Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Crohn's Disease
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
IND Number:	129646
EudraCT Number:	2016-002763-34
Clinical Trials.gov Identifier:	NCT02914600
Indication:	Crohn's Disease
Protocol ID:	GS-US-419-3896
Galapagos Medical Leader:	Name: [redacted]
Protocol Version/Date:	Original: 15 July 2016 Amendment 1: 07 September 2016 Amendment 2: 11 November 2016 Amendment 3: 15 June 2017 Amendment 4: 09 March 2018 Amendment 5: 09 November 2018 Amendment 5.1*: 17 April 2019 *Canada, Israel, France, UK, US, and VHP countries only Amendment 6: 05 September 2019 Amendment 7: 23 March 2020 Amendment 8: 02 December 2021 Amendment 9: 23 November 2022

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol/Amendment #	Date	Main Rationale General/Country-Specific
CSP Version 1.0	15-Jul-2016	Initial Clinical Study Protocol. General
Amendment 1	07-Sep-2016	Updated Study Procedures Table and footnotes to reflect changes made to weekly visits assessments/procedures in the protocol. Protocol GS-US-419-3896 title changed from Open-Label to Long-Term Extension study. General
Amendment 2	11-Nov-2016	Updated Study Procedures Table to reflect changes made to the study visit assessments/procedures in the protocol. General
Amendment 3	15-Jun-2017	Updates were made in response to the South Korean Ministry of Food and Drug Safety request for the use of 200 mg in males in Korea to be limited to male subjects who had failed 2 classes of biologic therapies (any tumor necrosis factor-alpha [TNFα] antagonist and vedolizumab). Updated sections with emerging relevant clinical and pipeline data, and ensured consistency with Investigator Brochure (IB) Ed 12. Updated Study Procedures Table to reflect changes made to the study visit assessments/procedures in the protocol. General
Amendment 4	09-Mar-2018	Clarification on inclusion/exclusion criteria including those surrounding hepatitis and tuberculosis (TB), clarified Day 1 visit procedures and provided additional flexibility for enhanced safety monitoring (suggested infectious workups for disease worsening). Updated the department name from Drug Safety and Public Health (DSPH) to Pharmacovigilance & Epidemiology (PVE) Updated the Study Procedures Table and footnotes to reflect changes made to the

Clinical Study Protocol/Amendment #	Date	Main Rationale General/Country-Specific
		study visit assessments/procedures in the protocol General
Amendment 5	09-Nov-2018	To allow study-wide unblinding of GS-US-419-3896 after the parent studies (GS-US-419-4015, GS-US-419-4016 and GS-US-419-3895) were unblinded. Inclusion criterion # 2 was amended to include a comprehensive list of the Gilead-sponsored Crohn's disease (CD) parent studies eligible for roll-over into this long-term extension (LTE) study. General
Amendment 5.1	17-Apr-2019	Updated to allow for continuation of concomitant vedolizumab use in subjects who were previously enrolled in study GS-US-419-4016. Canada, Israel, France, UK, US, and voluntary harmonisation procedure (VHP) countries
Amendment 6	05-Sep-2019	Updated duration of treatment to 432 weeks, or until filgotinib becomes commercially available, whichever comes first, to ensure continued access to filgotinib in subjects who have completed the parent study (GS-US-419-3896). Amended study drug interruption or discontinuation criteria to reflect that subjects with newly positive QuantiFERON® TB test (or centrally reported equivalent assay) are now considered for study drug interruption instead of permanent discontinuation. General
Amendment 7	23-Mar-2020	Updated study unblinding language to clarify the unblinding process and to allow subject unblinding once the corresponding parent study (GS-US-419-4015, GS-US-419-4016, or GS-US-419-3895) was unblinded. Updated study drug interruption criteria to allow the investigator to make the assessment of active or latent TB infection based on subject's individual risk factors and further evaluations per standard of

Clinical Study Protocol/Amendment #	Date	Main Rationale General/Country-Specific
		care upon seroconversion or sequential indeterminate QuantiFERON® TB tests. Changes were implemented at the request of the United States Food and Drug Administration (US FDA) regarding new safety information of other Janus kinase (JAK) inhibitors on the potential risk of thromboembolic events. A statement was added to clarify the procedures to be followed if the Data Monitoring Committee (DMC) recommended stopping the study due to lack of efficacy. General
Amendment 8	02-Dec-2021	Changed sponsorship from Gilead Sciences, Inc. to Galapagos NV. The Galapagos study number (GLPG0634-CL-310) was added. General
Amendment 9	23-Nov-2022	The duration of treatment and end of study were adapted due to the limited number of subjects expected to continue after 31 January 2025 and to allow subjects from other filgotinib treatment studies for CD to be enrolled into this study. Dose interruption criteria regarding renal impairment and lymphopenia were added to align with the IB Edition 17, 15 Jul 2022. The length of time women of childbearing potential should use effective contraception after cessation of filgotinib treatment was changed to align with the post-treatment visit. The requirements for male condom use and reporting of pregnancies in female partners were removed to align with the IB Edition 17, 15 Jul 2022. Monthly pregnancy testing in clinic was changed to allow at home testing for subjects outside the US to reduce the burden on subjects. General

SUMMARY OF CHANGES

Amendment 9 (23-Nov-2022)

The overall reasons for this amendment are:

a To adapt the duration of treatment and end of study due to the limited number of subjects expected to continue after 31 January 2025 and to allow subjects from other filgotinib treatment studies for Crohn's disease (CD) to be enrolled into this study.

b To add dose interruption criteria regarding renal impairment and lymphopenia to align with the Investigator's Brochure Edition (IB) 17, 15 Jul 2022.

c To change the length of time women of childbearing potential should use effective contraception after cessation of filgotinib treatment to align with the post-treatment visit.

d To remove the requirements for male condom use and for reporting pregnancies in female partners during this study to align with the IB Edition 17, 15 Jul 2022.

e To allow monthly pregnancy testing either in clinic (when it coincides with a scheduled visit) or at home with follow-up contact for subjects outside the US to reduce the burden on subjects.

In addition, minor updates and administrative corrections were made.

The changes made to the clinical study protocol (CSP) GS-US-419-3896 (GLPG0634-CL-310 [DIVERSITY LTE]) Version 8.0, 02 December 2021, are listed below, with a brief rationale of each change and the applicable sections.

Change and Rationale: The duration of treatment and end of study were adapted due to the limited number of subjects expected to continue after 31 January 2025 and to allow subjects from other filgotinib treatment studies for CD to be enrolled into this study.

Applicable Section:

Protocol Synopsis

Definition of Terms (new section)

1.3 Rationale for This Study

1.3.1 Rationale for Dose3.2 Study Design

3.3 Study Treatments

3.4 Duration of Treatment

3.7 End of Study

4.2 Inclusion Criteria

5.1 Randomization, Blinding and Treatment Codes

6.2.1 Day 1 Visit

6.3.2 (new section title) Every 4 Weeks From Day 1 (± 7 days)

6.3.3 (new section title) Week 12 and Then Every 12 Weeks Thereafter From Day 1 (± 7 days)

6.3.4 Every 24 Weeks From Day 1 (± 7 days)

6.3.5 Every 48 Weeks From Day 1 (± 7 days)

6.3.6 (new section) End of Treatment Visit

Appendix 2. Study Procedures Table

Change and Rationale: A study drug interruption criterion for subjects experiencing moderate renal impairment (estimated creatinine clearance ≥ 35 mL/min and < 60 mL/min per Cockcroft-Gault formula) was added to align with the IB Edition 17, 15 Jul 2022. **Applicable Section:** 3.5.1 Study Drug Interruption Considerations
Change and Rationale: A study drug interruption criterion for subjects with an absolute lymphocyte count (ALC) < 500 cells/mm^3 was added to align with the Investigator's Brochure Edition 17, 15 Jul 2022. **Applicable Section:** 3.5.1 Study Drug Interruption Considerations
Change and Rationale: The length of time women of childbearing potential should use effective contraception after cessation of filgotinib treatment was changed to 30 days to align with the post-treatment visit. **Applicable Sections:** Protocol Synopsis 4.3 Exclusion Criteria Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
Change and Rationale: The requirements for male subjects to use condoms and for pregnancies in female partners to be reported during this study were removed in alignment with the IB Edition 17, 15 Jul 2022. The use of a condom is not mentioned in the IB, as possible seminal transfer is not considered to lead to relevant systemic exposure in partners of childbearing potential. **Applicable Sections:** Protocol Synopsis 4.2 Inclusion Criteria 4.3 Exclusion Criteria 7.7.2.1 Instructions for Reporting Pregnancies Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
Change and Rationale: The requirement for female subjects to come to the clinic for monthly pregnancy testing was changed for subjects outside the US to allow for testing either in the clinic (when it coincides with a scheduled visit) or at home with a follow-up contact in order to reduce the burden on subjects. **Applicable Sections:** 6.3.2 (new section title) Every 4 Weeks From Day 1 (± 7 days) Appendix 2. Study Procedures Table Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

An overview of the changes introduced in previous amendments can be found in the separate protocol amendment summary of changes document for each amendment.

