Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Testicular Safety of Filgotinib in Adult Males with Moderately to Severely Active Inflammatory Bowel Disease
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
IND Number:	129647
EudraCT Number:	2017-000402-38
Clinical Trials.gov Identifier:	NCT03201445
Indication:	Inflammatory Bowel Disease
Protocol ID:	GS-US-418-4279
Medical Leader:	PPD
Protocol Version/Date:	Original: 31 January 2017 Amendment 1: 06 July 2017 Amendment 1.1 (VHP): 21 September 2017 Amendment 1.2 (CCI): 15 October 2018 Amendment 2: 22 August 2018 Amendment 3: 18 January 2019 Amendment 3.1 (CCI): 25 January 2019 Amendment 4: 17 March 2020 Amendment 4.1 (CCI): 27 March 2020 Amendment 5: 27 June 2022 Amendment 5.1 (CCI): 27 June 2022 Amendment 6: 09 September 2022 Amendment 6.1 (CCI): 09 September 2022

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

CLINICAL STUDY PROTOCOL HISTORY

Clinical study protocol (CSP)/Amendment #	**Date**	**Main Rationale** **General/Country-Specific**
CSP Version 1.0	31-Jan-2017	Initial CSP Version General
Amendment #1	06-Jul-2017	Update and/or clarification of study design, eligibility criteria, study procedures, study drug discontinuation considerations, and statistical analyses General
Amendment #1.1	21-Sep-2017	Update of study design and clarification of patient safety information Country-specific (voluntary harmonisation procedure countries)
Amendment #1.2	15-Oct-2018	Inclusion of sperm banking reimbursement language and details of new medical monitor and study director Country-specific ([redacted])
Amendment #2	22-Aug-2018	Expansion of study population to include subjects with Crohn's disease and update of eligibility criteria (note: this amendment was not implemented) General
Amendment #3	18-Jan-2019	Expansion of study population to include subjects with Crohn's disease and update of eligibility criteria General

Clinical study protocol (CSP)/Amendment #	**Date**	**Main Rationale** **General/Country-Specific**
Amendment #3.1	25-Jan-2019	Expansion of study population to include subjects with Crohn's disease and update of eligibility criteria Country-specific (CCI)
Amendment #4	17-Mar-2020	CCI request General
Amendment #4.1	27-Mar-2020	CCI request Country-specific (CCI)
Amendment #5	27-Jun-2022	Change in sponsorship from Gilead Sciences, Inc. to Galapagos NV General
Amendment #5.1	27-Jun-2022	Change in sponsorship from Gilead Sciences, Inc. to Galapagos NV Country-specific (CCI)
Amendment #6	09-Sep-2022	Change in wording about blinding General
Amendment #6.1	09-Sep-2022	Change in wording about blinding Country-specific (CCI)

SUMMARY OF CHANGES

Amendment 6 (09-Sep-2022)

The overall reason for this amendment:

This study has progressed beyond the analysis time points of the primary, secondary, and all exploratory endpoints, which were the scope of the second unblinded interim analysis (IA2). The Sponsor plans to disclose these data of scientific interest into a peer reviewed journal while the study is still ongoing, without compromising the data integrity and scientific validity. To this purpose, the wording about blinding was revised to allow disclosure of the treatment assignments of subjects who completed the study before IA2.

General minor administrative updates were made throughout the protocol, including terminology, punctuation, abbreviations, dates, numbers, and format for clarity and consistency.

The changes made to the clinical study protocol GS-US-418-4279 (GLPG0634-CL-228) Version 5.0, 27-Jun-2022 are listed below, reflecting a brief rationale for each change and the applicable sections.

Rationale: Text was revised to specify the decommissioning of the Data Monitoring Committee (DMC) and transfer the role of the DMC to the Sponsor Safety Management Team (SSMT). All planned DMC reviews have been completed and no additional reviews are expected. At this advanced stage of the study, treatment assignments have been unblinded for the majority of subjects, no longer requiring an external unblinded review committee in addition to the blinded Sponsor study team. Oversight by the SSMT will include regular reviews of safety summary updates and will provide similar options for escalated issue review as described in the DMC charter by following the SSMT standard procedures.

