

Subjects will return for an in-clinic FU visit on Day 15 (± 1 day). Study procedures and assessments are outlined in Table 6-1.

6.6. Assessments for Premature Discontinuation from Study

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

6.7. Study Stopping Criteria

If ≥ 2 subjects in any cohort experience the same or similar Grade 3 or Grade 4 treatment-emergent AE or confirmed laboratory abnormality that is not attributable to obvious alternative explanation (eg, hematuria occurring in a menstruating female, creatine kinase [CK] elevation after strenuous exercise, or triglyceride elevation that is non-fasting, etc), a review of all safety data generated in subjects dosed to date will be initiated. The decision as to whether and how to proceed with further enrollment will be determined based on the safety review.

6.8. Pharmacokinetic Assessments

Intensive PK sampling will occur relative to dosing of filgotinib at the following time points:

- Day 1: 0 (predose, ≤ 5 minutes prior to dosing), 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36, 48, 72, 96, and 120 hours postdose

A blood sample for PK analysis will be collected at the ET visit (if applicable) and may be analyzed.

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be measured and PK parameters determined. Plasma concentrations of other metabolites may be determined and PK explored.

Protein binding of filgotinib and its major metabolite (GS-829845) will be assessed at their T_{max} time point(s) as well as at another later time point.

6.9. Safety Assessments

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

6.9.1. Electrocardiogram Assessment

Subjects 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 subjects 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. 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.

6.9.2. Physical Examination

Physical examinations conducted throughout the study will be a complete physical examination or a symptom-directed physical examination, as outlined in Table 6-1. 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, or THC-containing products, alcohol and illegal drug use, and prior (within 30 days) and current medication use

6.9.3. Vital Signs

Vital sign measurements include blood pressure, heart rate, respiration rate, and temperature and should be taken once subjects have been seated or in the supine position. Subject position for measurement should be kept consistent throughout the study. Refer to Table 6-1 for vital signs collection time points.

6.9.4. Body Mass Index

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

6.9.5. Clinical Laboratory Tests/Assessments

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

6.9.5.1. Blood Sampling

Blood samples will be collected for the following laboratory analyses:

- Hematology: CBC with differential
- Chemistry (fasting): alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, total protein, albumin, lactic acid dehydrogenase (LDH), creatine kinase (CK), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine (see below), glucose, phosphorus, magnesium, potassium, sodium, uric acid, and amylase (reflex lipase testing is performed in subjects with total amylase > 1.5 × upper limit of normal [ULN]
- Coagulation: PT, PTT, INR
- α-fetoprotein
- HIV-1 and HIV- 2, HBV(sAg, cAb), and HCV (Ab; if positive, then reflex HCV RNA) testing
- Serum pregnancy test (females of childbearing potential only)
- Follicle-stimulating hormone (FSH) testing (female subjects < 54 years old with amenorrhea ≥ 12 months)

6.9.5.2. Urine Samples

Urine samples will be collected for urinalysis and alcohol, drug, and cotinine screen assessments.

6.9.6. Creatinine Clearance

Weight will be collected at screening to calculate creatinine clearance (CL_{cr}) for inclusion criteria.

6.9.7. 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. See Section 7 for more information regarding AEs and Sections 4.3 and 5.6.1 for more information about concomitant medications.

6.10. Sample Storage

PPD

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject 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 pre- or posttreatment complications that occur as a result of protocol-specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an 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 7.6)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and that is not related to a protocol-associated procedure is not an AE. It is considered to be preexisting and should be documented on the medical history eCRF.

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified subinvestigator is responsible for assessing the relationship to 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, or concomitant medication).
- **Yes**: There is reasonable possibility that the event 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 modified Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. For each episode, the highest grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the modified CTCAE, these intensity grades are defined in Table 7-1 and Appendix 4.

Table 7-1. Grading of Adverse Event Severity

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

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

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

7.3.1. Requirements for Collection Prior to Study Drug Initiation

After obtaining informed consent, but prior to initiation of study drug, all SAEs and AEs related to protocol-mandated procedures should be reported on the eCRF.

