



**GILEAD Galápagos**



**CLINICAL STUDY PROTOCOL**

**Study Title:** Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

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

**IND Number:** 129647  
**EudraCT Number:** 2016-001392-78  
**Clinical Trials.gov Identifier:** NCT02914522

**Indication:** Ulcerative Colitis

**Protocol ID:** GS-US-418-3898

**Gilead Study Director and Medical Monitor** Name: PPD  
Telephone: PPD  
Mobile: PPD  
Email: PPD  
Fax: PPD

**Protocol Version/Date:** Original: 15 July 2016  
Amendment 1: 07 September 2016  
Amendment 2: 27 October 2016  
Amendment 3: 15 June 2017  
Amendment 4: 05 March 2018  
Amendment 5: 02 April 2019

**CONFIDENTIALITY STATEMENT**

The information contained in this document, particularly unpublished data, is the property or under control of Gilead Sciences, Inc., and is provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an applicable Institutional Review Board or Independent Ethics Committee. The information is only to be used by you in connection with authorized clinical studies of the investigational drug described in the protocol. You will not disclose any of the information to others without written authorization from Gilead Sciences, Inc., except to the extent necessary to obtain informed consent from those persons to whom the drug may be administered.

## TABLE OF CONTENTS

TABLE OF CONTENTS .....	2
LIST OF IN-TEXT TABLES .....	5
LIST OF IN-TEXT FIGURES .....	5
PROTOCOL SYNOPSIS .....	6
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS.....	22
DEFINITION OF TERMS .....	26
1. INTRODUCTION .....	27
1.1. Background .....	27
1.2. Filgotinib (GS-6034) .....	28
1.2.1. General Information .....	28
1.2.2. Preclinical Pharmacology and Toxicology.....	28
1.2.3. Clinical Trials of Filgotinib .....	31
1.3. Rationale for This Study .....	32
1.3.1. Rationale for Endpoint and Timing .....	32
1.3.2. Rationale for Dose .....	33
1.4. Risk/Benefit Assessment for the Study .....	33
1.5. Compliance .....	35
2. OBJECTIVES .....	36
2.1. Cohort A Induction Study .....	36
2.2. Cohort B Induction Study .....	37
2.3. Maintenance Study .....	38
3. STUDY DESIGN.....	40
3.1. Endpoints .....	40
3.1.1. Cohort A Induction Study .....	40
3.1.2. Cohort B Induction Study.....	41
3.1.3. Maintenance Study .....	41
3.2. Study Design .....	43
3.3. Study Treatments .....	44
3.4. Duration of Treatment .....	45
3.5. Criteria for Study Drug Interruption or Discontinuation .....	46
3.5.1. Study Drug Interruption Considerations.....	46
3.5.2. Study Drug Discontinuation Considerations .....	46
3.6. Disease Worsening Criteria.....	48
3.7. End of Study.....	48
3.8. Post Study Care .....	49
3.9. Biomarker Testing.....	49
3.9.1. Biomarker Samples to Address the Study Objectives .....	49
<b>CCI</b> [REDACTED]	
4. SUBJECT POPULATION.....	51
4.1. Number of Subjects and Subject Selection .....	51
4.2. Induction Study (Cohorts A and B).....	51
4.2.1. Inclusion Criteria.....	51
4.2.2. Exclusion Criteria.....	54
4.3. Cohort A (Biologic-naïve) Induction Study .....	56



4.3.1.	Inclusion Criteria, Cohort A ONLY	56
4.3.2.	Exclusion Criteria, Cohort A ONLY	56
4.4.	Cohort B (Biologic-experienced) Induction Study	57
4.4.1.	Inclusion Criteria, Cohort B ONLY	57
4.4.2.	Exclusion Criteria Cohort B ONLY	58
4.5.	Maintenance Study	58
4.5.1.	Inclusion Criteria	58
4.5.2.	Exclusion Criteria	58
5.	INVESTIGATIONAL MEDICINAL PRODUCTS	59
5.1.	Randomization, Blinding and Treatment Codes	59
5.1.1.	Procedures for Breaking Treatment Codes	59
5.2.	Description and Handling of Filgotinib and Placebo to Match (PTM) Filgotinib	59
5.2.1.	Formulation	59
5.2.2.	Packaging and Labeling	60
5.2.3.	Storage and Handling	60
5.3.	Dosage and Administration	60
5.4.	Prior and Concomitant Medications	61
5.4.1.	Allowed Concomitant Medications	61
5.4.2.	Prohibited Concomitant Medications	62
5.4.3.	Corticosteroid Tapering	63
5.5.	Vaccine Guidelines	63
5.6.	Accountability for Study Drug	63
5.6.1.	Investigational Medicinal Product Return or Disposal	64
6.	STUDY PROCEDURES	65
6.1.	Subject Enrollment and Treatment Assignment	65
6.2.	Pretreatment Assessments	66
6.2.1.	Screening Visit	66
6.2.2.	Day 1	69
6.3.	Randomization	70
6.3.1.	Randomization and Study Drug Administration	70
6.4.	Study Assessments	70
6.4.1.	Priority of Assessments	70
6.4.2.	Efficacy	70
6.4.3.	Safety	71
6.4.4.	Pharmacokinetics Assessments	73
6.4.5.	Biomarker Assessments	73
6.5.	CCl [REDACTED] Post-Treatment Assessments	73
6.6.	Early Termination Assessments	74
6.7.	End of Study	74
6.8.	Post Study Care	74
7.	ADVERSE EVENTS AND TOXICITY MANAGEMENT	75
7.1.	Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events	75
7.1.1.	Adverse Events	75
7.1.2.	Serious Adverse Events	75
7.2.	Assessment of Adverse Events and Serious Adverse Events	76
7.2.1.	Assessment of Causality for Study Drugs and Procedures	76
7.2.2.	Assessment of Severity	76
7.3.	Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead	77
7.3.1.	Adverse Events	77

7.3.2.	Serious Adverse Events	77
7.4.	Gilead Reporting Requirements	79
7.5.	Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events	79
7.6.	Toxicity Management	79
7.6.1.	Grades 1 and 2 Laboratory Abnormality or Clinical Event	80
7.6.2.	Grade 3 Laboratory Abnormality or Clinical Event	80
7.6.3.	Grade 4 Laboratory Abnormality or Clinical Event	80
7.7.	Special Situations Reports	81
7.7.1.	Definitions of Special Situations	81
7.7.2.	Instructions for Reporting Special Situations	81
8.	STATISTICAL CONSIDERATIONS	83
8.1.	Analysis Objectives and Endpoints	83
8.1.1.	Analysis Objectives	83
8.1.2.	Primary Endpoint	86
8.1.3.	Secondary Endpoint	86
8.1.4.	Exploratory Endpoints	87
8.2.	Analysis Conventions	89
8.2.1.	Analysis Sets	89
8.3.	Data Handling Conventions	90
8.4.	Demographic Data and Baseline Characteristics	91
8.5.	Efficacy Analysis	91
8.5.1.	Primary Analysis	91
8.5.2.	Secondary Analyses	91
8.5.3.	Multiplicity Adjustments	91
8.5.4.	Exploratory Analyses	96
8.6.	Safety Analysis	97
8.6.1.	Extent of Exposure	97
8.6.2.	Adverse Events	97
8.6.3.	Laboratory Evaluations	98
8.6.4.	Other Safety Evaluations	98
8.7.	Pharmacokinetic Analysis	99
8.8.	Biomarker Analysis	99
8.9.	Sample Size	99
8.9.1.	Induction Studies (Cohorts A and B)	99
8.9.2.	Maintenance Study	100
8.10.	Data Monitoring Committee	100
8.11.	End of Induction Interim Analysis	101
9.	RESPONSIBILITIES	102
9.1.	Investigator Responsibilities	102
9.1.1.	Good Clinical Practice	102
9.1.2.	Institutional Review Board/Independent Ethics Committee Review and Approval	102
9.1.3.	Informed Consent	102
9.1.4.	Confidentiality	103
9.1.5.	Study Files and Retention of Records	103
9.1.6.	Case Report Forms	104
9.1.7.	Investigational Medicinal Product Accountability and Return	105
9.1.8.	Inspections	105
9.1.9.	Protocol Compliance	105
9.2.	Sponsor Responsibilities	106
9.2.1.	Protocol Modifications	106



9.2.2.	Study Report and Publications .....	106
9.3.	Joint Investigator/Sponsor Responsibilities .....	106
9.3.1.	Payment Reporting .....	106
9.3.2.	Access to Information for Monitoring .....	107
9.3.3.	Access to Information for Auditing or Inspections .....	107
9.3.4.	Study Discontinuation .....	107
10.	REFERENCES .....	108
11.	APPENDICES .....	109
Appendix 1.	Investigator Signature Page .....	110
Appendix 2.	Study Procedures Table .....	111
Appendix 3.	Management of Clinical and Laboratory Adverse Events .....	116
Appendix 4.	Mayo Scoring System for Assessment of Ulcerative Colitis Activity .....	117
Appendix 5.	CTCAE Grading Scale for Severity of Adverse Events .....	118
Appendix 6.	Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements .....	119
Appendix 7.	Clinical Laboratory Assessment Table .....	122

#### LIST OF IN-TEXT TABLES

Table 3-1.	Re-randomization for Maintenance Study .....	45
Table 5-1.	Prohibited Concomitant Medications .....	62
Table 7-1.	Grading of Adverse Event Severity .....	77

#### LIST OF IN-TEXT FIGURES

Figure 3-1.	Study Schema .....	43
Figure 8-1.	Induction Studies (Cohorts A and B): Testing Strategy for the Primary and Key Secondary Hypotheses .....	94
Figure 8-2.	Maintenance Study: Testing Strategy for the Primary and Key Secondary Hypotheses .....	96

## PROTOCOL SYNOPSIS

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

---

**Study Title:** Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

---

**IND Number:** 129647  
**EudraCT Number:** 2016-001392-78  
**Clinical Trials.gov Identifier:** NCT02914522

---

**Study Centers Planned:** Approximately 500 sites globally

---

**Objectives:** The overall objective of the study is to evaluate the effect of treatment with filgotinib on the induction and maintenance of remission in subjects with moderately to severely active ulcerative colitis (UC). Subjects who are biologic-naïve and biologic-experienced will be enrolled in Cohorts A and B respectively. Treatment assignments will be randomized within each Cohort.

### **Cohort A: Biologic-Naïve Subjects, Induction Study**

The primary objective of Cohort A Induction Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopy/bleeding/stool (EBS) remission at Week 10

The key secondary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing Mayo Clinic Score (MCS) remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10

The other secondary objectives of Cohort A are:

- To evaluate the safety and tolerability of filgotinib
- To assess the pharmacokinetic (PK) characteristics of filgotinib

The exploratory objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by Ulcerative Colitis Endoscopic Index of Severity (UCEIS) scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to C-reactive protein [CRP], fecal calprotectin, fecal lactoferrin, and fecal matrix metalloproteinase-9 [MMP-9]) with clinical outcomes
- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- To evaluate health-related quality of life (HRQoL)
- To evaluate the effect of filgotinib on health care resource utilization (HCRU)
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

#### **Cohort B: Biologic-Experienced Subjects, Induction Study**

The primary objective of Cohort B Induction Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 10

The key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10



The other secondary objectives of Cohort B Induction Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

**Maintenance Study:**

The primary objective of the Maintenance Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 58

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained EBS remission at Week 58, defined as EBS remission at both Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free EBS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 58

- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 58

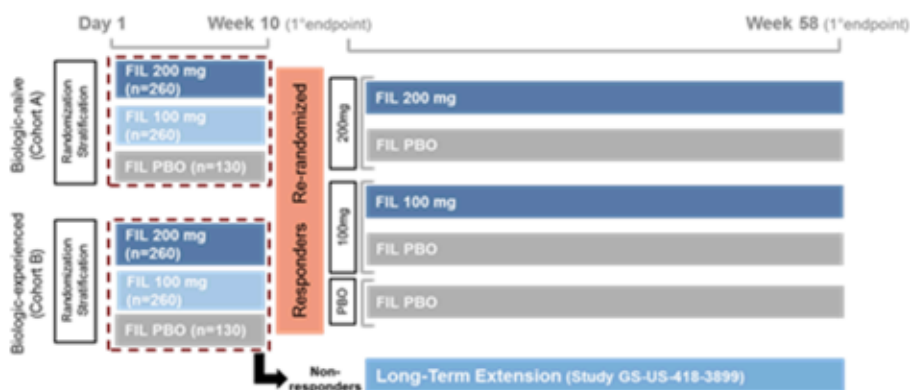
The other secondary objectives of the Maintenance Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 58
  - To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained MCS remission at Week 58, defined as MCS remission at both Weeks 10 and 58
  - To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free MCS remission at Week 58
  - To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
  - To evaluate stool microbiome
  - To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
  - To evaluate HRQoL
  - To evaluate the effect of filgotinib on HCRU
  - To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)
-

**Study Design:** These are combined Phase 2b/3, double-blind, randomized, placebo-controlled studies evaluating the efficacy and safety of filgotinib in the induction and maintenance of remission in subjects with moderately to severely active ulcerative colitis.



These studies include:

- Screening (Days -30 to -1)
- Randomization (Day 1)
- Blinded Induction Studies (Day 1 to Week 11)
  - Cohorts A and B Week 10 efficacy assessments:
  - At Week 10, MCS to assess MCS response or EBS remission
  - Blinded Bridge Phase (Week 10 to 11): Dosing will continue in a blinded fashion through the end of Week 10 until re-randomization at Week 11
- Re-randomization (Week 11)
  - Subjects in Cohorts A and B who complete the Induction Study and achieve either EBS remission or MCS response at Week 10 will be re-randomized into the Maintenance Study at Week 11
  - Subjects who achieve neither EBS remission nor MCS response at Week 10 will have the option to enter a separate, Long-Term Extension (LTE) study (GS-US-418-3899)
- Blinded Maintenance Study (Weeks 11 to 58)
- Post-Treatment (PTx) safety assessments:
  - Subjects who opt out of the LTE study (GS-US-418-3899) will return 30 days after the last dose of study drug for PTx safety assessments



- Subjects who complete all procedures per protocol, including the endoscopy, of the 58-week study will be offered the option to continue into the LTE study (GS-US-418-3899)
- Subjects who are eligible and opt to participate in the LTE study (GS-US-418-3899) can continue into the study without PTx safety assessments

#### **Treatment Regimen (Cohorts A and B Induction Studies)**

Based on protocol eligibility criteria, subjects will be screened for enrollment in *either* Cohort A or Cohort B.

Subjects who meet protocol eligibility criteria will be assigned to the respective Cohort and subsequently randomized in a blinded fashion in a 2:2:1 ratio to 1 of 3 treatments as follows:

**Treatment Group 1 (n = 260):** filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily

**Treatment Group 2 (n = 260):** filgotinib 100 mg and PTM filgotinib 200 mg, once daily

**Treatment Group 3 (n = 130):** PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

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

Within each Cohort, treatment assignments will be stratified according to the following factors in the Induction and Maintenance studies:

#### **Stratification Factors (Cohort A, Biologic-Naïve Induction Study)**

- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-mercaptopurine [6-MP], azathioprine, methotrexate [MTX]) at Day 1, (Yes or No)

#### **Stratification Factors (Cohort B, Biologic-Experienced Induction Study)**

- Exposure to one biologic agent versus more than one biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1, (Yes or No)

**Stratification Factors (Maintenance Study)**

- Participation in Cohort A or Cohort B
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1, (Yes or No)

**Re-randomization for Maintenance Study at Week 11**

- Subjects from Cohorts A and B who meet protocol-specified eligibility criteria for the Maintenance Study will be re-randomized to treatment as follows:

<b>Treatment Assignment Induction Studies Cohorts A and B</b>	<b>Maintenance Study Re-randomization:</b>
Treatment 1, filgotinib 200 mg	Treatment 1, 200 mg
	Treatment 3, Placebo
Treatment 2, filgotinib 100 mg	Treatment 2, 100 mg
	Treatment 3, Placebo
Treatment 3, Placebo	Continue Treatment 3, Placebo

Note: Subjects receiving Treatment 1 or 2 in the Induction study will be randomized in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance study.

Substudies:

**Pharmacokinetic (PK) Substudy**

An optional PK substudy will be performed in a subset of subjects (approximately 30 subjects each in Cohort A and Cohort B) who provide a separate informed consent. In the PK substudy, the daily dose of study drug should be administered under supervision in the clinic (at one visit between Week 2 and Week 10, inclusive), and additional PK samples should be collected predose and at 0.5, 1, 2, 3, 4, and 6 hours post dose.