Applicable sections: Synopsis

1.4 Risk/Benefit Assessment for the Study

8.8 Data Monitoring Committee/Sponsor Safety Management Team

Rationale: Text about blinding was revised to allow publication of the treatment assignments of subjects who completed the study before IA2.

Applicable sections: Synopsis

5.1.2 Blinding

8.11 Unblinded Interim Analysis

Rationale: A study drug interruption criterion for subjects experiencing moderate renal failure (estimated creatinine clearance ≥35 mL/min and <60 mL/min per Cockcroft-Gault formula) was added to align with Investigator's Brochure Edition 17, 15-Jul-2022.

Applicable Section: 3.3.1 Study Drug Interruption Considerations

Rationale: Text was added to specify the decommissioning of the Internal Independent Safety Review Team as of this amendment. The internal independent SSMT will cover the objectives of the DMC and the Internal Independent Safety Review Team.

Applicable Section: 8.10 Internal Independent Safety Review

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

PROTOCOL SYNOPSIS

Galapagos NV
Generaal De Wittelaan L11 A3
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Study Title:	A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Testicular Safety of Filgotinib in Adult Males with Moderately to Severely Active Inflammatory Bowel Disease
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	129647 2017-000402-38 NCT03201445
Study Centers Planned:	Approximately 175 centers worldwide
Main Objectives:	The primary objective of this study is: • To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 13 The secondary objectives of this study include: • To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 26 • To evaluate the effect of filgotinib on sperm total motility at Weeks 13 and 26 • To evaluate the effect of filgotinib on total sperm count at Weeks 13 and 26 • To evaluate the effect of filgotinib on the change from baseline in sperm concentration at Weeks 13 and 26 • To evaluate the effect of filgotinib on ejaculate volume at Weeks 13 and 26 • To evaluate the effect of filgotinib on sperm morphology at Weeks 13 and 26

The exploratory objectives of this study include:

- To evaluate the reversibility of observed effects of filgotinib on testicular function in subjects who experience a ≥ 50% decrease in sperm concentration and/or motility and/or morphology
- To evaluate the effect of filgotinib on sex hormones including luteinizing hormone (LH), follicle stimulating hormone (FSH), inhibin B, and total testosterone at Weeks 13 and 26
- To evaluate the safety and tolerability of filgotinib
- To characterize the plasma pharmacokinetics (PK) of filgotinib and its metabolite (GS-829845, formerly CCI)

Study Design:

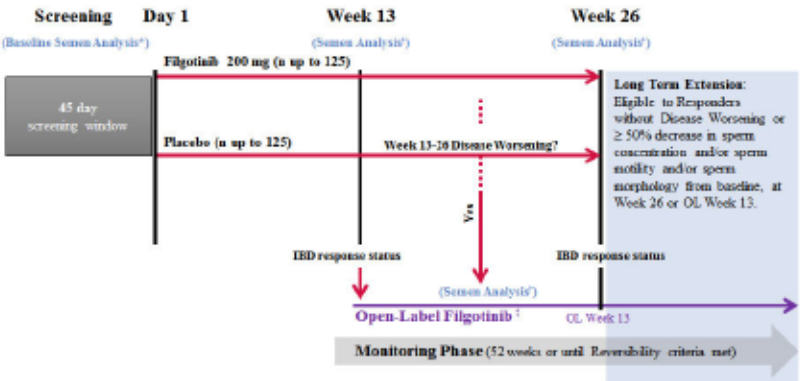
This is a randomized, double-blind, placebo-controlled Phase 2 study in adult males with moderately to severely active inflammatory bowel disease (IBD) who may be on protocol-specified therapy.

Up to 250 males between the age of 21 and 65 years (inclusive) at the time of consent will be randomized to receive 26 weeks of filgotinib 200 mg or placebo-to-match (PTM) filgotinib 200 mg once daily.