PROTOCOL SYNOPSIS

Galapagos NV
Generaal De Wittelaan L11 A3
2800 Mechelen, Belgium

Study Title:	A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Crohn's Disease
IND Number:	129646
EudraCT Number:	2016-002763-34
Clinical Trials.gov Identifier:	NCT02914600
Study Centers Planned:	Approximately 500 centers globally Study centers will consist of sites that previously participated in one or more filgotinib treatment studies for Crohn's disease (CD).
Objectives:	The primary objective of this study is: • To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD The secondary objective of this study is: • To evaluate the effect of filgotinib on Patient Reported Outcomes (PRO2) and Crohn's Disease Activity Index (CDAI) scores [redacted]
Study Design:	Long-term extension study to evaluate the safety of filgotinib administered to subjects with CD
Number of Subjects Planned:	Approximately 1000

Target Population:	Subjects with CD who have completed* or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD. *A subject is defined as completed if they have completed all study visits and procedures as defined in the protocol or have completed treatment up to the primary endpoint.
Duration of Treatment:	Subjects will receive filgotinib or placebo until filgotinib becomes commercially available in the country or until the end of study (31 January 2025), whichever comes first. All subject visits, including the post-treatment (PTx) visit, must be completed by 31 January 2025 at the latest. The maximum treatment duration will be approximately 7.5 years.
Diagnosis and Main Eligibility Criteria:	**Inclusion Criteria** Subjects will be eligible if they meet *all* of the following inclusion criteria: 1) Must have the ability to understand and sign a written informed consent form (ICF), which must be obtained prior to initiation of study procedures associated with this trial 2) Criterion modified per amendment 9 2.1) Must have enrolled in a CD parent protocol, GS-US-419-4015, GS-US-419-4016 or GS-US-419-3895 or any other Gilead/Galapagos-sponsored filgotinib treatment study for CD 3) Females of childbearing potential must have a negative pregnancy test at Day 1 and must agree to continued monthly pregnancy testing during use of filgotinib treatment 4) Criterion modified per amendment 9 4.1) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception for the duration described in Appendix 6 5) Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose of study drug 6) Must have completed all required procedures or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD **Exclusion Criteria** Subjects who meet *any* of the following exclusion criteria are not to be enrolled in the study.

1) Subjects who are discontinued from a parent study for reasons *other* than disease worsening or lack of response or remission; eg, subjects who discontinue for safety or tolerability issues are not eligible for this study
2) Known hypersensitivity to the study drug
3) Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease, alcohol or drug abuse) that, in the opinion of the Investigator or Sponsor, would make the subject unsuitable for the study or would prevent compliance with the study protocol
4) Criterion modified per amendment 9

   4.1) 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 for at least 30 days after the last dose of study drug
5) Criterion deleted per amendment 9
6) Criterion modified per amendment 9

   6.1) Females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined in Appendix 6
7) Use of prohibited concomitant medications as outlined in Section 5.4.2

Study Procedures/ Frequency:

Study visits with safety procedures will occur at Week 2, Week 4, Week 12, and then every 12 weeks thereafter. until the End of Treatment (EoT) visit. The EoT visit will be scheduled when filgotinib becomes commercially available in the country or prior to the end of study on 31 January 2025, whichever comes first.

Day 1 assessments will include medical history, symptom directed physical examination (PE) including body weight and height, vital signs, safety laboratory assessments, urine pregnancy test (for females of childbearing potential), PRO2 and CDAI, adverse events (AEs) and concomitant medication assessments.

PRO2, CDAI, symptom directed PE including body weight, vital signs, safety laboratory analyses, urine pregnancy test (for females of child-bearing potential), AEs and concomitant medications assessments will occur at each study visit.

Women of child-bearing potential will require urine pregnancy tests every 4 weeks starting from Day 1 for the entire duration of the study.

Subjects rolling over from GS-US-419-4016 will require complete perianal fistulae assessment every 12 weeks.

	Urine samples will be collected at Day 1 and once every 24 weeks. Peripheral Blood Mononuclear Cell (PBMC) (United States [US] and Canadian sites only), [redacted], [redacted], [redacted], and [redacted] will be collected at Day 1 and once every 24 weeks. Tuberculosis (TB) QuantiFERON® (or centrally reported equivalent assay) testing and [redacted] will be completed at Day 1 and once every 48 weeks. A standard 12-lead electrocardiogram (ECG) will be performed every 48 weeks. Flexible sigmoidoscopy/colonoscopy collection with biopsies is optional per standard of care. The date of the procedure may be requested for accuracy of data analysis. Other inflammatory bowel disease (IBD) therapies (eg, prednisone > 30 mg) not permitted in the parent protocol are not allowed in this study. Refer to Section 5.4 for further details. Increases to or the addition of oral medications for the treatment of CD are allowed provided their dose does not exceed what was allowed in the parent protocol. Subjects who complete all study treatment visits or discontinue early will return 30 days after the last dose of study drug for PTx safety assessments. All subject visits, including the PTx visit, must be completed by 31 January 2025 at the latest.
Test Product, Dose, and Mode of Administration:	Filgotinib 200 mg oral tablet, once daily Filgotinib 100 mg oral tablet, once daily Dosing regimen is determined by regimen in parent study and reason for exiting parent study, as noted in Section 3.3.
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match (PTM) filgotinib 200 mg oral tablet, once daily PTM filgotinib 100 mg oral tablet, once daily
Criteria for Evaluation:	
Safety:	Assessments of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of AEs, PE (symptom driven), vital signs, and clinical laboratory evaluations (hematology, chemistry, and urinalysis). An ECG will be performed every 48 weeks.
Efficacy:	Efficacy will be evaluated in terms of changes in PRO2 and CDAI scores.

[redacted]

Statistical Methods:	Safety and efficacy data from this study will be summarized descriptively. The primary end point is safety. Safety will be evaluated through AEs, clinical laboratory tests, and vital signs. Safety end points will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or standard descriptive statistics (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) for continuous data. The secondary efficacy end points of change from baseline in PRO2 and CDAI scores, and [redacted]ll be summarized using standard descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum). Interim analyses may be performed for regulatory submission purposes when the parent studies are unblinded.

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

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADL	Activities of Daily Living
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AP	abdominal pain
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration, drug versus time curve
[redacted]	[redacted]
BMI	body mass index
CC&G	Cockcroft-Gault
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CES	Carboxylesterases
CFR	Code of Federal Regulations
CI	confidence interval
CIA	collagen-induced arthritis
CK	creatine kinase
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMV	Cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRO	contract (or clinical) research organization
CRP	c-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP	Cytochrome
DAI	disease activity index
DMC	Data monitoring committee
DNA	deoxyribonucleic acid
DSS	dextran sodium sulfate
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EDC	Electronic Data Capture

e-Diary	electronic diary
EMA	European Medicines Agency
[redacted]	[redacted]
eSAE system	electronic SAE system
ET	early termination
EoT	end of treatment
EU	European Union
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
GI	Gastrointestinal
HBcAB	Hepatitis B virus core antibody
HBsAB	Hepatitis B virus surface antibody
HBsAG	Hepatitis B Virus surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
hERG	human ether-a-go-go
HLGT	High-Level Group Term
HLT	High-Level Term
[redacted]	[redacted]
IB	Investigator Brochure
IBD	inflammatory bowel disease
[redacted]	[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
IMP	investigational medicinal product
IND	Investigational new drug
INR	International Normalized Ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	Interactive Web Response System
JAK	Janus Kinase
[redacted]	[redacted]
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLOQ	Lower limit of quantitation

LLT	Lower-Level Term
LTE	long-term extension
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
MTX	Methotrexate
NOEL	no-observed-effect-levels
NSAID	Nonsteroidal Anti-inflammatory Drugs
O&P	ova and parasites test
OAT	organic anion transporters
PBMC	peripheral blood mononuclear cell
PD	Pharmacodynamic
PE	physical examination
PEG	polyethylene glycol
PI	principal investigator
PK	Pharmacokinetic
PRO2	Patient reported outcomes consisting of 2 items: abdominal pain severity and liquid stool frequency
PT	Preferred Term
PTM	Placebo-to-match
PTx	Post-Treatment
Q1	1st quartile
Q3	3rd quartile
RA	Rheumatoid Arthritis
RNA	ribonucleic acid
ROC	receiver operating characteristic
RT-PCR	reverse transcription polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
[redacted]	[redacted]
SI	international system of units
SOC	system organ class
SOP	standard operating procedure
STAT	signal transducer and activator of transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TgrasH2	Transgenic

TNFα	tumor necrosis factor-alpha
TYK	Tyrosine kinase
UC	ulcerative colitis
UGT	uridine 5’ diphosphate glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
[redacted]	[redacted]
WBC	white blood cell
[redacted]	[redacted]

DEFINITION OF TERMS

Completed in any other Gilead/Galapagos-sponsored filgotinib treatment parent study for CD	A subject is defined as completed if they have completed all study visits and procedures as defined in the protocol or have completed treatment up to the primary endpoint.

