GILEAD Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Perianal Fistulizing Crohn's Disease
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404, USA
IND Number:	129646
EudraCT Number:	2016-003153-15
Clinical Trials.gov Identifier:	NCT03077412
Indication:	Fistulizing Crohn's Disease
Protocol ID:	GS-US-419-4016
Contact Information:	The medical monitor name and contact information will be provided on the Key Study Team Contact List.
Protocol Version/Date:	Original: 12 September 2016 Amendment 1: 06 January 2017 Amendment 1.1: 28 February 2017 Amendment 2: 26 June 2017 Amendment 3: 11 October 2018 Amendment 4: 11 April 2019 Amendment 5: 04 February 2020

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PROTOCOL SYNOPSIS

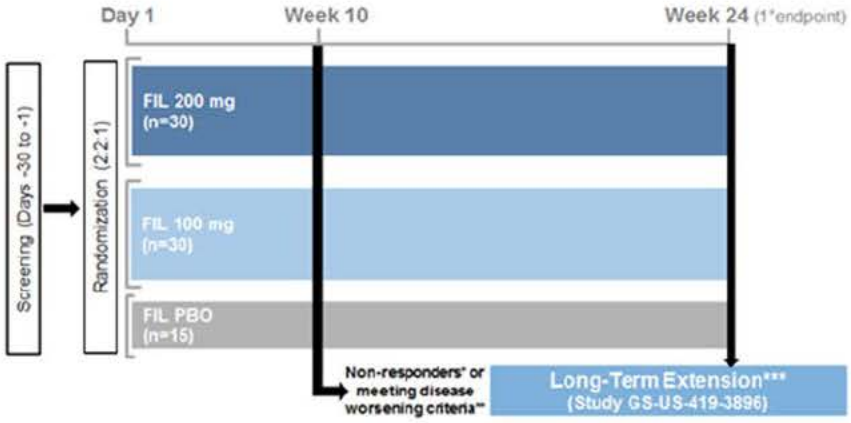
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Perianal Fistulizing Crohn's Disease
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	129646 2016-003153-15 NCT03077412
Study Centers Planned:	Approximately 60 centers across North America and Europe
Objectives:	The primary objective of this study is: • To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula response at Week 24 The secondary objectives of this study are: • To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula remission at Week 24 • To assess the time to clinical fistula response • To assess the time to clinical fistula remission • To evaluate the efficacy of filgotinib as compared to placebo in establishing proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline • To evaluate the safety and tolerability of filgotinib CCI [redacted]

[redacted]

Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of filgotinib in treating subjects with perianal fistulizing Crohn's disease (CD). Approximately 75 subjects aged 18 to 75 years with perianal fistulizing CD will be randomized to 1 of 3 treatment groups in a 2:2:1 ratio.



FIL = filgotinib; PBO = placebo; mg = milligram.

* Non-responders (luminal disease) are defined as subjects who either had a baseline CDAI score ≥ 220 and never achieve a ≥ 70-point CDAI reduction from baseline at any point up to and including Week 10 OR had a baseline CDAI score < 220 and have an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at Week 10. Non-responders (perianal fistulizing disease) are defined as subjects who meet the following criteria for PDAI symptom subscores : "Discharge" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10 OR "Pain/restriction of activities" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10

** Disease worsening is defined as an increase in CDAI of ≥ 100 points from the Week 10 value with CDAI score ≥ 220 points at 2 consecutive visits

*** Subjects who are non-responders, meeting disease worsening criteria, or complete the study at Week 24, will have the option to enter a separate LTE study, if eligible.

Treatment group 1 (n=30): filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily

Treatment group 2 (n=30): filgotinib 100 mg and PTM filgotinib 200 mg, once daily

Treatment group 3 (n=15): PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: United States (US) males who have not failed at least 2 prior biologic therapies (any tumor necrosis factor-alpha [TNFα] antagonist and vedolizumab) will be randomized in a 2:1 ratio to either filgotinib 100 mg or matching placebo.

For the purposes of this protocol, US males who have failed at least one prior TNF antagonist and present with actively draining perianal fistulae despite concomitantly taking vedolizumab at Day 1 will be considered as dual refractory patients. This assessment is based on recently published data from a subgroup analysis of the GEMINI-2 study, showing a beneficial effect of vedolizumab treatment for patients that were randomized with actively draining perianal fistulae at baseline {Feagan 2018}.

Treatment assignments will be stratified by:

- Anatomy of draining perianal fistulae at screening determined by MRI (simple *versus* complex)
- Receiving vedolizumab therapy concomitantly at Day 1 (Yes or No)
- Presence of moderately to severely active proctitis (Yes or No)

This study includes:

- Screening (Day -30 to -1)
- Randomization (Day 1)
- Blinded treatment (Day 1 to Week 24)

  Efficacy assessment: At Week 24, physical examination (PE), flexible sigmoidoscopy to assess presence of proctitis, and MRI of the pelvis to assess fistula response

  Subjects who complete all procedures per protocol, including the MRI at Week 24, may be offered the option to continue into a separate Long Term Extension (LTE) study (GS-US-419-3896), if deemed appropriate by the investigator

  Subjects who are non-responders at Week 10 (see Section 3.6 OR Section 3.7) or who meet disease worsening criteria (see Section 8) after Week 10 will have the option to enter the LTE study, if eligible.

- Post Treatment (PTx) safety assessments

  All subjects completing this study will be offered the option to continue study drug in a blinded fashion in the LTE study, if eligible

  Subjects who are eligible and opt to participate in the LTE study can continue into the LTE study without PTx safety assessments

  Subjects who opt out of the LTE study will return to clinic 30 days after the last dose of study drug for PTx safety assessments

  Subjects who are non-responders or meet disease-worsening criteria at or after Week 10 will complete MRI and flexible sigmoidoscopy prior to study discontinuation or entry into the LTE study

Non-responders for luminal disease activity are subjects who either had a baseline CDAI score ≥ 220 and never achieve a ≥ 70-point CDAI reduction from baseline at any point up to and including Week 10 OR had a baseline CDAI score < 220 and have an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at Week 10.

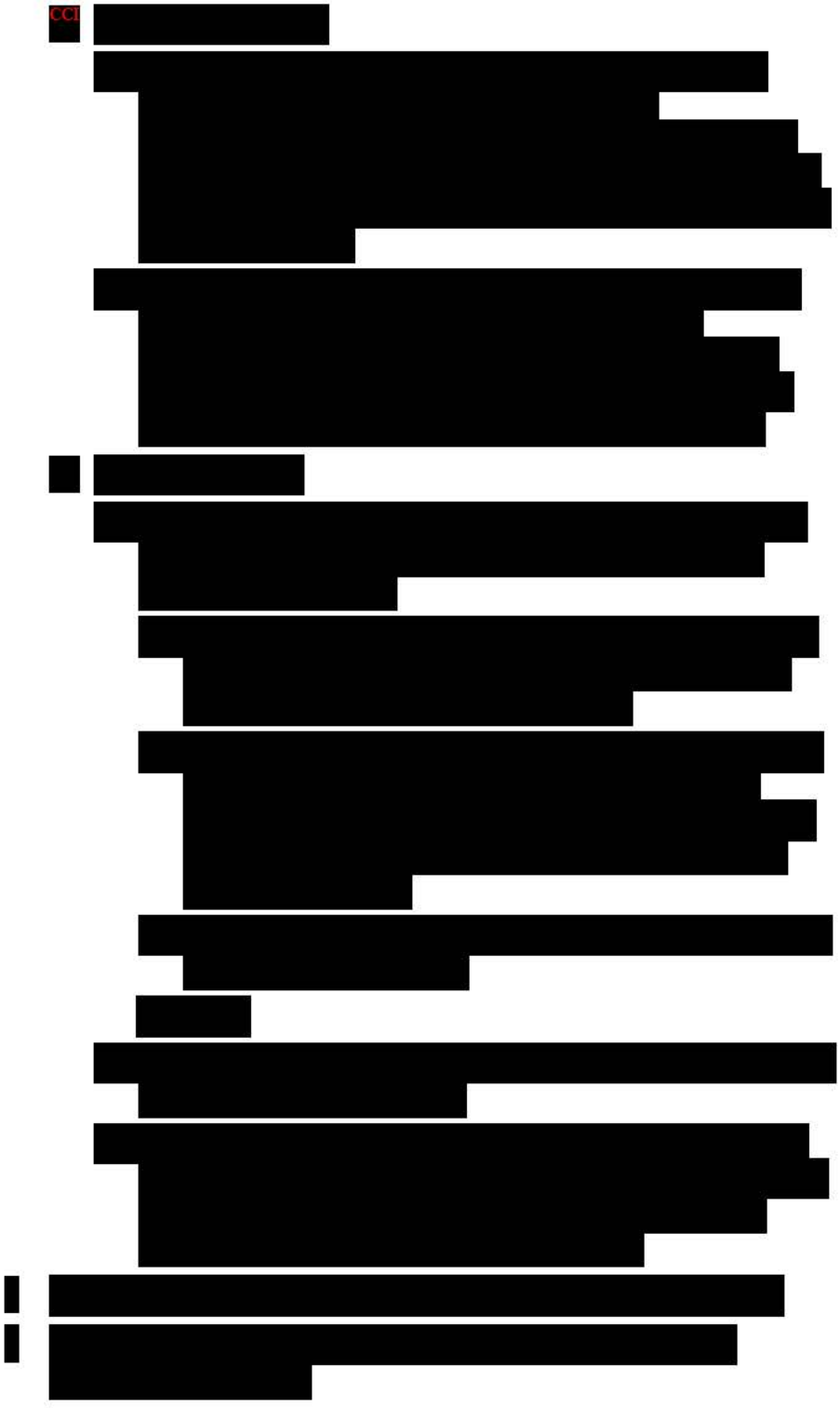
Non-responders (perianal fistulizing disease) are defined as subjects who meet the following criteria for PDAI symptom subscores: "Discharge" subscore of >1 and ≥ 1point increase from baseline at Week 6 and Week 10 OR "Pain/restriction of activities" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10.

Disease worsening is defined as an increase in CDAI of ≥ 100 points from the Week 10 value with CDAI ≥ 220 at 2 consecutive visits.

Steroid tapering must begin at Week 10 for subjects who are considered responders.

CCI [redacted]

CCI


CCI


CCI

	CCI [redacted]
Test Product, Dose, and Mode of Administration:	Filgotinib 200 mg oral tablet, once daily Filgotinib 100 mg oral tablet, once daily
Reference Therapy, Dose, and Mode of Administration:	PTM filgotinib 200 mg oral tablet, once daily PTM filgotinib 100 mg oral tablet, once daily
Criteria for Evaluation:	
Safety:	Assessment of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of AEs, PE (complete, symptom-driven, and perianal), vital signs, and clinical laboratory evaluations (hematology, chemistry, urinalysis). An ECG will be performed at screening and at Week 10 or ET if the subject terminates prior to Week 10. A data monitoring committee (DMC) will meet twice to evaluate all available safety data of the study. The initial meeting will occur after approximately 20% of the planned total number of subjects reaches Week 10 in the study. Following this, the next meeting will occur after approximately 50% of the subjects reach Week 10. Additionally, the DMC members may request an unscheduled review of the study data based on a concern for subject safety.

Efficacy:	Efficacy will be evaluated by combined fistula response (reduction of ≥1 from baseline in the number of draining external perianal fistula openings that were present at baseline and absence of fluid collection > 1cm on MRI pelvis) at Week 24. After a minimum of 35 subjects (estimated to be 7 from placebo group and 14 from each filgotinib treatment group based on randomization ratio) are enrolled and complete Week 10 visit or discontinue from the study, an interim futility analysis will be conducted to evaluate efficacy improvement in fistulizing disease. The summary statistics to evaluate perianal fistula closure of external openings, and CCI [redacted] improvement will be generated and provided to the DMC. The DMC will make a recommendation to either continue the study without modification or recommend that the study be halted due to lack of efficacy based on the totality of data available at the time of the interim analysis.
CCI [redacted]	[redacted]
[redacted]	[redacted]
	[redacted] CCI [redacted]
Statistical Methods:	The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), which includes all randomized subjects who received at least one dose of study drug. The primary efficacy endpoint is the proportion of subjects establishing combined fistula response at Week 24. Secondary efficacy endpoints include: • Proportion of subjects establishing combined fistula remission at Week 24 • Time to clinical fistula response • Time to clinical fistula remission • Proportion of subjects achieving proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline

For the primary efficacy endpoint, the number and proportion of subjects establishing combined fistula response at Week 24 for each treatment group will be summary zed with a corresponding 90% exact confidence interval (CI) based on the binomial distribution (Clopper-Pearson method). The difference in proportions between each filgotinib dose group and the placebo group will be presented, along with the associated 90% CI.

Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, non-responder imputation [NRI]). No formal hypothesis testing will be performed.

All time-to-event endpoints will be analyzed using the Kaplan-Meier method. The stratified Cox proportional hazards model will be used to estimate the hazard ratio with the corresponding 90% CI.

Safety will be evaluated by assessment of clinical laboratory tests, PEs, vital signs measurements at various time points during the study, and by the documentation of AEs. All safety data collected on or after the first dose of study drug administration (Day 1) up to 30 days after permanent discontinuation of study drug will be summarized by treatment group according to the study drug received.