Randomization will be stratified according to the type of IBD (ie, ulcerative colitis [UC] versus Crohn's disease [CD]), by concurrent use of methotrexate (MTX; yes or no), and by sperm concentration measured at Screening ("Baseline") according to the following strata:

- 15 to 25 million/mL
- > 25 to 50 million/mL
- > 50 million/mL

Study Schema



*A mean of 2 semen samples at Screening must meet the following minimum criteria: semen volume ≥ 1.5 mL, total sperm/ejaculate ≥ 39 million, sperm concentration ≥ 15 million/mL, sperm total motility ≥ 40%, and normal sperm morphology ≥ 30%
†All subjects with ≥ 50% decrease in sperm concentration and/or sperm motility and/or sperm morphology as compared to baseline will enter a Monitoring Phase (discontinue study drug and evaluate for Reversibility)
‡ At/after Week 13, protocol design allows a switch to open-label filgotinib for Non-responders or those with Disease Worsening; semen analysis is required to confirm that no pre-specified decrease threshold is met, prior to administration of open-label filgotinib

There are 5 distinct parts to the study which subjects may enter depending upon the individual subject's response of the underlying IBD to assigned treatment and/or observed changes in semen parameters. The 5 parts which are described in the following sections comprise of the following:

1) Part A (Day 1 through Week 13 Study Visit)
2) Part B (After Week 13 through Week 26 Study Visit)
3) Open-Label Filgotinib Phase
4) Monitoring Phase
5) Long Term Extension

The study parts are described in the following sections.

Part A (Day 1 through Week 13 Study Visit)

(Appendix 11 and Figure 3-2)

In Part A, all subjects will receive blinded study drug for the first 13 weeks, starting from the Day 1/Randomization Study Visit. At the Week 13 Study Visit, IBD response status (ie, Non-responder vs Responder, see Definition of Terms) will be determined based on the partial Mayo Clinic Score (partial MCS) for subjects with UC, or the Crohn's Disease Activity Index (CDAI) for subjects with CD. In addition, sperm parameters (see Section 6.13 Semen Collection Procedure) will be evaluated to determine whether any of the pre-specified decrease thresholds (see Definition of Terms) have been met.

- Subjects who are Responders and whose sperm parameters do not meet a pre-specified decrease threshold will continue blinded study drug in Part B.
- Subjects who are Non-responders and whose sperm parameters do not meet a pre-specified decrease threshold will discontinue blinded study drug and commence open-label (OL) filgotinib.
- Subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of IBD response status, will discontinue blinded study drug and enter the Monitoring Phase.

Part B (After Week 13 through Week 26 Study Visit)

(Appendix 11 and Figure 3-3)

In Part B, all subjects will continue blinded study drug for up to an additional 13 weeks. Subjects may experience Disease Worsening (see Definition of Terms) of their underlying IBD at any time during blinded study drug treatment (after Week 13 through Week 26). If Disease Worsening is confirmed, sperm parameters will be evaluated to determine whether a pre-specified decrease threshold has been met prior to a study drug change (changing from blinded study drug to OL filgotinib). Based upon the sperm parameters at this time point, subjects may follow one of the following pathways:

- All subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of IBD response status, will discontinue blinded study drug and enter the Monitoring Phase.
- Subjects who experience Disease Worsening after Week 13 and prior to Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold will discontinue blinded study drug and commence OL filgotinib.
- Subjects who do not experience Disease Worsening, and are Responders at Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold, will continue blinded study drug as part of the Long Term Extension (LTE).
- Subjects who do not experience Disease Worsening, but are Non-responders at Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold, will discontinue blinded study drug and complete a safety follow-up visit 30 days after last study drug dose.

Open-Label Filgotinib Phase (Open-Label Day 1 through Open-Label Week 13 Study Visit)

(Appendix 11 and Figure 3-4)

After exposure to 13 weeks of OL filgotinib, the subject's IBD response status will be determined and sperm parameters will be evaluated to determine whether a pre-specified decrease threshold has been met. Subjects will be evaluated during this phase as follows:

- All subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of Responder status, will discontinue OL filgotinib, complete a safety follow-up visit 30 days after last study drug dose, and enter the Monitoring Phase.