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. 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 Crohn's Disease 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 sub score cut off values of ≤1 for abdominal pain and ≤3 for stool frequency that define clinical remission. As yet, the stool frequency and abdominal pain sub scores of the CDAI have not been used on their own in prospective clinical trials.

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 [redacted] {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 US and European Union {EU}]) and certolizumab pegol (Cimzia® [approved in US]). Vedolizumab (Entivyo®, a monoclonal antibody against α4β71100 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 includes 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. Safe and effective treatment options which may be conveniently administered in a chronic setting would provide a significant treatment advance for patients with moderately to severely active 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 proinflammatory 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. Filgotinib is approved in the European Union (EU), Japan, and Great Britain for treatment of moderate to severe active RA in adult patients. It is also approved for the treatment of moderately to severely active ulcerative colitis (UC) in adults in the EU, Japan and Great Britain. The compound has shown good preliminary efficacy in CD patients in Phase 2 studies.

In humans, filgotinib is metabolized to form one 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 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 Dextran DSS model in two 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 end points 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'- diphosphate - glucuronosyltransferase (UGTs), and no relevant inhibition of key drug transporters, including organic anion transporters (OATs), by filgotinib or GS-829845. 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 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 and 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. Based on their clinical response in Part 1, subjects in Part 2 either continued their current treatment or were reassigned to a different treatment for an additional 10 weeks.

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 end point 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 and endoscopic response compared with placebo.

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

For additional details about the efficacy and safety of filgotinib in CD, reference is made to the IB.

1.3. Rationale for This Study

A need for safer, better tolerated, durable efficacious therapies for patients with CD exists. Despite significant uptake in the use of anti-TNF agents, tolerability of anti-TNFs due to allergic and autoimmune reactions, lack of durable response, and significant increased risk of infection remain problematic. Filgotinib is a once daily, oral therapy that may prove efficacious without the risk of allergic and autoimmune phenomena observed with anti-TNF agents.

This is a long-term extension study (GS-US-419-3896; Galapagos Study ID GLPG0634-CL-310 [DIVERSITY LTE]) to provide treatment with filgotinib for subjects with moderately to severely active CD (who have completed or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD) until filgotinib becomes commercially available in the country or until the end of study (31 January 2025), whichever comes first..

The purpose of this study is to observe the safety of long-term therapy and to ensure continued access to study drug for subjects who responded in the parent protocol of filgotinib. In addition, the study provides an open-label alternative at the highest possible dose (excluding males who are not dual-biologic refractory in the US and Korea, refer to Section 3.3 for further information) for subjects who had disease worsening or lack of response in the parent study.

1.3.1. 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, subjects treated in the 200 mg arm showed favorable response and remission rates (47% remission over 23% placebo and 59% response over 41% placebo). Remission rates 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 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. The presence of response in CD subjects in the exploratory 10 to 20 week arm of Study GLPG0634-CL-211, and study of multiple doses (ie, 100 mg and 200 mg once daily) in the present study will enable establishment of an appropriate nominal dose and determine the dose with the most favorable risk/benefit profile for CD subjects. The present study will ensure continued access to blinded dosing for specific subjects (those who complete a respective parent protocol through the end of that study). After the corresponding parent study (GS-US-419-4015, GS-US-419-4016, or GS-US-419-3895 [Galapagos Study ID: GLPG0634-CL-309]) is unblinded, subjects enrolled in the present study may be unblinded. Subjects who enroll from a parent study and receive blinded treatment in the DIVERSITY LTE study will have their DIVERSITY LTE treatment assignment unblinded when the parent study is unblinded. Subjects will continue on the same dose of open-label filgotinib as they had been receiving in blinded treatment. Subjects on placebo treatment will discontinue study drug and study participation. In addition, the present study allows open-label access at the highest possible dose for subjects who were non-responders or experienced disease worsening on blinded dosing in a parent study. At no time will males in the US and Korea who are not dual biologic refractory receive 200 mg.

Subjects enrolled from other filgotinib treatment studies for CD will receive open-label 200 mg filgotinib daily. Reference is made to Section 3.3 for details about dosing regimen and definition of being dual biologic refractory.

1.4. 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 moderate to severe disease. The lifelong nature of IBD increases the probability that subjects have cycled through various therapies, leaving few approved options.

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 (AUC at the NOAELs for dogs in the 26-week 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 US and Korea with CD or UC will be limited to subjects who have failed at least two biologic therapies (any TNFα antagonist and vedolizumab). Refer to the IB for further information about nonclinical and clinical testicular findings.

Filgotinib has shown an increase of embryofetal malformations in rats and rabbits at exposures similar to, or slightly higher than, exposures associated with a 200 mg once daily dose in CD subjects, the use of highly effective contraception in the subject population is expected to mitigate this risk.

JAK inhibition is expected to increase the risk of infection based on mechanism of action. Across the global studies in filgotinib, in general, active treated 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 clinically significant 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 inclusion criteria in the parent study. For further details about infections and malignancies, please refer to the IB.

The potential benefits of JAK inhibition include improvement in clinical symptoms and mucosal and [redacted]. JAK inhibition may be efficacious in the treatment of IBD based on

results from FITZROY. 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.

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 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.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD

The secondary objective of this study is:

- To evaluate the effect of filgotinib on PRO2 and CDAI scores

[redacted]

[redacted]

[redacted])

3. STUDY DESIGN

3.1. Endpoints

The primary end point is:

- Safety, evaluated through AEs, clinical laboratory tests, and vital signs

The secondary end points are:

- Change from baseline in PRO2 and CDAI scores

[redacted]

3.2. Study Design

This is a long-term extension study to evaluate the safety of filgotinib administered to subjects with CD.

This study includes:

- Day 1
- Treatment Visits: Week 2, Week 4, Week 12, and then every 12 weeks thereafter until filgotinib becomes commercially available in the country or until the end of study (31 January 2025), whichever comes first..
- PTx safety assessments (30 days after the last dose of study drug) for subjects who complete all study treatment visits or discontinue early. All subject visits, including the PTx visit, must be completed by 31 January 2025 at the latest.

3.3. Study Treatments

This is a long-term extension study. Some subjects will receive open-label drug and some will receive blinded dosing until subject's treatment in the corresponding parent study is unblinded. In general, subjects who fully complete a parent study blinded will continue blinded dosing at the same regimen in the present study on 200 mg filgotinib, 100 mg filgotinib, or placebo. After the corresponding parent study (GS-US-419-4015, GS-US-419-4016, or GS-US-419-3895, or other Gilead/ Galapagos-sponsored filgotinib treatment study) is unblinded, subjects enrolled in the present study may be unblinded. Subjects who enroll from a parent study and receive blinded treatment in the DIVERSITY LTE study will have their DIVERSITY LTE treatment assignment unblinded when the parent study is unblinded. Subjects will continue on the same dose of open-label filgotinib as they had been receiving in blinded treatment. Subjects on placebo treatment will discontinue study drug and study participation. Subjects who exit a parent study due to disease worsening or failure to meet response or remission criteria will receive open-label 200 mg filgotinib, with the exception of US and Korea males in this category who were not considered biologic refractory who will receive open-label 100 mg filgotinib. Subjects enrolled from other filgotinib treatment studies for CD will receive open-label 200 mg filgotinib daily.

For the purposes of this study, the definition of dual (or biologic) refractory includes subjects who:

1) Failed any TNFα antagonist and vedolizumab at the time of randomization in studies GS-US-419-3895, GS-US-419-4015, and GS-US-419-4016, or

2) Failed any TNFα antagonist and are taking vedolizumab at the time of randomization into the GS-US-419-4016 study.

Details on dosing regimen for LTE are noted below in Table 3-1.