**CCI** [REDACTED]

Number of  
Subjects  
Planned:

Approximately 650 subjects for each Cohort, for a total of 1300 subjects

Target Population:	Adult subjects with moderately to severely active UC as defined by an MCS criteria of a centrally read endoscopic subscore of $\geq 2$ , a rectal bleeding subscore of $\geq 1$ , a stool frequency subscore $\geq 1$ and a physician's global assessment subscore (PGA) of $\geq 2$ , with a total MCS of 6 to 12, inclusive.
Duration of Treatment:	58 weeks
Diagnosis and Main Eligibility Criteria:	<p>For a complete list of study inclusion and exclusion criteria, please refer to Section 4.</p> <p>A subject may enter either Cohort A <i>or</i> Cohort B based on prior exposure to biologic therapy.</p> <p><b><u>Main Eligibility Criteria (Cohorts A &amp; B):</u></b></p> <p>All subjects must meet <u>all</u> of the following criteria to be eligible for participation in either the Cohort A or B Induction Study.</p> <ul style="list-style-type: none"><li>• Males or non-pregnant, non-lactating females, ages 18 to 75 years, inclusive based on the date of the screening visit</li><li>• Documented diagnosis of UC of at least 6 months AND with a minimum disease extent of 15 cm from the anal verge. Documentation should include endoscopic and histopathologic evidence of UC as follows:<ol style="list-style-type: none"><li>a) The criteria for documentation of UC based on endoscopy will be medical record documentation of, or an ileocolonoscopy (full colonoscopy with the intubation of the terminal ileum) report dated <math>\geq 6</math> months before enrollment, which shows features consistent with UC, determined by the procedure performing physician</li><li>b) The criteria for documentation of UC based on histopathology will be medical record documentation of or a histopathology report indicating features consistent with UC as determined by the pathologist</li></ol></li><li>• A surveillance colonoscopy is required prior to screening in subjects with a history of UC for 8 or more years, if one was not performed in the prior 24 months</li><li>• Moderately to severely active UC as determined by a centrally read endoscopy score <math>\geq 2</math>, a rectal bleeding score <math>\geq 1</math>, a stool frequency score <math>\geq 1</math>, and PGA of <math>\geq 2</math> as determined by the Mayo clinic scoring system (reference <a href="#">Appendix 4</a>) with endoscopy occurring during screening; total score must be between 6 and 12, inclusive</li></ul>



- May be receiving the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted times):
  - a) Oral 5-aminosalicylate (5-ASA) compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization
  - b) Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization
  - c) Oral corticosteroid therapy (prednisone prescribed at a stable dose  $\leq 30$  mg/day or budesonide prescribed at a stable dose of  $\leq 9$  mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must remain stable for the first 14 weeks after randomization
- Must not have Crohn's disease, indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon
- Must not have active tuberculosis (TB) or history of latent TB that has not been treated (see inclusion criterion 8 for further information)
- Must not use any concomitant prohibited medications as described in Section 5.4.2

#### **Cohort A (Biologic-Naïve) Induction Study**

##### **Main Eligibility Criteria, Cohort A ONLY**

Subjects must meet all of the **additional** following criteria to be eligible for participation in Cohort A induction study.

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least 1 of the following agents (depending on current country treatment recommendations/guidelines):
  - a) Corticosteroids
    - i) Active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, OR
    - ii) Two failed attempts to taper steroids below a dose equivalent of 10 mg daily prednisone, OR
    - iii) History of steroid intolerance including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, serious infections, depression, allergic reactions, mood disturbances, or any other condition that contributed to discontinuation of the agent

b) Immunomodulators

- i) Active disease despite a history of at least a 12 week regimen of oral azathioprine ( $\geq 2$  mg/kg/day) or 6-MP ( $\geq 1$  mg/kg/day), or MTX (25 mg subcutaneously [SC] or intramuscularly [IM] per week for induction and  $\geq 15$ mg IM per week for maintenance) OR
  - ii) History of intolerance to at least one immunomodulator including, but not limited to, serious infections, hepatotoxicity, cytopenia, pancreatitis, thiopurine methyltransferase (TPMT) genetic mutation, allergic reactions, or any other condition that contributed to discontinuation of the agent
- No prior or current use of any TNF $\alpha$  antagonist including (but not limited to) infliximab, adalimumab, golimumab, certolizumab, or biosimilar agents at any time
  - No prior or current use of vedolizumab at any time

**Cohort B (Biologic-Experienced) Induction Study**

**Main Eligibility Criteria, Cohort B ONLY**

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least *one* of the following agents (depending on current country treatment recommendations/guidelines):
  - a) TNF $\alpha$  Antagonists
    - i) Active disease despite a history of at least 1 induction regimen of a TNF $\alpha$  Antagonist:
      - Infliximab: Minimum induction regimen of 5 mg/kg at 0, 2, and 6 weeks (in the European Union [EU], duration of treatment of 14 weeks)
      - Adalimumab: An 8-week induction regimen consisting of 160 mg (four 40-mg injections in one day or two 40-mg injections per day for two consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg and a 40 mg dose 2 weeks later (Day 29), followed by a 40 mg dose every other week until Week 8 (Day 57).
      - Golimumab: A minimum induction duration of 6 weeks (12 weeks in EU) is required for golimumab, which includes 200 mg SC injection at Week 0, followed by 100 mg at Week 2, and then 100 mg every 4 weeks OR

- ii) Recurrence of symptoms during maintenance therapy with the above agents, OR
  - iii) History of intolerance to any TNF $\alpha$  antagonists including, but not limited to, serious infections, hepatotoxicity, heart failure, allergic reactions, or any other condition that contributed to discontinuation of the agent
- b) Vedolizumab
- i) Active disease despite a history of at least a 14-week (10 weeks in EU) induction regimen of vedolizumab consisting of 300 mg IV at Weeks 0, 2, and 6 OR
  - ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent
- Must not have used any TNF $\alpha$  antagonist or vedolizumab  $\leq$  8 weeks prior to screening or any other biologic agent  $\leq$  8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer

### **Maintenance Study**

#### **Main Eligibility Criteria**

- Completion of Cohort A or Cohort B Induction Study with MCS response or EBS remission based on Week 10 assessments

Study  
Procedures/  
Frequency:

Study visits for all subjects will occur at screening, Day 1 and Week 2 to Week 11 (Induction) and Week 14 to Week 58 (Maintenance).

Screening assessments will include complete medical history and physical examination (PE), vital signs, laboratory assessment, MCS assessment with flexible sigmoidoscopy/colonoscopy with biopsies, pregnancy test (for females of childbearing potential as defined by [Appendix 6](#)), subject electronic diary (eDiary), HRQoL review, standard 12-lead electrocardiogram (ECG), adverse events (AEs) and concomitant medication assessment.

Mayo Clinic Score assessment with flexible sigmoidoscopy/colonoscopy and biopsies must be performed during screening, and at the Weeks 10 and 58 visits. If normal margins are not apparent from sigmoidoscopy or if proximal colonic involvement is suspected, a full colonoscopy should be performed at all-time points where endoscopic evaluation is performed.

Sparse plasma PK samples will be collected prior to dose at Weeks 10 and 58, post dose at Week 4 (at least 30 minutes and up to 3 hours after dosing), and at any time at Week 26.



Adverse events and concomitant medications will be assessed at each visit.

Non-responding subjects completing all Week 10 assessments will be eligible to enter the LTE study (GS-US-418-3899).

Subjects who opt out of the LTE study (GS-US-418-3899) will return 30 days after the last dose of study drug for PTx safety assessments.

Subjects who are eligible and opt to participate in the LTE study (GS-US-418-3899) can continue into the study without PTx safety assessments.

Subjects who complete the Week 58 visit will have the option to continue study drug in a blinded fashion in the LTE study (GS-US-418-3899).

**Concomitant Ulcerative Colitis Medication Management:**

Subjects on permitted concomitant medications for UC that are described in the inclusion criteria (eg, 5-ASA, and immunomodulators) must remain on stable doses until Week 10. Steroids must remain stable to Week 14.

Starting at Week 14, subjects who are on concomitant steroids must begin tapering steroid therapy. The dose should be reduced at a rate starting at 2.5 mg per week up to 5 mg per week (or equivalent taper if not prednisone). Subjects who are on budesonide should have their daily dose reduced by 3 mg every 3 weeks until they are completely off steroids. For subjects undergoing taper, steroids may be increased or restarted at doses up to and including their baseline dose if return of symptoms is apparent. These subjects will not be considered treatment failures. Subjects who need to restart or increase steroid treatment at a dose that exceeds their baseline dose of steroids (dose may not exceed 30 mg prednisone [or equivalent] or budesonide 9 mg/day) will be considered treatment failures for all clinical endpoints but will be permitted to remain in the study.

For additional prohibited UC medications, reference [Table 5-1](#).

---

<b>Test Product, Dose, and Mode of Administration:</b>	Filgotinib 200 mg oral tablet, once daily Filgotinib 100 mg oral tablet, once daily
<b>Reference Therapy, Dose, and Mode of Administration:</b>	PTM filgotinib 200 mg oral tablet, once daily PTM filgotinib 100 mg oral tablet, once daily

---

---

**Criteria for  
Evaluation:**

- Safety:** Assessment of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of AEs, PE (complete or symptom driven), vital signs, and clinical laboratory evaluations (hematology, chemistry, urinalysis). An ECG will be performed at screening, Week 10 (or at Early Termination (ET) if subject terminates prior to Week 10), Week 26 and Week 58.
- A data monitoring committee (DMC) will meet to evaluate all available safety data accumulated during the study. The initial meeting for each induction study (Cohorts A and B, separately) will occur after approximately 100 subjects (20 from placebo group and 40 from each filgotinib treatment group) reach Week 10. The second meeting for each induction study will include an interim futility analysis and occur after approximately 175 subjects (35 from placebo group and 70 from each filgotinib treatment group) reach Week 10. Following the interim futility analysis meeting, subsequent meetings will occur approximately once every 4 months or at a frequency determined by the DMC.
- Efficacy:** Primary efficacy will be assessed by EBS remission, defined as an endoscopic subscore (based on central reading) of 0 or 1 (referencing the Mayo Score), rectal bleeding subscore of 0, and at least a 1 point decrease in stool frequency from baseline to achieve a subscore of 0 or 1. Efficacy will also be assessed using the full MCS composed of 4 sub-scores (stool frequency, rectal bleeding, endoscopic findings, and PGA), ranging from 0 to 12. Assessments during non-endoscopic visits may use the *partial* MCS, which includes all components except flexible sigmoidoscopy/colonoscopy. Geboes histologic remission will be assessed using the Geboes histologic scores composed of 6 different grades for evaluation of disease severity in UC.
- Pharmacokinetics:** Plasma concentrations of filgotinib and its metabolite GS-829845 (formerly G254445) will be determined.
- Biomarkers:** Blood samples will be collected (predose, if applicable) at Day 1, and Weeks 4, 10, 26, and 58 for assessment of markers of inflammation, immune status, peripheral blood mononuclear cell (PBMC), and the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway. Histopathologic and immunohistochemistry (IHC) assessments will be performed on biopsies at screening and Weeks 10 and 58. Microbiome samples will be collected at screening and Weeks 10, 26, and 58. **CCI**
-



**Statistical  
Methods:**

**Induction Studies (Cohorts A and B)**

The primary analysis set for efficacy analyses is the Full Analysis Set (FAS), which includes all randomized subjects who received at least 1 dose of study drug in the corresponding induction study (Day 1 to Week 10).

The primary analysis will compare each filgotinib dose group to placebo on the proportion of subjects achieving EBS remission at Week 10. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of the primary endpoint.

The graphical approach {Bretz 2009} to sequentially rejective multiple test procedures will be used to control a family-wise type I error rate (FWER) at 5% (ie,  $\alpha = 0.05$ ) for hypothesis testing on primary and key secondary endpoints: Once all hypotheses within the same filgotinib dosing regimen are rejected, then the respective alpha can be passed on to the other regimen's hypotheses. See Section 8.5.3 for details and the significance level that will be used to declare a statistical significant treatment effect for each filgotinib dose group when compared to placebo. Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, non-responder imputation [NRI]).

**Interim Futility Analysis: Induction Studies (Cohorts A and B)**

After 175 subjects (35 from placebo group and 70 from each filgotinib treatment group) complete Week 10 assessments or discontinue from the study, an interim futility analysis will be conducted to evaluate endoscopic efficacy and safety. The proportion of subjects who achieve endoscopic response (endoscopic subscore of 0 or 1) for each treatment group will be evaluated. For each filgotinib dose group comparison with placebo, the DMC may recommend to terminate that respective filgotinib dose group if the observed proportion of subjects who achieve endoscopic response in that filgotinib dose group is less than that in the placebo group. If both filgotinib dose group comparisons meet the futility criteria, the DMC may recommend stopping the study.



### **Cohorts A and B End of Induction Analysis**

Efficacy and safety data will be evaluated by the DMC and a pre-specified sponsor's executive team after *all* subjects in Cohorts A and B complete Week 10 dosing (or prematurely discontinue study drug but complete PT assessments). Data from Cohorts A and B (examined independently) will be used to evaluate the study overall for possible discontinuation (See Section 8.10 and Section 8.11 for details).

### **Maintenance Study**

The primary analysis set for efficacy analyses is the FAS, which includes all re-randomized subjects who met the protocol definition of EBS remission or MCS response at Week 10, and received at least 1 dose of study drug in the Maintenance Study (Weeks 11 to 58).

The primary analysis will compare each filgotinib dose group to placebo on the proportion of subjects achieving EBS remission at Week 58. The CMH approach adjusting for stratification factors will be used for hypothesis testing of the primary endpoint. See Section 8.5.3 for details and the significance level that will be used to declare a statistical significant treatment effect for each filgotinib dose group when compared to placebo. Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, NRI).

### **Pharmacokinetics:**

- Plasma concentrations of filgotinib and its metabolite GS-829845 will be listed and summarized using descriptive statistics.

Sample Size:

### **Induction Studies (Cohorts A and B)**

The sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at Week 10 could be detected when comparing filgotinib to placebo within each Induction Study.

A sample size of 130 subjects in the placebo group and 260 subjects in each filgotinib dose (200 mg or 100 mg) group ( $n = 650$  per cohort) will provide 90% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in EBS remission rate of 15% (25% on filgotinib and 10% on placebo).

### **Maintenance Study**

Assuming an induction response rate (ie, proportion of subjects achieving either EBS remission or MCS response at Week 10) of 55% among subjects receiving filgotinib 200 mg or 100 mg treatment, approximately 285 subjects from each filgotinib dose group from Cohorts A and B Induction Studies combined would be eligible to be re-randomized into the Maintenance Study.

The sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at Week 58 could be detected when comparing each filgotinib dose group (200 mg or 100 mg) to placebo in the Maintenance Study.

A sample size of 95 subjects in the placebo group and 190 subjects in the filgotinib group at the same dose level as the induction dose will provide more than 85% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in maintenance EBS remission rate of 20% (40% on filgotinib and 20% on placebo).

---

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
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration, drug versus time curve
BAP	Biomarker Analysis Plan
BLQ	below the limit of quantitation
BMI	body mass index
<i>C.diff</i>	<i>clostridium difficile</i>
CC&G	Cockcroft-Gault
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CES	Carboxylesterase
CFR	Code of Federal Regulations
CI	confidence interval
CIA	collagen-induced arthritis
CK	creatine kinase
Cmax	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CrCl	creatinine clearance
CRF	case report form(s)
CRO	contract (or clinical) research organization
CRP	c-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAI	Disease Activity Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DSS	dextran sulfate sodium



<i>E.coli</i>	<i>Escherichia coli</i>
EBS	endoscopy/bleeding/stool
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form(s)
EDC	Electronic Data Capture
eDiary	electronic diary
EMA	European Medicines Agency
EQ-5D	EuroQol five dimensions
eSAE	electronic SAE system
ET	early termination
EU	European Union
EudraCT	European clinical trials database
FAS	full analysis set
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
GI	gastrointestinal
GSI	Gilead Sciences, Inc.
GU	genitourinary
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCRU	health care resource utilization
HCV	hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
hERG	human ether-a-gogo
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
HRQoL	health related quality of life
IB	Investigator Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC <sub>50</sub>	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

IL-12	interleukin
IM	intramuscular
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
JAK-STAT	Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT)
LAM	lactational amenorrhea method
LDL	low-density lipoprotein
LLOQ	lower limit of quantitation
LLT	Lower-Level Term
LOCF	Last Observation Carried Forward
LTE	long-term extension
MCS	Mayo Clinic Score
MedDRA	Medical Dictionary for Regulatory Activities
MMP-9	matrix metalloproteinase-9
MTX	methotrexate
NOEL	no-observed-effect-levels
NRI	non-responder imputation
NSAID	nonsteroidal anti-inflammatory drugs
O&P	ova and parasites test
OAT	organic anion transporters
PBMC	peripheral blood mononuclear cell
PCP	pneumocystis pneumonia
PD	pharmacodynamics
PE	physical examination
PEG	polyethylene glycol
PGA	physician's global assessment
P-gp	p glycoprotein
PI	principal investigator
PK	pharmacokinetic
PTM	placebo to match
PTx	pPost-tTreatment
PVE	Pharmacovigilance and Epidemiology
Q1	1 <sup>st</sup> quartile
Q3	3 <sup>rd</sup> quartile

RA	rheumatoid arthritis
RNA	ribonucleic acid
RT-PCR	reverse transcription polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF-36	Short Form Health Survey
SI	international system of units
SOC	system organ class
SOP	standard operating procedure
spp	species
STAT	signal transducer and activator of transcription
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TgrasH2	transgenic mouse
TNF $\alpha$	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
TYK	tyrosine kinase
UC	ulcerative colitis
UCEIS	ulcerative colitis endoscopic index of severity
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
vfPBMC	visibly frozen peripheral blood mononuclear cell
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment



## DEFINITION OF TERMS

Corticosteroid-Free Remission	EBS remission with no corticosteroid use for at least 6 months prior to Week 58 among subjects who are on corticosteroid at Baseline
EBS Remission	An endoscopic subscore of 0 or 1, rectal bleeding subscore of 0, and at least a one point decrease in stool frequency from baseline to achieve a subscore of 0 or 1
Endoscopic Response	Endoscopic subscore of 0 or 1
Geboes histologic remission	Based on the Geboes Scale, all of the following must be met to be considered in Geboes histologic remission. Grade 0        ≤ 0.3 Grade 1        ≤ 1.1 Grade 2a       ≤ 2A.3 Grade 2b       2B.0 Grade 3        3.0 Grade 4        4.0 Grade 5        5.0
Mayo Clinic Score*	Composed of sub-scores from endoscopy, rectal bleeding, stool frequency, and PGA
Mayo Clinic Score Remission	MCS of ≤ 2 points and no individual subscore > 1 point
Mayo Clinic Score Remission (Alternative Definition)	Rectal bleeding, stool frequency, and PGA subscore of 0 and an endoscopic subscore of 0 or 1; overall MCS of ≤ 1
Mayo Clinic Score Response	A Mayo Clinic Score (MCS) reduction of ≥ 3 points and at least 30% from baseline score with an accompanying decrease in rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1
Partial Mayo Clinic Score	Composed of sub-scores from rectal bleeding, stool frequency, and PGA

\* Rectal bleeding and stool frequency subscores will be rounded to the nearest integer for determination of eligibility and calculation of endpoints

## 1. INTRODUCTION

### 1.1. Background

Ulcerative colitis (UC) is a chronic, intermittent, relapsing disease characterized by inflammation of the colonic mucosa, which is limited to the colon and rectum. The disease characteristically commences in the rectum and may extend proximally in an uninterrupted pattern into the colon. It can involve the entire colon (pan-colitis), the left colon, or isolated recto-sigmoid disease with patients being equally distributed in those 3 phenotypes. In the United States (US), the prevalence of UC has been estimated to be 238 per 100,000 adults {Kappelman 2007}. Europe has the highest reported prevalence values for inflammatory bowel disease (IBD; 505 per 100,000 persons for UC and 322 for Crohn's Disease [CD]). The annual incidence of UC is 24.3 per 100,000 person-years in Europe and the incidence is 6.3 per 100,000 person-years for UC in Asia {Molodecky 2012}. The incidence and prevalence of IBD appear to be increasing over time globally. The hallmark symptoms of the disease are bloody diarrhea, rectal urgency, and tenesmus. The clinical course tends to wax and wane with periods of remission interspersed with periods of active disease. Ulcerative colitis may also be associated with extra-intestinal manifestations including ocular lesions, skin lesions, arthritis, and primary sclerosing cholangitis. The exact pathophysiology is not known but in general, genetic predisposition in conjunction with environmental and social factors (such as history of tobacco use, medication history, and geography) may impact development of disease. Discoordinated activity of both innate and adaptive immune responses in combination with epithelial barrier defects and dysbiosis lead to an inflammatory cascade resulting in clinical signs and symptoms of UC {Ungaro 2016}.

In addition to abdominal pain and rectal bleeding that both impact activities of daily living and quality of life for patients with UC, the disease also carries an increased risk of colorectal cancer {Ungaro 2016}. With poorly controlled disease, the rate of developing colorectal cancer increases with time. The risk of colorectal cancer in UC patients is decreasing over time partially due to better control of inflammation and colonoscopic surveillance {Beaugerie 2015}. Overall, UC patients still experience a greater risk of colorectal cancer; in one meta-analysis of population based cohorts the risk was 2.4-fold {Jess 2012}. Thus, UC represents a serious, life-threatening disease for which new therapies are needed to interrupt the inflammatory process to prevent disease progression, restore quality of life, and reduce the risk of colorectal cancer.

Treatment of UC is dependent on the severity and the location of disease. Goals of treatment include improved quality of life, reduction in long-term corticosteroid use, and minimization of cancer risk. Mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids {Kornbluth 2010}. For moderate disease, oral corticosteroids, and immunomodulators such as azathioprine and 6-mercaptopurine (6-MP) may be utilized {Danese 2011}. For more moderate to severe disease, patients are commonly treated with a tumor necrosis factor-alpha (TNF $\alpha$ ) antagonist infusion or injection such as infliximab (Remicade<sup>®</sup>), adalimumab (Humira<sup>®</sup>), and golimumab (Simponi<sup>®</sup>). Vedolizumab (Entyvio<sup>®</sup>), an injectable integrin  $\alpha 4\beta 7$  monoclonal antibody, is also approved for moderately to severely active

disease. Ustekinumab (Stelara<sup>®</sup>, CNTO 1275; an IL-12 and IL-23 monoclonal antibody), upadacitinib (JAK inhibitor), etrolizumab (PRO145223; monoclonal antibody targeting the  $\beta 7$  subunit of the heterodimeric integrins  $\alpha 4\beta 7$  and  $\alpha E\beta 7$ ), risankizumab (IL-23 antibody) and ozanimod (RPC1063; selective S1P1 and S1P5 receptor agonist) are currently being tested in Phase 3 clinical trials. Tofacitinib, a JAK 1/3 inhibitor, was effective in a Phase 3 UC study {Sandborn 2017}. Leukocytapheresis therapy may be used in Japan {Fukunaga 2012}. Despite several classes of treatment options for patients with UC, there remains an unmet medical need, particularly in the treatment of moderately to severely active disease. Agents with novel mechanisms of action that target the inflammatory cascade, with oral dosing and acceptable immunomodulatory and hematologic effects, remain the most promising option to address these unmet needs.

## 1.2. Filgotinib (GS-6034)

### 1.2.1. General Information

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine interleukin (IL)-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including rheumatoid arthritis (RA) and CD.

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

In humans, filgotinib is metabolized to form 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 rat juvenile toxicity study and a 6-month carcinogenicity study in transgenic (TgrasH2) mice. Ongoing studies include carcinogenicity studies in rats and mice, a rat pre- and post-natal development study, and a 4-week impurity qualification study in rats.



#### 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  $\geq 179$  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  $\geq 50\%$  at 50-fold higher concentration than  $IC_{50}$  for JAK1. Broad receptor profiling ( $\sim 70$  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 endpoints evaluated across the DSS colitis model studies confirmed the suppression of various inflammatory markers including serum levels of C-reactive protein (CRP) and myeloperoxidase (MPO) and expression of IL-6 and TNF $\alpha$  (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-gogo [hERG] and dog telemetry studies), apart from a slight non-adverse increase in heart rate and arterial pressure with GS-829845 at exposures 8-fold that of the peak serum concentration ( $C_{max}$ ) in subjects with CD treated with 200 mg once daily filgotinib. There were no relevant effects on electrocardiogram (ECG) and QT. Filgotinib and GS-829845 had no effects on the respiratory system and central nervous system (CNS).



### 1.2.2.3. Key Nonclinical Distribution, Metabolism, and Excretion Data

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

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

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

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

In vitro metabolism studies in all species revealed one major metabolite (GS-829845). The formation of GS-829845 is mediated by carboxylesterases (CES) and is not dependent on cytochrome P450 (CYP).

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'-diphospho-glucuronosyltransferase (UGTs), and no relevant inhibition of key drug transporters, including organic anion transporters (OATs), by filgotinib or GS-829845. OCT2 was inhibited by both filgotinib (IC<sub>50</sub>: 8.7 μM) and GS-829845 (IC<sub>50</sub>: 67 μM). The clinical relevance of the IC<sub>50</sub> values for inhibition of OCT2 will be further evaluated. MATE1 was also weakly inhibited by filgotinib (IC<sub>50</sub>: 94 μM) and GS-829845 (IC<sub>50</sub>: >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 embryoletality 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 Crohn's Disease Activity Index [CDAI] score < 150), clinical response (defined as a decrease in CDAI of at least 100 points from baseline), and endoscopic response (defined as a decrease of at least 50% from baseline in the SES-CD score).

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

There remains a significant unmet need in the treatment of moderately to severely active UC despite multiple classes of treatment regimens. Goals of treatment include improved quality of life, reduction in long-term corticosteroid use, mucosal healing, and minimization of risk of malignancy. To date, no oral agent has been approved for moderately to severely active UC, and the use of corticosteroids and oral immunomodulators has been in combination with biologic therapies. Patient response to primary TNF $\alpha$  inhibition is variable, and the risk of secondary biologic failure is significant. Though surgery may be curative, avoidance of surgical risks is equally desirable. Oral therapy with efficacy comparable to TNF $\alpha$ -inhibition and anti-integrin therapy is highly desirable. JAK inhibition with filgotinib represents a significant opportunity to achieve long-term mucosal healing with an acceptable safety profile and with added ease of oral administration.

JAK inhibition as a therapeutic modality for UC is supported by preclinical evidence of efficacy in the DSS-induced colitis mouse model, Phase 2 clinical trial results in moderately to severely active CD, and by evidence of tofacitinib (pan-JAK inhibitor) efficacy in a similar population with moderately to severely active UC {Sandborn 2017}. In a well-established preclinical model of UC {Chassaing 2014}, the DSS-induced mouse model, filgotinib was efficacious at 30 mg/kg in protecting mice from colitis development, neutrophil recruitment, and macrophage infiltration. Markers of inflammation including CRP and IL-1 $\beta$  normalized after filgotinib administration. Findings with tofacitinib {Sandborn 2017} validate JAK inhibition as a therapeutic intervention for UC and consequently but indirectly also support development of filgotinib in this population. Additionally, filgotinib selectivity for JAK1 with consequent minimal effects on hemoglobin (with increases up to 4% in Phase 2b studies in RA and increases in the CD population based on 10-week data) suggests that filgotinib may demonstrate an acceptable safety profile in the UC population.

#### 1.3.1. Rationale for Endpoint and Timing

Previous UC induction studies have evaluated initial endpoints at 8 to 12 weeks and the present study proposes that Week 10 assessments for biologic naïve and experienced subjects be used to assess for continuation into the maintenance phase. A Week 10 induction endpoint for UC is considered appropriate based on the rapid and sustained clinical responses induced by filgotinib in RA and CD. Ten weeks is sufficient time for some degree of mucosal healing to occur and for clinical symptoms to improve. The use of endoscopy/bleeding/stool (EBS) remission, which includes all subset of scores from the MCS but excludes the subjective physician global assessment (PGA) maximizes objectivity in assessment of drug effect. Use of centrally read endoscopy will further reduce bias in assessment of endoscopic healing. Maintenance and durability of response and remission will be explored in the 48-week maintenance phase using a traditional model of induction-maintenance design.

### 1.3.2. 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). The remission rate at Week 20 for subjects who failed placebo for the first 10 weeks and commenced 100 mg from Weeks 10 to 20 was slightly lower (32%) though the response rate was comparable (59%), indicating some level of efficacy at the 100 mg dose. These results are consistent with the relationship observed between filgotinib exposures and inhibition of pSTAT1 activation (ex-vivo) following single and multiple filgotinib doses, where maximal inhibition of pSTAT1 activation (~78%) was achieved at or above 200 mg total daily dose and intermediate inhibition (~47%) at 100 mg {[Namour 2015](#)}. pSTAT1 data, in conjunction with considerations around the margin for nonclinical testicular findings, suggests assessing doses above 200 mg is not indicated. Given the absence of definitive data for filgotinib in UC, and the presence of response in CD subjects in the exploratory 10 to 20 week arm of 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 UC subjects.

The induction portion of the study will evaluate 2 doses of filgotinib. The purpose of the maintenance phase is to evaluate the ability of drug to sustain remission in subjects who have responded at a given dose. Therefore, the re-randomization will occur into 2 arms for active treated subjects: continuation of the induction dose or re-randomization to placebo.

In conclusion, JAK inhibition represents a promising target in the treatment of moderate to severe UC, and filgotinib, a safe and well tolerated oral therapy based on Phase 2 data. The present study is intended to establish the safety and efficacy of JAK-selective inhibition on a life threatening disease with presently inadequate treatment options.

### 1.4. Risk/Benefit Assessment for the Study

Ulcerative colitis 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 2 biologic therapies (any TNF $\alpha$  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. For further details about infections and malignancies, please reference the IB.

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

An independent and experienced data monitoring committee (DMC) appointed to monitor the study will provide an additional level of risk mitigation. The DMC may advise to continue the study unchanged, to modify the study, or to discontinue the study. The initial meeting will occur after approximately 100 subjects (20 from placebo group and 40 from each filgotinib group) reach Week 10. The second meeting for each induction study will include an interim futility analysis and occur after approximately 175 subjects (35 from placebo group and 70 from each filgotinib treatment group) reach Week 10. After the futility analyses, the DMC meetings for safety review will be held approximately once every 4 months or at a frequency determined by the DMC. In addition, an end of induction analysis will be performed to evaluate efficacy in induction of both dose groups in both cohorts.

Taking all of these considerations into account with respect to the filgotinib program, the early signals for efficacy demonstrated in clinical trials of CD, 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 UC. 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

### 2.1. Cohort A Induction Study

The primary objective of Cohort A Induction Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 10

The key secondary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10

The other secondary objectives of Cohort A Induction Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)



## 2.2. Cohort B Induction Study

The primary objective of Cohort B Induction Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 10

The key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10

The other secondary objectives of Cohort B Induction Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)



### 2.3. Maintenance Study

The primary objective of the Maintenance Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 58 in subjects

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained EBS remission at Week 58, defined as EBS remission at both Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free EBS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 58

The other secondary objectives of the Maintenance Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained MCS remission at Week 58, defined as remission at both Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free MCS remission at Week 58
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes

- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression and treatment response to filgotinib in subjects with UC
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

### **3. STUDY DESIGN**

#### **3.1. Endpoints**

##### **3.1.1. Cohort A Induction Study**

The primary endpoint is:

- The proportion of subjects achieving EBS remission at Week 10

The key secondary endpoints are:

- The proportion of subjects achieving MCS remission at Week 10
- The proportion of subjects achieving an endoscopic subscore of 0 at Week 10
- The proportion of subjects achieving Geboes histologic remission at Week 10
- The proportion of subjects achieving MCS remission (alternative definition) at Week 10

The other secondary endpoints are:

- PK characteristics for filgotinib and its metabolite GS-829845

The exploratory endpoints are:

- Change from baseline in UCEIS at Week 10
- Association between changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- Change from baseline in HRQoL scores at Week 10
- HCRU assessments at Week 10
- The proportion of subjects achieving novel histologic outcomes at Week 10

### **3.1.2. Cohort B Induction Study**

The primary endpoint is:

- The proportion of subjects achieving EBS remission at Week 10

The key secondary endpoints are:

- The proportion of subjects achieving MCS remission at Week 10
- The proportion of subjects achieving an endoscopic subscore of 0 at Week 10
- The proportion of subjects achieving Geboes histologic remission at Week 10
- The proportion of subjects achieving MCS remission (alternative definition) at Week 10

The other secondary endpoints are:

- PK characteristics for filgotinib and its metabolite GS-829845

The exploratory endpoints are:

- Change from baseline in UCEIS at Week 10
- Association between changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- Change from baseline in HRQoL scores at Week 10
- HCRU assessments at Week 10
- The proportion of subjects achieving novel histologic outcomes at Week 10

### **3.1.3. Maintenance Study**

The primary endpoint is:

- The proportion of subjects achieving EBS remission at Week 58



The key secondary endpoints are:

- The proportion of subjects achieving MCS remission at Week 58
- The proportion of subjects achieving sustained EBS remission, defined as EBS remission at both Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free EBS remission at Week 58
- The proportion of subjects achieving endoscopic remission at Weeks 58
- The proportion of subjects achieving Geboes histologic remission at Week 58
- The proportion of subjects achieving MCS remission (alternative definition) at Week 58

The other secondary endpoints are:

- PK characteristics for filgotinib and its metabolite GS-829845

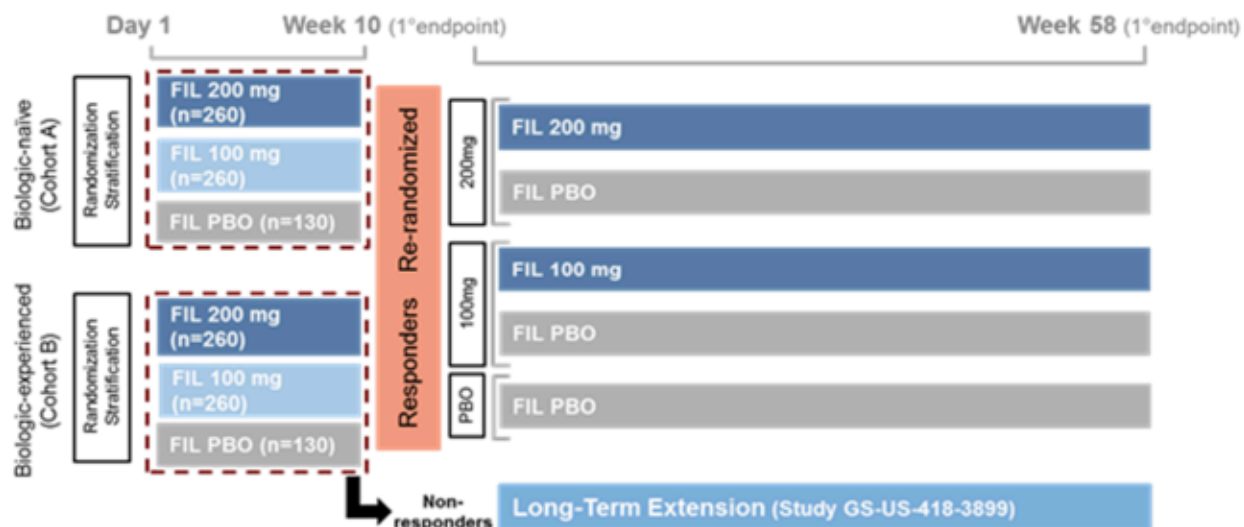
The exploratory endpoints are:

- Change from baseline in UCEIS at Week 58
- The proportion of subjects achieving sustained MCS remission, defined as MCS remission at both Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free MCS remission at Week 58
- Association between changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib in subjects with UC
- Change from baseline in HRQoL scores at Week 58
- HCRU assessments at Week 58
- The proportion of subjects achieving novel histologic outcomes at Week 58

### 3.2. Study Design

These are combined Phase 2b/3, double-blind, randomized, placebo-controlled studies evaluating the efficacy and safety of filgotinib in the induction and maintenance of remission in subjects with moderately to severely active UC. A schematic of this study is provided in Figure 3-1.