- Subjects who experience Disease Worsening and whose sperm parameters do not meet a pre-specified decrease threshold will discontinue OL filgotinib, complete Early Termination (ET) and a safety follow-up visit 30 days after last study drug dose.

- Subjects who do not experience Disease Worsening, and are Responders at OL Week 13 after exposure to 13 weeks of OL filgotinib, and whose sperm parameters do not meet a pre-specified decrease threshold, may continue receiving OL filgotinib as part of the LTE.

- Subjects who do not experience Disease Worsening, but are Non-responders after exposure to 13 weeks of OL filgotinib, and whose sperm parameters do not meet a pre-specified decrease threshold, will discontinue OL filgotinib and complete a safety follow-up visit 30 days after last study drug dose.

Monitoring Phase (up to 52 weeks) (Appendix 11 and Figure 3-5.)

All subjects who enter the Monitoring Phase will undergo semen evaluations every 13 weeks from the day of study drug discontinuation, for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first. Subjects will be offered locally approved standard of care (SOC) therapy during the Monitoring Phase.

Long Term Extension (up to 195 weeks)

(Appendix 11 and Figure 3-6.)

All subjects who enter the LTE will undergo scheduled visits for safety assessments every 13 weeks from the start of LTE, for up to 195 weeks, and semen monitoring (every 13 weeks) until the Week 13 primary study results are analyzed. Subjects will receive either OL filgotinib or blinded study drug based on the individual's response criteria described above. If a subject experiences Disease Worsening during the LTE, the treatment (either OL filgotinib or blinded study drug) will be discontinued and the subject will complete an ET visit, followed by a safety follow-up visit 30 days after last study drug dose.

Data Monitoring Committee (DMC)/Sponsor Safety Management Team (SSMT)

An external, multidisciplinary DMC, including an expert in male fertility, will review the progress of the study and perform interim unblinded reviews of safety data (details in Section 8.8).

The DMC has monitored the study until the date of protocol amendment 6, including the data for the second unblinded interim analysis (IA2). As of amendment 6, the DMC will be decommissioned. The safety and progress of the remainder of the study will continue to be

	monitored by the Sponsor medical leader and medical monitor or designee, providing updates during regular Sponsor medical monitoring oversight meetings across the filgotinib program. If needed, safety issues will be escalated to the SSMT per internal standard procedures. The SSMT can consult external experts, if deemed necessary, and can review data in an unblinded fashion. **Key Concomitant Medication Considerations** Subjects may be treated with 5-aminosalicylic acid (5-ASA), conventional immunomodulators, and/or corticosteroid therapy, as defined by the inclusion criteria. Subjects are prohibited from receiving sulfasalazine, beginning 26 weeks prior to Screening until the end of study, as defined by Exclusion Criteria. A list of permitted and prohibited medications is provided in the exclusion criteria and Section 5.3.
Number of Subjects Planned:	Up to 250 subjects for 200 evaluable subjects
Target Population:	Males between the ages of 21 and 65 years (inclusive) with moderately to severely active IBD
Duration of Treatment:	The duration of treatment is approximately up to 26 weeks of blinded study drug, and up to 13 weeks of OL filgotinib (if eligible). Subsequently, for those subjects qualifying, this will be followed by an LTE lasting up to 195 weeks. Subjects whose sperm parameters meet a pre-specified decrease threshold at any time during the study will discontinue study drug, and should be managed with allowed standard of care therapy. These subjects will be followed in the Monitoring Phase of the study, for up to 52 weeks or until Reversibility (see Definition of Terms) of all parameters meeting sperm decrease threshold is met, whichever is achieved first.
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3. **Key Inclusion Criteria** • Males between the age of 21 and 65 (inclusive) on the day of signing informed consent • Documented diagnosis of UC or CD of at least 4 months duration. Documentation must include endoscopic and histopathologic documentation of either UC or CD, as follows:

— UC

- Medical record documentation of, or an endoscopy report dated ≥ 4 months before randomization, which shows features consistent with UC, determined by the procedure performing physician, AND
- Medical record documentation of, or a histopathology report indicating features consistent with UC as determined by the pathologist

Note: Subjects also need to have minimum disease extent of 15 cm from the anal verge

— **CD**

- Medical record documentation of, or an ileocolonoscopy (full colonoscopy with intubation of terminal ileum) reported dated ≥ 4 months before randomization, which shows features consistent with CD, determined by the procedure performing physician, AND
- Medical record documentation of, or a histopathology report indicating features consistent with, CD as determined by the pathologist

- Moderately to severely active UC, or moderately to severely active CD, assessed locally and defined by:

— **UC**

- Mayo Clinic Score (MCS; Appendix 3) ≥ 6, Physician's Global Assessment (PGA) of 2 or 3, and endoscopic subscore ≥ 2, at Screening or in the prior 90 days

— **CD**

- CDAI total score (Appendix 9) ≥ 220, AND
- Evidence of active inflammation, with a total score of ≥ 6 by the Simple Endoscopic Activity Score in Crohn's Disease (SES-CD; Appendix 10), OR if disease is limited to the ileum and/or right colon, a combined SES-CD score ≥ 4 in these 2 segments, at Screening or in the prior 90 days

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of at least 1 of the following 5 classes of agents, as individually defined in Section 4.2 Inclusion Criteria, #6
  - Corticosteroids
  - Azathioprine, 6-mercaptopurine, or methotrexate
  - TNFα antagonists (infliximab, adalimumab, golimumab [UC only], or certolizumab [CD only])
  - Vedolizumab
  - Ustekinumab (CD only)
- The mean of 2 separate semen samples collected at the Screening visit must meet the following minimum criteria (in accordance with Section 6.14 and Figure 6-1): semen volume ≥ 1.5 mL, total sperm/ejaculate ≥ 39 million, sperm concentration ≥ 15 million/mL, sperm total motility ≥ 40%, and normal sperm morphology ≥ 30%

Key Exclusion Criteria

- Previously or currently documented problems with male reproductive health, including but not limited to primary hypogonadism, secondary hypogonadism, or reduced fertility
- Current use of sulfasalazine or its use within the 26 weeks leading up to Screening; sulfasalazine is not permitted at any point during the study
- Current use of corticosteroids at a dosage of > 20 mg/day of prednisone or equivalent at randomization
- Active tuberculosis or untreated latent tuberculosis (Section 4.2 Inclusion Criteria, #12)

Infection with active Hepatitis B, Hepatitis C, or HIV (Section 4.3 Exclusion Criteria, #31-33)

Study Procedures/ Frequency:

After written informed consent is obtained, screening procedures will commence, including but not limited to evaluation of eligibility criteria, medical history, routine blood and urine collection for laboratory analyses and semen sample collection. All subjects meeting eligibility criteria will be randomized 1:1 to receive filgotinib 200 mg once daily or PTM filgotinib 200 mg once daily, for up to 26 weeks.

All subjects will return to the clinical study center to be evaluated for clinical and laboratory assessments at Week 2, Week 4, Week 8, and Week 13, including semen sample collection during Week 13 visits. Subjects continuing on blinded study drug will return for Week 20 and

Week 26 assessments, including semen sample collection during Week 26 visits. Subjects who are Non-responders at Week 13 or who show Disease Worsening between the Week 13 and Week 26 Study Visits will switch to OL filgotinib. After starting OL filgotinib, subjects will return for study assessments at OL Day 1, OL Week 2, OL Week 4, OL Week 8, and OL Week 13, including a semen sample collection at OL Week 13. Subjects continuing on to the LTE will undergo scheduled visits for safety assessments and semen sample collection, every 13 weeks up to 195 weeks.