Table 3-1. Dosing Regimens in LTE

Dose in parent study	Reason for exiting parent study	Dose in LTE	Dose in LTE after LTE Unblinding
All Females, Non-US males and US & Korea dual refractory males			
200 mg filgotinib, blinded	Study completed to end	200 mg filgotinib + PTM 100 mg (blinded dosing)	200 mg filgotinib, open- label
100 mg filgotinib, blinded	Study completed to end	100 mg filgotinib + PTM 200 mg (blinded dosing)	100 mg filgotinib, open-label
Placebo, blinded	Study completed to end	PTM 100 mg + PTM 200 mg (blinded dosing)	Discontinue study drug
200 mg filgotinib, open-label/ blinded	Completed treatment up to primary endpoint	200 mg filgotinib, open-label	200 mg filgotinib, open-label
Placebo, open-label/ blinded	Completed treatment up to primary endpoint	200 mg filgotinib, open-label	200 mg filgotinib, open-label
200 mg filgotinib, blinded	Disease worsening and/or failure to meet response/remission criteria	200 mg filgotinib, open-label	200 mg filgotinib, open-label
100 mg filgotinib, blinded	Disease worsening and/or failure to meet response/remission criteria	200 mg filgotinib, open-label	200 mg filgotinib, open-label
Placebo, blinded	Disease worsening and/or failure to meet response/remission criteria	200 mg filgotinib, open-label	200 mg filgotinib, open-label
200 mg filgotinib, open-label	Study completed to end	200 mg filgotinib, open-label	200 mg filgotinib, open-label
100 mg filgotinib, open-label	Study completed to end	100 mg filgotinib, open-label	100 mg filgotinib, open-label
200 mg filgotinib, open-label	Disease worsening and/or failure to meet response/remission criteria	200 mg filgotinib, open-label	200 mg filgotinib, open-label
100 mg filgotinib, open-label	Disease worsening and/or failure to meet response/remission criteria	200 mg filgotinib, open-label	200 mg filgotinib, open-label

Dose in parent study	Reason for exiting parent study	Dose in LTE	Dose in LTE after LTE Unblinding
US & Korea Males who have not failed at least two biologic therapies (any TNFα and vedolizumab)			
100 mg filgotinib, blinded	Study completed to end	100 mg filgotinib (blinded dosing)	100 mg filgotinib, open-label
Placebo, blinded	Study completed to end	PTM 100 mg (blinded dosing)	Discontinue study drug
100 mg filgotinib, blinded	Disease worsening and/or failure to meet response/remission criteria	100 mg filgotinib, open-label	100 mg filgotinib, open-label
Placebo, blinded	Disease worsening and/or failure to meet response/remission criteria	100 mg filgotinib, open-label	100 mg filgotinib, open-label
100 mg filgotinib, open-label	Study completed to end	100 mg filgotinib, open-label	100 mg filgotinib, open-label
100 mg filgotinib, open-label	Disease worsening and/or failure to meet response/remission criteria	100 mg filgotinib, open-label	100 mg filgotinib, open- label

Abbreviations: LTE=long-term extension; PTM=placebo-to-match

3.4. Duration of Treatment

Subjects will receive filgotinib or placebo until filgotinib becomes commercially available in the country or until the end of study (31 January 2025), whichever comes first. All subject visits, including the PTx visit, must be completed by 31 January 2025 at the latest. The maximum treatment duration will be approximately 7.5 years.

3.5. Criteria for Study Drug Interruption or Discontinuation

3.5.1. Study Drug Interruption Considerations

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

Study drug interruption should be considered in the following circumstances; prior to resumption of study drug, the investigator should discuss the case with the medical monitor:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug pausing should be determined in consultation with the 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.

- Subjects with newly positive (converted) or 2 indeterminate QuantiFERON® TB test (or centrally reported equivalent assay) result(s) should interrupt study drug dosing and be evaluated for active TB and latent TB by the investigator per local standard of care. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Positive or negative results must not be repeated.

- Subjects diagnosed with latent TB (ie, a subject who has newly identified positive diagnostic TB test result, in which active TB has been ruled out) may initiate an adequate course of prophylaxis as per local standard of care; appropriate, ongoing, prophylactic treatment for latent TB must be initiated for a minimum of 4 weeks prior to the continuation of study medication. Subjects may resume study drug after investigator's consultation with medical monitor.

- Subjects with positive or 2 indeterminate QuantiFERON® test result(s) who are determined as having neither latent nor active TB infection may continue participation in the study after consultation and approval from medical monitor. Any subject with active TB must be discontinued from the study. Subjects who were previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator do not need to have yearly QuantiFERON® tests. Subjects previously treated for TB should be screened at least yearly for signs and symptoms consistent with reactivation of TB. Any subject with active TB should be discontinued from the study.

- After a confirmed laboratory change representing moderate renal impairment (estimated creatinine clearance [CrCl] ≥ 35 mL/min and < 60 mL/min per Cockcroft-Gault [CC&G] formula) at any time during the study, the following actions should be taken by the investigator and documented:

  — Establish possible underlying condition and initiate appropriate action to resolve.

  — Retest CrCl within 8 weeks.

  — Carefully consider individual benefit/risk of continuation of filgotinib 200 mg once daily in relation to the observation.

  — If continuation of filgotinib 200 mg once daily is not considered appropriate, interrupt treatment until retest confirms CrCl ≥ 60 mL/min.

  — The investigator/designee should assess individual subject benefit/risk with regards to re-initiation of treatment after repeat or prolonged interruptions, or if re-initiation is not considered appropriate.

- For subjects with confirmed absolute lymphocyte count (ALC) less than 500 cells/mm^3, retest within 3 to 7 days, filgotinib should be interrupted until grade returns to ≤ Grade 2 (more than 500 cells/mm^3). If ALC does not return to ≤ Grade 2 within 4 weeks or returns to less than 500 cells/mm^3 following re-challenge with filgotinib, then filgotinib should be permanently discontinued and the subject managed according to local practice.

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.

The medical monitor should consult the medical leader as needed.

3.5.2. Study Drug Discontinuation Considerations

The 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 HCV during the study, as evidenced by HCV RNA positivity
- Evidence of active 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 and Appendix 6
- Discontinuation of the study at the request of the Sponsor, 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 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).

  — 2 sequential neutrophil counts < 750 neutrophils/mm^3 (international system units [SI]: < 0.75×10^9 cells/L)

  — 2 sequential platelet counts < 75,000 platelets/mm^3(SI: < 75.0×10^9 cells/L)

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

    ■ total bilirubin > 2× ULN

    ■ international normalized ratio (INR) > 1.5

    ■ or accompanied by symptoms consistent with hepatic injury.

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

  — 2 sequential AST or ALT elevations > 5× ULN

  — 2 sequential values for estimated CrCl < 35 mL/min based on the Cockcroft-Gault (CC&G) formula

    Male [(140–age in years) × (weight in kg)]/[72 × (serum creatinine in mg/dL)] = CLcr (mL/min)

    Female [(140–age in years) × (weight in kg) × 0.85]/[72 × (serum creatinine in mg/dL)] = CLcr (mL/min)

- Subjects who were receiving blinded placebo at the time of study unblinding

- 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 physicians.

- 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.

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.

The medical monitor should consult the medical leader as needed.

3.6. Disease Worsening Criteria

Subjects meeting the following criteria should be considered to be discontinued from the study.

- Any subject with significant disease worsening or lack of response to therapy based on investigator judgment may discontinue study drug at any time during the LTE
- Disease worsening based on change in CDAI score may also be used to guide discontinuation of the subject: eg, increase in CDAI ≥100 from Day 1 in present study and CDAI >220 at 2 consecutive visits.
  - The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits).
- 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).
- A stool sample will be obtained for culture for pathogenic bacteria, ova and parasite evaluation, and *C. difficile* toxin assay, when a subject becomes symptomatic, including worsening or return of disease activity.

3.7. End of Study

End of Study is defined as last subject last visit. This will be when filgotinib becomes commercially available in the country or 31 January 2025, whichever comes first. All subject visits, including the PTx visit, must be completed by 31 January 2025 at the latest.

3.8. Post Study Care

Post study care is at the discretion of the treating investigator or physician.

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Approximately 1000 subjects who meet eligibility criteria at Day 1 will receive filgotinib or placebo.

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 ICF, which must be obtained prior to initiation of study procedures associated with this trial

2) Criterion modified per amendment 9

    2.1) Must have enrolled in a CD parent protocol, GS-US-419-4015, GS-US-419-4016, GS-US-419-3895 or any other Gilead/Galapagos-sponsored filgotinib treatment study in CD

3) Females of childbearing potential must have a negative pregnancy test at Day 1 and must agree to continued monthly pregnancy testing during use of filgotinib treatment

4) Criterion modified per amendment 9

    4.1) Female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception for the duration described as described in Appendix 6

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

6) Must have completed all required procedures or met protocol specified efficacy discontinuation criteria in a prior filgotinib treatment study for CD

4.3. Exclusion Criteria

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

1) Subjects who are discontinued from a parent study for reasons other than disease worsening, or lack of response or remission; eg, subjects who discontinue for safety or tolerability issues are not eligible for the present study

2) Known hypersensitivity to the study drug

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

4) Criterion modified per amendment 9

   4.1) 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 for at least 30 days after the last dose of study drug

5) Criterion deleted per amendment 9

6) Criterion modified per amendment 9

   6.1) Females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined in Appendix 6

7) Use of prohibited concomitant medications as outlined in Section 5.4.2

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and 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. The Sponsor recommends but does not require that the investigator contact the 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 medical monitor promptly in case of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial; therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued (unless study-wide unblinding occurs or is specific to subjects previously enrolled in a given parent study [GS-US-419-4015, GS-US-419-4016, GS-US-419-3895, or any other Gilead/Galapagos-sponsored filgotinib treatment study for CD]). All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

The Sponsor may independently unblind cases for expedited reporting of suspected unexpected serious adverse reactions (SUSARs).