Figure 3-1. Study Schema



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

Non-responders are subjects who achieve neither EBS remission nor MCS response at Week 10

Subjects in the Maintenance Study that meet disease worsening criteria (see Section 3.6) will be offered open-label filgotinib.

This study includes:

- Screening (Days -30 to -1)
- Randomization (Day 1)
- Blinded Induction Studies (Day 1 to Week 11)
  - Cohorts A and B Week 10 efficacy assessments
    - At Week 10, MCS to assess MCS response or EBS remission
  - Blinded Bridge Phase (Week 10 to 11): Dosing will continue in a blinded fashion through the end of Week 10 until re-randomization at Week 11
- Re-randomization (Week 11)
  - Subjects in Cohorts A and B who complete the Induction Study and achieve either EBS remission or MCS response at Week 10 will be re-randomized into the Maintenance Study at Week 11
  - Subjects who achieve neither EBS remission nor MCS response at Week 10 will have the option to enter a separate, Long-Term Extension (LTE) study (GS-US-418-3899)

- Blinded Maintenance Study (Weeks 11 to 58)
- Post-Treatment (PT) safety assessments:
  - Subjects who opt out of the LTE study (GS-US- 418-3899) will return 30 days after the last dose of study drug for PTx safety assessments
  - Subjects who complete all procedures per protocol, including the endoscopy, of the 58-week study will be offered the option to continue into the LTE study (GS-US-418-3899)
  - Subjects who are eligible and opt to participate in the LTE study (GS-US-418-3899) can continue into the study without PTx safety assessments

### 3.3. Study Treatments

Based on protocol eligibility criteria, subjects will be screened for enrollment in *either* Cohort A or Cohort B.

Subjects who meet protocol eligibility criteria will be assigned to the respective Cohort and subsequently randomized in a blinded fashion in a 2:2:1 ratio to 1 of 3 treatments as follows:

#### Treatment Groups (Induction Study)

**Treatment Group 1 (n = 260):** filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily

**Treatment Group 2 (n = 260):** filgotinib 100 mg and PTM filgotinib 200 mg, once daily

**Treatment Group 3 (n = 130):** PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: US and Korea males who have not failed at least two biologic therapies (any TNF $\alpha$  antagonist and vedolizumab) will be randomized in a 2:1 ratio to either filgotinib 100 mg or matching placebo.

Within each Cohort, treatment assignments will be stratified according to the following factors in the Induction and Maintenance studies:

#### Stratification Factors (Cohort A, Biologic Naïve Induction Study)

- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-mercaptopurine (6-MP), azathioprine, MTX) at Day 1 (Yes or No)



**Stratification Factors (Cohort B, Biologic Experienced Induction Study)**

- Exposure to *one* biologic agent versus more than *one* biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1 (Yes or No)

**Stratification Factors (Maintenance Study)**

- Participation in Cohort A or Cohort B
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1 (Yes or No)
- Subjects from Cohorts A and B who are eligible for the Maintenance Study will be re-randomized to treatment as follows:

**Table 3-1. Re-randomization for Maintenance Study**

<b>Treatment Assignment Induction Studies Cohorts A and B</b>	<b>Maintenance Study Re-randomization:</b>
Treatment 1, filgotinib 200 mg	Treatment 1, 200 mg
	Treatment 3, Placebo
Treatment 2, filgotinib 100 mg	Treatment 2, 100 mg
	Treatment 3, Placebo
Treatment 3, Placebo	Continue Treatment 3, Placebo

Note: Subjects receiving Treatment 1 or 2 in the Induction study will be randomized in a 2:1 manner to either continue on the assigned filgotinib regimen or to placebo for the duration of the Maintenance study.

**3.4. Duration of Treatment**

Randomized subjects will receive a maximum of 58 weeks of study drug. Subjects who are non-responders based on the results of the Week 10 assessments will be offered the option to receive open-label filgotinib by entering into the LTE study (GS-US-418-3899).

Subjects meeting disease worsening criteria at Week 11 or later must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib in the LTE study (See Section 3.6, Disease Worsening Criteria).

Subjects who complete the Week 58 visit will have the option to continue study drug in a blinded fashion in the LTE study.

### 3.5. Criteria for Study Drug Interruption or Discontinuation

#### 3.5.1. Study Drug Interruption Considerations

The Gilead Medical Monitor should be consulted prior to study drug interruption when medically feasible. Study drug interruption should be considered in the following circumstances; *prior to resumption of study drug, the investigator should discuss the case with the Gilead Medical Monitor:*

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for 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 Gilead Medical Monitor.
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored.

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

#### 3.5.2. Study Drug Discontinuation Considerations

The Gilead 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  $> 38.3^{\circ}\text{C}$  or a sustained temperature of  $> 38^{\circ}\text{C}$  for more than one hour) with absolute neutrophil count of  $< 1,000/\text{mm}^3$
- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue ) with hemoglobin  $< 7.5 \text{ g/dL}$  , 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

- Unacceptable toxicity or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.7.2.1
- Discontinuation of the study at the request of Gilead, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subject use of prohibited concurrent therapy *may* trigger study drug discontinuation; consultation should be made with the Gilead 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<sup>3</sup> (SI: < 0.75x10<sup>9</sup> cells/L)

— 2 sequential platelet counts < 75,000 platelets/mm<sup>3</sup> (SI: < 75.0x10<sup>9</sup> cells/L)

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

- total bilirubin >2x ULN

- INR > 1.5

- or accompanied by symptoms consistent with hepatic injury

For any subject with an **initial** AST or ALT elevation > 3x the 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 > 5xULN

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

Male  $[(140 - \text{age in years}) \times (\text{weight in kg})] / [72 \times (\text{serum creatinine in mg/dL})] = \text{CLcr (mL/min)}$

Female  $[(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85] / [72 \times (\text{serum creatinine in mg/dL})] = \text{CLcr (mL/min)}$



- Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF).
- Subjects who permanently discontinue study drug for any reason should discuss their continued care plan with their 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 Post-Treatment (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.

### 3.6. Disease Worsening Criteria

Subjects meeting the following disease worsening criteria evaluated starting at Week 11 must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib by entering into the separate LTE study (GS-US-418-3899).

- Disease worsening starting at 11 weeks of therapy is based on the following criteria: partial MCS score (all components of MCS except for endoscopic subscore) increase of  $\geq 3$  points to at least 5 points from the Week 10 value on two consecutive visits, or an increase to 9 points on two consecutive visits if the Week 10 value is  $> 6$ .
  - The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits anytime from Week 11 onward).
- Disease worsening to the extent that the subject clinically requires medications prohibited by the study (at investigator discretion, with discussion with medical monitor if feasible); these subjects do not qualify for the LTE study.

### 3.7. End of Study

End of Study is defined as when the last subject has completed 58 weeks of treatment plus 30 days follow-up.


### 3.8. Post Study Care

All subjects completing all study related procedures including endoscopy at Week 58 will be offered an opportunity to participate in the LTE study (GS-US-418-3899). For those subjects who do not participate in the LTE study, after the subject has completed their study participation, the long-term care of the participant will remain the responsibility of their primary treating physicians.

### 3.9. Biomarker Testing

#### 3.9.1. Biomarker Samples to Address the Study Objectives

The following biological specimens will be collected in this study and will be used to evaluate the association of exploratory systemic and/or tissue specific biomarkers with study drug response, including efficacy and/or AEs and to help inform the mechanism of action and mechanism of intrinsic and acquired resistance to filgotinib in UC. The specific analyses will include, but will not be limited to, the biomarker sample and assays listed below.

- Colon biopsies to assess the association of JAK signaling, inflammation, immune status and clinical outcomes. The potential biomarker analyses include the expression of pSTAT and MMP-9, tissue lymphocyte subsets and transcriptome.
- Stool microbiome to understand how changes of gut flora correlate with mucosal healing, immune status and treatment effect
- Plasma and serum samples for potential analysis of circulating factors including but not limited to cytokines, miRNA and metabolome
- Paxgene blood samples for leukocyte gene expression analyses
- Whole blood sample for potential B-cell/T-cell receptor repertoire sequencing
- 
- Viable frozen peripheral blood mononuclear cells (vPBMCs) to assess inflammatory signaling pathway and immune cell subset analysis (vPBMC sample collection at US and Canadian sites only)

Because biomarker science is a rapidly evolving area of investigation, and AEs in particular are difficult to predict, it is not possible to specify prospectively all tests that will be done on the specimens provided. The testing outlined above is based upon the current state of scientific knowledge. It may be modified during or after the end of the study to remove tests no longer indicated and/or to add new tests based upon the growing state of art knowledge.

Specimens will be collected from all subjects who provide consent.

Biomarker sample collection frequency is listed in [Appendix 2](#).

CCI

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]



## **4. SUBJECT POPULATION**

### **4.1. Number of Subjects and Subject Selection**

#### **Cohort A Induction Study**

Approximately 650 subjects who meet eligibility criteria at screening will be randomized in a blinded fashion to receive filgotinib 200 mg, filgotinib 100 mg, or matching placebo in a 2:2:1 ratio, respectively.

#### **Cohort B Induction Study**

Approximately 650 subjects who meet eligibility criteria at screening will be randomized in a blinded fashion to receive filgotinib 200 mg, filgotinib 100 mg, or matching placebo in a 2:2:1 ratio, respectively.

#### **Maintenance Study**

Subjects from Cohorts A and B who meet either MCS response or EBS remission criteria will be re-randomized at Week 11 in a blinded fashion in a 2:1 ratio to either the same dose of filgotinib or placebo. Refer to Section 3.3, [Table 3-1](#).

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

### **4.2. Induction Study (Cohorts A and B)**

#### **4.2.1. Inclusion Criteria**

Subjects must meet all of the following inclusion criteria to be eligible for participation in either the Cohort A or B Induction Study.

- 1) Must have the ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures
- 2) Males or non-pregnant, non-lactating females, ages 18 to 75 years, inclusive based on the date of the screening visit
- 3) Females of childbearing potential (as defined in [Appendix 6](#)) must have a negative pregnancy test at screening and baseline
- 4) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in [Appendix 6](#)

- 5) Documented diagnosis of UC of at least 6 months AND with a minimum disease extent of 15 cm from the anal verge. Documentation should include endoscopic and histopathologic evidence of UC as follows:
  - a) The criteria for documentation of UC based on endoscopy will be medical record documentation of, or an ileocolonoscopy (full colonoscopy with the intubation of the terminal ileum) report dated  $\geq 6$  months before enrollment, which shows features consistent with UC, determined by the procedure performing physician
  - b) The criteria for documentation of UC based on histopathology will be medical record documentation of or a histopathology report indicating features consistent with UC as determined by the pathologist
- 6) A surveillance colonoscopy is required prior to screening in subjects with a history of UC for 8 or more years, if one was not performed in the prior 24 months
- 7) Moderately to severely active UC as determined by a centrally read endoscopy score  $\geq 2$ , a rectal bleeding score  $\geq 1$ , a stool frequency score  $\geq 1$  and PGA of  $\geq 2$  as determined by the Mayo clinic scoring system (reference [Appendix 4](#)) with endoscopy occurring during screening; total score must be between 6 and 12, inclusive.
- 8) Meet one of the following TB screening criteria:
  - a) No evidence of active or latent TB:
    - i) A negative QuantiFERON<sup>®</sup> TB-Gold In-Tube test (or centrally reported equivalent assay) at screening, AND
    - ii) A chest radiograph (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection, AND
    - iii) No history of either untreated or inadequately treated latent or active TB infection
  - b) Previously treated for TB: ie, if a subject has previously received an adequate course of therapy as per local standard of care for either latent TB (eg, 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are  $< 5\%$  or an acceptable alternative regimen) or active TB (acceptable multi-drug regimen). In these cases, no QuantiFERON<sup>®</sup> TB-Gold In-Tube test (or centrally reported equivalent assay) need be obtained, but a chest radiograph must be obtained if not done so within 3 months prior to screening (with the report or films available for investigator review). It is the responsibility of the investigator to verify the adequacy of previous anti- TB treatment and provide appropriate documentation.

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

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

- 9) Laboratory parameters (subjects who fail to meet the below reference laboratory tests may be re-tested once at discretion of investigator prior to being considered a screen failure):
- a) Hepatic panel (AST, ALT, total bilirubin)  $\leq 2$  times the ULN
  - b) Estimated CrCl  $\geq 40$  ml/min as calculated by the CC&G equation
  - c) Hemoglobin  $\geq 8$  g/dL
  - d) Absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/L$  ( $1,500/mm^3$ )
  - e) Platelets  $\geq 100 \times 10^9/L$
  - f) White blood cells (WBC)  $\geq 3.0 \times 10^9/L$
  - g) Absolute Lymphocyte count  $> 750/mm^3$
- 10) May be receiving the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted times):
- a) Oral 5-aminosalicylate (5-ASA) compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for first 10 weeks after randomization
  - b) Azathioprine, 6-MP or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for first 10 weeks after randomization
  - c) Oral corticosteroid therapy (prednisone prescribed at a stable dose  $\leq 30$  mg/day or budesonide prescribed at a stable dose of  $\leq 9$  mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must be stable for first 14 weeks after randomization
- 11) Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose



#### 4.2.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in either the Cohort A or B Induction Study.

- 1) Pregnant or lactating females
- 2) Males and females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined by [Appendix 6](#)
- 3) Females who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 35 days after last dose of the study drug
- 4) Male subjects unwilling to refrain from sperm donation for at least 90 days after last dose of the study drug
- 5) Known hypersensitivity to filgotinib, its metabolites, or formulation excipients
- 6) Exhibit acute severe UC as defined by the following criteria:
  - a)  $\geq 6$  bloody stools daily AND 1 or more of the following:
    - i) Body temperature  $\geq 100.4^{\circ}\text{F}$  (or  $38^{\circ}\text{C}$ )
    - ii) Pulse  $> 90$  beats per minute
- 7) Use of rectal formulations of 5-ASA compounds or rectal corticosteroids 2 weeks prior to screening
- 8) History of major surgery or trauma within 30 days prior to screening
- 9) Presence of CD, indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon
- 10) Prior surgical intervention for UC (eg, total colectomy, subtotal colectomy, partial or hemicolectomy, ileostomy, or colostomy) or likely requirement for surgery during the study
- 11) Dependence on parenteral nutrition
- 12) History or evidence of incompletely resected colonic mucosal dysplasia
- 13) Stool sample positive for *Clostridium difficile* (*C. diff*) toxin, pathogenic *Escherichia coli* (*E. coli*), *Salmonella* species (spp), *Shigella* spp, *Campylobacter* spp or *Yersinia* spp
- 14) Stool sample positive for ova and parasites test (O&P) unless approved by the medical monitor

- 15) Active clinically significant infection, or any infection requiring hospitalization or treatment with intravenous anti-infectives within 30 days of screening (or 8 weeks of Day 1); or any infection requiring oral anti-infective therapy within 2 weeks of screening (or 6 weeks of day 1)
- 16) Infection with HIV, hepatitis B or hepatitis C
- 17) Presence of Child-Pugh Class C hepatic impairment
- 18) Active TB or history of latent TB that has not been treated (See inclusion criterion 8 for further information)
- 19) History of malignancy in the last 5 years except for subjects who have been successfully treated for non-melanoma skin cancer or cervical carcinoma in situ
- 20) History of lymphoproliferative disorder, lymphoma, leukemia, myeloproliferative disorder, or multiple myeloma
- 21) History of treatment with lymphocyte-depleting therapies, including but not limited to alemtuzumab, cyclophosphamide, total lymphoid irradiation, and rituximab
- 22) History of cytapheresis  $\leq$  2 months prior to screening
- 23) Use of prohibited concomitant medications as described in Section 5.4.2.
- 24) Any chronic medical condition (including, but not limited to, cardiac or pulmonary disease, or substance abuse) or psychiatric problem 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 procedures
- 25) Administration of a live or attenuated vaccine within 30 days of randomization
- 26) History of opportunistic infection or immunodeficiency syndrome
- 27) Currently on any chronic systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis (PCP), cytomegalovirus (CMV), herpes zoster, atypical mycobacteria)
- 28) History of disseminated *Staphylococcus aureus*
- 29) History of symptomatic herpes zoster or herpes simplex within 12 weeks of screening, or any history of disseminated herpes simplex, disseminated herpes zoster, ophthalmic zoster, or central nervous system zoster

### **4.3. Cohort A (Biologic-naïve) Induction Study**

#### **4.3.1. Inclusion Criteria, Cohort A ONLY**

Subjects must meet all of the additional following inclusion criteria to be eligible for participation in Cohort A Induction Study.