Subjects who are Responders at Week 26 or at OL Week 13 and choose not to continue to the LTE, as well as subjects who discontinue study participation for any reason prior to Week 26, OL Week 13, reaching Reversibility or Monitoring Phase Week 52 (whichever occurs first), or LTE Week 195, will complete an ET visit in addition to a routine safety follow-up visit 30 days (± 5 days) after the last dose of study drug.

Sparse Plasma PK Sample Collection:

In Parts A and B, sparse plasma PK samples will be collected at least 30 minutes post dose at the Week 2 visit, anytime at the Week 4 visit, and predose during visits at Weeks 13 and 26. In the OL Filgotinib Phase, sparse plasma PK samples will be collected at least 30 minutes post dose at the OL Week 2 visit, anytime at the OL Week 4 visit, and predose during visits at OL Week 13.

Semen Collection and Analysis:

At each of the following time points, subjects will provide 2 semen samples, collected within a 14-day period. Each semen sample must be collected with an ejaculation free period of ≥ 48 hours and ≤ 7 days (Section 6.13):

- Screening (Baseline)
- After Part A (Week 13 Study Visit)
- After Part B (Week 26 Study Visit)

  OR

  For Subjects who experience confirmed Disease Worsening between Weeks 13-26 in Part B, prior to beginning OL Filgotinib Phase and at the OL Week 13 Study Visit
- Every 13 weeks during the Monitoring Phase (if applicable)
- Every 13 weeks during the LTE

In select instances where the semen sample with questioned value(s) is found to be non-assessable or invalid (eg, collection without adherence to ejaculation-free periods; intercurrent illness or dehydration at time of

	collection; incomplete capture of semen sample; and/or sample processing or semen analysis that deviates from standardized procedure), a third semen sample, when indicated, must be collected within 14 days of the prior sample, with an ejaculation free period of ≥ 48 hours and ≤ 7 days. All decisions of retesting any semen/sperm parameter (ie, obtaining a third semen sample at any of the above time points) must be approved by the Sponsor Medical Monitor or designee before the retest.
Test Product, Dose, and Mode of Administration:	200 mg filgotinib tablet orally once daily
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match filgotinib 200 mg tablet orally once daily
Required Background Medication:	Permitted medication as described in the inclusion criteria, and administered according to the local product label.
Criteria for Evaluation:	
Safety	Semen samples will be collected as outlined in Section 6.13. Sex hormones, including LH, FSH, inhibin B, and total testosterone will be measured at various time points during this study. Other aspects of safety will be assessed by the reporting of AEs, clinical laboratory evaluations (hematology, chemistry and urinalysis), physical examination, vital signs, and at various time points during the study. Concomitant medication usage will also be assessed throughout the study.
Pharmacokinetics	Plasma concentrations of filgotinib and its metabolite (GS-829845) will be analyzed.
Statistical Methods:	The primary endpoint is the proportion of subjects with a ≥ 50% decrease in sperm concentration from baseline at Week 13. A cumulative distribution plot for the percent change from baseline in sperm concentration at Week 13 for each treatment group will be constructed. The x-axis will display percent changes from baseline sperm concentration ranging from 100% decrease (ie, -100% or azoospermia) to the maximal observed increase. The y-axis will display

the proportion of subjects who experienced a percentage change in sperm concentration equal to or less than the corresponding x-axis value at Week 13. This method is suggested in FDA's Guidance for Industry: Testicular toxicity: Evaluation During Drug Development (October 2018).

The proportion of subjects experiencing at least a 50% decrease in sperm concentration from baseline will be calculated together with the associated 95% confidence interval for the difference between the filgotinib and placebo groups. Additional assessments of semen parameters may be conducted.

All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by dosing group.

A sample size of 100 evaluable subjects per group, where evaluable is defined as subjects in the Semen Analysis Set (Section 8.2.1.2), is adequate for the purposes of estimating cumulative distribution curves and producing a 95% confidence interval width that is reasonably narrow for the percentage of subjects in each group who experience a $\geq$ 50% decrease in sperm concentration compared to baseline. Assuming a 20% rate of non-evaluable subjects at Week 13, up to 125 subjects per arm may be enrolled.