7.3.1.1. Adverse Events

Following initiation of study treatment, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug must be reported 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 FU period.

7.3.1.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment FU period, must be reported to the eCRF database and Pharmacovigilance & Epidemiology (PVE) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the posttreatment FU visit but within 30 days of the last dose of study drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after days of the last dose of study drug; however, if an investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, the investigator should promptly document and report the event to Gilead PVE

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

7.3.1.3. Electronic Serious Adverse Event Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of an investigator's knowledge of the event. Detailed instructions may be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically (eg, the eCRF database is not functioning), record the SAE on the paper SAE reporting form and submit within 24 hours as described above.

Gilead PVE
Fax: PPD
Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

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

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by email or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States (US) 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, serious adverse drug reactions (SADRs), or SUSARs. In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant independent ethics committee (IEC) in concerned member states of applicable SUSARs as outlined in current regulations.

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

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

7.5. Clinical Laboratory Abnormalities

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

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Severity should be recorded and graded according to the modified CTCAE, version 4.03 (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.

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

For study specific stopping criteria, please refer to Section 6.7.

7.6. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically, when feasible, 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.

Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results and followed until resolution or until stable, if possible. Refer to Appendix 2 for additional details on toxicity management.

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

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

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

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

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

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

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Sections 7.1.1 and 7.1.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead PVE using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE by emailing PPD or faxing PPD

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to Gilead PVE using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of pregnancy should continue until its conclusion. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead PVE by faxing PPD or emailing PPD

Refer to Appendix 3, Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

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

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is as follows:

- To evaluate the PK of filgotinib and its metabolite GS-829845 in subjects with impaired hepatic function relative to matched, healthy controls

The secondary objective of this study is as follows:

- To evaluate the safety and tolerability of filgotinib in subjects with normal and impaired hepatic function

8.1.2. Primary Endpoint

The primary endpoints are PK parameters (e.g., AUC_{last}, AUC_{inf}, and C_{max}) for filgotinib and GS-829845.

8.1.3. Secondary Endpoint

The secondary endpoints include incidences of AEs, laboratory abnormalities, abnormal findings in vital signs and safety ECG monitoring.

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Enrolled

The All Enrolled Analysis Set will include all subjects enrolled into the study after screening. This is primary analysis set for listings.

8.2.1.2. Safety

The Safety Analysis Set will include all enrolled subjects who received 1 dose of filgotinib.

8.2.1.3. Pharmacokinetics

The PK Analysis Set will include all enrolled subjects who received 1 dose of filgotinib and had at least 1 nonmissing PK concentration datum of filgotinib or its metabolite GS-829845 reported by PK lab.

8.3. 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, such as height, weight and BMI, will be summarized and descriptive statistics will be provided.

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

8.5. Interim Analysis

Review of available safety and PK data will be conducted by the sponsor to facilitate the decision on whether or not to conduct the adaptive cohorts.

8.6. Safety Analysis

All safety data collected on or after the date that study drug was first administered up to the date of last dose of study drug plus 30 days will be summarized by hepatic function group using Safety Analysis Set.

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the current version of 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.

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

8.6.3. Laboratory Evaluations

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

8.6.4. Other Safety Evaluations

Vital signs and ECG data will be summarized by hepatic function group.

8.7. Pharmacokinetic Analysis

Plasma concentrations over sampling time and PK parameters (C_{max}, T_{max}, C_{last}, T_{last}, λ_z, AUC_{last}, AUC_{inf}, $\%AUC_{exp}$, $t_{½}$, CL/F, and V_z/F, as appropriate)for filgotinib and GS-829845 will be listed and summarized by hepatic function group using descriptive statistics (eg, sample size, mean, SD, %CV, median, first quartile, third quartile, minimum, and maximum).