A total of approximately 75 subjects are planned to be randomized (2:2:1 ratio); 30 subjects to each of the filgotinib dose groups and 15 subjects to the placebo group. This sample size is considered adequate to assess the safety, tolerability, and efficacy of filgotinib in a descriptive manner.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

°C	degrees Celsius
°F	degrees Fahrenheit
5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration, drug versus time curve
BAP	Biomarker Analysis Plan
BLQ	below the limit of quantitation
BMI	body mass index
CC&G	Cockcroft-Gault
C. diff	*Clostridium difficile*
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CES	Carboxylesterases
CI	confidence interval
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form(s)
CRP	c-reactive protein
CRPhs	c-reactive protein, high sensitivity
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSS	dextran sodium sulfate
EC	ethics committee
E.coli	*Escherichia coli*
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	Electronic Data Capture
EMA	European Medicines Agency

CCI	[redacted]
ET	early termination
EU	European Union
EudraCT	European clinical trials database
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FDA	Fistula Drainage Assessment
GCP	Good Clinical Practice (Guidelines)
GHAS	Global Histologic Disease Activity Score
GSI	Gilead Sciences, Inc.
h	Hours
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
CCI	[redacted]
IB	investigator brochure
IBD	inflammatory bowel disease
CCI	[redacted]
IC_{50}	concentration of an inhibitor that is required for 50-percent inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IM	Intramuscular
IMP	investigational medicinal product
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
JAK	Janus Kinase
JAK-STAT	Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT)
LDL	low-density lipoprotein
LLT	Lower-Level Term
LLOQ	lower limit of quantification
LOCF	Last Observation Carried Forward
LTE	long-term extension

MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
MPO	Myeloperoxidase
MTX	Methotrexate
CCI	[redacted]
NOEL	No-observed-effect-levels
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drugs
nM	nanomolar
OAT	organic anion transporters
O&P	ova and parasites test
OLE	Open Label Extension
P-gp	p-glycoprotein
PBMC	peripheral blood mononuclear cell
PBO	placebo
PD	pharmacodynamics
PDAI	Perianal Disease Activity Index
PE	physical examination
PEG	polyethylene glycol
PI	principal investigator
CCI	[redacted]
CCI	[redacted]
PT	preferred term
PTx	Post-Treatment
PTM	placebo to match
PVE	Pharmacovigilance & Epidemiology
RA	rheumatoid arthritis
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
CCI	[redacted]
SOC	system organ class
SOP	standard operating procedure
spp	species

SUSAR	suspected unexpected serious adverse reaction
STAT	signal transducer and activator of transcription
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor-alpha
TYK	Tyrosine Kinase
UC	ulcerative colitis
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
CCI	[redacted]
WBC	white blood cell
CCI	[redacted]

DEFINITION OF TERMS

Simple Fistula (for stratification purposes)	Single, unbranched submucosal or intersphincteric fistula tract, no extensions, no inflammatory mass/collections, single external opening
Complex Fistula(e) (for stratification purposes)	Multiple simple fistulae **OR** Single branched (multiple external openings arising from one fistula tract), trans-, extra-, or suprasphincteric fistulae tracts, possible extensions, and/or focal to small collections
Perianal Fistula Closure	No fistula drainage despite gentle external compression
Clinical Fistula Remission	Perianal fistula closure of all external openings that were draining at baseline
Clinical Fistula Response	Reduction of ≥ 1 from baseline in the number of draining external perianal fistula openings that were present at baseline
Combined Fistula Remission	Perianal fistula closure of all external openings that were draining at baseline, and absence of fluid collections > 1cm on MRI pelvis
Combined Fistula Response	Reduction of ≥ 1 from baseline in the number of draining external perianal fistulae openings that were present at baseline, and absence of fluid collections > 1cm on MRI pelvis
Proctitis SES-CD Score	Sum of ulcer size and ulcerated surface SES-CD endoscopy subscores for the rectum and anal canal, assessed by centrally read flexible sigmoidoscopy
Anal Canal Segmental SES-CD score	Sum of ulcer size and ulcerated surface SES-CD endoscopy subscores for the anal canal segment only, assessed by centrally read flexible sigmoidoscopy
Moderately to Severely Active Proctitis	Proctitis SES-CD Score > 2
Proctitis Remission	A Proctitis SES-CD Score of 0
Disease Worsening	An increase in CDAI of ≥ 100 points from the Week 10 value with CDAI ≥ 220 at 2 consecutive visits
Non-responder (Luminal Disease)	Subject who had a baseline CDAI score ≥ 220 and never achieves a ≥ 70-point CDAI reduction from baseline at any point up to and including Week 10 OR had a baseline CDAI score < 220 and have an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at Week 10
Non-Responder (Perianal Fistulizing Disease)	Subjects who meet the following criteria for PDAI symptom subscores: • "Discharge" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10 OR • "Pain/restriction of activities" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10

1. INTRODUCTION

1.1. Background

Crohn's disease (CD) is a relapsing and remitting form of inflammatory bowel disease (IBD) that causes gastrointestinal signs and symptoms of diarrhea, abdominal pain, weight loss, and the passage of blood or mucous per rectum. The inflammation of CD can involve the mucosal surface of the gastrointestinal tract and penetrate through the full thickness of the gastrointestinal wall, including the serosal surface. Crohn's disease is characterized by phenotype and location of involved bowel. The phenotypes include inflammatory, stricturing, and penetrating subtypes. Stricture formation can result in intestinal obstruction requiring surgical management. Over time, patients with repeated surgeries are at risk for developing short bowel syndrome and/or intestinal failure. Penetrating disease is characterized by fistula formation, which can be bowel to bowel, bowel to skin, or bowel to adjacent organ. Depending on location, penetrating disease can also require surgical management. Penetrating disease can also manifest with intra-abdominal abscess, a condition which can be life threatening if not treated early with systemic antibiotics (and/or drainage). In addition, CD may affect other organ systems leading to rashes, joint pain and stiffness, fever, and weight loss {Baumgart 2012}.

The incidence and prevalence of CD has been increasing, with bimodal peaks affecting young adults (15 to 35 years of age) and older adults aged 50 to 70 with the age of onset often occurring in children < 12 years of age. Although geographic variation does occur, the overall incidence of CD in the northern hemisphere ranges from 7 to 20 per 100,000 person years, with a prevalence of up to 300 per 100,000 people. In the United States (US) and Europe, up to 1.5 million individuals may be affected and the incidence is on the rise in parts of Asia and the Middle East {Molodecky 2012}.

The cause of CD is poorly understood, however a complex interplay of genetic predisposition, aberrant immune activation, and early infection during childhood may be involved. The importance of environmental triggers is suggested by increasing rates due to industrialization and improved domestic hygiene and sanitation. This "hygiene hypothesis" has also been implicated in various other autoimmune disorders {Ventham 2013}.

To assess disease severity, a number of clinical scoring systems are utilized based upon signs, symptoms, laboratory parameters, imaging modalities, and endoscopy. The CD Activity Index (CDAI) is one such scoring tool with scores ranging from 0 to over 600 based upon a composite of symptoms (eg, abdominal pain), signs (the presence of abdominal mass and weight), laboratory values (eg, hematocrit), and physician assessment amongst others. In this scoring system, patients with a score > 220 are defined as moderate to severe; these comprise the patients with the greatest unmet medical need. The CDAI can also be used to determine how well a therapy is working, with therapeutic remission defined as a CDAI of < 150 points {Dignass 2010}.

The CDAI has 2 patient reported outcomes of interest in CD drug development: liquid or very soft stool frequency and abdominal pain. In the Patient Reported Outcomes (PRO2) for the current study, these symptoms are recorded daily for 7 days and averaged to determine subscore cut off values of ≤ 1 for abdominal pain and ≤ 3 for stool frequency that define clinical remission. As yet, stool frequency and abdominal pain subscores of the CDAI have not been used on their own in prospective clinical trials.

Fistulae are frequent manifestations of the transmural nature of CD and it is estimated that up to 50% of patients with CD are affected by fistulae according to population-based studies {Schwartz 2002, Solomon 1996}. One of these studies showed the high cumulative incidence of fistulae (33% 10 years after the diagnosis of CD, and 50% after 20 years), demonstrating the extent of this complication in patients with CD {Schwartz 2002}.

Fistulae are classified according to their location and their connection with continuous organs. They can be external (eg, perianal and enterocutaneous), or internal (eg, enteroenteric, enterovesical, enterouterine, enterovaginal, etc). Perianal is the most common form, which comprises approximately 50% of these fistulae {Schwartz 2002}. Perianal fistulae can be further classified as simple (a single submucosal or intersphincteric fistula tract with a single external opening, no branching or extensions and no evidence of rectovaginal involvement or anorectal stricture) or complex (trans-, extra-, or suprasphincteric fistula tract, possible extensions or branching that can potentially involve multiple external openings, a rectovaginal fistula, or is associated with an anorectal stricture, or active inflammatory rectal disease, as assessed by endoscopy). Complex fistulae are more difficult to treat, have decreased healing rates and are associated with less successful outcomes. Overall, perianal fistulae represent a major clinical problem in the management of inflammatory bowel disease as they often cause severe impairment in the affected patient's quality of life, are refractory to conventional treatment, and require surgery.

A significant change in CD management and therapeutic strategy has occurred over the last decade. Recent therapeutic goals extend beyond symptomatic control and include long term mucosal and endoscopic remission {Cheifetz 2013}. The ultimate aim is to change the natural course of the disease by slowing down or halting its progression, thus avoiding surgery or hospitalization. This is achieved by utilizing earlier, aggressive, and goal-directed therapy. Risk assessment and prediction by means of complex clinical, biochemical, and endoscopic markers has become the key to patient management, therapy optimization, and prediction of the outcome and side effects of medical therapy.

Currently available biologic therapies focus on neutralizing cytokine activity or altering T-cell differentiation and homing. Three monoclonal antibodies which inhibit tumor necrosis factor-alpha (TNFα), are currently marketed for the treatment of CD: infliximab (Remicade®), adalimumab (Humira® [approved in United States (US) and European Union {EU}]) and certolizumab pegol (Cimzia® [approved in US]). Vedolizumab (Entivyo®), a monoclonal antibody against α4β7 integrin, is also approved for moderately to severely active CD. Recently, ustekinumab (Stelara®), a monoclonal antibody directed against the p40 subunit of IL-23 and therefore an antagonist for both IL-12 and IL-23 signaling, has been approved for the treatment

of CD. Leukocytapheresis therapy may be used in Japan {Fukunaga 2012}. Other investigational treatment approaches still in development include the administration of cytokines to stimulate innate immunity, the use of prebiotics to alter the gut flora, and blocking the IL-6 signaling pathway {Ito 2004, Korzenik 2016}. New treatments being tested in clinical trials include janus kinase (JAK) inhibitors (eg, upadacitinib) and new biologic agents such as IL-23 p19 antagonists (eg, risankizumab) and a monoclonal antibody directed against β_7 integrin (eg, etrolizumab).

While the introduction of biologic therapies has significantly improved response rates in patients with moderately to severely active CD, long-term or durable remission rates are still low at approximately 20%. Many patients receiving biologic therapies develop neutralizing antibodies with resulting loss of efficacy. These agents may be associated with specific safety issues including but not limited to anaphylaxis, increased risk of infection including progressive multifocal leukoencephalopathy, and liver injury. Among these therapies, only infliximab was shown to be effective for the treatment of fistulizing CD in a double-blind, placebo-controlled, randomized and multicenter trial {Present 1999}. However, less than 40% of patients who received infliximab maintenance therapy had a durable fistula closure at 54 weeks {Sands 2004}. Safe and effective treatment options which may be conveniently administered in a chronic setting would provide a significant treatment advance for patients with perianal fistulizing CD.

This study is designed to evaluate the safety and efficacy of filgotinib for 24 weeks in perianal fistulizing CD.

1.2. Filgotinib (GS-6034)

1.2.1. General Information

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK 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, JAK1, JAK2, JAK3, and TYK2 which interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including rheumatoid arthritis (RA) and CD.

Filgotinib (GS-6034, formerly known as GLPG0634) is a potent and selective inhibitor of JAK1. The compound has shown good preliminary efficacy in RA and CD patients in Phase 2 studies.

In humans, filgotinib is metabolized to form 1 major active metabolite, GS-829845. Though the potency of this metabolite is lower than the parent molecule, the overall exposure and peak plasma concentration in humans is higher than seen in all tested animal species. As a consequence, dedicated pharmacology and toxicology studies have been performed with GS-829845. Results from pharmacodynamics (PD) testing in healthy volunteers suggest that the clinical activity of filgotinib could result from the combination of the parent molecule and the metabolite.

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

1.2.2. Preclinical Pharmacology and Toxicology

Filgotinib and its metabolite, GS-829845 have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1; efficacy studies in rats and mice; repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), in vitro and in vivo safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study. A definitive juvenile toxicology study in rats is ongoing.