- 1) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least 1 of the following agents (depending on current country treatment recommendations/guidelines):
  - a) Corticosteroids
    - i) Active disease despite a history of at least an induction regimen of a dose equivalent to oral prednisone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, OR
    - ii) Two failed attempts to taper steroids below a dose equivalent of 10 mg daily prednisone, OR
    - iii) History of steroid intolerance including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, serious infections, depression, allergic reactions, mood disturbances, or any other condition that contributed to discontinuation of the agent
  - b) Immunomodulators
    - i) Active disease despite a history of at least a 12-week regimen of oral azathioprine ( $\geq 2$  mg/kg/day) or 6-MP ( $\geq 1$  mg/kg/day), or MTX (25 mg subcutaneously [SC] or intramuscularly [IM] per week for induction and  $\geq 15$ mg IM per week for maintenance) OR
    - ii) History of intolerance to at least 1 immunomodulator including, but not limited to, serious infections, hepatotoxicity, cytopenia, pancreatitis, thiopurine methyltransferase (TPMT) genetic mutation, allergic reactions, or any other condition that contributed to discontinuation of the agent

#### **4.3.2. Exclusion Criteria, Cohort A ONLY**

Subjects who meet any of the following exclusion criteria are not to be enrolled in Cohort A Induction Study.

- 1) Prior use of any TNF $\alpha$  antagonist including (but not limited to) infliximab, adalimumab, golimumab, certolizumab, or biosimilar agents at any time
- 2) Prior or current use of vedolizumab at any time



#### 4.4. Cohort B (Biologic-experienced) Induction Study

##### 4.4.1. Inclusion Criteria, Cohort B ONLY

Subjects must meet all the additional following inclusion criteria to be eligible for participation in Cohort B Induction Study.

- 1) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least one of the following agents (depending on current country treatment recommendations/guidelines):
  - a) TNF $\alpha$  Antagonists
    - i) Active disease despite a history of at least one induction regimen of a TNF $\alpha$  Antagonist:
      - Infliximab: Minimum induction regimen of 5 mg/kg at 0, 2, and 6 weeks (in the EU, duration of treatment of 14 weeks)
      - Adalimumab: An 8-week induction regimen consisting of 160 mg (four 40-mg injections in 1 day or two 40-mg injections per day for 2 consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg and a 40 mg dose 2 weeks later (Day 29), followed by a 40 mg dose every other week until Week 8 (Day 57).
      - Golimumab: Minimum induction duration of 6 weeks (12 weeks in EU) is required for golimumab, which includes 200 mg SC injection at Week 0, followed by 100 mg at Week 2 and then 100 mg every 4 weeks. OR
    - ii) Recurrence of symptoms during maintenance therapy with the above agents, OR
    - iii) History of intolerance to any TNF $\alpha$  antagonists including, but not limited to, serious infections, hepatotoxicity, heart failure, allergic reactions, or any other condition that contributed to discontinuation of the agent
  - b) Vedolizumab
    - i) Active disease despite a history of at least a 14 week (10 weeks in EU) induction regimen of vedolizumab consisting of 300 mg IV at weeks 0, two, and six, OR
    - ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent
- 2) Must not have used any TNF $\alpha$  antagonist or vedolizumab  $\leq$  8 weeks prior to screening or any other biologic agent  $\leq$  8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer

#### 4.4.2. Exclusion Criteria Cohort B ONLY

Subjects who meet the following exclusion criterion are not eligible to be enrolled in Cohort B Induction Study.

- 1) Have used any TNF $\alpha$  antagonist or vedolizumab within  $\leq 8$  weeks prior to screening, or any other biologic agent  $\leq 8$  weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer

#### 4.5. Maintenance Study

##### 4.5.1. Inclusion Criteria

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

- 1) Completion of Cohort A or B induction study with MCS response or EBS remission based on Week 10 assessments
- 2) Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose
- 3) May be on oral corticosteroid therapy (prednisone prescribed at a stable dose  $\leq 30$  mg/day or budesonide at a dose of  $\leq 9$  mg/day); dose must remain stable to Week 14

##### 4.5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria are not to be enrolled in the Maintenance Study:

- 1) Males and Females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined by [Appendix 6](#)
- 2) Females who may wish to become pregnant and/or plan to undergo egg donation or egg harvesting for the purpose of current or future fertilization during the course of the study and up to 35 days after last dose of the study drug
- 3) Male subjects unwilling to refrain from sperm donation during the study and for at least 90 days after last dose of the study drug
- 4) Use of prohibited concomitant medications as described in Section [5.4.2](#).

## **5. INVESTIGATIONAL MEDICINAL PRODUCTS**

### **5.1. Randomization, Blinding and Treatment Codes**

#### **5.1.1. Procedures for Breaking Treatment Codes**

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the investigator may obtain treatment assignment directly from the interactive web response system (IWRS) for that subject. Gilead recommends but does not require that the investigator contact the Gilead 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 Gilead 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. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

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

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

#### **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 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 for oral administration, and PTM 200 mg and 100 mg filgotinib tablets for oral administration.

The following treatments will be evaluated:

- **Treatment 1:** filgotinib 200 mg and PTM filgotinib 100 mg, once daily
- **Treatment 2:** filgotinib 100 mg and PTM filgotinib 200 mg, once daily
- **Treatment 3:** PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Subjects who are non-responders based on Week 10 assessments will be offered the option to receive open-label filgotinib by entering into the LTE study (GS-US-418-3899). Subjects meeting disease worsening criteria at Week 11 or later must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib 200 mg, (See Section 3.6, Disease Worsening Criteria), except for US and Korea males who will be offered filgotinib 100 mg unless they have failed at least 2 other biologic therapies (any TNF $\alpha$  antagonist and vedolizumab). Subjects who complete the Week 58 visit will have the option to continue study drug in a blinded fashion in the LTE study.

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

#### **5.4. Prior and Concomitant Medications**

All medications taken up to 30 days prior to the screening visit through the end of study (30 days after the last dose of study drug), need to be recorded in the source documents and on the eCRF. At each study visit, the study center will record any and all 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 Gilead Medical Monitor should be consulted prior to initiation of the new medication. In instances where an excluded medication is initiated prior to discussion with the Sponsor, the Investigator should notify Gilead as soon as he/she is aware of the use of the excluded medication.

##### **5.4.1. Allowed Concomitant Medications**

The allowed concomitant medication(s) for UC must be maintained at a stable dose for the noted time without dosing alteration or discontinuation.

The allowed medications for UC are as follows:

- Oral 5-ASA compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization
- Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization
- Oral corticosteroid therapy (prednisone prescribed at a stable dose  $\leq$  30 mg/day or budesonide prescribed at a stable dose of  $\leq$  9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must be stable for the first 14 weeks after randomization

#### 5.4.2. Prohibited Concomitant Medications

The prohibited medications are as follows:

**Table 5-1. Prohibited Concomitant Medications**

Drug Class	Agents Disallowed	Prohibited Period
<b>Strong P-gp Inducers<sup>a</sup></b>		
Anticonvulsants	Phenobarbital, phenytoin, carbamazepine	30 days prior to screening through the end of the study
Antimycobacterials	Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort, danshen ( <i>Salvia Miltiorrhiza</i> )	
<b>Prohibited IBD Medications</b>		
Corticosteroids	Dose equivalent to > 30mg/day of prednisone	30 days prior to screening through the end of the study
TNF $\alpha$ antagonist	Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent	8 weeks prior to screening through the end of the study
Integrin antagonist	Vedolizumab and natalizumab	8 weeks prior to screening through the end of the study
Interleukin antagonist	Ustekinumab	12 weeks prior to screening through the end of the study
Rectal compounds	Rectal 5-ASA or rectal corticosteroids	2 weeks prior to screening through the end of the study
Antidiarrheal agents	Loperamide and diphenoxylate/atropine	2 weeks prior to screening through the end of the study
Other (non-biologic)	Cyclosporine, thalidomide, tacrolimus, leflunomide, and any investigational agent	30 days prior to screening through the end of the study
	Any JAK inhibitor	Any time before and through the end of the study
Investigational biologics	Any investigational biologic agent	8 weeks prior to screening through the end of the study (or at least 5 half-lives)
Lymphocyte-depleting therapies	Alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte depleting therapy	Any time before and through the end of the study
<b>Other Prohibited Medications</b>		
Chronic Nonsteroidal Anti-inflammatory Drugs (NSAIDs) <sup>b</sup>	Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, COX-2 inhibitors	From screening through the end of the study
Other biologics <sup>c</sup>	Antibody based or other systemic biologics, eg, denosumab, trastuzumab	Requires medical monitor consultation

a May decrease study drug exposure and are excluded to avoid potential reduction in study drug activity. PK results indicate filgotinib is a P-gp substrate, as a single dose of 200 mg itraconazole (a potent P-gp inhibitor) increased filgotinib C<sub>max</sub> by 64% and AUC<sub>inf</sub> by 45% and had no effect on the major, active metabolite GS-829845.

b Occasional use of NSAIDs for transient symptoms and daily use of aspirin up to 162.5 mg for the purpose of cardiovascular prophylaxis are permitted

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



### 5.4.3. Corticosteroid Tapering

Starting at Week 14, subjects who are on concomitant steroids must begin tapering steroid therapy. The dose should be reduced at a rate starting at 2.5 mg per week up to 5 mg per week (or equivalent taper if not prednisone) until subject is no longer on steroids. Subjects who are on budesonide should have their daily dose reduced by 3 mg every 3 weeks until they are completely off steroids. For subjects undergoing taper, steroids may be increased or restarted at doses up to and including their baseline dose if return of symptoms is apparent. These subjects will not be considered treatment failures. Subjects who need to restart or increase steroid treatment at a dose that exceeds their baseline dose of steroids (dose may not exceed 30 mg prednisone [or equivalent] or budesonide 9 mg/day) will be considered treatment failures for all clinical end points but will be permitted to remain in the study.

### 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

Based on protocol eligibility criteria, subjects will be screened for enrollment in *either* Cohort A or Cohort B.

Subjects who meet the protocol criteria will be assigned to the respective cohort and subsequently randomized in a blinded fashion in a 2:2:1 ratio to 1 of 3 treatments as follows:

- **Treatment 1 (n = 260):** filgotinib 200 mg and PTM filgotinib 100 mg, once daily
- **Treatment 2 (n = 260):** filgotinib 100 mg and PTM filgotinib 200 mg, once daily
- **Treatment 3 (n = 130):** PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

Note: US and Korea males who have not failed at least two biologic regimens (any TNF $\alpha$  antagonist and vedolizumab) will be randomized in a 2:1 ratio to either filgotinib 100 mg or matching placebo.

Within each Cohort, treatment assignments will be stratified according to the following factors in the Induction and Maintenance studies:

#### Stratification Factors (Cohort A, Biologic-Naïve Induction Study)

- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1 (Yes or No)

#### Stratification Factors (Cohort B, Biologic-Experienced Induction Study)

- Exposure to one biologic agent versus more than one biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1 (Yes or No)



### Stratification Factors (Maintenance Study)

- Participation in Cohort A or Cohort B
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1 (Yes or No)
- Concomitant use of immunomodulators (eg, 6-MP, azathioprine, MTX) at Day 1 (Yes or No)
- Refer to Section 3.3, Table 3-1 for re-randomization in the Maintenance Study

## 6.2. Pretreatment Assessments

### 6.2.1. Screening Visit

Subjects will be screened within 30 days before randomization to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent
  - Additional consent will be required from subjects participating in the PK substudy [REDACTED]
- Review inclusion/exclusion criteria and other protocol restrictions (Section 4)
- Obtain medical history, including UC disease and treatment history
- Complete physical examination (PE) including vital signs, body weight and height
- Perform 12-lead ECG
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.
- Instruct subjects to maintain concomitant medication at a stable dose
- Provide subject with the electronic diary (e-Diary) and instructions for daily documentation of stool frequency and rectal bleeding. **Subjects should be counseled to enter the Normal Stool Count (NSC) as the stool count the subject experiences when disease free (eg, in remission). If the subject has never been in remission, the subject should enter in normal stool count when healthy (eg, prior to diagnosis).**
- Conduct phone call approximately 4 days after screening visit to encourage compliance with daily documentation of stool frequency and rectal bleeding

- If warranted, based on the review of compliance and average scores from the subject e-Diary reports for rectal bleeding and stool frequency, perform flexible sigmoidoscopy/colonoscopy and biopsy during screening. If a colonoscopy is performed, flexible sigmoidoscopy is not required. **Subject diary data and lab results should be reviewed to ensure eligibility is met prior to scheduling endoscopy. Endoscopy should not be performed unless subject has met eligibility criteria for stool frequency and rectal bleeding.**
  - Record investigator endoscopic value
- Subjects will need a full colonoscopy only if the investigator chooses to do so for disease management
- Four biopsy samples will be collected. These biopsies will be sent to central laboratory for storage and then to specialty laboratories for subsequent analysis.
- Collect the variables to calculate complete MCS (reference [Appendix 4](#))
  - Site collects patient assessments at each visit
  - MCS calculated centrally after all components have been captured electronically
- TB Assessment– Must have negative QuantiFERON® test (or centrally reported equivalent assay) during screening, and negative chest x-ray within 3 months of or during screening for those with no evidence or history of TB. Positive or negative results must not be repeated. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Two sequential indeterminate results constitute a screen failure. Subjects with previously treated or latent TB require sponsor approval (See inclusion criterion 8 for details). Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Gilead medical monitor.
- Obtain blood samples (reference Study Procedure Table in [Appendix 2](#))
  - **HCV Screening Guidelines**
    - Subjects with positive HCV antibody at Screening require reflex testing for HCV RNA. Subjects with HCV RNA  $\geq$  lower limit of quantification (LLOQ) at Screening will be excluded. Subjects with positive HCV antibody but HCV RNA  $<$  LLOQ are eligible.
  - **HBV Screening and Surveillance Guidelines**
    - Subjects with positive HBV surface antigen (HBsAg) at Screening are excluded.
    - Subjects who are positive for HBV surface antibody (HBsAb), but negative for both HBsAg and HBV core antibody (HBcAb) at Screening are eligible.

- Subjects with positive HBcAb require reflex testing for HBV DNA. Subjects with HBV DNA  $\geq$  LLOQ at Screening will be excluded. Subjects with positive HBcAb and HBV DNA  $<$  LLOQ are eligible, but will require ongoing HBV DNA monitoring every 3 months during this study. These subjects may 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 will require reflex testing for HBV DNA at Screening. Subjects with positive HBcAb and/or HBsAb but with HBV DNA  $<$  LLOQ at Screening are eligible for the study. These subjects will require ongoing HBV DNA monitoring every 4 weeks in accordance with local guidelines during this study.
- Any subject who has HBV DNA  $\geq$  LLOQ during the study will be discontinued (reference Section 3.5.2).

— **HIV Screening Guidelines**

- Subjects who have HIV infection, regardless of virologic status, are excluded from the study.
- Obtain blood sample for serum pregnancy test (for females of childbearing potential only)
- Obtain stool sample (reference Study Procedure Table in [Appendix 2](#))
  - A stool sample will be obtained for culture for pathogenic bacteria, ova and parasite evaluation, and *C. difficile* toxin assay during screening for the purposes of determining eligibility.
- Obtain urine sample (reference Study Procedure Table in [Appendix 2](#))
- Obtain urine sample for urine drug screen (reference Study Procedure Table in [Appendix 2](#))

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


Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for randomization into the study. Subjects may be randomized more than 30 days after initial screening if they receive permission from the Gilead Medical Monitor. If the subject does not begin the treatment within this 30-day window, specific screening evaluation procedures may need to be repeated at the direction of the Gilead Medical Monitor. No more than one repeat screening visit is allowed for each subject, unless prior written approval has been provided by the Sponsor.



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

### 6.2.2. Day 1

The following tests and procedures must be completed prior to randomization and dosing/dispensing:

- Review inclusion/exclusion criteria and other protocol restrictions
- Symptom directed PE including body weight
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Review AEs and concomitant medications
- Review e-Diary reports for compliance and scores – remind subjects of diary instructions at every visit
- Collect the variables to calculate partial MCS (see [Appendix 4](#))
  - Site collects patient assessments at each visit
  - MCS calculated centrally after all components have been captured electronically
- Have subject complete HRQoL questionnaires
- Administer HCRU questionnaire
- Obtain fasting blood samples (reference Study Procedure Table in [Appendix 2](#))
- Obtain blood sample for vFPBMC and leukocyte subsets (US and Canadian sites only)
- 
- Obtain urine sample (reference Study Procedure Table in [Appendix 2](#))
  - Sample will be used for urinalysis and pregnancy test (for females of childbearing potential only)

### **6.3. Randomization**

Please refer to Section 6.1.

#### **6.3.1. Randomization and Study Drug Administration**

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

### **6.4. Study Assessments**

#### **6.4.1. Priority of Assessments**

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

#### **6.4.2. Efficacy**

Efficacy assessments will be performed at the time points indicated in the Study Procedures Table ([Appendix 2](#)).