5.1.1. Blinding

During the blinded treatment 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. Individuals in Clinical Packaging & Labeling or Clinical Supply

Management who have an Unblinded Inventory Manager role in the IWRS for purposes of study drug inventory management will remain unblinded. Individuals 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 verify treatment assignment and to support data monitoring committee data review if needed. 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)

5.2.1. Formulation

Filgotinib is available 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 to the respective active tablets, in appearance. 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 US 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. 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

The study medication will consist of 200 mg and 100 mg filgotinib tablets and PTM 200 mg and 100 mg filgotinib tablets for oral administration, to be taken once a day.

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 Medications

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 medications 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 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 the Sponsor as soon as he/she is aware of the use of the excluded medication.

5.4.1. Allowed Concomitant Medications

Doses for allowed concomitant medications for CD must remain within the acceptable dose limits from the parent protocol. Steroids cannot exceed prednisone at a prescribed dose of 30 mg/day equivalents. Discontinuation or dose modifications within the limits of allowed doses are permitted at the discretion of the investigator.

The allowed medications for CD are as follows:

- Oral 5-ASA compounds
- Azathioprine, 6-MP, or MTX*
- Oral corticosteroid therapy (prednisone at ≤ 30 mg/day or budesonide at a dose of ≤ 9 mg/day)

- Antidiarrheals for chronic diarrhea

- Antibiotics for the treatment of CD (eg, metronidazole, ciprofloxacin) consistent with subject's standard low-dose regimen or cyclic therapy

*Subjects enrolling into this study from the GS-US-419-4016 study and are taking concomitant vedolizumab may continue to take vedolizumab during their participation in this study. These subjects cannot take concomitant azathioprine, 6-MP, or MTX.

5.4.2. Prohibited Concomitant Medications

The prohibited medications are as follows:

Table 5-1. Prohibited Concomitant Medications

Drug Class	Agents Disallowed
Strong P-gp Inducers[a]	
Anticonvulsants	Phenobarbital, phenytoin, carbamazepine
Antimycobacterials	Rifabutin, rifapentine, rifampin
Herbal/Natural Supplements	St. John's wort, danshen (Salvia Miltiorrhiza)
Prohibited IBD Medications	
Corticosteroids	Dose equivalent to > 30 mg/day of prednisone
TNFα antagonist	Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent
Integrin antagonist	Vedolizumab[b] and natalizumab
Interleukin antagonist	Ustekinumab
JAK inhibitor	Any JAK inhibitors including but not limited to tofacitinib, baricitinib, and upadacitinib
Other (non-biologic)	Cyclosporine, thalidomide, tacrolimus, leflunomide and any investigational agent
Investigational biologics	Any investigational biologic agent
Lymphocyte-depleting therapies	Alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte-depleting therapy
Other Prohibited Medications	
Chronic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[c]	Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, COX-2 inhibitors
Other biologics[d]	Antibody based or other systemic biologics, eg, denosumab, trastuzumab

Abbreviations: COX-2=Cyclooxygenase-2; JAK=Janus Kinase; NSAID=Nonsteroidal Anti-inflammatory Drugs; TNFα=tumor necrosis factor-alpha

a May decrease study drug exposure and are excluded to avoid potential reduction in study drug activity. Pharmacokinetic (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 Subjects enrolling into this study from the GS-US-419-4016 study and are taking concomitant vedolizumab may continue to take vedolizumab during their participation in this study.

c 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.

d Other biologics may be allowed with the approval of the medical monitor

5.5. 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.

5.6. 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 dispensed to subjects must be returned to the site.

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

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

5.6.1. 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 presented in tabular form in Appendix 2 and described in the text that follows.

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

6.1. Subject Enrollment and Treatment Assignment

Subjects who meet the eligibility criteria at Day 1 will be enrolled. Dosing regimen is determined by regimen in parent study and reason for exit (reference Section 3.3. for details).

6.2. Pretreatment Assessments

6.2.1. Day 1 Visit

LTE Day 1 Rollover from GS-US-419-3895

Subjects that meet protocol specified non-response criteria based on Week 10 assessments in the GS-US-419-3895 study may enter this study after completing the Week 11 visit procedures in the GS-US-419-3895 study. After LTE consent is obtained, complete all Day 1 LTE procedures that are not duplicates of Week 11 procedures in the GS-US-419-3895 study.

Subjects that meet the protocol specified disease worsening criteria in the GS-US-419-3895 study may enter the LTE study after completing the visit procedures on the GS-US-419-3895 study. The Day 1 LTE visit must occur within a 10 day window from the confirmatory visit that determined their disease worsening status in the GS-US-419-3895 study. After LTE consent is obtained, complete all Day 1 LTE procedures.

Subjects that potentially meet protocol specified disease worsening criteria based on Week 58 assessments in the GS-US-419-3895 study must have their Day 1 LTE within a 10 day window from the Week 58 visit, while awaiting laboratory results in order to complete the CDAI calculation. The potential meeting of protocol specified disease worsening criteria occurs if the second consecutive visit coincides with the Week 58 visit. All Week 58 procedures must be completed from the GS-US-419-3895 study. After LTE consent is obtained, complete all Day 1 LTE procedures that are not duplicates of Week 58 procedures in the GS-US-419-3895 study.

Subjects that complete Week 58 and do not meet protocol specified disease worsening criteria in the GS-US-419-3895 study may enter this study after completing the Week 58 procedures in the GS-US-419-3895 study. After LTE consent is obtained, complete all Day 1 LTE procedures that are not duplicates of Week 58 procedures in the GS-US-419-3895 study.

LTE Day 1 Rollover from GS-US-419-4015 or GS-US-419-4016

Subjects that are non-responders based on Week 10 assessments in the prior study must return for the Day 1 LTE visit within 10 days of Week 10. All Day 1 LTE procedures must be completed.

Subjects that met protocol specified disease worsening criteria in the prior study should have their Day 1 LTE visit within a 10 day window from the confirmatory visit that determined their disease worsening status. All Day 1 LTE procedures must be completed.

Subjects that have completed the prior study up to and including Week 24 and did not meet protocol specified disease worsening criteria in the prior study should have their Day 1 LTE visit on the same day as Week 24. All Week 24 procedures must be completed along with any non-duplicate Day 1 LTE procedures.

Subjects that flare at the time of their Week 24 visit may require visit rescheduling in order to have confirmation of disease worsening status. Under these circumstances, the Day 1 LTE visit cannot be scheduled until their final status is known. At this time, the Day 1 LTE visit should be scheduled within a 10 day window from the confirmatory visit to determine disease worsening status.

LTE Day 1 Rollover from any other filgotinib treatment study for CD

Subjects that have completed* a Gilead/Galapagos-sponsored parent study may enter this study up to 30 days after completing the end of study procedures in the parent study. After LTE consent is obtained, complete all Day 1 LTE procedures.

*A subject is defined as completed if they have completed all study visits and procedures as defined in the protocol or have completed treatment up to the primary endpoint.

Please refer to the Phase 2 studies' subject rollover manual for details on rollover procedures.

Day 1 LTE Procedures

Subjects will be screened to ensure eligibility, and if confirmed, subjects will be enrolled on the same day and study drug dispensed. The following will be performed and documented at this visit:

- Obtain written informed consent
- Review inclusion/exclusion criteria and other protocol restrictions (Sections 4.2 and 4.3)
- Review medical history (ongoing AEs from prior filgotinib treatment studies should be recorded as medical history)
- Review AEs and concomitant medications
- TB Assessment QuantiFERON® (or centrally reported equivalent assay)
- Review electronic diary (e-Diary) for completion from prior filgotinib treatment study when available and remind subjects of diary instructions
- Collect the variables to calculate CDAI score (reference Appendix 4)
    - Site enters patient assessments from Day 1 visit
    - CDAI score calculated centrally after all components have been captured electronically

- Baseline PRO2 (reference Appendix 4) – centrally calculated using the patient reported symptoms of stool frequency and abdominal pain captured in the electronic diary
- Symptom-directed physical examination (PE)
- Transfer a copy of the subject's last perianal fistulae assessment into source documentation (for subjects rolling over from GS-US-419-4016 **only**)
- Obtain weight and height
- Obtain vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
  - HBV Surveillance Guidelines
    - Subjects with positive HBcAb and HBV DNA < LLOQ in a parent CD protocol will require ongoing HBV DNA monitoring every 3 months during this study. These subjects may also require prophylactic treatment per investigator discretion in accordance with local guidelines/standard of care.
    - In Japan and where required by local guidelines, subjects with positive HBcAb and/or positive HBsAb but with HBV DNA < LLOQ in a parent CD protocol will require ongoing HBV DNA monitoring every 4 weeks for at least 12 months after starting study drug in accordance with local guidelines during this study.
    - Any subject who has HBV DNA ≥ LLOQ during the study will be discontinued (reference Section 3.5.2).
- [redacted]
- Obtain stool samples (reference Study Procedures Table [Appendix 2])
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
  - Sample will be used for urinalysis and pregnancy test (for females of childbearing potential only)
- Administer [redacted] surveys to subject
- Enter subject information in the IWRS to receive assignment
- Dispense study drug as directed by the IWRS
- Instruct the subject on the packaging, storage, and administration of the study drug
- Document first dose in LTE for the subject–If a subject has already taken study drug for that day within the parent protocol, first dose should take place on Day 2.