An analysis of variance appropriate for a parallel design will be fitted to the natural logarithmic transformation of PK parameters (AUC_{last}, AUC_{inf}, and C_{max}) for filgotinib and GS-829845. Two-sided 90% CIs will be calculated for the GLSM ratios of PK parameters between hepatic impairment group versus the matched control (normal hepatic function) group. If the 2-sided 90% CIs of the GLSM ratio for AUC_{last}, AUC_{inf}, and C_{max} of filgotinib or GS-829845 falls within the [50%, 200%] bound, the null hypothesis that subjects with hepatic impairment exhibit PK parameter change of at least 2-fold for filgotinib or GS-829845 compared with subjects with normal liver function will be rejected.

Protein binding of filgotinib and GS-829845 at their T_{max} and another later time point will be summarized by hepatic function group using descriptive statistics. Unbound PK parameters such as CLu/F, and Vzu/F will be calculated as appropriate and summarized by hepatic function group. Relationships between measures of hepatic function (ie, CPT score, serum albumin, total bilirubin, prothrombin time, and International Normalized Ratio [INR]) and primary filgotinib/GS-829845 PK parameters will be evaluated.

8.8. Sample Size

With 16 (8 per group) evaluable subjects, the estimated two-sided 90% CI of the geometric least-square mean (GLSM) ratio of test vs reference groups, with regards to PK parameters (AUC and C_{max}) would be within (50%, 200%) with over 95% probability, if the estimated GLSM ratio were 1.0. This is assuming the SDs for PK parameters between subjects within each group is no more than 0.347 (or 0.203) for the natural logarithm-transformed PK parameters for filgotinib (or GS-829845). Such assumptions are supported by PK data from a prior Gilead study of filgotinib (GS-US-417-3900) with 100 mg dose in healthy volunteers. An overage of 2 subjects per group will be enrolled in order to accommodate subject drop-outs, so a total sample size of 20 subjects (10 per group) for each cohort 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 the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the EU Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, Part 50, "Protection of Human Subjects," and 21 CFR, Part 56, "Institutional Review Boards."

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, "Financial Disclosure by Clinical Investigators," providing 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 subject completes the protocol-defined activities.

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

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

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

9.1.3. Informed Consent

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

9.1.4. Confidentiality

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

The investigator agrees that all information received from Gilead, including but not limited to the IB, this protocol, eCRF, the study drug, 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) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF, IRB/EC and 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 subject:

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number)
- Study discussed and date of informed consent
- Dates of all visits
- Documentation that protocol specific procedures were performed
- Results of efficacy parameters, as required by the protocol
- Start and end dates (including dose regimen) of study drug, including dates of dispensing and return
- Record of all AEs and other safety parameters (start and end dates, and including causality and severity)
- 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 until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

9.1.6. Case Report Forms

For each subject 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 subject 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 subject has been enrolled. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture 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. Study Drug Accountability and Return

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

A copy of the site's IMP Disposal SOP or written procedure (signed and dated by the investigator or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead (or Gilead's representative) for return of unused study drug supplies. If IMP is destroyed on site, the investigator must maintain accurate records for all IMPs destroyed. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to Gilead.

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to IRB/EC in accordance with local requirements and receive documented IRB/EC 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(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met: the results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

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

No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol (eg, attendance at investigator's meetings). If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to federal and state agencies any expenses paid or reimbursed for such services, including any clinical 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 study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

10. REFERENCES

Clark JD, Flanagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem 2014;57 (12):5023-38.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.

U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling. May, 2003.

11. APPENDICES

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 1 Open-Label Study to Evaluate the Pharmacokinetics of Filgotinib in Subjects with Impaired Hepatic Function

GS-US-417-4048, Original, 19 December 2017

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

PPD

Medical Monitor

PPD

Signature

12/21/2017

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.