##### **6.4.2.1. Mayo Clinic Score (MCS)**

Mayo Scoring system for assessment of ulcerative colitis activity. Refer to [Appendix 4](#).

##### **6.4.2.2. 36-Item Short Form Healthy Survey**

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

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

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

#### 6.4.2.3. Work Productivity and Activity Impairment Questionnaire (WPAI)

The WPAI is designed to measure the effect of general health and symptom severity on work productivity and regular activities during the past seven days.

#### 6.4.2.4. EQ-5D

The EQ-5D is a standardized instrument developed by the EuroQol Group as a measure of health-related quality of life that can be used in a wide range of health conditions and treatments.

#### 6.4.2.5. IBDQ

This disease-specific questionnaire comprises 32 questions divided into four health subscales: bowel symptoms (10 questions); systemic symptoms, including sleep disorders and fatigue (5 questions); emotional function such as depression, aggression and irritation (12 questions); and social function, meaning the ability to participate in social activities and to work (5 questions).

### 6.4.3. Safety

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

#### 6.4.3.1. Clinical Laboratory Evaluations

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

Blood samples will be collected by venipuncture (or optional indwelling catheter for PK sampling days) in the arm at the time points indicated in the Study Procedures Table ([Appendix 2](#)). In addition, urine samples for the clinical laboratory assessments will be collected. An overnight fast (no food or drinks, except water) of at least 8 hours will be required prior to collection of blood samples for lipid testing.

A stool sample should also be collected at any time during the study for culture for pathogenic bacteria, ova and parasites, and *C. diff* toxin assay when a subject becomes symptomatic, including worsening or return of disease activity.

Refer to [Appendix 7](#) for table of clinical laboratory tests.

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



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

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

#### 6.4.3.2. Pregnancy Testing (for females of childbearing potential)

All females meeting the childbearing potential criteria must have a serum pregnancy testing at screening and an in-clinic urine pregnancy test must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic that will be centrally reported.

#### 6.4.3.3. Vital Signs

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

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

#### 6.4.3.4. Physical Examination

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

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

#### 6.4.3.5. 12-lead Electrocardiogram

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

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

#### 6.4.4. Pharmacokinetics Assessments

The PK sample at Week 4 is collected post-dose (at least 30 minutes and up to 3 hours after study drug dosing). For this visit, it is preferred that study drug dosing is done in clinic. The PK sample at Weeks 26 can be collected at any time without regard to dosing. The PK sample at Weeks 10 and 58 are collected at pre-dose (within 2 hours prior to dosing).

Subjects who consent to the optional PK substudy will have additional plasma PK samples at any single visit from Week 2 to Week 10, collected pre-dose, and at 0.5, 1, 2, 3, 4 and 6 hours after supervised dosing in the clinic. If a sub-study PK sample is scheduled to be collected at the same time as a sparse PK sample, only one sample should be collected.

For all visits with PK sampling, the time of dose taken prior to and on the day of visit will be noted in the eCRF. Plasma concentrations of filgotinib and its metabolite (GS-829845) will be analyzed.

#### 6.4.5. Biomarker Assessments

Blood samples will be collected on Day 1 and at Weeks 4, 10, 26, and 58.

Blood samples may be analyzed for assessment of markers of inflammation, immune status, and JAK-STAT pathway activation.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

#### 6.5. Post-Treatment Assessments

All subjects must complete the PTx assessments 30 days after the last dose of study drug. Subjects who enter into the LTE study (GS-US-418-3899) will not complete PTx assessments associated with this protocol.

The following will be performed and documented:

- Symptom directed PE
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Review AEs and concomitant medications

- Obtain blood samples (reference Study Procedure Table in [Appendix 2](#))
- Obtain urine sample (reference Study Procedures Table [[Appendix 2](#)])
  - Pregnancy test (for females of child bearing potential only)

#### **6.6. Early Termination Assessments**

The following will be performed and documented:

- Symptom directed PE
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Perform 12-Lead ECG (for subjects who terminate prior to Week 10)
- Review AEs and concomitant medications
- Collect e-Diary back from subject
- Collect the variables to calculate partial MCS (see [Appendix 4](#))
  - Site collects patient assessments at each visit
  - MCS calculated centrally after all components have been captured electronically
- Obtain fasting blood samples (reference Study Procedure Table in [Appendix 2](#))
- Obtain urine sample (reference Study Procedures Table [[Appendix 2](#)])
  - Pregnancy test (for females of child bearing potential only)

#### **6.7. End of Study**

Please refer to Section [3.7](#).

#### **6.8. Post Study Care**

Please refer to Section [3.8](#).



## 7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

#### 7.1.1. Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. 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 medicinal product will be considered a medically important event and subject to expedited reporting requirements.

## **7.2. Assessment of Adverse Events and Serious Adverse Events**

The investigator or qualified 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 Gilead**

Requirements for collection prior to study drug initiation:

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

#### **7.3.1. Adverse Events**

Following initiation of study medication, all AEs, regardless of cause or relationship, until 30 days after last administration of study IMP must be reported to the eCRF database as instructed.

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

#### **7.3.2. Serious Adverse Events**

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



Any SAEs and deaths that occur after the post treatment follow-up visit but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period. However, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead PVE.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- At the time of study start, SAEs may be reported using a paper serious adverse event reporting form. During the study conduct, sites may transition to an electronic SAE (eSAE) system. Gilead will notify sites in writing and provide training and account information prior to implementing an eSAE system.

#### Electronic Serious Adverse Event Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead PVE within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.
- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours as described above.

**Gilead Sciences PVE**

**Fax:**  
**E-mail:**

PPD  
PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.
- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

#### 7.4. Gilead Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the 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.

To minimize the possibility of exposing study subjects to unusual risk, the safety information from this study will also be reviewed periodically by an independent DMC (as described in Section 8.10). The DMC may have access to partially blinded or unblinded data and will make recommendations regarding the study according to the DMC charter.

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

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, ECG, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (ie, anemia) not the laboratory result (ie, decreased hemoglobin).

Severity should be recorded and graded according to the CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 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 supercede below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The Gilead 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  $\leq$  Grade 2.
- If a laboratory abnormality recurs to  $\geq$  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 Gilead Medical Monitor, who will have a discussion with the investigator and decide the appropriate course of action. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

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



## **7.7. Special Situations Reports**

### **7.7.1. Definitions of Special Situations**

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

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

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

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

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

Occupational exposure with an AE is defined as exposure to medicinal product as result of one's professional or non-professional occupation.

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

### **7.7.2. Instructions for Reporting Special Situations**

#### **7.7.2.1. Instructions for Reporting Pregnancies**

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

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

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

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

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

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

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

Refer to [Appendix 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 Gilead PVE within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

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

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

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

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

## 8. STATISTICAL CONSIDERATIONS

### 8.1. Analysis Objectives and Endpoints

Unless otherwise specified, all the efficacy endpoints based on MCS will utilize the central read endoscopic subscore. The local read endoscopic subscore will be utilized into the sensitivity analysis with details being included in the statistical analysis plan (SAP).

#### 8.1.1. Analysis Objectives

##### Cohort A Induction Study

The primary objective of Cohort A is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 10

The key secondary objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10

The other secondary objectives of Cohort A are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome



- To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

### **Cohort B Induction Study**

The primary objective of Cohort B is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 10

The key secondary objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 10

The other secondary objectives of Cohort B are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in improving endoscopic appearance as determined by UCEIS scoring system at Week 10
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome

- To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

### **Maintenance Study**

The primary objective of the Maintenance Study is:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing EBS remission at Week 58

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained EBS remission at Week 58, defined as EBS remission at both Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free EBS remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing an endoscopic subscore of 0 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing Geboes histologic remission at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing MCS remission (alternative definition) at Week 58

The other secondary objectives of the Maintenance Study are:

- To evaluate the safety and tolerability of filgotinib
- To assess the PK characteristics of filgotinib

The exploratory objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib in improving endoscopic appearance as determined by UCEIS scoring system at Week 58

- To evaluate the efficacy of filgotinib in establishing sustained MCS remission at Week 58, defined as MCS remission at both Weeks 10 and 58
- To evaluate the efficacy of filgotinib in establishing 6-month corticosteroid-free MCS remission at Week 58
- To evaluate the association of changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- To evaluate stool microbiome
- To characterize the association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- To evaluate HRQoL
- To evaluate the effect of filgotinib on HCRU
- To evaluate the efficacy of filgotinib as compared to placebo in achieving novel histologic outcomes (eg, resolution of basal plasmacytosis)

#### 8.1.2. Primary Endpoint

##### Cohort A Induction Study

- The proportion of subjects achieving EBS remission at Week 10

##### Cohort B Induction Study

- The proportion of subjects achieving EBS remission at Week 10

##### Maintenance Study

- The proportion of subjects achieving EBS remission at Week 58

#### 8.1.3. Secondary Endpoint

##### Cohort A Induction Study

The key secondary endpoints of Cohort A are:

- The proportion of subjects achieving MCS remission at Week 10
- The proportion of subjects achieving endoscopic subscore of 0 at Week 10
- The proportion of subjects achieving Geboes histologic remission at Week 10
- The proportion of subjects achieving MCS remission (alternative definition) at Week 10



The other secondary endpoint of Cohort A is:

- PK characteristics for filgotinib and its metabolite GS-829845

#### **Cohort B Induction Study**

The key secondary endpoints of Cohort B are:

- The proportion of subjects achieving MCS remission at Week 10
- The proportion of subjects achieving endoscopic subscore of 0 at Week 10
- The proportion of subjects achieving Geboes histologic remission at Week 10
- The proportion of subjects achieving MCS remission (alternative definition) at Week 10

The other secondary endpoint of Cohort B is:

- PK characteristics for filgotinib and its metabolite GS-829845

#### **Maintenance Study**

The key secondary endpoints of the Maintenance Study are:

- The proportion of subjects achieving MCS remission at Week 58
- The proportion of subjects achieving sustained EBS remission, defined as establishing EBS remission at both Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free EBS remission at Week 58
- The proportion of subjects achieving endoscopic subscore of 0 at Week 58
- The proportion of subjects achieving Geboes histologic remission at Week 58
- The proportion of subjects achieving MCS remission (alternative definition) at Week 58

The other secondary endpoint of the Maintenance Study is:

- PK characteristics for filgotinib and its metabolite GS-829845

#### **8.1.4. Exploratory Endpoints:**

##### **Cohort A Induction Study**

The exploratory endpoints for Cohort A are:

- Change from baseline in UCEIS at Week 10

- Association between changes in systemic or localized inflammatory biomarkers (eg including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- Change from baseline in HRQoL scores at Week 10
- HCRU assessments at Week 10
- The proportion of subjects achieving novel histologic outcomes at Week 10

#### **Cohort B Induction Study**

The exploratory endpoints for Cohort B are:

- Change from baseline in UCEIS at Week 10
- Association between changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- Change from baseline in HRQoL scores at Week 10
- HCRU assessments at Week 10
- The proportion of subjects achieving novel histologic outcomes at Week 10

#### **Maintenance Study**

The exploratory endpoints for the Maintenance study are:

- Change from baseline in UCEIS at Week 58
- The proportion of subjects achieving sustained MCS remission, defined as MCS remission at both Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free MCS remission at Week 58

- Association between changes in systemic or localized inflammatory biomarkers (eg, including but not limited to CRP, fecal calprotectin, fecal lactoferrin, and fecal MMP-9) with clinical outcomes
- Stool microbiome assessments
- Association of host genetics and other markers with disease severity, disease progression, and treatment response to filgotinib
- Change from baseline in HRQoL scores at Week 58
- HCRU assessments at Week 58
- The proportion of subjects achieving novel histologic outcomes at Week 58

## 8.2. Analysis Conventions

### 8.2.1. Analysis Sets

#### 8.2.1.1. Efficacy

The primary analysis set for efficacy is the Full Analysis Set (FAS).

- The FAS for each Induction Study (Cohorts A and B) includes all randomized subjects who received at least one dose of study drug in the corresponding Induction Study (Day 1 to Week 10).
- The FAS for Maintenance Study includes all re-randomized subjects who met the protocol definition of EBS remission or MCS response at Week 10, and received at least one dose of study drug in the Maintenance Study (Weeks 11 to 58).

Subjects will be analyzed according to the treatment group they were randomized to for the analysis period.

#### 8.2.1.2. Safety

The primary analysis set for safety is the Safety Analysis Set.

- The Safety Analysis Set for each Induction Study (Cohorts A and B) includes all subjects who received at least one dose of study drug in the corresponding Induction Study (Day 1 to Week 10).
- The Safety Analysis Set for the Maintenance Study includes all subjects who receive at least one dose of study drug in the Maintenance Study (Weeks 11 to 58).
- The Overall Safety Analysis Set for the study includes all subjects who received at least one dose of study drug from Day 1 to Week 58.

Subjects will be analyzed according to the study drug they actually received for the analysis period.



### 8.2.1.3. Pharmacokinetics

#### 8.2.1.3.1. Pharmacokinetic Substudy Analysis Set

The primary analysis set for intensive PK analyses will be the PK substudy analysis set for each Induction Study (Cohorts A and B), which includes all subjects in the Safety Analysis Set from the corresponding Induction Study who have enrolled into the PK substudy, and have intensive concentration data to provide interpretable results for the specific parameters of interest for the analyte under evaluation.

#### 8.2.1.3.2. Pharmacokinetic Analysis Set

The primary analysis set for general PK analyses will be defined separately for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study). For each study, the PK analysis set includes all subjects in the corresponding Safety Analysis Set who have at least one nonmissing plasma concentration data for filgotinib and/or its metabolite GS-829845.

#### 8.2.1.4. Biomarker Analysis Set

The Biomarker Analysis Set will be defined separately for each individual study (Cohort A Induction Study, Cohort B Induction Study and Maintenance Study). For each study, the Biomarker Analysis Set includes all subjects in the corresponding Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

### 8.3. Data Handling Conventions

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

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

PK concentration values and PK parameter values below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listings. BLQ values that occur prior to the first dose will be treated as 0, BLQ values at all other time points will be treated as 1/2 of the lower limit of quantitation (LLOQ).

Laboratory data that are continuous in nature but are less than the 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).

Procedures for handling missing data for MCS (and components) will be described in the SAP.

#### 8.4. Demographic Data and Baseline Characteristics

Demographic and baseline measurements for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study) will be summarized separately by treatment group using standard descriptive statistics (n, mean, standard deviation [SD], median, 1<sup>st</sup> quartile [Q1], 3<sup>rd</sup> 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), MCS, number of years since UC diagnosed, concomitant use of oral corticosteroids, concomitant use of immunomodulators, fecal calprotectin, serum CRP, and other variables of interest.

#### 8.5. Efficacy Analysis

##### 8.5.1. Primary Analysis

For each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study), the primary analysis will compare each filgotinib dose group to placebo on the proportion of subjects achieving EBS remission at Week 10 (Induction Studies, Cohort A and B) and at Week 58 (Maintenance Study), respectively. The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of the primary endpoint within each study. See Section 8.5.3 for the significant level that will be used to declare a statistical significant treatment effect for each filgotinib dose group when compared to placebo for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study). For evaluation of EBS remission at Weeks 10 and 58, MCS score at screening will be used as baseline value.

Subjects who do not have sufficient measurements to determine efficacy endpoints will be considered failures (ie, non-responder imputation [NRI]). Sensitivity analyses will be described in the SAP.

##### 8.5.2. Secondary Analyses

The same statistical methods used for testing the primary efficacy endpoint will be utilized for testing the key secondary endpoints in each study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study) separately. Subjects who do not have sufficient measurements to determine the efficacy endpoints will be considered failures (ie, NRI).

##### 8.5.3. Multiplicity Adjustments

The graphical approach {Bretz 2009} to sequentially rejective multiple test procedures will be used to control a family-wise type I error rate (FWER) at 5% (ie,  $\alpha = 0.05$ ) for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study). This procedure strongly protects the FWER on all the primary and key secondary endpoints.

### **Induction Studies (Cohorts A and B)**

For each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study), a Bonferroni approach with equal alpha allocation of 0.025 (2-sided) to each filgotinib dose group comparison with placebo will be used to control the overall study-wide type I error rate at 0.05 within each study. To protect the integrity of the study due to the unblinded interim futility analysis planned for each induction study (Cohort A and Cohort B) (details in Section 8.10), an alpha of 0.00001 will be spent for each filgotinib dose group comparison to placebo within each induction study. As a result, a nominal p-value of less than 0.02499 (2-sided) will be needed to declare statistical significance for the final primary analysis of each filgotinib dose group when compared to placebo to control the study-wise type I error rate at 0.05. If one filgotinib dose group is discontinued for futility at the interim futility analysis, the overall alpha error rate stays unchanged at a 2-sided 0.02499 level for the continuing filgotinib dose group at the primary analysis.

The hypotheses to be tested for the induction studies are outlined below.