1.2.2.1. Nonclinical Pharmacology

In cellular assays, filgotinib inhibits JAK1 signaling with the concentration of an inhibitor that is required for 50% inhibition (IC_{50}) values of ≥ 179 nM, and demonstrates 30-fold selectivity over JAK2 in a human whole blood assay. Filgotinib has been profiled against 451 kinases and it is highly selective for JAK1; only 2.5% of kinases were inhibited ≥ 50% at 50-fold higher concentration than IC_{50} for JAK1. Broad receptor profiling (~70 receptors, ion channels, transporters and enzymes) did not reveal any off-target liabilities of the compound. Filgotinib demonstrated high potency in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulfate sodium (DSS)-induced colitis model, the latter of which is detailed below. The major human metabolite of filgotinib, GS-829845, exhibits a similar JAK1 selectivity profile but is approximately 10-fold less potent as compared to parent filgotinib in vitro.

The efficacy of filgotinib was evaluated in a prophylactic setting of the chronic mouse DSS dextran model in 2 separate studies. Both studies evaluated oral dose levels of 10 and 30 mg/kg once daily. In addition to assessments of clinical score (disease activity index [DAI] and colon lesion score), serum markers of inflammation, immunohistochemical analysis, and expression of various chemokines and cytokines known to be altered in CD and UC patients were also evaluated in the distal colon of these mice.

In both studies, the DAI score, which takes into account body weight loss, rectal bleeding, and stool consistency, was reduced by filgotinib in a dose-dependent manner, demonstrating that filgotinib protected mice against colitis induced by DSS. Histology of the colon revealed a filgotinib-mediated dose-related reduction in colon lesion score, correlating with reductions in DAI score.

Additional endpoints evaluated across the DSS colitis model studies confirmed the suppression of various inflammatory markers including serum levels of C-reactive protein (CRP) and myeloperoxidase (MPO) and expression of IL 6 and TNFα (by reverse transcription polymerase chain reaction [RT-PCR]) by filgotinib. Immunohistochemical analysis of the colon confirmed inhibition of the JAK-STAT pathway by filgotinib as evidenced by a reduction of DSS-induced STAT3 phosphorylation.

1.2.2.2. Safety Pharmacology

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human-ether-a-go-go [hERG] and dog telemetry studies), apart from a slight non adverse increase in heart rate and arterial pressure with GS-829845 at exposures 8-fold that of the peak serum concentration (C_{max}) in subjects with CD treated with 200 mg once daily filgotinib. There were no relevant effects on electrocardiogram (ECG) and QT. Filgotinib and GS-829845 had no effects on the respiratory system and central nervous system (CNS).

1.2.2.3. Key Nonclinical Distribution, Metabolism, and Excretion Data

Filgotinib demonstrates good oral bioavailability in mice, rats, dogs, and mini-pigs but less in monkeys. Plasma protein binding is low (< 70%) in all species, including humans.

The pharmacokinetics (PK) of filgotinib is generally dose proportional without gender differences. No accumulation occurs with repeated dosing. The mean terminal half-life after oral administration is 4 hours and 5 hours in rats and dogs, respectively.

In the rat, filgotinib showed a rapid and even distribution throughout the body. High concentrations were observed only in the gastrointestinal (GI) tract and urinary bladder. Filgotinib does not penetrate into CNS tissues. The distribution of filgotinib indicates some affinity for melanin-containing tissues.

Excretion is nearly complete within 24 hours (rat) and 48 hours (dog) post-dosing. In the rat, fecal and urinary excretion accounted for 40% and 53% of the administered dose, respectively, with a bile secretion of about 15%. In the dog, fecal excretion was the primary route of excretion, accounting for 59% of the administered dose, with urinary excretion accounting for 25%.

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of 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 5'-diphospho-glucuronosyltransferase (UGTs), and no relevant inhibition of key drug transporters, including organic anion transporters (OATs), by filgotinib or GS-829845. Organic cation transporter 2 (OCT2) was inhibited by both filgotinib (IC_{50}: 8.7 μM) and GS-829845 (IC_{50}: 67 μM). The clinical relevance of the IC_{50} values for inhibition of OCT2 will be further evaluated. MATE1 was also weakly inhibited by filgotinib (IC_{50}: 94 μM) and GS-829845 (IC_{50}: > 100 μM). Filgotinib was found to be a substrate of P-glycoprotein (P-gp).

1.2.2.4. Nonclinical Toxicology

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 only. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility; however, sperm counts remained low. When using the mean exposure (AUC) at the NOAELs for the most sensitive species (the dog), the exposure margins compared to a 200 mg once daily dose of filgotinib in CD subjects are 2.5, 1.9, and 3.6-fold for the 26-week and 39-week chronic toxicity studies and the 39-week targeted exposure toxicity study, respectively.

GS-829845-related findings in the repeat-dose toxicity studies were generally similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

Filgotinib and GS-829845 were non-genotoxic when evaluated in the bacterial mutagenicity assay, the in vitro mouse lymphoma mutagenicity assay, and the rat bone marrow micronucleus assay.

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in pregnant rats and rabbits. Teratogenicity was observed at exposures slightly higher or similar to the human exposure at 200 mg once daily of filgotinib in subjects with CD. Administration of filgotinib did not affect female fertility but impaired fertility was observed in male rats at exposures approximately 12-fold the human exposure at 200 mg of filgotinib in subjects with CD. GS-829845 did not have any effects on fertility parameters in either male or female rats.

In an in vitro phototoxicity study in 3T3 cells, the metabolite GS-829845 was positive for phototoxic potential and results with filgotinib were equivocal. A follow-up in vivo rat phototoxicity assay revealed a lack of phototoxic potential for both compounds.

1.2.3. Clinical Trials of Filgotinib

An overview of exposure, safety, and efficacy in clinical studies conducted with filgotinib is available in the IB.

1.2.3.1. Phase 2 Study in Crohn's Disease (GLPG0634-CL-211, FITZROY)

A Phase 2, randomized, double-blind, placebo-controlled, multicenter study with filgotinib was performed in subjects with active CD with evidence of mucosal ulceration {Vermeire 2017}. In Part 1, a total of 174 subjects were randomized (3:1) to receive either filgotinib 200 mg once daily or placebo for 10 weeks. CCI [redacted]

The efficacy of filgotinib was assessed by evaluating clinical remission (defined as CDAI score < 150), clinical response (defined as a decrease in CDAI of at least 100 points from baseline), and endoscopic response (defined as a decrease of at least 50% from baseline in the SES-CD score).

The primary endpoint of the study was met: at Week 10, 60 of 128 subjects (46.9%) who received filgotinib achieved clinical remission versus 10 of 44 subjects (22.7%) who received placebo, a difference of 24.1% (p-value = 0.0077). In addition, filgotinib treatment was associated with increases in the proportion of subjects with clinical response and endoscopic response compared with placebo.

Overall, the safety profile of filgotinib in CD subjects was consistent with prior studies.

1.3. Rationale for This Study

Accurate assessments of perianal disease activity may help to improve treatment and prognosis, and therefore the patient's quality of life. The Fistula Drainage Assessment (FDA) is one of the most widely used methods for the assessment, which takes the presence of purulent drainage from the cutaneous orifice after gentle compression as an index of activity. However, it does not take into account patient-reported outcomes. The Perianal Disease Activity Index (PDAI) is more comprehensive, as it evaluates perianal disease morbidity, particularly the presence of fistula discharge, pain and the restriction of daily activities, the restriction of sexual activity, the type of perianal disease, and the degree of induration. It is based on a simple 5-point scale, which can be easily used in an office setting, and is capable of quantifying the severity of perianal disease. A prospective study on 62 patients with perianal CD showed that the optimal PDAI cutoff value discriminating active and inactive perianal disease was > 4, which had an accuracy of 87% detecting active disease when the clinical examination was considered the reference standard for comparison {Losco 2009}. In the same study, the PDAI cutoff was shown to be well-correlated with the clinical outcome as it indicated that a PDAI of ≤ 4 identified inactive disease requiring no therapy. This study will evaluate changes in PDAI score to assess the treatment response of perianal fistulizing CD to filgotinib.

Evaluation of the presence and severity of proctitis is critical in the management of patients with perianal fistulizing CD as it determines further treatment strategy and prognosis. The absence of proctitis is an independent predictor for increased healing and reduced recurrence rates of perianal fistulae. However, rectal involvement is associated with a higher proctectomy rate compared with rectal sparing. In this study, centrally read flexible sigmoidoscopy will be conducted at baseline to assess the rectum and anal canal and the severity of proctitis determined by SES-CD will be used as one of the stratification factors. At Week 24, endoscopic appearance of the rectum and anal canal will be assessed again by centrally read flexible sigmoidoscopy.

Diagnostic modalities for fistulizing CD have improved over the last decade. An accurate assessment of each fistula's anatomy before treatment is essential, and enables the physician to choose the most appropriate therapy. Inadequate characterization of the fistula and associated pathology can result in potentially poor clinical outcomes. MRI is now considered the gold standard imaging tool to evaluate the perianal complication of CD as it offers excellent soft tissue discrimination with a wide field of view and it carries no radiation hazard {Gecse 2004}. Previous studies have shown that MRI is particularly sensitive for the detection of pelvic abscesses in CD patients, even in the absence of clinical signs {Lunniss 1994, Myhr 1994}. Use of MRI as preinclusion clinical evaluation will ensure accurate characterization of the fistulae and detect any abscess which may require drainage.

With the advent of anti-TNF therapy, the goal of treatment for fistulizing CD has evolved from symptomatic improvement (eg, by drainage) of the fistula to complete cessation of drainage and, in some patients, fistula closure and fibrosis of the fistula tract {Gecse 2004}. However, the optimal clinical index for assessing perianal CD is still under debate. Even though the endpoint adopted in previous trials in perianal fistulizing CD (ie, disappearance of drainage from at least 50% of the fistulae) {Present 1999, Sands 2004} is clinically relevant, it has been shown that cessation of drainage from external orifices does not accurately reflect what is happening to the fistula track. A small prospective cohort study including 18 subjects with perianal CD showed that persistent inflammatory activity in the fistula track is observed even after long-term (46 weeks) infliximab therapy, whereas external orifices are observed to heal and to stop draining rapidly after the therapy {Van Assche 2003}. A primary endpoint at 6 months into the treatment course was chosen to allow healing of the fistulae.

Residual inflammation of the fistula tract may be responsible for the occurrence of *de novo* perianal abscesses and for fistula recurrence in patients treated for fistulizing CD. The undetected pelvic abscess may become clinically apparent only after cessation of drainage from external orifices, and becomes a source of continuous inflammatory reaction. Given these challenges in assessing the activity and complications of the perianal CD, it may be warranted to combine MRI assessment with clinical examination to evaluate the efficacy of study treatment. A 2 cm cutoff for fluid collection as entry criteria was chosen as it represents the clinical threshold which warrants drainage. A cutoff of ≤ 1 cm for fluid collection was chosen as part of the combined primary endpoint to ensure a more stringent definition of response to treatment was used that is differentiated from the clinical threshold for drainage.

In conclusion, this study will use MRI to evaluate healing of fistulae in addition to clinical assessment of drainage and fistula closure. MRI images will be centrally read in a blinded manner. These measures will provide a comprehensive and objective assessment of disease activity and treatment response in fistulizing CD.

1.4. Rationale for Dose

In Phase 2 trials in RA, pooled data with an exposure – response analysis demonstrated a dose-dependent increase in efficacy up to 200 mg total daily dose. In the Phase 2 study of CD (GLPG0634-CL-211), subjects treated in the 200 mg arm showed favorable response and remission rates (47% remission over 23% placebo and 59% response over 41% placebo). The remission rate at Week 20 for subjects who failed placebo for the first 10 weeks and commenced 100 mg from Weeks 10 to 20 was slightly lower (32%) though the response rate was comparable (59%), indicating some level of efficacy at the 100 mg dose. These results are consistent with the relationship observed between filgotinib exposures and inhibition of pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 activation (~78%) was achieved at or above 200 mg total daily dose and intermediate inhibition (~47%) at 100 mg {Namour 2015}. pSTAT1 data, in conjunction with considerations around the margin for nonclinical testicular findings, suggests assessing doses above 200 mg is not indicated. CCI

1.5. Risk/Benefit Assessment for the Study

Crohn's disease is a progressive and potentially life-threatening disease with few treatment options, many of which result in primary or secondary nonresponse. Inflammatory bowel disease may lead to increased risk of gastrointestinal malignancies, impairment in quality of life, and ultimate need for life-altering surgery. Current treatment options are limited in ability to establish mucosal healing and clinical remission and have significant safety and efficacy limitations; for example, biologics have significant immunogenic risks and steroids are associated with increased morbidity and mortality. Remission rates are generally low when compared to placebo rates across most therapies for IBD. There remains substantial unmet need in IBD, particularly in fistulizing CD among all phenotypes of CD. Despite the high cumulative occurrence and recurrence rates and significant morbidity associated with it, there is only 1 approved therapy for fistulizing CD.