Results of this study may be pooled with the results of a separate study being conducted in subjects with rheumatic diseases (GLPG0634-CL-227) with the same objective. The total planned number of subjects in both studies combined will be approximately 250 subjects.

Unblinded interim analyses of the clinical trial data will be performed by the Sponsor for regulatory submissions when 200 subjects (eg, pooled data from GS-US-418-4279 and GLPG0634-CL-227), and/or when some defined subset(s) of subjects, have completed the Week 13 and Week 26 (or OL Week 13) assessments (first unblinded interim analysis [IA1]), and when complete reversibility data for all subjects who entered the Monitoring Phase at these time points is available (IA2; see Definition of Terms). A Data Integrity and Communication Plan for the interim analysis will be developed prior to unblinding. The analyses will

	be conducted primarily to evaluate the testicular safety and further details will be described in the statistical analysis plan (SAP). For ongoing subjects, the study teams and study staff at the sites and all other staff directly involved in the conduct of the study will remain blinded to the treatment assignments until the final analysis when the database has been locked. Publication of the IA2 data is planned by the Sponsor. This publication will contain group level data for the entire study population, but will unblind the study teams and staff directly involved in the conduct of the study to the individual baseline treatment assignment of subjects who completed the study before IA2.

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

DEFINITION OF TERMS

Disease Worsening	For subjects with UC, Disease Worsening is defined by a partial MCS after Week 13 consisting of: an increase of ≥ 3 points to at least 5 points from the Week 13 value on 2 consecutive visits, OR an increase to 9 points from the Week 13 value on 2 consecutive visits, if the Week 13 value was > 6 points For subjects with CD, Disease Worsening is defined by a total CDAI score after Week 13 consisting of: a score ≥ 220 on 2 consecutive visits, AND an increase of ≥ 100 points from the Week 13 value on 2 consecutive visits Disease Worsening is confirmed at the time of the second consecutive visit.
Mayo Clinic Score (MCS)	Composite score of UC activity consisting of sub-scores from endoscopy, rectal bleeding, stool frequency, and PGA. Subject recall for the last 24 hours will be used for the patient reported components of the complete MCS.
Partial Mayo Clinic Score (partial MCS)	Composite score of UC activity consisting of sub-scores from rectal bleeding, stool frequency, and PGA. Subject recall for the last 24 hours will be used for the patient reported components of the partial MCS.
Crohn's Disease Activity Index (CDAI)	Composite score of CD activity consisting of gastrointestinal symptoms (eg, abdominal pain), signs (eg, abdominal mass), laboratory values (ie, hematocrit), and complications (eg, arthritis/arthralgia), among other patient attributes. Subject recall for the last 7 days will be used for the patient reported outcome of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.
Simple Endoscopic Activity Score in Crohn's Disease (SES-CD)	Composite score of mucosal inflammation in CD consisting of four endoscopic variables (ulcer presence and size; luminal surface covered by ulcers; luminal surface with disease involvement; and stenosis presence and severity).