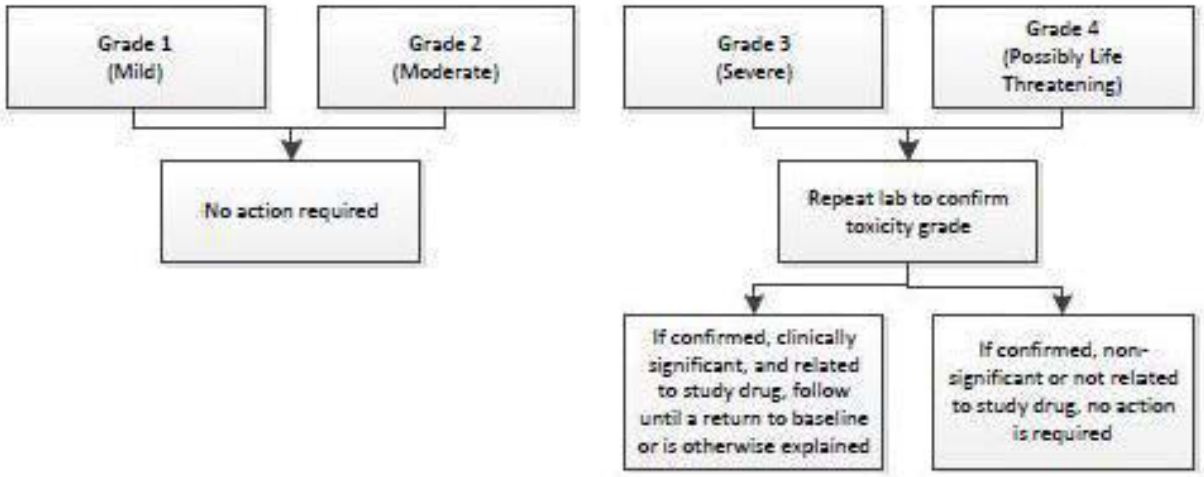
Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Management of Clinical and Laboratory Adverse Events



Appendix 3. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

The administration of filgotinib in embryo-fetal animal development studies resulted in decreased numbers of viable rat fetuses, increased resorptions, and visceral and skeletal malformations. Similar effects were noted in the rabbit. A safety margin relative to human exposure has not been identified. Filgotininb is contraindicated during pregnancy.

For participation in this study, all subjects of childbearing potential must agree to the use of *highly effective* contraception as outlined below.

1) Definitions

a) Definition of Childbearing Potential

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

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

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age. Bilateral tubal ligation is not considered permanent sterilization.

b) Definition of Male Fertility

For the purposes of this study, a male born subject is considered of fertile after the initiation of puberty unless the subject is permanently sterile by bilateral orchidectomy or medical documentation. Vasectomy is not considered permanent sterilization.

2) Contraception Requirements for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Data from a drug-drug interaction study of filgotinib and hormonal contraceptives (GS-US-417-3916) demonstrated that filgotinib does not alter the pharmacokinetics of a representative hormonal contraceptive levonorgestrel/ethinyl estradiol.

For female subjects, hormonal contraceptives will be permitted as a form of contraception when used a conjunction with a barrier method (preferably a male condom). For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

Please refer to the latest version of the filgotinib IB for additional information.

b) Contraception Requirements for Female Subjects

The inclusion of female subjects of childbearing potential requires the use of highly effective contraceptive measures. Women must have a negative serum pregnancy test at Screening and on Day -1 prior to study drug treatment. Pregnancy tests will be performed throughout the study period (refer to Table 6-1).

Female subjects must agree to use one of the following methods (where permitted and used per local prescribing label) from Screening until 35 days following the last dose of study drug.

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

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
  - Intrauterine device (IUD) with a failure rate of <1% per year
  - Tubal sterilization
  - Essure micro-insert system (provided confirmation of success 3 months after procedure)
  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success at least 3 months after procedure, with documentation of sperm-free ejaculate)

These above described methods are considered *preferred methods* of highly effective contraception in this protocol.

Female subjects who wish to use a hormonally based method must agree to use it in conjunction with a barrier method (used either by the female subject or by her male partner). Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing.

Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (subject must agree to use with a barrier method, preferably, with a male condom)
  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods (subject must agree to use with a hormonal method)
  - Male or female condom, with or without spermicide
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide
- All female subjects must also agree to refrain from egg donation and in vitro fertilization during study participation and for at least 35 days after the last study drug dose.

3) Contraception Requirements for Male Subjects

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

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

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 35 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant within 90 days of the last dose of study drug must report the information to the investigator.

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

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

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

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

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

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

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