Nonclinical studies in rats and dogs identified lymphoid tissues and testes as target organs for filgotinib in long-term repeat-dose toxicity studies. Although decreased lymphocyte numbers observed in nonclinical studies have not been seen in clinical studies, hematological assessment will be performed throughout the present study to ensure this potential risk is appropriately monitored. In both rats and dogs, microscopic findings in the testes included germ cell depletion and degeneration, with reduced sperm content and increased cell debris in the epididymis and reduction in fertility in male rats. The dog was determined to be the most sensitive species. When using the mean exposure (AUC) at the NOAELs for dogs in the 26- and 39-week chronic toxicity studies, and the 39-week targeted exposure toxicity study, the exposure margins compared with the highest proposed clinical dose of 200 mg once daily are 2.5-, 1.9-, and 3.6-fold respectively, in subjects with CD. A male safety study is planned to examine the potential effect of filgotinib on sperm/ejaculate parameters. Pending those results, the use of 200 mg in males in the United States with CD or UC will be limited to subjects who have failed at least two biologic therapies (TNFα antagonists or vedolizumab). Reference is made to the IB for further information about nonclinical testicular findings.

Administration of filgotinib produces an increase in embryofetal malformations in pregnant rats and rabbits at exposures similar to, or slightly higher than, exposures associated with a 200 mg once daily dose in CD subjects; this risk will be mitigated with the use of highly effective contraception for subjects of child-bearing potential.

JAK inhibition is expected to increase the risk of infection based on mechanism of action. Across global studies with filgotinib, in general, active treatment arms have increased incidences of infection versus placebo. In the present protocol, treatment interruption and discontinuation considerations surrounding infections are incorporated and sites and investigators will be trained regarding such circumstances. All subjects will be screened for tuberculosis (TB) and subjects with active infections will be excluded. Malignancy has been reported in subjects on filgotinib; in the present trial, subjects will be required to have up to date colorectal cancer screening and surveillance and subjects with recent malignancies will be excluded as outlined in the eligibility criteria. For further details about infections and malignancies, please reference the IB.

The potential benefits of JAK inhibition include improvement in clinical symptoms and mucosal and endoscopic healing. JAK inhibition may be efficacious in the treatment of IBD based on results from FITZROY. A lack of response contingency after Week 10 will enable early access to active drug when clinically indicated. In FITZROY, an increase in mean hemoglobin concentration was observed, without difference between filgotinib and placebo. No clinically significant changes from baseline in mean neutrophil counts or liver function tests were observed at 10 weeks. Filgotinib treated subjects showed an increase in HDL and no significant change in LDL. Lipid and hemoglobin effects represent potential benefits in this population.

An independent data monitoring committee (DMC) appointed to monitor the study will provide an additional level of risk mitigation. The DMC may advise to continue the study unchanged, to modify the study, or to discontinue the study. The initial meeting will occur after approximately 20% of the planned total number of subjects reach the Week 10 visit. Following this, the next meeting will occur after approximately 50% of subjects reach the Week 10 visit. Additional DMC meetings may be convened, if needed.

Taking all of these considerations into account with respect to the filgotinib program, the early signals for efficacy demonstrated in the CD clinical trials, as well as the beneficial findings in nonclinical models of disease and the overall safety, tolerability, and PK characteristics of filgotinib that have been elucidated to date, there is a favorable benefit-risk profile for this agent in continued development as a treatment for fistulizing CD. The overall risk/benefit balance of this study is considered favorable.

For additional information about the risks of filgotinib, reference is made to the filgotinib IB.

1.6. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula response at Week 24

The secondary objectives of this study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula remission at Week 24
- To assess the time to clinical fistula response
- To assess the time to clinical fistula remission
- To evaluate the efficacy of filgotinib as compared to placebo in establishing proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline
- To evaluate the safety and tolerability of filgotinib

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3. STUDY DESIGN

3.1. Endpoints

The primary efficacy endpoint is:

- Proportion of subjects establishing combined fistula response at Week 24

The secondary efficacy endpoints are:

- Proportion of subjects establishing combined fistula remission at Week 24
- Time to clinical fistula response
- Time to clinical fistula remission
- Proportion of subjects achieving proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline

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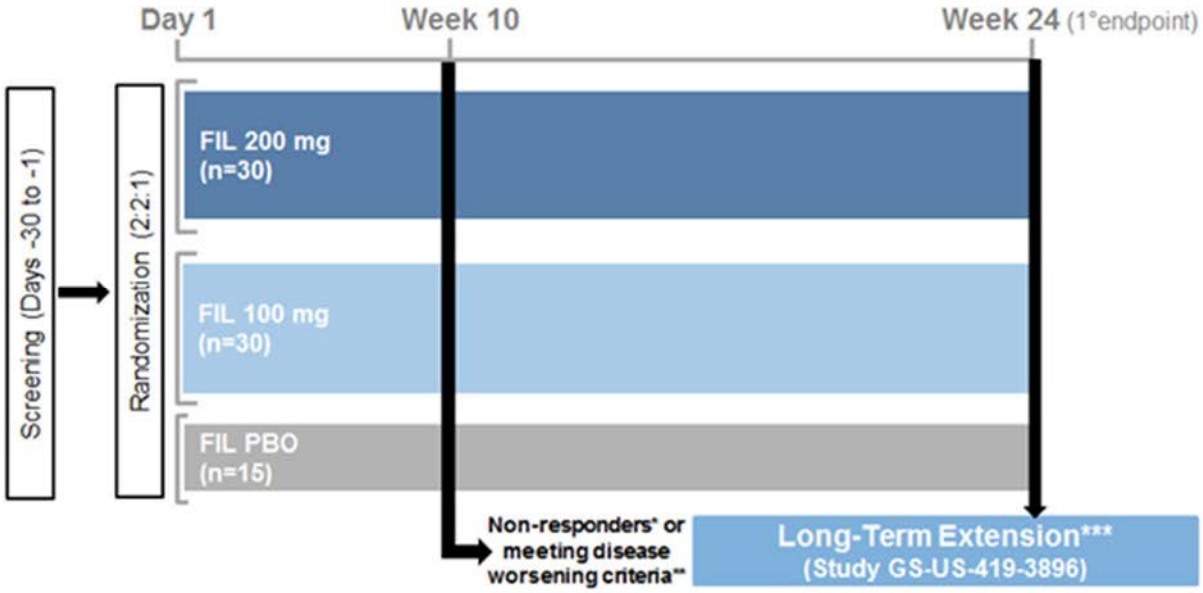
[redacted]

3.2. Study Design

This study is a Phase 2, double-blind, randomized, multicenter study evaluating the efficacy and safety of filgotinib versus placebo in the treatment of perianal fistulizing CD. A schematic of this study is provided in Figure 3-1.

Figure 3-1. Study Design Schematic



FIL = filgotinib; PBO = placebo; mg = milligram.

* Non-responders (luminal disease) are defined as subjects who either had a baseline CDAI score ≥ 220 and never achieve a ≥ 70-point CDAI reduction from baseline at any point up to and including Week 10 OR had a baseline CDAI score < 220 and have an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at Week 10.
Non-responders (perianal fistulizing disease) are defined as subjects who meet the following criteria for PDAI symptom subscores: "Discharge" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10 OR "Pain/restriction of activities" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10

** Disease worsening is defined as an increase in CDAI of ≥100 points from the Week 10 value with CDAI score ≥ 220 points at 2 consecutive visits

*** Subjects who are non-responders, meeting disease worsening criteria, or complete the study at Week 24, will have the option to enter a separate LTE study, if eligible.

This study includes:

- Screening (Day -30 to -1)
- Randomization
- Blinded Treatment Period (Day 1 to Week 24)

  Efficacy assessment: At Week 24, physical examination, flexible sigmoidoscopy to assess presence of proctitis, and MRI to assess fistula response

  Subjects who complete all procedures per protocol, including the MRI at Week 24, may be offered the option to continue into a separate Long Term Extension (LTE) study (GS-US-419-3896), if deemed appropriate by the investigator

- Subjects who are non-responders at Week 10 (see Section 3.6 OR Section 3.7) or who meet disease worsening criteria (see Section 3.8) after Week 10 will have the option to enter the LTE study, if eligible.

- Post Treatment (PTx) safety assessments:

  All subjects completing this study will be offered the option to continue study drug in a blinded fashion in the LTE study, if eligible

  Subjects who are eligible and opt to participate in the LTE study can continue into the LTE study without PTx safety assessments

  Subjects who opt out of the LTE study will return to clinic 30 days after the last dose of study drug for PTx safety assessments

3.3. Study Treatments

Based on protocol eligibility criteria, subjects will be screened for enrollment and randomized into 1 of 3 treatment groups in a blinded fashion in a 2:2:1 ratio as follows:

Treatment group 1 (n = 30): filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Treatment group 2 (n = 30): filgotinib 100 mg and PTM filgotinib 200 mg, once daily

Treatment group 3 (n = 15): PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: US males who are not dual refractory will be randomized in a 2:1 ratio to either filgotinib 100 mg or matching placebo. For the purposes of this protocol, US males who have failed at least one prior TNF antagonist AND either previously failed vedolizumab induction therapy or are concomitantly taking vedolizumab at Day 1 and present with actively draining perianal fistulae despite continued vedolizumab therapy will be considered as dual refractory patients. This assessment is based on recently published data from a subgroup analysis of the GEMINI-2 study, showing a beneficial effect of vedolizumab treatment for patients that were randomized with actively draining perianal fistulae at baseline (Feagan 2018).

Treatment assignments will be stratified according to the following factors:

- Anatomy of draining perianal fistulae at screening determined by MRI (simple *versus* complex)

- Receiving vedolizumab therapy concomitantly at Day 1 (Yes or No)

- Presence of moderately to severely active proctitis (Yes or No)

3.4. Duration of Treatment

Randomized subjects will receive a maximum of 24 weeks of study drug. Subjects who are non-responders based on the results of the Week 10 assessments (see Section 3.6 OR Section 3.7 or meeting disease worsening criteria after Week 10 (see Section 3.8) must be discontinued from blinded treatment (see Section 3.5.2).

3.5. Criteria for Study Drug Interruption or Discontinuation

3.5.1. Study Drug Interruption Considerations

The Study Medical Monitor should be consulted prior to study drug interruption when medically feasible.

Study drug interruption should be considered in the following circumstances (*prior to resumption of study drug, the investigator should discuss the case with the Study Medical Monitor*):

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug interruption should be determined in consultation with the Study Medical Monitor
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored

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

3.5.2. Study Drug Discontinuation Considerations

The Study Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

Study drug must be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
- Febrile neutropenia (temperature > 38.3°C or a sustained temperature of > 38°C for more than one hour) with absolute neutrophil count of < 1,000/mm^3

- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin < 7.5 g/dL, or if transfusion is indicated regardless of hemoglobin value

- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)

- Evidence of active Hepatitis C Virus (HCV) during the study, as evidenced by HCV RNA positivity

- Evidence of active Hepatitis B Virus (HBV) during the study, as evidenced by HBV DNA positivity

- Any thromboembolic event that meets SAE reporting criteria

- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest

- Subject request to discontinue for any reason

- Subject noncompliance

- Pregnancy during the study; refer to Section 7.7.2.1

- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)

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

- Laboratory Criteria: After becoming aware of any of the below described abnormal laboratory changes occurring at any one time, an unscheduled visit (ie, sequential visit) should occur to retest within 3 to 7 days (except creatinine, which should be retested 7 to 14 days apart).

  Two sequential neutrophil counts < 750 neutrophils/mm^3 (SI: < $0.75x10^9$ cells/L)

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

Two sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3 times the upper limit of normal range (x ULN) and at least one of the following confirmed values:

- total bilirubin > 2 x ULN
- INR > 1.5
- or accompanied by symptoms consistent with hepatic injury

For any subject with an **initial** AST or ALT elevation > 3x ULN, at the time of the **second confirmatory draw**, an INR, prothrombin time (PT), and partial thromboplastin time (PTT) must also be drawn.

Two sequential AST or ALT > 5 x ULN

Two sequential values for estimated creatinine clearance (CL_{cr}) < 35 mL/min based on the Cockcroft-Gault (CC&G) formula

Male: $\frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times (\text{serum creatinine in mg/dL})}$ CL_{cr} (mL/min)

Female: $\frac{(140 - \text{age in years}) \times (\text{wt in kg}) \times 0.85}{72 \times (\text{serum creatinine in mg/dL})}$ CL_{cr} (mL/min)

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).

Subjects who permanently discontinue study drug for any reason should discuss their continued care plan with their physician.

Subjects who permanently discontinue study drug for pregnancy should not continue in the study; if there are any questions regarding permanent discontinuation, these should be discussed with the Sponsor.

Subjects withdrawing from the study should complete Early Termination (ET), followed by PTx assessments 30 days after the last dose of study drug (Refer to Section 6.13 for Post Treatment assessments).

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

The Sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study medication or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

3.6. Luminal Disease Activity - Non-Response Criteria

Subjects who are non-responders to study treatment for luminal disease activity are subjects who either:

- Had a baseline CDAI ≥ 220 and never achieve a ≥ 70-point CDAI reduction from baseline at any point up to and including Week 10 OR
- Had a baseline CDAI score < 220 and have an increase in CDAI of ≥ 100 points from baseline, with CDAI ≥ 220 at Week 10

These subjects will be offered the option to receive open-label filgotinib by entering into the separate LTE study. Subjects will remain blinded to their treatment allocation in the current study. Subjects meeting non-response criteria should undergo a pelvic MRI and flexible sigmoidoscopy prior to exiting the study (Refer to Sections 6.5 and 6.6 for details regarding the flexible sigmoidoscopy and MRI).