The primary null hypotheses to be tested:

- H1: The EBS remission rate in the filgotinib 200 mg group is equal to the EBS remission rate in the placebo group at Week 10
- H2: The EBS remission rate in the filgotinib 100 mg group is equal to the EBS remission rate in the placebo group at Week 10

The key secondary null hypotheses to be tested:

- H3: The MCS remission rate in the filgotinib 200 mg group is equal to the MCS remission rate in the placebo group at Week 10
- H4: The MCS remission rate in the filgotinib 100 mg group is equal to the MCS remission rate in the placebo group at Week 10
- H5: The endoscopic subscore of 0 rate in the filgotinib 200 mg group is equal to the endoscopic subscore of 0 rate in the placebo group at Week 10
- H6: The endoscopic subscore of 0 rate in the filgotinib 100 mg group is equal to the endoscopic subscore of 0 rate in the placebo group at Week 10
- H7: The Geboes histologic remission rate in the filgotinib 200 mg group is equal to the Geboes histologic remission rate in the placebo group at Week 10
- H8: The Geboes histologic remission rate in the filgotinib 100 mg group is equal to the Geboes histologic remission rate in the placebo group at Week 10

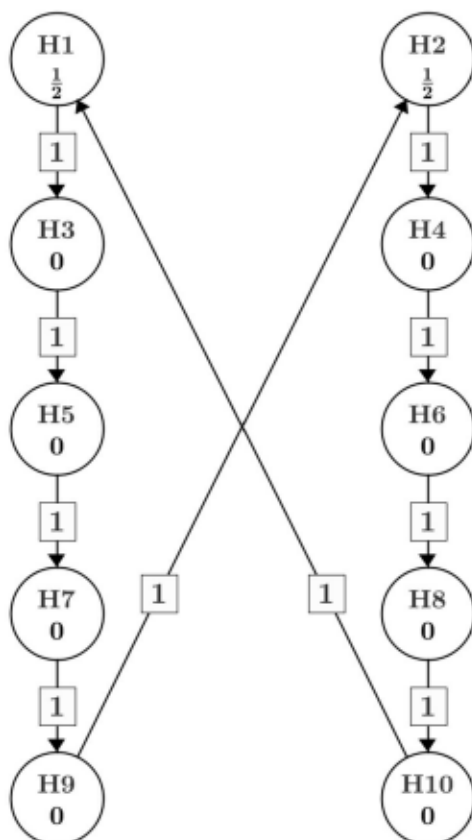


- H9: The MCS remission (alternative definition) rate in the filgotinib 200 mg group is equal to the MCS remission (alternative definition) rate in the placebo group at Week 10
- H10: The MCS remission (alternative definition) rate in the filgotinib 100 mg group is equal to the MCS remission (alternative definition) rate in the placebo group at Week 10

If the primary null hypothesis is rejected, then the next key secondary hypothesis in the same filgotinib dosing regimen will be tested at the same alpha level. Testing of the hypotheses will be performed in the order outlined in [Figure 8-1](#) (Induction Studies) in the same filgotinib dosing regimen. Once all hypotheses within the same filgotinib dosing regimen are rejected, then the respective 0.02499 alpha can be passed on to the other regimen's hypotheses, that is, all hypotheses in the other filgotinib dosing regimen will be tested at 0.04998 (2-sided) for Induction Studies. If an endpoint within a filgotinib dosing regimen fails to reach statistical significance, then formal sequential testing will stop and only nominal significance will be reported for the remaining endpoints within that filgotinib dosing regimen. If not all primary and key secondary hypotheses within the same filgotinib dosing regimen can be rejected, all hypotheses in the other filgotinib dosing regimen will still be tested at 0.02499 (2-sided) for Induction Studies.

A graphical illustration of the testing strategy for the primary and key secondary hypotheses in the Induction Studies is shown in [Figure 8-1](#).

**Figure 8-1. Induction Studies (Cohorts A and B): Testing Strategy for the Primary and Key Secondary Hypotheses**



### Maintenance Study

Since there is no interim analysis planned for the maintenance study, the significance level for the final primary analysis will be at 0.025 (2-sided) level for each filgotinib dose group when compared to placebo for the maintenance study.

The hypotheses to be tested for the maintenance study are outlined below.

The primary null hypotheses to be tested:

- H1: The EBS remission rate in the filgotinib 200 mg group is equal to the EBS remission rate in the placebo group at Week 58
- H2: The EBS remission rate in the filgotinib 100 mg group is equal to the EBS remission rate in the placebo group at Week 58

The key secondary null hypotheses to be tested:

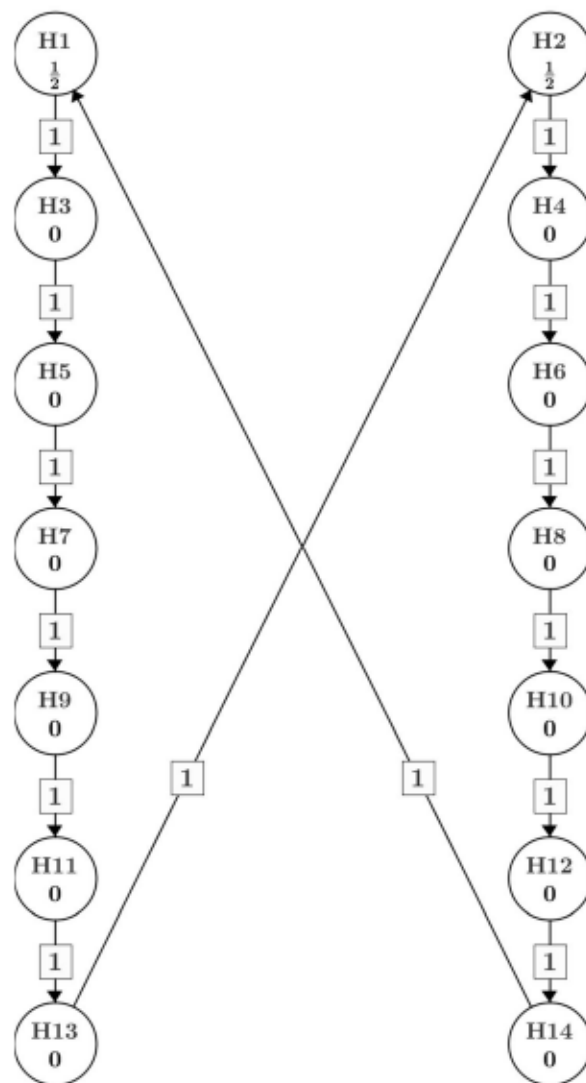
- H3: The 6-month corticosteroid-free EBS remission rate in the filgotinib 200 mg group is equal to the 6-month corticosteroid-free EBS remission rate in the placebo group at Week 58
- H4: The 6-month corticosteroid-free EBS remission rate in the filgotinib 100 mg group is equal to the 6-month corticosteroid-free EBS remission rate in the placebo group at Week 58
- H5: The sustained EBS remission rate in the filgotinib 200 mg group is equal to the sustained EBS remission rate in the placebo group at Week 58
- H6: The sustained EBS remission rate in the filgotinib 100 mg group is equal to the sustained EBS remission rate in the placebo group at Week 58
- H7: The MCS remission rate in the filgotinib 200 mg group is equal to the MCS remission rate in the placebo group at Week 58
- H8: The MCS remission rate in the filgotinib 100 mg group is equal to the MCS remission rate in the placebo group at Week 58
- H9: The endoscopic subscore of 0 rate in the filgotinib 200 mg group is equal to the endoscopic subscore of 0 rate in the placebo group at Week 58
- H10: The endoscopic subscore of 0 rate in the filgotinib 100 mg group is equal to the endoscopic subscore of 0 rate in the placebo group at Week 58
- H11: The Geboes histologic remission rate in the filgotinib 200 mg group is equal to the Geboes histologic remission rate in the placebo group at Week 58
- H12: The Geboes histologic remission rate in the filgotinib 100 mg group is equal to the Geboes histologic remission rate in the placebo group at Week 58
- H13: The MCS remission (alternative definition) rate in the filgotinib 200 mg group is equal to the MCS remission (alternative definition) rate in the placebo group at Week 58
- H14: The MCS remission (alternative definition) rate in the filgotinib 100 mg group is equal to the MCS remission (alternative definition) rate in the placebo group at Week 58

The same approach described for Induction Studies will be applied to the Maintenance Study at the alpha level of 0.025 (2-sided) for each filgotinib dose group when compared to placebo.

Graphical illustrations for the testing strategies for the primary and key secondary hypotheses in the Maintenance Study are shown in [Figure 8-2](#).



**Figure 8-2. Maintenance Study: Testing Strategy for the Primary and Key Secondary Hypotheses**



#### 8.5.4. Exploratory Analyses

The same statistical methods used for analyzing the primary endpoint will be utilized for analyzing the exploratory endpoints for proportions in each study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study) separately. The difference in proportions between each filgotinib dose group and placebo, along with the corresponding 95% 2-sided confidence interval (CI), will be provided.

Difference of mean change from baseline between each filgotinib dose group and placebo for continuous variables will be tested using an analysis of variance (ANOVA) model adjusting for stratification factors. Last Observation Carried Forward (LOCF) approach will be used to impute the missing values. Detailed analyses will be provided in the SAP.

## 8.6. Safety Analysis

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

### **Induction Studies (Cohorts A and B)**

All safety data collected on or after the first dose of study drug administration for each Induction Study (Day 1) up to:

- 30 days after last dose date, for subjects who prematurely discontinued study drug prior to or at Week 10 OR
- Week 10, for subjects who completed Week 10 dosing and continued on study drug will be summarized by treatment group according to the study drug received.

### **Maintenance Study**

All safety data collected on or after the first dose of study drug administration for the Maintenance study (Week 11) up to 30 days after permanent discontinuation of study drug will be summarized by treatment group according to the study drug received.

### **Overall (Induction and Maintenance)**

All safety data collected on or after the first dose of study drug administration for the entire study (Day 1) up to 30 days after permanent discontinuation of study drug will be summarized by treatment group according to the study drug received.

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

#### 8.6.1. Extent of Exposure

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

#### 8.6.2. Adverse Events

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

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

### **Induction Studies (Cohorts A and B)**

- Any AEs with an onset date of on or after the study drug start date for each Induction study (Day 1) and prior to:
  - 30 days after last dose date, for subjects who prematurely discontinued study drug prior to or at Week 10 OR

- Week 10, for subjects who completed Week 10 dosing and continued on study drug
- Any AEs leading to premature discontinuation of study drug prior to Week 10.

### **Maintenance Study**

- Any AEs with an onset date of on or after the study drug start date for the Maintenance study (Week 11) and up to 30 days after permanent discontinuation of study drug.
- Any AEs leading to premature discontinuation of study drug after first dose of study drug administration for the Maintenance study (Week 11).

### **Overall (Induction and Maintenance)**

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

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

#### **8.6.3. Laboratory Evaluations**

Select 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 in [Appendix 5](#).

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

#### **8.6.4. Other Safety Evaluations**

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



## 8.7. Pharmacokinetic Analysis

For each individual study (Cohort A Induction Study, Cohort B Induction Study and Maintenance Study), plasma concentrations of filgotinib and its metabolite GS-829845 will be listed and summarized by treatment group using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). Plasma concentrations over time may also be plotted in semi-logarithmic and linear formats as mean  $\pm$  SD and median (Q1, Q3).

For subjects enrolled in the optional PK substudy, pharmacokinetic parameters of filgotinib and its metabolite GS-829845 will be listed and summarized by treatment; and plasma concentrations of the filgotinib and GS-829845 over time will be plotted in semi logarithmic and linear formats as mean  $\pm$  SD and median (Q1, Q3) by treatment.

Exposure-response relationships for efficacy and safety may also be evaluated.

## 8.8. Biomarker Analysis

For each individual study (Cohort A Induction Study, Cohort B Induction Study and Maintenance Study), descriptive statistics of baseline and change in biomarkers will be provided at each sampling time by treatment. To evaluate treatment effect, a mixed-effect analysis of variance model will be used to calculate a point estimate and 2-sided 95% CI for the mean percent change from baseline in biomarker level for each treatment group at individual time points. The estimate and 95% CI of difference in mean percent change from baseline between each filgotinib dose group and placebo will be provided as well.

Exploratory analyses will also be performed to evaluate the association of individual biomarkers, including the systemic or localized inflammatory biomarkers, or combination of biomarkers with clinical outcomes.

Additional exploratory analyses may be described in the Biomarker Analysis Plan (BAP) if necessary.

## 8.9. Sample Size

### 8.9.1. Induction Studies (Cohorts A and B)

The sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at Week 10 could be detected when comparing filgotinib to placebo within each Induction Study.

A sample size of 130 subjects in the placebo group and 260 subjects in each filgotinib dose group (n = 650 total per cohort) will provide 90% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in EBS remission rate of 15% (25% on filgotinib and 10% on placebo).

### 8.9.2. Maintenance Study

Assuming an induction response rate (ie, proportion of subjects achieving EBS remission or MCS response at Week 10) of 55% among subjects receiving filgotinib 200 mg or filgotinib 100 mg treatment, approximately 285 subjects from each filgotinib dose group from Cohorts A and B Induction Studies combined would be eligible to be re-randomized into the Maintenance Study.

The sample size was chosen to ensure that a clinically meaningful difference in EBS remission rate at Week 58 could be detected when comparing each filgotinib dose group (200 mg or 100 mg) to placebo in the Maintenance Study. A sample size of 95 subjects in the placebo group and 190 subjects in the filgotinib group at the same dose level as the induction dose will provide more than 85% power for each filgotinib dose group comparison to placebo at a 2-sided 0.025 significance level to detect a treatment difference in maintenance EBS remission rate of 20% (40% on filgotinib and 20% on placebo).

### 8.10. Data Monitoring Committee

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

The initial meeting for each induction study will occur after approximately 100 subjects (20 from placebo group and 40 from each filgotinib group) reach Week 10.

The second meeting for each induction study will include an interim futility analysis and occur after approximately 175 subjects (35 from placebo group and 70 from each filgotinib treatment group) reach Week 10. The futility analysis will be conducted to evaluate endoscopic efficacy and overall safety. The proportion of subjects who achieve endoscopic response (endoscopic subscore of 0 or 1) for each treatment group will be evaluated. The DMC may recommend to terminate a filgotinib dose group if the observed proportion of subjects who achieve endoscopic response in the filgotinib group is lower than that in the placebo group. If both filgotinib dose groups meet the futility criteria, the DMC may recommend stopping the study.

After the futility analyses, DMC meetings for safety review will be held approximately once every 4 months or at a frequency determined by the DMC.

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

While the DMC will be asked to advise Gilead regarding future conduct of the study, including possible early study termination, Gilead retains final decision-making authority on all aspects of the study.

### **Cohorts A and B End-of-Induction Analysis**

Efficacy and safety data will be evaluated by DMC after *all* subjects in both cohorts complete Week 10 dosing (or prematurely discontinue study drug but complete post-treatment assessments).

Both cohorts will be examined independently.

- Taking into account data in Cohort A and Cohort B, if both filgotinib dose groups (200 mg and 100 mg) in both cohorts (independently examined) fail to reach statistical significance compared to placebo on EBS remission, the DMC may recommend overall study discontinuation.
- If the above condition above is not met, the DMC may recommend that the study continue without modification.

### **Ad-hoc DMC Meetings**

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

- $\geq 2$  subjects develop the same (by preferred term) related, Grade 4, unexpected adverse event (AE) in the infections and infestations system organ class
- Any subject develops a Grade 5, related, unexpected AE. The definition of an unexpected AE will be based on the Reference Safety Information that is on file at the time the event occurs.

### **8.11. End of Induction Interim Analysis**

After all subjects from Cohorts A and B have completed the Week 10 visit or have terminated prior to Week 10 and corresponding data entry is complete, an End of Induction safety and efficacy analysis will be performed including cumulative safety analysis that has been provided for DMC safety review and analyses on primary endpoint and key secondary endpoints as well endoscopic response and MCS response.

In parallel with DMC review, a prespecified sponsor's executive team will review the unblinded group level safety analysis results and group level efficacy analysis results from the Induction Studies for the purpose of sponsor decision making and future development planning. Members of the Study Management Team with direct involvement in the conduct of the study will not have access to the unblinded results from the induction studies.

The unblinded End of Induction analysis results of Study GS-US-418-3898 will not be shared externally with the exception of Health Authority or DMC requests for information, until after the Week 58 database lock is completed and the study is unblinded.

Follow up actions may be taken based on the data from this analysis including study design change, with communication with regulatory authorities, if indicated.

Further details will be specified in the SAP and an Interim Analysis Communication Plan.



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

#### **9.1.2. Institutional Review Board/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. The consent form will inform subjects about genomic testing and sample retention.

#### **9.1.4. Confidentiality**

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

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

#### **9.1.5. Study Files and Retention of Records**

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

The investigator's study file will contain the protocol/amendments, 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 Gilead. The investigator must notify Gilead before destroying any clinical study records.