Please refer to Section 7 Adverse Events and Toxicity Management for details regarding the reporting of AEs and SAEs.

6.3. Treatment Assessments

6.3.1. Week 2 and Week 4 (± 3 days)

On Week 2 and Week 4, the following evaluations are to be completed:

- Review AEs and concomitant medications
- Review e-Diary for completion and remind subjects of diary instructions
- Collect the variables to calculate CDAI score (reference Appendix 4)
  - Site enters patient assessments at each visit
  - CDAI score calculated centrally after all components have been captured electronically
- PRO2 (reference Appendix 4) – calculated centrally
- Symptom-directed PE
- Obtain weight
- Obtain vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
  - Pregnancy test (for females of child-bearing potential only) –Week 4 only
- Dispense study drug as directed by the IWRS–Week 4 only

6.3.2. Every 4 Weeks From Day 1 (± 7 days)

Once every 4 weeks from Day 1 until EoT or early discontinuation, women of childbearing potential must have a urine pregnancy test. The test will be performed at home or in the clinic if it coincides with a scheduled visit. In case of home urine pregnancy testing, the site will contact the subject to obtain the results and will record the information in the eCRF. For subjects in the US, all pregnancy tests will be carried out in the clinic. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic.

6.3.3. Week 12 and Then Every 12 Weeks Thereafter From Day 1 (± 7 days)

On Week 12 and then every 12 weeks thereafter from Day 1 until EoT or early discontinuation, the following evaluations are to be completed:

- Review AEs and concomitant medications
- Review e-Diary for completion and remind subjects of diary instructions
- Collect the variables to calculate CDAI score (reference Appendix 4)
  - Site enters patient assessments at each visit
  - CDAI score calculated centrally after all components have been captured electronically
- PRO2 (reference Appendix 4) – calculated centrally
- Symptom-directed PE
- Complete perianal fistulae assessment (for subjects rolling over from GS-US-419-4016 **only**)
- Obtain weight
- Obtain vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
- Dispense study drug as directed by the IWRS

6.3.4. Every 24 Weeks From Day 1 (± 7 days)

Once every 24 weeks from Day 1 until EoT or early discontinuation, the following evaluations are to be completed:

- Obtain fasting (8 hours with no food or drink except water) blood samples (reference Study Procedures Table [Appendix 2])
- Obtain stool samples (reference Study Procedures Table [Appendix 2])

[redacted]

- Obtain urine sample for urinalysis (reference Study Procedures Table [Appendix 2])

6.3.5. Every 48 Weeks From Day 1 (± 7 days)

Once every 48 weeks from Day 1 until EoT or early discontinuation, the following evaluations are to be completed:

- TB Assessment (See Section 3.5.1 for further information)
- Perform 12-lead ECG

[redacted]

6.3.6. End of Treatment Visit

The EoT visit will be scheduled when filgotinib becomes commercially available in the country or prior to the end of study on 31 January 2025, whichever comes first.

The same assessments as for the Early Termination visit should be performed at the EoT visit (Section 6.6).

6.4. Safety

6.4.1. 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).

6.5. Post-Treatment Assessments (± 3 days)

All subjects must complete the Post-Treatment (PTx) assessments 30 days after the last dose of study drug.

The following evaluations are to be completed:

- Symptom-directed PE
- Complete perianal fistulae assessment (for subjects rolling over from GS-US-419-4016 **only**)
- Obtain weight
- Review AEs and concomitant medications
- Obtain vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
- Obtain urine sample (reference Study Procedures Table [Appendix 2])

— Sample will be used for pregnancy test (for females of childbearing potential only)

6.6. Early Termination Assessments

Early termination assessments should occur after the corresponding parent study is unblinded for all subjects who were receiving placebo. In addition, early termination assessments should occur for any subject who discontinues the study due to meeting study drug discontinuation criteria (see Section 3.5.2 Study Drug Discontinuation Considerations).

The following evaluations are to be completed:

- Review AEs and concomitant medications
- Obtain vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Symptom-directed PE
- Complete perianal fistulae assessment (for subjects rolling over from GS-US-419-4016 **only**)
- Obtain weight
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
  - — Sample will be used for pregnancy test (for females of childbearing potential only)
- Collect the variables to calculate CDAI score (reference Appendix 4)
  - — Site enters patient assessments at each visit
  - — CDAI score calculated centrally after all components have been captured electronically
- PRO2 (reference Appendix 4) – calculated centrally

6.7. Assessments After Study Unblinding

After study unblinding, subjects who were receiving placebo will discontinue study drug and study participation. Subjects should attend the clinic at their next scheduled study visit or earlier during an unscheduled visit and undergo the early termination assessments as described in Section 6.6 followed by the PTx assessments 30 days after the last dose of study drug (see Section 6.5).

After study unblinding, subjects who were receiving active filgotinib will continue to receive the same dose (as received blinded) of open-label filgotinib dosing. Subjects should attend the clinic at their next scheduled study visit and complete study procedures as per their next scheduled study visit.

6.8. End of Study

Please refer to Section 3.7.

6.9. Post Study Care

Please refer to Section 3.8.

6.10. Clinical Laboratory Assessments

Please refer to Appendix 7.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered an investigational 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 an investigational product, whether or not considered related to the investigational product. Adverse Events may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae (See Section 7.7.1)
- 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 eCRF.

7.1.2. Serious Adverse Events

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

- Death
- Life-threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated investigational 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 sub-investigator 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 sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

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

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

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

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

7.2.2. Assessment of Severity

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

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

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 the Sponsor

Requirements for collection prior to initiation of Day 1 LTE IMP:

After informed consent, but prior to initiation of Day 1 LTE IMP, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol mandated procedures.

7.3.1. Adverse Events

Non-serious Adverse Events that occur prior to initiation of Day 1 LTE IMP:

After LTE informed consent is signed, but prior to initiation of Day 1 LTE IMP, all non-serious AEs related to LTE protocol-mandated procedures must be reported on the LTE electronic case report form (eCRF).

All other non-serious events that occur after LTE informed consent is signed, but prior to initiation of Day 1 LTE IMP, should be reported on the parent Study eCRFs.

Non-serious Adverse Events that occur after initiation of Day 1 LTE IMP:

Following initiation of Day 1 LTE IMP, all non-serious AEs, regardless of cause or relationship, until 30 days after last administration of LTE IMP, must be reported on the LTE eCRF.

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

7.3.2. Serious Adverse Events

Serious Adverse Events that occur prior to initiation of Day 1 LTE IMP:

After LTE informed consent is signed, but prior to initiation of Day 1 LTE IMP, all SAEs related to LTE protocol-mandated procedures must be reported on the LTE eCRF.

All other SAEs that occur after informed consent is signed for the parent study, but prior to initiation of Day 1 of the LTE IMP must be reported in the parent study eCRF.

Serious Adverse Events that occur after initiation of Day 1 LTE IMP:

All SAEs, regardless of causal relationship, must be reported to LTE study eCRF and the Sponsor from initiation of Day 1 of the LTE IMP and throughout the duration of the LTE study (including the protocol-required post treatment follow-up period).

General SAE Guidance:

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 the Sponsor.

- 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 the Sponsor within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described below.

  Email: DIVERSITYLTE_safety@glpg.com

- 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. Sponsor 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, the Sponsor 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), the Sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IRB/IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by the Sponsor or designee using reference safety information specified in the investigator's brochure (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 and 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 5). 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 below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The 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 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 medical monitor. The medical monitor should consult the medical leader as needed.

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 labeling (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 an 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 DIVERSITYLTE_safety@glpg.com 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. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to DIVERSITYLTE_safety@glpg.com.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to DIVERSITYLTE_safety@glpg.com 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 DIVERSITYLTE_safety@glpg.com.

Refer to Appendix 6 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 DIVERSITYLTE_safety@glpg.com within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to concomitant medications.

Special situations involving concomitant medications do not need to be reported on the special situations report form; however, special situations that result in AEs due to a concomitant medication, 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 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 analysis objective is:

- To observe the long-term safety of filgotinib in subjects who have completed or met protocol specified discontinuation criteria in a prior filgotinib treatment study for CD

The secondary analysis objective is:

- To evaluate the effect of filgotinib on PRO2 and CDAI scores

[redacted]

- [redacted]
- [redacted]

8.1.2. Primary Endpoint

The primary end point is safety, evaluated through AEs, clinical laboratory tests, and vital signs.

8.1.3. Secondary Endpoint

The secondary end points are:

- Change from baseline in PRO2 and CDAI scores

[redacted]

[redacted]

[redacted]

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Safety/Efficacy

The primary analysis set for safety and efficacy is the Safety Analysis Set, which includes all enrolled subjects who received at least one dose of study drug.

[redacted]

[redacted]

8.3. Data Handling Conventions

Values for missing safety laboratory data will not be imputed. 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.