3.7. Perianal Fistulizing Disease Activity - Non-Response Criteria

Subjects who are non-responders to study treatment for symptoms relating to their perianal fistulae must meet the following criteria for PDAI symptom subscores:

- "Discharge" subscore of >1 and ≥ 1-point increase from baseline at Week 6 and Week 10 **OR**
- "Pain/restriction of activities" subscore of >1 and ≥ 1-point increase at Week 6 and Week 10 from baseline

These subjects will be offered the option to receive open-label filgotinib by entering into the separate LTE study. Subjects will remain blinded to their treatment allocation in the current study. Subjects meeting non-response criteria should undergo a pelvic MRI and flexible sigmoidoscopy prior to exiting the study (Refer to Sections 6.5 and 6.6 for details regarding the flexible sigmoidoscopy and MRI).

3.8. Luminal Disease Activity - Disease Worsening Criteria

Subjects meeting the following disease worsening criterion after Week 10 must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib by entering into the separate LTE study:

- An increase in CDAI of ≥ 100 points from the Week 10 value with CDAI ≥ 220 at 2 consecutive visits

  Determination of disease worsening may be made at scheduled or unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits anytime subsequent to the Week 10 visit).

- All subjects meeting disease worsening criteria should undergo a pelvic MRI and flexible sigmoidoscopy prior to exiting the study (Refer to Sections 6.5 and 6.6 for details regarding the flexible sigmoidoscopy and MRI).
- If a subject experiences significant worsening of underlying CD, which requires any of the prohibited medications (refer to Section 5.4.2), or surgical intervention at any point during the study, treatment discontinuation should be considered at investigator's discretion, in consultation with medical monitor if feasible (refer to Section 3.5.2); these subjects do not qualify for LTE study.

3.9. End of Study

End of Study is defined as 30 days after the last dose administered to the last subject.

3.10. Post Study Care

All subjects completing 24 weeks of treatment will be given the opportunity to participate in the LTE study. For those subjects who do not participate in the LTE study, after the subject has completed their study participation, the long-term care of the participant will remain the responsibility of their primary treating physicians.

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4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 75 subjects who meet the eligibility criteria at screening will be randomized in a blinded fashion in a 2:2:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or matching placebo.

In order to manage the total study enrollment, Gilead, at its sole discretion, may suspend screening and/or enrollment at any site or study-wide at any time.

4.2. Inclusion Criteria

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

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

2) Males or non-pregnant, non-lactating females, ages 18 to 75 years, inclusive based on the date of screening visit

3) Females of childbearing potential (as defined in Appendix 9) must have a negative pregnancy test at screening and baseline

4) 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 9)

5) Documented diagnosis of Crohn's disease with a minimum disease duration of 3 months documented by the following:

   a) Medical record documentation of, or an ileocolonoscopy (full colonoscopy with the intubation of terminal ileum) report dated ≥ 3 months before enrollment, which shows features consistent with CD, determined by the procedure performing physician; AND

   b) Medical record documentation of, or a histopathology report showing features consistent with CD, determined by the pathologist

6) At screening, has a minimum of 1 (maximum of 3) draining perianal fistulae external openings of ≥ 4 weeks duration as a complication of CD, confirmed by MRI.

   At least 1 (maximum of 3) of the draining perianal fistulae external openings present at screening must still be draining at the time of randomization.

   Subjects with other fistula types (enterocutaneous, abdominal) in addition to the required minimum number of perianal fistula may be permitted on discussion with and approval by the Sponsor's Medical Monitor.

7) May have concurrent noncutting perianal seton(s) at screening, which must be removed ≥ 14 days prior to randomization

8) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least 1 of the following agents (depending on current country treatment recommendations/guidelines):

   a) Antibiotics

      i) Active disease (draining perianal fistulae) despite at least a 4-week regimen of antibiotics (ciprofloxacin or metronidazole per local treatment guidelines) for the purpose of treating perianal fistulae

   AND/OR

   b) Immunomodulators

      i) Active disease despite a history of at least a 12-week regimen of oral azathioprine (≥ 2 mg/kg) or 6-mercaptopurine (6-MP) (≥ 1 mg/kg), or methotrexate (25 mg per week subcutaneously [SC] or intramuscularly [IM] per week for induction and ≥ 15 mg IM per week for maintenance), OR

      ii) History of intolerance to at least one immunomodulator including, but not limited to, serious infections, hepatotoxicity, cytopenia, pancreatitis, TPMT genetic mutation, allergic reactions, or any other condition that contributed to discontinuation of the agent

   AND/OR

   c) TNFα Antagonist

      i) Active disease despite a history of at least one induction regimen of infliximab, adalimumab, certolizumab or biosimilar as follows:

         (1) Infliximab: A 14-week induction regimen of 5 mg/kg IV at Weeks 0, 2, and 6 (6 week induction regimen with 2 doses at Weeks 0 and 2 in EU)

         (2) Adalimumab: A 4-week induction regimen consisting of 160 mg SC (four 40-mg injections in 1 day or two 40-mg injections per day for 2 consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg.

         (3) Certolizumab: A 8-week induction regimen of 400 mg SC at Weeks 0, 2, and 4

      AND/OR

      ii) Recurrence of symptoms during maintenance therapy with the above agents,

      AND/OR

      iii) History of intolerance to any TNFα inhibitors including, but not limited to, serious infections, hepatotoxicity, heart failure, allergic reactions, or any other condition that contributed to discontinuation of the agent

9) Is willing and able to undergo MRI per protocol requirements

10) Is willing and able to undergo flexible sigmoidoscopy per protocol requirements

11) Meet one of the following tuberculosis (TB) screening criteria:

    a) No evidence of active or latent TB ie,

        i) A negative QuantiFERON® TB-Gold In-Tube test at screening, AND

        ii) A chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection, AND

        iii) No history of either untreated or inadequately treated latent or active TB infection

    b) Previously treated for TB: ie, if a subject has previously received an adequate course of therapy as per local standard of care for either latent TB (eg, 9 months of isoniazid in a location where rates of primary multi drug resistant TB infections are < 5% or an acceptable alternative regimen) or active TB (acceptable multi-drug regimen). In these cases, no QuantiFERON® TB-Gold In-Tube test need be obtained, but a chest radiograph must be obtained if not done so within 3 months prior to screening (with the report or films available for investigator review). It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

    c) Newly identified latent TB during screening: ie, a subject who has a newly identified positive diagnostic TB test result (defined as a positive QuantiFERON® TB Gold in Tube test) in which active TB has been ruled out and for which appropriate, ongoing, prophylactic treatment for latent TB has been initiated for a minimum of 4 weeks prior to the first administration of study medication. Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised subjects. Quantiferon testing may not be repeated except in the case of a single repeat for indeterminate results.

Cases falling under category “b” and “c” need to be approved by the Sponsor prior to enrollment in this study. No subject with currently active TB may be enrolled in the study, regardless of past or present anti-TB medication use.

12) Laboratory parameters (subjects who fail to meet the parameters of any of the below reference laboratory tests may be retested once at discretion of investigator prior to being considered a screen failure):

    a) Hepatic panel (AST, ALT, total bilirubin) ≤ 2 x ULN

    b) Estimated CL_{cr} ≥ 40 ml/min as calculated by the CC&G equation

    c) Hemoglobin ≥ 8 g/dL (both males and females)

d) Absolute neutrophil count (ANC) ≥ 1.5×10^9/L (1,500/mm^3)

e) Platelets ≥ 100×10^9/L

f) White blood cells (WBC) ≥ 3.0 x 10^9/L

g) Absolute lymphocyte count > 750/mm^3

13) May be receiving the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted times):

a) Oral 5-aminosalicylate (5-ASA) compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization

b) Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 20 mg/day or budesonide prescribed at a dose of ≤ 6 mg/day) provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization

c) Azathioprine or 6-MP or methotrexate provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization

d) Antibiotics for the treatment of perianal fistulizing CD (eg, metronidazole, ciprofloxacin) provided the dose prescribed has been stable for the 2 weeks prior to randomization. Dose must remain stable for the first 10 weeks after randomization. Subjects who are on cyclic therapy must continue their standard low-dose regimen without change for the first 10 weeks after randomization.

e) Vedolizumab therapy (300 mg IV) for the treatment of concurrent luminal disease activity provided the dose has been stable for 14 weeks prior to randomization; subjects must remain on vedolizumab for the duration of their participation in the study. Subjects on concurrent vedolizumab therapy must not be taking concurrent azathioprine or 6-MP or methotrexate.

14) Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose of study drug

15) Must be up to date on colorectal cancer screening and surveillance as standard of care according to local guidelines.

4.3. Exclusion Criteria

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

1) Pregnant or lactating females.

2) Males and females of reproductive potential who are unwilling to adhere to contraceptive guidance as outlined by Appendix 9.

3) Females who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 35 days after the last dose of the study drug.

4) Male subjects unwilling to refrain from sperm donation during the study and for at least 90 days after the last dose of study drug.

5) Known hypersensitivity to filgotinib, its metabolites, or formulation excipients

6) Claustrophobia to a degree that prevents tolerance of MRI scanning procedure (sedation is permitted at discretion of investigator).

7) Metallic implant of any sort that prevents MRI examination, not limited to but including aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, body piercing that cannot be removed, cochlear implant; or other contraindication to MRI examination.

8) Known hypersensitivity to gadolinium

9) Currently have complications of CD as any of the following:

   a) Symptomatic strictures, OR

   b) Severe (impassable) rectal/anal stenosis, OR

   c) Short bowel syndrome, OR

   d) Any other complications which could preclude the use of the CDAI to assess response to therapy, or would possibly confound the evaluation of benefit from treatment with filgotinib

10) Presence of current rectovaginal, anovaginal, or enterovesicular fistulae

11) Has an abscess > 2 cm or an abscess that the Investigator feels requires drainage based on either clinical assessment or MRI, unless drained and treated at least 4 weeks prior to Day 1, and are not anticipated to require surgery during the study

12) Has a CDAI score > 300

13) History of major surgery or trauma within 30 days prior to screening

14) Presence of ulcerative colitis (UC), indeterminate colitis, ischemic colitis, fulminant colitis, or toxic mega-colon

15) History of total proctocolectomy, total colectomy, presence of ileostomy or colostomy, or likely requirement for surgery during the study

16) Dependence on parenteral nutrition

17) History or evidence of incompletely resected colonic mucosal dysplasia

18) Infection with human immunodeficiency virus (HIV), HBV or HCV

19) Presence of Child-Pugh Class C hepatic impairment

20) Stool samples positive for *Clostridium difficile* (*C. difficile*) toxin, pathogenic *Escherichia coli* (*E. coli*), *Salmonella* species (spp), *Shigella* spp, *Campylobacter* spp, or *Yersinia* spp.

21) Stool sample positive for ova and parasites test (O&P) unless approved by the medical monitor

22) Use of any prohibited concomitant medications as described in Section 5.4.2

23) Has used any TNFα antagonist ≤ 8 weeks prior to screening, ustekinumab IV or SC ≤12 weeks prior to screening, or any other biologic agent ≤ 8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer. Subjects who have an undetectable serum level of a biologic agent since its last dose using a commercially available assay can undergo study screening without the above-mentioned waiting period.

24) Active clinically significant infection or any infection requiring hospitalization or treatment with intravenous anti-infectives within 30 days of screening (or 8 weeks of Day 1); or any infection other than related to the fistula(s) requiring oral anti-infective therapy within 2 weeks of screening (or 6 weeks of Day 1)

25) Active TB or history of latent TB that has not been treated (see inclusion criterion 11 for further information)

26) History of opportunistic infection or immunodeficiency syndrome

27) History of disseminated *Staphylococcus aureus*

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

29) Administration of live or attenuated vaccine within 30 days of randomization

30) Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease) or psychiatric problem (including, but not limited to alcohol or drug abuse) that, in the opinion of the Investigator, would make the subject unsuitable for the study or would prevent compliance with the study protocol

31) History of malignancy within the last 5 years except for subjects who have been treated or resected for non-melanoma skin cancer or cervical carcinoma in situ

32) History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma

33) History of treatment with lymphocyte-depleting therapies, including but not limited to alemtuzumab, cyclophosphamide, total lymphoid irradiation, and rituximab

34) History of leukocytapheresis ≤ 6 months prior to Screening

35) Prior exposure to any Janus kinase (JAK) inhibitor (including but not limited to tofacitinib, baricitinib, and upadacitinib)

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

5.1.1. Procedures for Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the interactive web response system (IWRS) for that subject. Gilead recommends but does not require that the investigator contact the Study Medical Monitor before breaking the blind. Treatment assignment should remain blinded unless that knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was obtained. The investigator is requested to contact the Study Medical Monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

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

5.1.2. Blinding

During the randomized phase, subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, CCI [redacted] Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the interactive voice/web response system for purposes of study drug inventory management will remain unblinded. Individuals in PVE responsible for safety signal detection, investigational new drug safety reporting, and/or expedited reporting of SUSARs may be unblinded to individual case data and/or group-level summaries. External (ie, contract research organizations) Biostatisticians and Programmers will be unblinded to support data monitoring committee data review CCI [redacted]. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

5.2. Description and Handling of Filgotinib and Placebo to Match (PTM) Filgotinib

5.2.1. Formulation

Filgotinib is provided as 200 mg and 100 mg strength tablets. Filgotinib tablets, 200 mg and 100 mg are beige, debossed with "GSI" on one side and "200" or "100" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg or 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/ polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo to match (PTM) filgotinib 200 mg and 100 mg tablets are identical in appearance to the respective active tablets. PTM filgotinib 200 mg and 100 mg tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/PEG 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

5.2.2. Packaging and Labeling

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

Study drugs to be distributed to centers in the US, EU and other participating countries 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 and PTM 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 and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

To ensure the stability and proper identification, study drugs should not be stored in a container other than the container in which they were supplied. Keep the container tightly closed to protect from moisture. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling.