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

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

#### **9.1.6. Case Report Forms**

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility 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 internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

#### **9.1.7. Investigational Medicinal Product Accountability and Return**

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

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

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

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

#### **9.1.8. Inspections**

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

#### **9.1.9. Protocol Compliance**

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

## **9.2. Sponsor Responsibilities**

### **9.2.1. Protocol Modifications**

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

### **9.2.2. Study Report and Publications**

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of 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 Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.
- No such communication, presentation, or publication will include Gilead's confidential information (See Section 9.1.4).
- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

## **9.3. Joint Investigator/Sponsor Responsibilities**

### **9.3.1. Payment Reporting**

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

### **9.3.2. Access to Information for Monitoring**

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

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

### **9.3.3. Access to Information for Auditing or Inspections**

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

### **9.3.4. Study Discontinuation**

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



## 10. REFERENCES

- Beaugerie L, Itzkowitz SH. Cancers Complicating Inflammatory Bowel Disease. *N Engl J Med* 2015;372 (15):1441-52.
- Bretz F, Maurer W, Brannath W, Posch M. A Graphical Approach to Sequentially Rejective Multiple Test Procedures. *Stat Med* 2009;28:586-604.
- Chassaing B, Aitken JD, Malleshappa M, Vijay-Kumar M. Dextran sulfate sodium (DSS)-induced colitis in mice. *Current Protocols in Immunology* 2014;104.
- Danese S, Fiocchi C. Ulcerative colitis. *N Engl J Med* 2011;365 (18):1713-25.
- Fukunaga K, Matsumoto T. Current status and future perspectives of leukocytapheresis for inflammatory bowel disease. *J Gastroenterol Hepatol* 2012;27 (6):997-1003.
- Jess T, Rungoe C, Peyrin-Biroulet L. Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-analysis of Population-Based Cohort Studies. *Clin Gastroenterol Hepatol* 2012;10 (6):639-45.
- Kappelman MD, Rifas-Shiman SL, Kleinman K, Ollendorf D, Bousvaros A, Grand RJ, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. *Clin Gastroenterol Hepatol* 2007;5 (12):1424-9.
- Kornbluth A, Sachar DB. Erratum: Ulcerative Colitis Practice Guidelines in Adults: American College of Gastroenterology, Practice Parameters Committee. *The American Journal of Gastroenterology* 2010.
- 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, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. *N Engl J Med* 2017;376 (18):1723-36.
- Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet* 2016:1-15.
- 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
- Appendix 2. Study Procedures Table
- Appendix 3. Management of Clinical and Laboratory Adverse Events
- Appendix 4. Mayo Scoring System for Assessment of Ulcerative Colitis Activity
- Appendix 5. CTCAE Grading Scale for Severity of Adverse Events
- Appendix 6. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements
- Appendix 7. Clinical Laboratory Assessment Table

**Appendix 1. Investigator Signature Page**

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

**STUDY ACKNOWLEDGEMENT**

Combined Phase 2b/3, Double-Blind, Randomized, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Filgotinib in the Induction and Maintenance of Remission in Subjects with Moderately to Severely Active Ulcerative Colitis

**GS-US-418-3898, Amendment 5, 02 April 2019**

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

**PPD**

PPD  
Medical Monitor/Study Director

**PPD**

03-Apr-2019

Date

**INVESTIGATOR STATEMENT**

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number



**Appendix 2. Study Procedures Table**

Period	Screen	Treatment																			Follow-up	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PTx <sup>a</sup>
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20		
Week		0	2	4	6	10	11	14	17	20	23	26	30	34	38	42	46	50	54	58		
Study Day	-30 to -1	1	15	29	43	71	78	99	120	141	162	183	211	239	267	295	323	351	379	407		
Visit Window			±3	±3	±3	±2	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±3	±3
Written Informed Consent	X																					
Medical History & Demographics	X																					
Ulcerative Colitis Treatment History and disease extent	X																					
12-lead ECG	X					X						X									X	X <sup>b</sup>
Review of Inclusion/Exclusion Criteria	X	X																				
Complete Physical Exam <sup>c</sup>	X																					
Symptom directed physical exam <sup>c</sup> (as needed)		X	X	X	X	X	X	X		X		X		X		X		X		X	X	X
Vital Signs	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X
Height	X																					
Weight	X	X	X	X	X	X		X		X		X		X		X		X		X	X	X
Adverse Events	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X		X		X		X		X		X		X	X	X
Randomization		X					X															

Period	Screen	Treatment																			Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PTx <sup>a</sup>	ET
Week		0	2	4	6	10	11	14	17	20	23	26	30	34	38	42	46	50	54	58		
Study Day	-30 to -1	1	15	29	43	71	78	99	120	141	162	183	211	239	267	295	323	351	379	407		
Visit Window			±3	±3	±3	±2	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±3	±3
Study Drug Dispensing		X		X			X	X		X		X		X		X		X				
Colonoscopy/Flexible Sigmoidoscopy with biopsy	X <sup>d</sup>					X															X	
Investigator Endoscopic Value (0,1,2,or 3) <sup>e</sup>	X					X															X	
Mayo Score (Partial) <sup>f</sup>		X	X	X	X		X	X		X		X		X		X		X				X
Mayo Score (Complete)	X					X															X	
eDiary instruction & review <sup>g</sup>	X	X	X	X	X	X	X	X		X		X		X		X		X			X	
Stool for <i>C. diff</i> toxin, pathogenic <i>E. coli</i> , <i>Salmonella</i> spp, <i>Shigella</i> spp, <i>Campylobacter</i> spp or <i>Yersinia</i> spp testing	X																					
Stool O&P <sup>h</sup>	X																					
Stool microbiome	X					X						X									X	
Fecal MMP-9	X					X						X									X	
Fecal Lactoferrin, Calprotectin	X					X						X									X	

Period	Screen	Treatment																			Follow-up		
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PTx <sup>a</sup>	ET	
Visit	1																						
Week		0	2	4	6	10	11	14	17	20	23	26	30	34	38	42	46	50	54	58			
Study Day	-30 to -1	1	15	29	43	71	78	99	120	141	162	183	211	239	267	295	323	351	379	407			
Visit Window			±3	±3	±3	±2	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±3	±3		
Urine drug screen <sup>i</sup>	X																						
Urinalysis	X	X				X														X			
Pregnancy Test <sup>j</sup>	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
TB <sup>k</sup>	X																						
Chest x-ray <sup>l</sup>	X																						
HBV, HCV, HIV screening <sup>m</sup>	X																						
HBV DNA monitoring (Japan) <sup>n</sup>				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
HBV monitoring (other regions) <sup>n</sup>						X				X				X				X		X			
Hematology	X	X	X	X	X	X		X		X		X		X		X		X		X	X	X	
Chemistry	X	X	X	X	X	X		X		X		X		X		X		X		X	X	X	
Lipid profile (fasting) <sup>o</sup>		X				X						X								X		X	
CRP	X	X	X	X	X	X		X		X		X		X		X		X		X	X	X	
Serum immunoglobulin		X		X		X						X								X	X	X	
Blood TCR/BCR repertoire samples <sup>p</sup>		X		X		X						X								X			
Plasma biomarker sample		X		X		X						X								X			

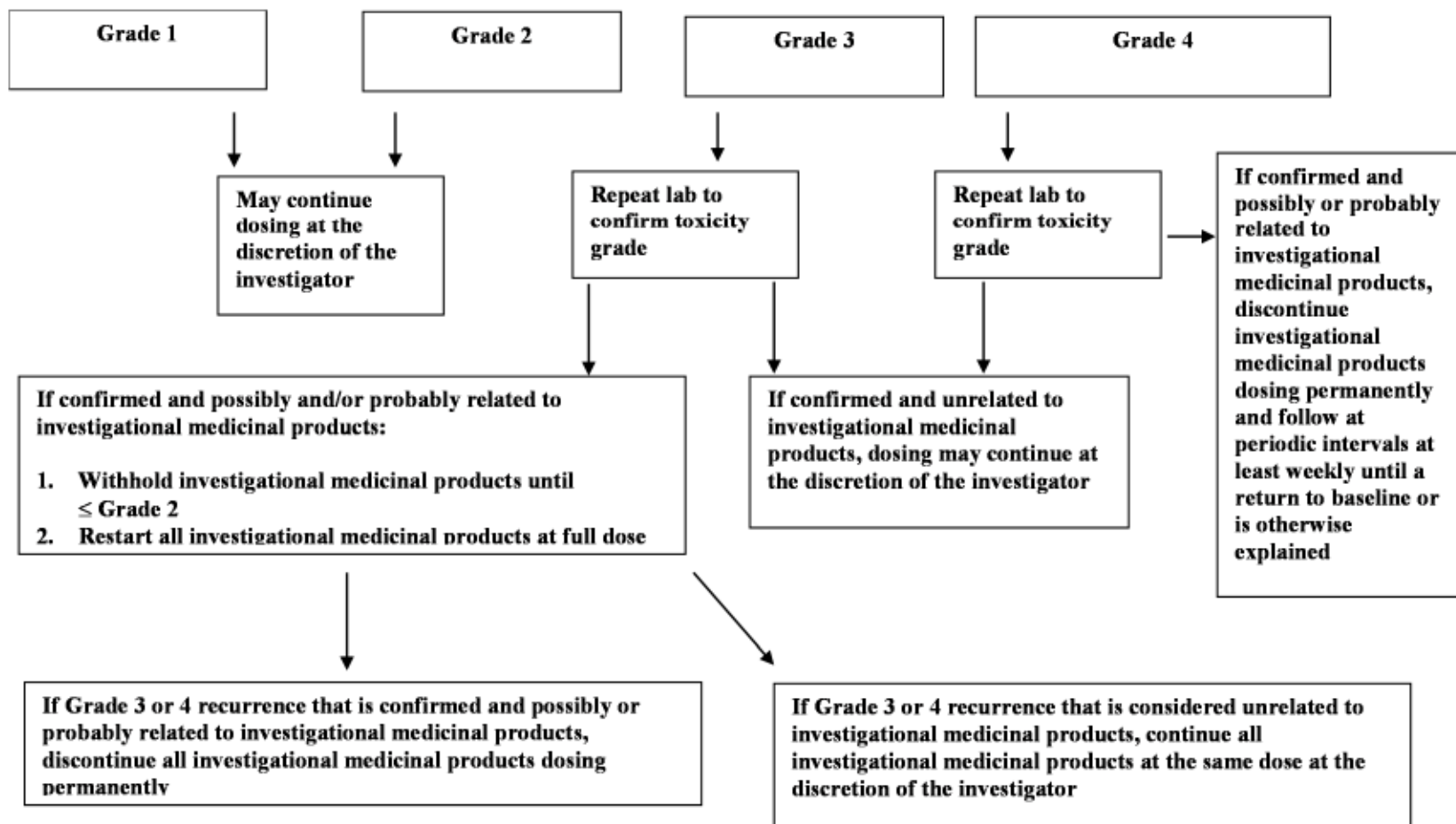


Period	Screen	Treatment																				Follow-up		
		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	PTx <sup>a</sup>	ET		
Visit	1																							
Week		0	2	4	6	10	11	14	17	20	23	26	30	34	38	42	46	50	54	58				
Study Day	-30 to -1	1	15	29	43	71	78	99	120	141	162	183	211	239	267	295	323	351	379	407				
Visit Window			±3	±3	±3	±2	±3	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±3	±3			
Serum biomarker sample		X		X		X						X								X				
Blood transcriptome sample		X		X		X						X								X				
PK collection (sparse) <sup>g</sup>				X		X						X								X				
vfPBMC <sup>c</sup>		X		X		X						X								X				
PK substudy <sup>d</sup>				X																				
<b>CCI</b>																								
HRQoL Surveys <sup>a</sup>		X				X						X								X				
HCRU questionnaire		X	X	X	X	X	X	X		X		X		X		X		X		X				

- a The Post Treatment (PTx) visit should occur 30 days after the last dose of study drug. Only subjects who roll over into the LTE study (GS-US-418-3899) will not complete PTx assessments.
- b For subjects who terminate prior to Week 10
- c A complete physical examination (PE) including, vital signs, body weight, and height will be performed at screening. (GU exam at investigator discretion). A symptom directed PE may be done as needed at other time points.
- d Diary data and other eligibility criteria should be reviewed prior to scheduling endoscopy. Perform the screening colonoscopy/flexible sigmoidoscopy within 2 weeks of Day 1 (Day -14 to -1). Subject should meet stool frequency and rectal bleeding requirements based on diary data prior to endoscopy performance.
- e The investigator (ie, local endoscopist) should enter in an endoscopic subscore (0, 1, 2, or 3) based on the Mayo Clinic Scoring System endoscopic scale (Appendix 4); this will be entitled the Investigator Endoscopic Value. The locally read score entered may not be used for eligibility or Mayo Clinic Score calculation purposes, and is not a substitute for the centrally read score, but is collected solely for exploratory purposes.
- f Includes all parts of the Mayo score except endoscopy
- g Subjects should begin filling out the eDiary the day after their initial screening visit and continue to fill it out throughout the remainder of the study.
- h Stool samples should be collected to rule out infectious causes when disease worsens.
- i Positive cocaine test disqualifies subject; positive amphetamines, barbiturates, benzodiazepines, and opioids require medical monitor review.
- j All females meeting the childbearing potential criteria must have a serum pregnancy testing at screening and a urine pregnancy test must be completed in clinic every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic.

- k Proof of no active or untreated latent TB at screening. Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the medical monitor.
- l Chest x-ray (views as per local guidelines) taken at screening or within the 3 months prior to screening (with the report or films available for investigator review) without evidence of active or latent TB infection
- m Hepatitis B surface Ag, surface Ab and core Ab, reflex HBV DNA, Hepatitis C Ab, reflex HCV RNA, HIV Ag/Ab, reflex HIV 1/2 Ab at Screening (Section 6.2.1).
- n In Japan, subjects with negative HBsAg, positive HBcAb and/or positive HBsAb at Screening require HBV DNA monitoring every 4 weeks in accordance with local guidelines (Section 6.2.1). 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)
- o Fasting means no food or drink, except water, for 8 hours
- p TCR: T-cell receptor; BCR: B-cell receptor
- q This PK sample at Weeks 10 and 58 are collected at pre-dose (within 2 hours prior to dosing). The PK sample at Week 4 is collected post-dose (at least 30 minutes and up to 3 hours after study drug dosing). For this visit, it is preferred that study drug dosing is in clinic. The PK sample at Weeks 26 can be collected at any time without regard to dosing. For these visits, the time of dose taken on the day of and the dose taken prior to the PK sample being drawn will be noted in the eCRF.
- r vfpBMC collection at US and Canadian sites only.
- s Subjects who consent to optional PK substudy will have an additional plasma PK sample at any single visit from Week 2 and 10, collected pre-dose and at 0.5, 1, 2, 3, 4 and 6 hours after supervised dosing in the clinic. For all visits with PK sampling, the time of dose taken prior to and on the day of visit will be noted in the eCRF
- t [REDACTED]
- u HRQoLs include SF-36, WPAI, EQ-5D, IBDQ

### Appendix 3. Management of Clinical and Laboratory Adverse Events





**Appendix 4. Mayo Scoring System for Assessment of Ulcerative Colitis Activity**

<p><b>Stool Frequency</b> – <i>Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency</i></p>	<p><input type="checkbox"/> 0 Normal number of stools for subject</p> <p><input type="checkbox"/> 1 1 to 2 stools per day more than normal</p> <p><input type="checkbox"/> 2 3 to 4 stools more than normal</p> <p><input type="checkbox"/> 3 <math>\geq 5</math> stools more than normal</p>
<p><b>Rectal Bleeding</b> – <i>The daily bleeding score represents the most severe bleeding of the day.</i></p>	<p><input type="checkbox"/> 0 No blood seen</p> <p><input type="checkbox"/> 1 Streaks of blood with stool less than half the time</p> <p><input type="checkbox"/> 2 Obvious blood with stool half or more than half of the time</p> <p><input type="checkbox"/> 3 Blood alone passes</p>
<p><b>Endoscopic findings</b> – <i>Assessed by Central Reader (include only for MCS assessment)</i></p>	<p><input type="checkbox"/> 0 Normal or inactive disease</p> <p><input type="checkbox"/> 1 Mild Disease (<i>erythema, decreased vascular pattern</i>)</p> <p><input type="checkbox"/> 2 Moderate Disease (<i>marked erythema, lack of vascular pattern, friability, erosions</i>)</p> <p><input type="checkbox"/> 3 Severe Disease (<i>spontaneous bleeding, ulceration</i>)</p>
<p><b>Physician's Global Assessment</b> – <i>The physician's global assessment acknowledges the three other criteria, the subject's daily recollection of abdominal discomfort and general sense of well-being, and other observation, such as physical findings and the subject's performance status.</i></p>	<p><input type="checkbox"/> 0 Normal</p> <p><input type="checkbox"/> 1 Mild disease</p> <p><input type="checkbox"/> 2 Moderate disease</p> <p><input type="checkbox"/> 3 Severe disease</p>

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

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

### **1) Definitions**

#### **a) Definition of Childbearing Potential**

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

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

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

#### **b) Definition of Male Fertility**

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

### **2) Contraception for Female Subjects**

#### **a) Study Drug Effects on Pregnancy and Hormonal Contraception**

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



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). For male subjects, male condom should be used; for their female partners of childbearing potential, an accepted contraceptive method should also be considered. Details are outlined below.

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

#### **b) Contraception for Female Subjects of Childbearing Potential**

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

Female subjects must agree to use one of the following methods from screening until 35 days following the last dose of study drug.

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

Or

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

Female subjects who wish to use a hormonally based method, must use it in conjunction with a barrier method; the barrier method is to be used either by the female subject or by her male partner. Female subjects who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally-based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Hormonal methods (each method *must* be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel

- Transdermal contraceptive patch
- Contraceptive vaginal ring
- Barrier methods (each method *must* be used with a hormonal method)
  - Male or female condom with or without spermicide
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

All female subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 35 days after the last study drug dose.

### 3) Contraception Requirements for Male Subjects

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

### 4) Unacceptable Birth Control Methods

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

### 5) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study are to report the information to the investigator.

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

### 6) Pregnancy Testing

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