Laboratory data that are continuous in nature but are less than the lower limit of quantitation (LLOQ) 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).

Procedure for handling missing data for PRO2 and CDAI scores will be described in the statistical analysis plan (SAP).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized 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), PRO2 score, CDAI score, serum [redacted], [redacted], and other variables of interest.

8.5. Efficacy Analysis

Change from baseline in PRO2 and CDAI scores, and change in [redacted] will be summarized using standard descriptive statistics (n, mean, SD, median, Q1, Q3, minimum, maximum).

[redacted]

8.6. Safety Analysis

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 up to 30 days after the last dose of study drug will be summarized. 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. Exposure data will be summarized descriptively.

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 and no later than 30 days after permanent discontinuation of study drug
- Any AEs leading to premature discontinuation of study drug

Summaries (number and percentage of subjects) of TEAEs by SOC and PT will be provided. 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 CTCAE.

Incidence of treatment-emergent laboratory abnormalities defined as values that increase at least one toxicity grade from baseline at any time post baseline will be summarized. 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 PE findings, prior and concomitant medications and medical history will be provided. Vital signs measurements will be listed by subject and summarized by incidence of events/abnormalities or descriptive statistics as appropriate.

8.7. Pharmacokinetic Analysis

Not applicable.

8.8. [redacted]

[redacted]

[redacted]

[redacted].

8.9. Sample Size

No formal hypothesis testing is planned for this study and sample size calculation is not conducted. All subjects who have completed or met protocol specified discontinuation criteria in a prior filgotinib treatment study for CD may enroll in this long-term extension study.

8.10. Interim Analysis

Interim analyses may be performed for regulatory submission purposes when the parent studies (GS-US-419-4015, GS-US-419-4016 and GS-US-419-3895) are unblinded. Further details of the interim analysis will be described in the SAP.

8.11. Data Monitoring Committee

While there are subjects receiving blinded treatment in this study, selected safety data from this study (DIVERSITY LTE) may be reviewed by the DMC for study GS-US-419-3895. After the present study is unblinded, safety monitoring will continue per the Sponsor's ongoing internal processes.

If the DMC recommends stopping the study for lack of efficacy, the Sponsor's Executive Team will be unblinded to confirm the DMC recommendation.

Ad-hoc DMC Meetings

An ad-hoc convening of DMC may be triggered by the following condition:

- ≥ 2 subjects develop any related, Grade 4, thromboembolic event that has been positively adjudicated by the adjudication committee (See Section 8.12)

8.12. Cardiovascular Safety Endpoint Adjudication Committee

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 Cardiovascular Safety Endpoint Adjudication Committee (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 EU Clinical Trials Directive 2001/20/EC and GCP Directive 2005/28/EC.

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

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

The investigator (or Sponsor as appropriate according to local regulations) will submit this protocol, ICF, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/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 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.

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 the Sponsor, including but not limited to the IB, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of the Sponsor 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 the Sponsor. 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, eCRF 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 the Sponsor. The investigator must notify the Sponsor before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor 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 the Sponsor 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. Electronic 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 have 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 the data management 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, the Sponsor 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 the Sponsor, 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 the Sponsor site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and the Sponsor (or the Sponsor's representative) for return of unused study drug supplies.

If IMP is destroyed on site, the investigator must maintain accurate records for all IMPs destroyed. Upon study completion, copies of the IMP accountability records must be filed at the site. Another copy will be returned to the Sponsor.

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 the Sponsor'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 the Sponsor. 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). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of CSRs (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 the Sponsor 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 the Sponsor 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 the Sponsor's confidential information (See Section 9.1.4).

- The investigator will comply with the Sponsor'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, the Sponsor 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 the Sponsor 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 medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or the Sponsor 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, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380 (9853):1590-605.

Cheifetz AS. Management of active Crohn disease. JAMA 2013;309 (20):2150-8.

Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. Journal of Crohn's & colitis 2010;4 (1):28-62.

Fukunaga K, Matsumoto T. Current status and future perspectives of leukocytapheresis for inflammatory bowel disease. J Gastroenterol Hepatol 2012;27 (6):997-1003.

Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, et al. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology 2004;126 (4):989-96; discussion 47.

Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et al. A retrospective analysis: the development of patient reported outcome measures for

the assessment of Crohn's disease activity. Aliment Pharmacol Ther 2015;41 (1):77-86.

Korzenik JR. Investigational therapies in the medical management of Crohn disease. Available at: www.uptodate.com/contents/4076. UpToDate 2016.

Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142 (1):46-54 e42; quiz e30.

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

Sandborn WJ, Feagan BG, Hanauer SB, Lochs H, Lofberg R, Modigliani R, et al. A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease. Gastroenterology 2002;122 (2):512-30.

Ventham NT, Kennedy NA, Nimmo ER, Satsangi J. Beyond gene discovery in inflammatory bowel disease: the emerging role of epigenetics. Gastroenterology 2013;145 (2):293-308.

Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017;389:266-75.

11. APPENDICES

Appendix 1.Investigator Signature Page

GALAPAGOS NV
GENERAAL DE WITTELAAN L11 A3
2800 MECHELEN
BELGIUM

STUDY ACKNOWLEDGEMENT

A Long-Term Extension Study to Evaluate the Safety of Filgotinib in Subjects with Crohn's Disease

GS-US-419-3896 (GLPG0634-CL-310 [DIVERSITY LTE]),
Amendment 9, 23 November 2022

This protocol has been approved by Galapagos NV. The following investigator signature documents this approval. An electronic signature of the sponsor's responsible person is provided at the end of the document.

[redacted]

Signature

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 Galapagos NV. 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

Study Procedures	Day 1[a]	Week 2 ± 3 days	Week 4 ± 3 days	Every 4 Weeks from Day 1 ± 7 days	Week 12 and then every 12 Weeks from Day 1 Clinic Visit ± 7 days	Every 24 Weeks from Day 1 Clinic Visit ± 7 days	Every 48 Weeks from Day 1 Clinic Visit ± 7 days	Early Termination (ET) / End of Treatment Visit	Post-Treatment (PTx)[b] ± 3 days
Written Informed Consent	X								
Review Inclusion/Exclusion Criteria	X								
Medical History	X								
Symptom-Directed Examination (as needed)	X	X	X		X			X	X
Perianal fistulae assessment (for subjects rolling over from GS-US-419-4016 **only**) [c]					X			X	X
Vital Signs[d]	X	X	X		X			X	X
Height	X								
Weight	X	X	X		X			X	X
Hematology	X	X	X		X			X	X
Chemistry	X	X	X		X			X	X
Lipid Profile (fasting)[e]						X			
Urinalysis	X					X			
Pregnancy Test[f]	X		X	X				X	X
HBV DNA monitoring (Japan)[g]	X		X	X					
HBV DNA monitoring (other regions)[h]	X				X				

Study Procedures	Day 1[a]	Week 2 ± 3 days	Week 4 ± 3 days	Every 4 Weeks from Day 1 ± 7 days	Week 12 and then every 12 Weeks from Day 1 Clinic Visit ± 7 days	Every 24 Weeks from Day 1 Clinic Visit ± 7 days	Every 48 Weeks from Day 1 Clinic Visit ± 7 days	Early Termination (ET) / End of Treatment Visit	Post-Treatment (PTx)[b] ± 3 days
TB Assessment[i]	X						X		
12-lead ECG							X		
Serum immunoglobulin	X					X			
[redacted]									
e-Diary Instruction & Review[l]	X	X	X		X				
PRO2[m]	X	X	X		X			X	
CDAI[m]	X	X	X		X			X	
[redacted]									
Enrollment	X								
Study Drug Dispensation	X		X		X				
Adverse Events[o]	X	X	X		X			X	X
Concomitant Medications	X	X	X		X			X	X

a Day 1 visit for this study may occur at the same time as the final scheduled treatment visit of the prior filgotinib study or up to 30 days after completing the end of study procedures in the parent study, see Section 6.2.1. All procedures necessary for the final visit in the prior filgotinib study will be completed as well as any additional procedures required for this study. Procedures that are duplicates of the final visit from prior filgotinib study do not need to be performed again for this protocol. Day 1 may be delayed up to 10 days. If Day 1 of LTE is not the same as the last study visit of the prior study, a full set of Day 1 procedures should be performed. If a subject has already taken study drug for that day within the parent protocol, first dose should take place on Day 2.

b The Post-Treatment (PTx) Visit should occur 30 days after the last dose of study drug.

c The perianal fistula assessment entails tracking the clinical status of draining external openings of perianal fistulae that were identified at baseline of Study GS-US-419-4016. For additional details on the perianal assessment, refer to the Perianal Fistula Assessment Manual

d Vital signs include resting blood pressure, respiratory rate, pulse, and temperature.