5.3. Dosage and Administration of Study Drug

The study medication will consist of 200 mg and 100 mg filgotinib tablets for oral administration and PTM 200 mg and 100 mg filgotinib tablets for oral administration.

The following treatments will be evaluated:

- **Treatment group 1**: 1 tablet of 200 mg filgotinib daily, 1 tablet of PTM filgotinib 100 mg daily
- **Treatment group 2**: 1 tablet of 100 mg filgotinib daily, 1 tablet of PTM filgotinib 200 mg daily
- **Treatment group 3**: 1 tablet of PTM filgotinib 200 mg daily, 1 tablet of PTM filgotinib 100 mg daily

Subjects who are non-responders based on the results of the Week 10 assessments (see Section 3.6, Luminal Disease Activity – Non-Response Criteria OR Section 3.7, Perianal Fistulizing Disease Activity – Non-Response Criteria) will be offered the option to receive open-label filgotinib by entering into the LTE study (GS-US-419-3896); prior to entering the LTE study, subjects **must** complete MRI and flexible sigmoidoscopy early termination procedures. Subjects meeting disease worsening criteria after Week 10 must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib 200 mg (see Section 3.8, Disease Worsening Criteria), except for US males who will be offered filgotinib 100 mg unless they are considered to be 'dual refractory' prior to entering the LTE study, subjects **must** complete MRI and flexible sigmoidoscopy early termination procedures. Subjects who complete all procedures per protocol up to the Week 24 visit (including the Week 24 MRI and flexible sigmoidoscopy) will have the option to continue study drug in a blinded fashion in the LTE study.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose(s) of study medication as soon as possible during the same day. If the missed dose is not taken on the original day, then subjects should not take the missed dose and the missed dose should be returned to the study drug bottle. Subjects should be cautioned not to double the next dose (ie, taking the missed dose of study drug with that day's dose).

5.4. Prior and Concomitant Medication

All medications taken up to 30 days prior to the screening visit through the end of study (30 days after the last dose of study drug), need to be recorded in the source documents and on the eCRF. At each study visit, the study center will record any and all concomitant medications taken by the subject since the last visit or during the visit (as applicable). All concomitant medications (prescription, peri-procedural medications, over-the-counter medications, including vaccines, vitamins, herbal, dietary supplements, and minerals) must be recorded in the concomitant therapy section of the eCRF.

Effective current therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medication as supportive care or to treat AEs as deemed necessary by the Investigator or the subject's physician. Should subjects have a need to initiate treatment with any excluded concomitant medication, the Study Medical Monitor should be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator should notify Gilead as soon as he/she is aware of the use of the excluded medication.

5.4.1. Allowed Concomitant Medication

The allowed concomitant medication(s) for CD must be maintained at a stable dose for the noted time without dose alteration or discontinuation. Subjects should not initiate new induction therapy prior to the screening visit. If a new therapy has been recently initiated, the full induction course should be completed prior to screening consideration.

The allowed medications for CD are as follows:

- Oral 5-ASA compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization

- Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization

- Oral corticosteroid therapy (prednisone prescribed at a stable dose of ≤ 20 mg/day or budesonide prescribed at a stable dose of ≤ 6 mg/day) provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization.

- Antidiarrheals for chronic diarrhea are allowed throughout the study as necessary for control of chronic diarrhea; stable doses are encouraged.

- Occasional use of non-steroidal anti-inflammatory drugs (NSAIDs) for transient symptoms is permitted; daily use of aspirin up to 162.5 mg for the purpose of cardiovascular prophylaxis is permitted.

- Antibiotics for the treatment of perianal fistulizing CD (eg, metronidazole, ciprofloxacin) provided the dose prescribed has been stable for the 2 weeks prior to randomization. Dose must remain stable for the first 10 weeks after randomization. Subjects who are on cyclic therapy must continue their standard low-dose regimen without change for the first 10 weeks after randomization

- Vedolizumab therapy (300 mg IV) for the treatment of concurrent luminal disease activity provided the dose has been stable for 14 weeks prior to randomization; subjects must remain on vedolizumab for the duration of their participation in the study. Subjects on concurrent vedolizumab therapy must not be taking concurrent azathioprine or 6-MP or methotrexate.

5.4.2. Prohibited Concomitant Medication

The prohibited medications are as follows:

Table 5-1. Prohibited Concomitant Medication

Drug Class	Agents Disallowed	Prohibited Period
Strong P-gp Inducers[a]		
Anticonvulsants	Phenobarbital, phenytoin, carbamazepine,	30 days prior to screening through the end of the study
Antimycobacterials	Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort, danshen (salvia miltiorrhiza)	
Prohibited IBD Medication		
Corticosteroids	Dose equivalent to > 20 mg/day of prednisone	30 days prior to screening through the end of the study
TNFα antagonist	Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent	8 weeks prior to screening through the end of the study
Integrin antagonist	Natalizumab	8 weeks prior to screening through the end of the study
Interleukin antagonist	Ustekinumab	12 weeks prior to Screening through the end of the study
JAK inhibitors	any JAK inhibitors, including but not limited to tofacitinib, baricitinib, and upadacitinib	Any time before and through the end of the study
Other (non-biologic)	Cyclosporine, thalidomide, tacrolimus, leflunomide, and any investigational agent	30 days prior to screening through the end of the study
Investigational biologics	Any investigational biologic agent	8 weeks prior to screening through the end of the study (or at least 5 half-lives)
Lymphocyte-depleting therapies	Alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte depleting therapy	Any time before and through the end of the study
Other Prohibited Medication		
Chronic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[b]	Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, COX-2 inhibitors	From screening through the end of the study
Other biologics[c]	Antibody based or other systemic biologics, eg, denosumab, trastuzumab	Requires medical monitor consultation

a May decrease study drug exposure and are excluded to avoid potential reduction in study drug activity. PK results indicate that filgotinib is a P-gp substrate, as a single dose of 200 mg itraconazole (a potent P-gp inhibitor) increased filgotinib C_{max} by 64% and AUC_{inf} by 45% and had no effect on the major, active metabolite GS-829845.
b Occasional use of NSAIDs for transient symptoms and daily use of aspirin up to 162.5 mg for the purpose of cardiovascular prophylaxis are permitted.
c Other biologics may be allowed with the approval of the medical monitor.

5.5. Corticosteroid Tapering

Starting at Week 10, subjects who are on concomitant steroids must begin tapering steroid therapy. The dose should be reduced at a rate starting at 2.5 mg per week up to 5 mg per week (or equivalent taper if not prednisone) until the subject is no longer on steroids. Subjects who are on budesonide should have their daily dose reduced by 3 mg every 3 weeks until they are completely off steroids. For subjects undergoing taper, steroids may be increased or restarted at doses up to and including their baseline dose if return of symptoms is apparent. These subjects will not be considered treatment failures. Subjects who need to restart or increase steroid treatment at a dose that exceeds their baseline dose of steroids (dose may not exceed 20 mg/day prednisone [or equivalent] or budesonide 6 mg/day) will be considered treatment failures for all clinical endpoints but will be permitted to remain in the study and continue to receive study drug.

5.6. Vaccine Guidelines

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

- Live or attenuated vaccines (including, but not limited to varicella and inhaled flu vaccine) are prohibited within 30 days of Day 1, throughout the study, and for 12 weeks after the last dose of study drug.

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

- Varicella or attenuated typhoid fever vaccination – avoid contact for 4 weeks following vaccination

- Oral polio vaccination -- avoid contact for 6 weeks following vaccination

- Attenuated rotavirus vaccine -- avoid contact for 10 days following vaccination

- Inhaled flu vaccine -- avoid contact for 1 week following vaccination

- Inactivated vaccines (such as inactivated flu vaccines) should be administered according to local vaccination standards whenever medically appropriate; however, there are no available data on the concurrent use of filgotinib and its impact on immune responses following vaccination.

5.7. Accountability for Study Drug

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

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

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

5.7.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are detailed in tabular form in Appendix 2. Key procedures are described in the text that follows.

Written informed consent must be obtained from each subject before initiation of any screening procedure. CCI [redacted]

From the time of obtaining informed consent through the Week 10 visit, subjects must maintain allowed concomitant medications at a stable dose (see Section 5.4.1).

The investigator must document any deviation from protocol procedures and notify the Sponsor or contract research organization.

6.1. Subject Enrollment and Treatment Assignment

Subjects who meet protocol eligibility criteria will be randomized in a blinded fashion in a 2:2:1 ratio to 1 of 3 treatment groups as described in Section 5.3.

6.2. Sequence of Assessments at Study Visits

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

CCI [redacted]

CCI [redacted]

6.4. Randomization and Study Drug Administration

- Enter subject information in the IWRS to receive treatment assignment
- Dispense study drug as directed by the IWRS
- Instruct the subject on the packaging, storage, and administration of the study drug
- Observe the subject taking the first dose of study drug and record the time of first dose

6.5. Flexible Sigmoidoscopy

A centrally read flexible sigmoidoscopy will be conducted at screening to assess the rectum and anal canal and determine the severity of proctitis via SES-CD (refer to Appendix 5). At Week 24, endoscopic appearance of the rectum and anal canal will be assessed again by centrally read flexible sigmoidoscopy.

Screening flexible sigmoidoscopy should be performed only after subject eligibility based on CDAI is confirmed. If there are any outstanding screening clinical laboratory assessments at the time the baseline CDAI is calculated, these results must also be confirmed as being within eligibility requirements prior to conducting the flexible sigmoidoscopy. Consideration should be given to central reader review turnaround times to ensure results are available prior to Day 1.

Week 24 flexible sigmoidoscopy should be performed no earlier than 14 days prior to the Week 24 visit. If possible, flexible sigmoidoscopy should be performed on the same day as the MRI procedure.

An early termination (ET) flexible sigmoidoscopy must be performed prior to the subject leaving the study for subjects that early ET due to either:

1) non-response of their moderately active luminal disease at Week 10, OR

2) non-response of their perianal fistulizing disease at Week 10, OR

3) meeting disease worsening criteria after Week 10.

For additional details on the flexible sigmoidoscopy procedure, refer to the Endoscopy Manual.

6.6. Magnetic Resonance Imaging

A centrally read MRI will be conducted at screening to determine the anatomy of draining perianal fistulae. At Week 24, MRI will be used to evaluate healing of fistulae in addition to clinical assessment of drainage and fistula closure.

Screening MRI should be performed only after subject eligibility based on CDAI is confirmed. If there are any outstanding screening clinical laboratory assessments at the time the baseline CDAI is calculated, these results must also be confirmed as being within eligibility requirements prior to conducting the MRI. Consideration should be given to central reader review turnaround times to ensure results are available prior to Day 1.

Week 24 MRI should be performed no earlier than 14 days prior to the Week 24 visit. Glomerular filtration rate (GFR) using the Cockcroft-Gault Model for creatinine clearance from the Week 18 visit should be reviewed prior to the Week 24 MRI. Since this procedure involves the use of a gadolinium-based contrast, subjects with an eGFR < 40 mL/min at Week 18 require approval from the Medical Monitor to undergo MRI.

An ET MRI must be performed prior to the subject leaving the study for subjects that early ET due to either:

1) non-response of their moderately active luminal disease at Week 10, OR

2) non-response of their perianal fistulizing disease at Week 10, OR

3) meeting disease worsening criteria after Week 10.

GFR using the Cockcroft-Gault Model for creatinine clearance from the Week 10 visit (for Week 10 non-responders) or the last scheduled study visit prior to disease worsening, should be reviewed prior to the ET MRI. Since this procedure involves the use of a gadolinium-based contrast, subjects with an eGFR < 40 mL/min require approval from the Medical Monitor to undergo MRI.

For additional details on the MRI procedure, refer to the MRI Manual.

6.7. Perianal Assessment

The perianal assessment entails identification of external openings of perianal fistulae and evaluation of their status.

For additional details on the perianal assessment and how to document it using the Perianal Fistula Assessment Worksheet, refer to the Perianal Fistula Assessment Manual.

CCI [redacted]

6.11. Safety

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

6.11.1. Clinical Laboratory Evaluations

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

Blood samples will be collected by venipuncture CCI [redacted] in the arm at the time points indicated in the Study Procedures Table (Appendix 2). In addition, urine samples for the clinical laboratory assessments will be collected.

An overnight fast (no food or drinks, except water) of at least 8 hours will be required prior to collection of blood samples for lipid testing.

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

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and/or withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days [except creatinine, which should be retested 7 to 14 days apart]).

Refer to Appendix 10 for table of clinical laboratory tests. The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

6.11.1.1. Tuberculosis Testing

Subjects must have negative QuantiFERON® test during screening, and negative chest X ray within 3 months of or during screening for those with no evidence or history of TB. Positive or negative QuantiFERON® test results must not be repeated. An indeterminate result should be repeated once and the second result (if positive or negative) will be considered final.
Two sequential indeterminate results constitute a screen failure. Subjects with previously treated latent or active TB require sponsor approval. Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Study Medical Monitor.

6.11.1.2. HBV Screening and Surveillance Guidelines

- Subjects with positive HBV surface antigen at screening are excluded.
- Subjects who are positive for HBV surface antibody but negative for both HBV surface antigen and HBV core antibody (HBcAb) at screening are eligible.
- Subjects with positive HBcAb require reflex testing for HBV DNA (conducted locally). Subjects with HBV DNA ≥ lower limit of quantitation (LLOQ) at screening will be excluded. Subjects with positive HBcAb and HBV DNA < LLOQ are eligible, but will require ongoing HBV DNA monitoring (conducted locally) every 3 months during this study. These subjects may require prophylactic treatment per investigator discretion in accordance with local guidelines/standard of care.

6.11.1.3. Thromboembolic Events

Subjects experiencing a thromboembolic event should be evaluated for the overall risk of recurrent thromboembolism and referred to a specialist for further testing as appropriate (including but not limited to evaluation for an underlying inherited hypercoagulable state).

6.11.2. Repeat Screening Assessments

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

Flexible sigmoidoscopy or MRI may be repeated with prior written approval provided by the Sponsor, if the original imaging assessment was not considered acceptable due to technical reasons (e.g. poor quality or missing sequences).

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for randomization into the study. Subjects may be randomized more than 30 days after initial screening if they receive permission from the Gilead Study Director in consultation with the Study Medical Monitor. If the subject does not begin

treatment within this 30-day window, specific screening evaluation procedures may need to be repeated at the direction of the Study Medical Monitor. No more than 1 repeat screening visit is allowed for each subject, unless prior written approval has been provided by the Sponsor.

6.11.3. Pregnancy Testing (for females of childbearing potential only)

All females meeting the childbearing potential criteria (Appendix 9) must have a serum pregnancy test at screening that will be centrally reported, and an in-clinic urine pregnancy test must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic that will be centrally reported. Confirmed pregnancies should be reported as outlined in Section 7.7.2.1.

6.11.4. Vital Signs

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

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

6.11.5. Physical Examination

A physical examination should be performed at the time points indicated in the Study Procedures Table (Appendix 2). Any changes from screening will be recorded. Weight will be measured at all visits, except Week 20. Height will be measured at screening only. Subjects should be instructed to remove shoes prior to measurement of height.

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

6.11.6. 12-lead Electrocardiogram

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

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

CCI [redacted]

[redacted]

[redacted]

6.13. Post-Treatment Assessments

All subjects must complete the PTx assessments 30 days after the last dose of study drug. Only subjects who choose to participate in the LTE study will not complete PTx assessments associated with this protocol:

- Symptom-directed PE including perianal assessment
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Review AEs and concomitant medications
- Obtain blood samples (see Study Procedures Table [Appendix 2])
- Obtain urine sample for pregnancy test (for females of childbearing potential only)

6.14. Early Termination Assessments

For subjects who early terminate from the study, the following tests and procedures will be performed and documented:

- Symptom-directed PE including perianal assessment
- MRI Pelvis
- Flexible sigmoidoscopy
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Perform 12-Lead ECG (for subjects who terminate prior to Week 10)
- Review AEs and concomitant medications
- Collect eDiary back from subject

[redacted]

- Obtain blood samples (see Study Procedures Table [Appendix 2])
- Obtain urine sample for pregnancy test (for females of childbearing potential only) (see Study Procedures Table [Appendix 2])

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 medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (see Section 7.7.1)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

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

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of 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 AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 8

Table 7-1. Grading of Adverse Event Severity

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

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

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

Requirements for collection prior to study drug initiation:

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

7.3.1. Adverse Events

Following initiation of study drug, all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP 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 follow up period.

7.3.2. Serious Adverse Events

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

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

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

- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system.

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 the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit via fax and/or email within 24 hours to:

Gilead PVE: Fax: PPD
E-mail: PPD

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

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

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

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

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

7.4. Gilead Reporting Requirements

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

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

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

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

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 investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 8). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

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

Refer to Section 3.5, Criteria for Study Drug Interruption or Discontinuation, for additional specific discontinuation criteria. Specific toxicity discontinuation criteria in Section 3.5 supersede the below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria should apply. The Study Medical Monitor should be consulted prior to study drug discontinuation when medically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

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

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

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

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

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

Investigational medicinal product may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (eg, Grade 4 creatine kinase [CK] after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to IMP.

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Study 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 until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Any questions regarding toxicity management should be directed to the Study 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, drug interactions, exposure via breastfeeding, unexpected benefit, transmission of infectious agents via the product, product complaints, counterfeit or falsified medicine, and pregnancy reports regardless of an associated AE.

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

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

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

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

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

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

Transmission of infectious agents is defined as any suspected transmission of an infected agent through a GSI investigational product.

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

Counterfeit or falsified medicine: Any investigational product with a false representation of: a) its identity, b) its source, or c) its history.

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3.2. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead PVE.

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

Gilead PVE:	Fax:	PPD
	E-mail:	PPD

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

Gilead PVE:	Fax:	PPD
	E-mail:	PPD

Refer to Appendix 9 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

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

Special situations involving non-Gilead concomitant medications do 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 must be reported as an AE.

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 f 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 is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula response at Week 24

The secondary objectives are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing combined fistula remission at Week 24
- To assess the time to clinical fistula response
- To assess the time to clinical fistula remission
- To evaluate the efficacy of filgotinib as compared to placebo in establishing proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline
- To evaluate the safety and tolerability of filgotinib

CCI

8.1.2. Primary Endpoint

The primary efficacy endpoint is the proportion of subjects establishing combined fistula response at Week 24

8.1.3. Secondary Endpoints

The secondary efficacy endpoints are:

- Proportion of subjects establishing combined fistula remission at Week 24
- Time to clinical fistula response
- Time to clinical fistula remission
- Proportion of subjects achieving proctitis remission at Week 24, in subjects that had moderately to severely active proctitis at baseline

CCI [redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

The primary analysis set for efficacy analyses will be the Full Analysis Set (FAS), defined as all randomized subjects who received at least one dose of study drug.

8.2.1.2. Safety

The primary analysis set for safety analyses is the Safety Analysis Set, defined as all subjects who received at least one dose of study drug.

CCI [redacted]

CCI [redacted]

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available. If no pre-treatment laboratory value is available, the baseline value will be assumed to be normal (ie, no grade [Grade 0]) for the summary of graded laboratory abnormalities. If safety laboratory results for a subject are missing for any reason at a time point, the subject will be excluded from the calculation of summary statistics for that time point.

Values for missing vital signs data will not be imputed. However, a missing baseline result will be replaced with a screening result, if available.

CCI [redacted]

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

CCI [redacted]

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized separately by treatment group using standard descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) for continuous variables and number and percentage of subjects for categorical variables.

Demographic summaries will include age, sex, race and ethnicity. Baseline characteristics may include height, weight, body mass index (BMI), CCI [redacted], number of years since diagnosis of CD, anatomy of draining perianal fistulae (simple *versus* complex), presence of moderately to severely active proctitis (Yes or No), Receiving vedolizumab therapy concomitantly at Day 1 (Yes or No), fecal calprotectin, fecal lactoferrin, serum CRP, and other variables of interest.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The number and proportion of subjects establishing combined fistula response at Week 24 for each treatment group will be summarized with corresponding exact 90% CI based on binomial distribution (Clopper-Pearson method). The difference in proportions between each filgotinib dose group and the placebo group will be presented along with the associated 90% CI. Subjects who do not have sufficient measurements to determine efficacy endpoint will be considered failures (ie, non-responder imputation [NRI]). No formal hypothesis testing will be performed.

8.5.2. Secondary Analyses

The same summaries used for the primary endpoint will be utilized for the proportion of subjects establishing combined fistula remission at Week 24. Subjects who do not have sufficient measurements to determine efficacy endpoint will be considered failures (ie, NRI).

For time-to-event secondary endpoints, the summary statistics (eg, median, Q1, Q3) from the Kaplan-Meier method will be provided for each treatment group. The stratified Cox proportional hazards model will be used to estimate the hazard ratio with the corresponding 90% CI.

CCI [redacted]

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, PE, ECG and vital signs measurements at various time points during the study, and by the documentation of AEs. All safety data collected on or after the first dose of study drug administration (Day 1) up to 30 days after permanent discontinuation of study drug will be summarized by treatment group according to the study drug received.

All data collected during the course of the study will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. The number of doses administered and the level of adherence will be summarized by treatment group.

8.6.2. Adverse Events

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

Treatment-Emergent Adverse Events (TEAEs) are defined as 1 or both of the following:

- Any AEs with an onset date of on or after the study drug start date for the entire study (Day 1) and up to 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug.

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

8.6.3. Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Absolute value and change from baseline at all scheduled time points will be summarized.

Graded laboratory abnormalities will be defined using the grading scheme defined in the Common Terminology Criteria for Adverse Events (CTCAE).

Incidence of treatment-emergent laboratory abnormalities defined as values that increase at least 1 toxicity grade from baseline at any time post baseline will be summarized by treatment group. If baseline data are missing, then any graded abnormality (ie, at least a Grade 1) will be considered treatment-emergent.

8.6.4. Other Safety Evaluations

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

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.8. Sample Size

A total of approximately 75 subjects are planned to be randomized (2:2:1 ratio); 30 subjects to each of the filgotinib dose groups and 15 subjects to the placebo group. This sample size is considered adequate to assess the safety, tolerability, and efficacy of filgotinib in a descriptive manner.

Table 8-1 provides the exact 90% CI using the binomial distribution for a given combined fistula response rate ranging from 20% to 80%:

Table 8-1. Combined Fistula Response Rates (90% CI)

Number Randomized	Number of Responders	Response rate	Lower Limit of 90% CI	Upper Limit of 90% CI
30	6	20%	9%	36%
30	9	30%	17%	47%
30	12	40%	25%	57%
30	15	50%	34%	66%
30	18	60%	43%	75%
30	21	70%	53%	83%
30	24	80%	64%	91%

CI = confidence interval

8.9. Data Monitoring Committee

An external data monitoring committee (DMC) comprised of an independent statistician and two independent gastroenterologists will review the progress of the study and perform interim reviews of safety data and provide recommendation to Gilead whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications.

The DMC will meet twice to evaluate all available safety data of the study. The initial meeting will occur after approximately 20% of the planned total number of subjects complete their Week 10 visit. Following this, the next meeting will occur after approximately 50% of the subjects reach Week 10. Additionally, the DMC members may request an unscheduled review of the study data based on a concern for subject safety. An ad hoc DMC meeting may be triggered by the following conditions:

- ≥ 2 subjects develop the same (by PT) related, Grade 4, unexpected AE in the infections and infestations SOC
- ≥ 2 subjects develop any related, Grade 4, thromboembolic events that have been positively adjudicated by the adjudication committee (see Section 8.10)
- Any subject develops a Grade 5, related, unexpected AE. The definition of an unexpected AE will be based on the reference safety information that is on file at the time the event occurs

After a minimum of 35 subjects (estimated to be 7 from placebo group and 14 from each filgotinib treatment group based on randomization ratio) are enrolled and complete Week 10 visit or discontinue from the study, an interim futility analysis will be conducted to evaluate efficacy improvement in fistulizing disease. The cumulative safety analysis and summary statistics to evaluate perianal fistula closure of external openings, and CCI [redacted] improvement will be generated and provided to the DMC. The DMC will make a recommendation to either continue the study without modification or recommend that the study be halted due to lack of efficacy, and will be based on the totality of data available at the time of the interim analysis.

The DMC's specific activities will be defined by a mutually agreed upon charter, which will define the DMC's membership, conduct and meeting schedule.

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study. If the DMC recommends stopping the study for lack of efficacy, a Gilead executive team will be unblinded to confirm the DMC recommendation.

8.10. Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

An independent adjudication committee will be formed to periodically review and adjudicate all potential major adverse cardiovascular events (MACE) and thromboembolic events in a blinded manner.

The CVEAC's specific activities will be governed by a mutually agreed charter, which will define the CVEAC's membership, conduct, and meeting schedule.

The following events will be adjudicated and classified by the CVEAC:

- Cardiovascular death
- Myocardial infarction
- Stroke
- Arterial thromboembolism
- Venous thromboembolism (eg, deep venous thrombosis, pulmonary embolism)

Further details will be specified in the CVEAC charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

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

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, 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/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. **The study investigator must ensure that the potential risk of infertility is discussed with all male subjects during the informed consent process**. The investigator must use the most current

IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention.