e Fasting means no food or drink except water, for 8 hours

f Females who are of childbearing potential only. A urine pregnancy test must be completed every 4 weeks at a minimum. The test will be performed at home or in the clinic if it coincides with a scheduled visit. In case of home urine pregnancy testing, the site will contact the subject to obtain the results and will record the information in the eCRF. For subjects in the US, all pregnancy tests will be carried out in the clinic. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic.

g In Japan, subjects with negative HBsAg, positive HBcAb and/or positive HBsAb in a parent CD protocol require HBV DNA monitoring every 4 weeks in accordance with local guidelines (Section 6.2.1).

h In other regions, subjects with negative HBsAg and positive HBcAb require HBV DNA monitoring every 3 months in accordance with local guidelines (Section 6.2.1)

i Subjects who were previously treated for TB do not need to have yearly QuantiFERON® (or centrally reported equivalent assay) tests but should be screened at least yearly for signs and symptoms of reactivation.

j [redacted]

k [redacted]

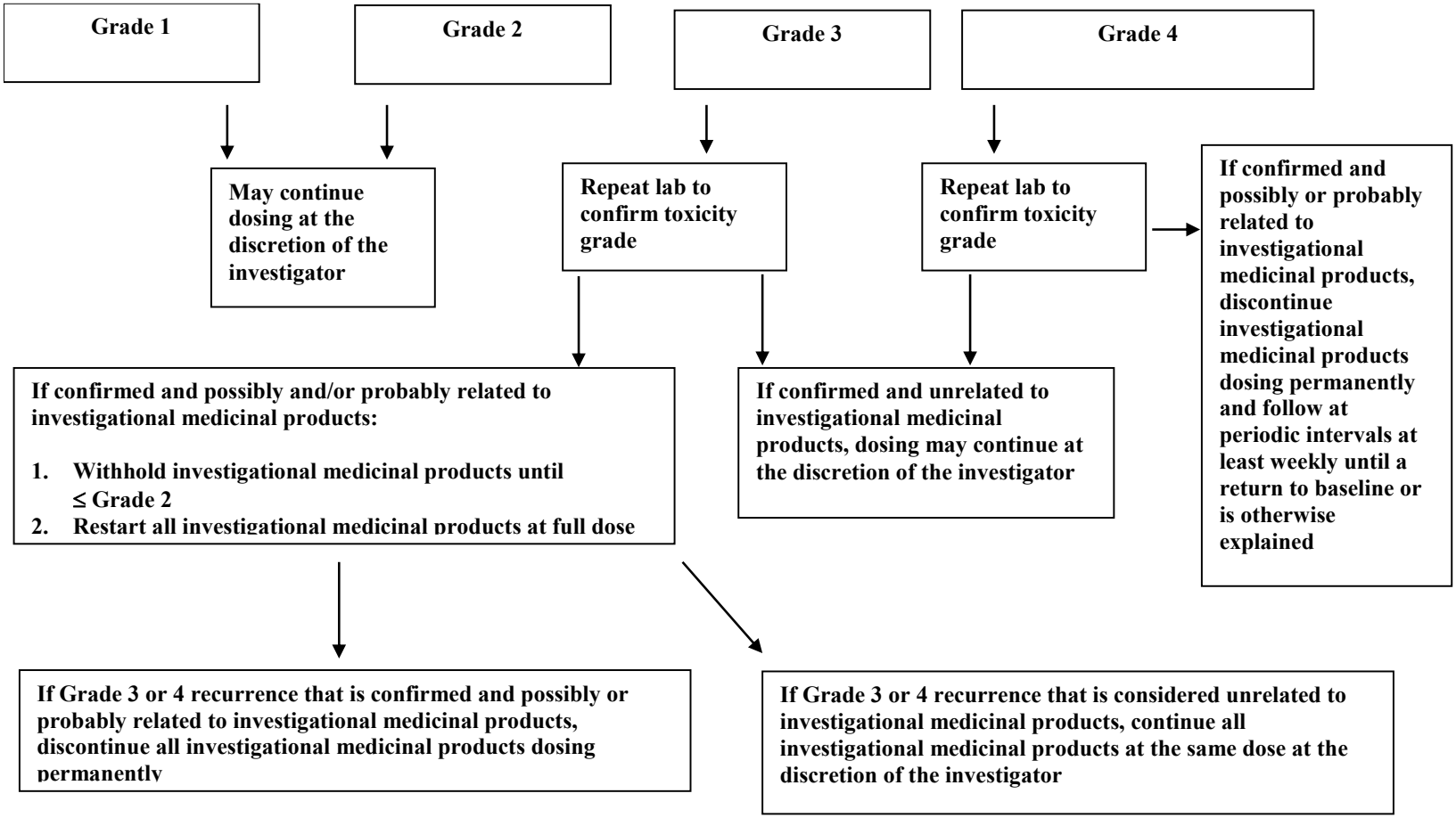
l At Day 1 visit, review diary of subject reported components from parent study, if available. Subjects should begin filling out the Diary at the Day 1 visit and continue to fill it out throughout the study.

m Colonoscopy with biopsies is optional per standard of care. The date of the procedure may be requested for accuracy of data analysis.

n [redacted]

o Ongoing AEs from previous filgotinib studies should be recorded as medical history. Collection of AEs and SAEs related to protocol-mandated procedures will begin once informed consent is signed and will continue through the Post-Treatment (PTx) Visit.

Appendix 3.Management of Clinical and Laboratory Adverse Events



Appendix 4. Crohn's Disease Activity Index (CDAI) and Patient Reported Outcomes – 2 items (PRO2)

The Crohn's Disease Activity Index (CDAI) will be calculated as follows:

Variable no.	Variable	Variable description	Multiplier
1	Liquid or very soft stool	Daily stool count is summed for 7 days	2
2	Abdominal pain	Sum of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe	5
3	General wellbeing	Sum of 7 days of daily ratings as 0 = generally well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible	7
4	Complications	Number of listed complications: Arthritis or arthralgia Erythema nodosum, pyoderma gangrenosum or aphthous stomatitis Iritis or uveitis Anal fissures or fistulae or abscess Other fistula Fever over 37.8°C [100°F] during past week	20 each
5	Use of anti-diarrheal medications	Use of diphenoxylate or loperamide or other opiate for diarrhea 0 = No, 1 = Yes	30
6	Abdominal mass	0 = none, 2 = questionable, 5 = definite	10
7	Hematocrit*	Males: 47 – Hct [%] Females: 42 – Hct [%] * Result must be greater than or equal to 0. If negative result enter 0	6 × difference
8	Weight*	Percentage deviation from standard weight (1 – weight / standard weight) × 100 * Limit of -10	1
CDAI score			TOTAL

CDAI = Crohn's Disease Activity Index; Hct = hematocrit
{Sandborn 2002}

The patient reported outcomes of liquid or very soft stool and abdominal pain (PRO2) score will be assessed as follows:

Variable no.	Variable	Variable description
1	Liquid or very soft stool	**Mean** of the daily stool count for 7 days
2	Abdominal pain	**Mean** of 7 days of daily ratings as 0 = none, 1 = mild, 2 = moderate, 3 = severe

{Khanna 2015}
Each PRO2 score will be rounded to the nearest integer for determination of eligibility and calculation of endpoints.

Appendix 5.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 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

The administration of filgotinib in embryofetal 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.

- **Definitions**

  - **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.

- **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.

- **Contraception for Female Subjects**

  - **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 coadministration with filgotinib did not alter the pharmacokinetics of representative hormonal contraceptives levonorgestrel/ethinyl estradiol.

For female subjects, hormonal contraceptives will be permitted as a form of contraception when used in conjunction with a barrier method (preferably a male condom). Details are outlined below.

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

— **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 pregnancy test at the Day 1 visit of the LTE. 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 continue to use one of the following methods from Screening (parent study) until 30 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 30 days after the last study drug dose.

- **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.

- **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.

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

- **Pregnancy Testing**

All females of childbearing potential will have urine pregnancy testing every 4 weeks during their study participation. The test will be performed at home or in the clinic if it coincides with a scheduled visit. In case of home urine pregnancy testing, the site will contact the subject to obtain the results and will record the information in the eCRF. For subjects in the US, all pregnancy tests will be carried out in the clinic. If a urine pregnancy test is positive, the subject should stop study drug immediately, contact the investigator, and have confirmatory serum pregnancy test in clinic.

Appendix 7.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) **Fasting Lipids** Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low density lipoprotein [LDL])	Appearance: Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen **Pregnancy** *In females of childbearing potential:* Urine pregnancy Serum pregnancy	[redacted] ([redacted]) [redacted] [redacted] [redacted] [redacted] Bacterial stool culture C-diff toxin Ova and parasites (O&P) [redacted] [redacted] [redacted] Serum Immunoglobulin QuantiFERON® (or centrally reported equivalent assay) Prothrombin time (PT) Partial Thromboplastin time (PTT) International Normalized Ratio (INR) HBV DNA

Signature Page for glpg0634-cl-310-protocol-amend9 21162

Approval	[redacted] 24-Nov-2022 13:48:54 GMT+0000

Signature Page for glpg0634-cl-310-protocol-amend943952_40834_108642