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

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

- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility has been received. Subsequent to data entry, a study monitor will perform source data

verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF 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 trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

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

If IMP is destroyed on site, the investigator must maintain accurate records for all 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 IMP supplies and associated records at periodic intervals.

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

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

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

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (see Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, eg, attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

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Appendix 3. Management of Clinical and Laboratory Adverse Events
CCI [redacted]
Appendix 5. Simple Endoscopic Score for Crohn's Disease (SES-CD)
CCI [redacted]
CCI [redacted]
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Appendix 10. Clinical Laboratory Assessment Table

Appendix 1. Investigator Signature Page

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

STUDY ACKNOWLEDGEMENT

A Phase 2, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Efficacy and Safety of Filgotinib in the Treatment of Perianal Fistulizing Crohn's Disease

GS-US-419-4016, Amendment 5, 04 February 2020

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

PPD

PPD (Printed)
PPD

PPD

Signature

07FEB2020

Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

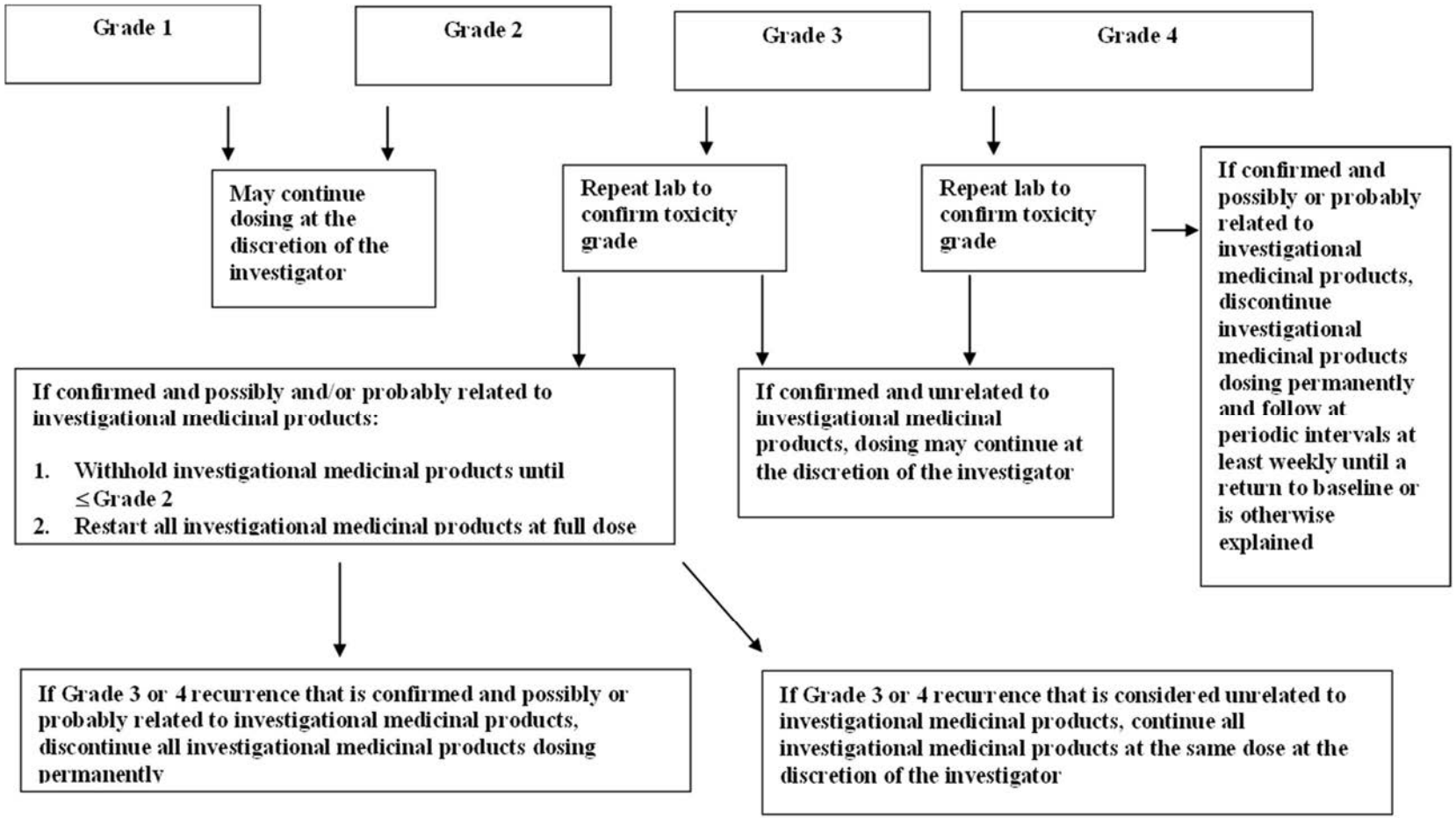
Period	Screening	Treatment									Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**PTx[a]**	**ET**
Week		**0**	**2**	**4**	**6**	**10**	**14**	**18**	**20**	**24**		
Study Day	**-30 to -1**	**1**	**15**	**29**	**43**	**71**	**99**	**127**	**141**	**169**		
Visit Window (±)			**±3**	**±3**	**±3**	**±2**	**±3**	**±3**	**±5**	**±5**	**±3**	
Written Informed Consent	X											
Medical History & Demographics	X											
Crohn's Disease & Treatment History	X											
12-lead ECG	X					X						X[b]
Review of Inclusion/ Exclusion Criteria	X	X										
Physical Exam (Complete including perianal)[c]	X											
Physical Exam (symptom-based) and perianal assessment[c]		X	X	X	X	X	X	X		X	X	X
Vital Signs	X	X	X	X	X	X	X	X		X	X	X
Weight	X	X	X	X	X	X	X	X		X	X	X
Height	X											
Adverse Events	X	X	X	X	X	X	X	X		X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X
Randomization		X										
Study Drug Dispensing		X		X		X	X	X				
CCI [redacted]												
CCI [redacted]												
eDiary instruction & review[e]	X	X	X	X	X	X	X	X		X		
Flexible Sigmoidoscopy[o]	X									X		X[r]
MRI[f]	X									X		X[s]

Period	Screening	Treatment									Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**PTx[a]**	**ET**
Week		**0**	**2**	**4**	**6**	**10**	**14**	**18**	**20**	**24**		
Study Day	**-30 to -1**	**1**	**15**	**29**	**43**	**71**	**99**	**127**	**141**	**169**		
Visit Window (±)			**±3**	**±3**	**±3**	**±2**	**±3**	**±3**	**±5**	**±5**	**±3**	
Stool for *C. diff* toxin, pathogenic *E. coli*, *Salmonella*, *Shigella*, *Campylobacter* and *Yersinia* testing	X											
Stool O&P	X											
CCI												
Fecal Lactoferrin, Calprotectin	X									X		
Urine drug screen[g]	X											
Urinalysis[q]	X									X		
Pregnancy Test[h]	X	X		X	X	X	X	X	X	X	X	X
TB screening[i]	X											
Chest x-ray[q]	X											
HBV, HCV, HIV screening[j]	X											
Hematology	X	X	X	X	X	X	X	X		X	X	X
Chemistry	X	X	X	X	X	X	X	X		X	X	X
Fasting Lipids[p]		X				X				X		
CRP	X	X	X	X	X	X	X	X		X	X	X
Blood TCR/BCR repertoire sample[k]		X		X		X				X		
Plasma biomarker sample		X		X		X				X		
Serum biomarker sample		X		X		X				X		
Blood transcriptome sample		X		X		X				X		
CCI												
Serum immunoglobulin		X		X		X				X	X	X
CCI												

Period	Screening	Treatment									Follow-Up	
Visit	1	2	3	4	5	6	7	8	9	10	PTx[a]	ET
Week		0	2	4	6	10	14	18	20	24		
Study Day	-30 to -1	1	15	29	43	71	99	127	141	169		
Visit Window (±)			±3	±3	±3	±2	±3	±3	±5	±5	±3	
CCI												
CCI												

a The Post-Treatment (PTx) visit should occur 30 days after the last dose of study drug. Only subjects who roll over into the LTE study will not complete PTx assessments.
b For subjects who terminate prior to Week 10
c A complete physical examination (PE) including; vital signs, body weight, height, and perianal assessment (including completion of the Perianal Fistula Assessment Worksheet) will be performed at screening. A symptom-directed PE and perianal assessment(including completion of the Perianal Fistula Assessment Worksheet) should be performed at all other time points.
CCI [redacted]
e Subjects should begin filling out the eDiary the day of their initial screening visit and continue to fill it out throughout the remainder of the study.
f Refer to Section 6.6 for details on the MRI procedure
g Positive cocaine test disqualifies subject; positive amphetamines, barbiturates, benzodiazepines, and opioids require medical monitor review
h All females meeting the childbearing potential criteria must have a serum pregnancy testing at screening and a urine pregnancy test must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug must be immediately interrupted and the subject should come to the site for serum pregnancy test in clinic.
i Proof of no active or untreated latent TB at screening. Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care, for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Study Medical Monitor.
j An HIV-1/HIV-2 antibody test, a HCV antibody test, a HBV surface antigen test, a HBV surface antibody test, and a HBV core antibody test will be performed on all subjects. Subjects with positive HBcAb require reflex testing for HBV DNA (conducted locally). Refer to section 6.11.1.2 for further details.
k TCR: T-cell receptor; BCR: B-cell receptor
CCI [redacted]
o Refer to Section 6.5 for details on the flexible sigmoidoscopy procedure
p Subjects should fast (no food or drinks, except water) for at least 8 hours prior to blood sample collection at Day 1, Week 10, and Week 24
q Chest x-ray (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection
r Subjects meeting non-response or disease worsening criteria should undergo a flexible sigmoidoscopy assessment prior to exiting the study.
s Subjects meeting non-response or disease worsening criteria should undergo a pelvic MRI prior to exiting the study.

Appendix 3. Management of Clinical and Laboratory Adverse Events



CCI

Appendix 5. Simple Endoscopic Score for Crohn's Disease (SES-CD)

Variables	Score			
	0	**1**	**2**	**3**
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter >0.5-2)	Very large ulcers (diameter > 2)
Ulcerated Surface (%)	None	< 10	10-30	> 30
Affected surface (%)	Unaffected segment	< 50	50-75	> 75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Total SES-CD: sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (eg, rectum, left colon, transverse colon, right colon, and ileum); note Total SES-CD will not be calculated during Study GS-US-419-4016
{Daperno 2004}
For Study GS-US-419-4016, the Proctitis SES-CD score (which includes an overall assessment of both rectum and anal canal) and Anal Canal Segmental SES-CD score will only score **size of ulcers** and **ulcerated surface**. The Proctitis SES-CD score will be used to provide an endoscopic measure of proctitis. CCI [redacted]


CCI

CCI

Appendix 8. CTCAE Grading Scale for Severity of Adverse Events

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

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

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

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

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

Appendix 9. 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. Pregnancy is contraindicated during use of filgotinib.

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

1) Definitions

a) Definition of Childbearing Potential

For the purposes of this study, a female-born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure. Women who do not meet below criteria for being post-menopausal, are not permanently sterile, or do not have medically documented ovarian failure must have pregnancy testing as outlined by the protocol.

Women are considered to be in a postmenopausal state when they are $\geq$ 54 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause.

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

b) Definition of Male Fertility

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

2) Contraception for Female Subjects

a) Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

b) Contraception for Female Subjects of Childbearing Potential

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

Female subjects must agree to use one of the following methods 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 3 months after procedure)

- Female subjects, who wish to use a hormonally based method, must use it in conjunction with a barrier method; the barrier method is to be 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 (each method *must* be used with a barrier method, preferably male condom)

  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Barrier methods (each method *must* be used 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 refrain from egg donation and in vitro fertilization during treatment and until at least 35 days after the last study drug dose.

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 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 during the study are to report the information to the investigator.

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

6) Pregnancy Testing

All females of childbearing potential will have urine pregnancy testing every 4 weeks (in clinic) during their study participation. If a urine pregnancy test is positive, the subject should stop study drug immediately, contact the investigator, and have a confirmatory serum pregnancy test in clinic.

Appendix 10. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Creatinine clearance (CC&G) Glucose Phosphorus Magnesium Potassium Sodium Creatine Phosphokinase (CPK)	Appearance Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen Microscopy	Urine drug screen for: Amphetamines Cocaine Barbiturates Opiates Benzodiazepines C-reactive protein (CRP) QuantiFERON® TB – Gold In-Tube Analysis (if required per inclusion criteria) Serum immunoglobulin Prothrombin Time (PT) Partial thromboplastin time (PTT) International Normalized Ratio (INR)
Serology	**Fasting lipids**	**Stool**	**Pregnancy**
Hepatitis B surface antigen (HBsAg) Hepatitis B surface antibody (Ab) Hepatitis B Core Ab Hepatitis C Ab HIV Ag/Ab CCI [redacted]	Triglycerides Total Cholesterol High-density lipoprotein cholesterol [HDL-C] Low-density lipoprotein cholesterol [LDL-C])	Bacterial stool culture C-Diff Toxin Ova and Parasites (O&P)	*In females of childbearing potential:* Serum pregnancy Urine pregnancy