Monitoring Phase	A subject who experiences a ≥ 50% decrease in sperm concentration, and/or motility, and/or morphology at any time after 13 weeks on study drug will discontinue the study drug, complete a routine safety follow up visit 30 days (± 5 days) after the last dose of study drug and start the Monitoring Phase. Semen samples will be collected every 13 weeks from the date of the study drug discontinuation, for up to 52 weeks or until Reversibility is met, whichever is achieved first.
Responder	For UC, a subject who has a reduction of ≥ 2 in partial Mayo Clinic Score compared to baseline at the specified assessment time (Appendix 2). For CD, a subject who has a reduction of ≥ 100 points in total CDAI score compared to baseline at the specified assessment time (Appendix 2). A subject with a baseline total CDAI score of ≥ 220 to ≤ 250 will be considered to be a Responder if a CDAI score of < 150 is attained at the specified assessment time.
Non-responder	For UC or CD, a subject who does not fulfill the definition of Responder at the specified assessment time (Appendix 2).
Pre-specified decrease threshold	A ≥ 50% decrease in sperm concentration, and/or motility, and/or morphology in comparison to Baseline. The mean of values for each of the sperm parameters (measured from 2 separate semen samples) will be used in all analyses. Samples will be collected within a 14-day period, with an ejaculation-free period of ≥ 48 hours and ≤ 7 days.
Reversibility	Reversibility is met when all sperm parameter(s) qualifying the subject to enter into the Monitoring Phase return(s) to greater than 50% of Baseline (ie, to greater than [0.50 x mean of 2 sperm collections collected at the Screening visit (eg, Baseline)]).
Week 13	The Week 13 Study Visit occurs once a subject completes the first 13 weeks of blinded study drug, and is inclusive of all study assessments performed at the clinic visit and the semen sample collection visits associated with this time point.
Week 26	The Week 26 Study Visit occurs once a subject completes the second 13 weeks of blinded study, and is inclusive of all study assessments performed at the clinic visit and the semen sample collection visits associated with this time point.
OL Week 13	The OL Week 13 Study Visit occurs once a subject completes the first 13 weeks of OL filgotinib, and is inclusive of all study assessments performed at the clinic visit and the semen sample collection visits associated with this time point.

First unblinded interim analysis (IA1)	Unblinded Week 26 analysis to be performed after at least 200 evaluable subjects pooled across studies GS-US-418-4279 (GLPG0634-CL-228) and GLPG0634-CL-227 complete Week 13 and evaluable subjects from Study GS-US-418-4279 complete Week 26 (or OL Week 13) or permanently discontinue from study drug. Referred to as 'Week 26 Analysis' in the SAP.
Second unblinded interim analysis (IA2)	Unblinded Week 26 analysis to be performed after all subjects reach Week 26 and all subjects with a $\geq$ 50% decrease in sperm concentration, and/or motility, and/or morphology up to Week 26 (or OL Week 13) enter the Monitoring Phase and either meet reversibility criteria or are followed off-treatment for 52 weeks, whichever occurs first. Referred to as 'Week 26 and Reversibility Analysis for Pre-specified Sperm Decreases Up to Week 26' in the SAP.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
Ab	antibody
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
$AUC_{0-\tau}$	area under the plasma drug concentration-time curve of a dosing interval
BUN	blood urea nitrogen
C_τ	trough plasma concentration (just before the next dosing ie, predose sample)
CC&G	Cockcroft-Gault
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CES	carboxylesterases
CI	confidence interval
CIA	collagen-induced arthritis
C_{max}	maximum observed plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CRO	Contract Research Organization
CRP	C-reactive protein
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	cardiovascular safety endpoint adjudication committee
CXR	chest x-ray
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DSS	dextran sulfate sodium
E.coli	*Escherichia coli*
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
EU	European Union
EudraCT	European Clinical Trials Database

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Galapagos NV
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HDL	high density lipoprotein
hERG	human ether-a-go-go-related gene
HIV	human immunodeficiency virus
HLGT	high-level group term
HLT	high-level term
HR	heart rate
IA1/2	first/second unblinded interim analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	independent ethics committee
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
IWRS	interactive web response system
JAK	janus kinase
LAM	lactational amenorrhea method
LDL	low density lipoprotein
LH	luteinizing hormone
LLT	low level term
LTE	long term extension
MACE	major adverse cardiovascular events
MCS	Mayo Clinic Score
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate

NOEL	no-observed-effect-level
NSAIDs	nonsteroidal anti-inflammatory drugs
O&P	ova & parasites
OATs	organic anion transporters
OL	open label
P-gp	p-glycoprotein
PD	pharmacodynamic(s)
PEG	polyethylene glycol
PGA	Physician's Global Assessment of disease activity
PK	pharmacokinetic(s)
PT	prothrombin time
PTM	placebo-to-match
PTT	partial thromboplastin time
Q1	1st quartile
Q3	3rd quartile
RA	rheumatoid arthritis
RNA	ribonucleic acid
RR	respiratory rate
RT-PCR	reverse transcription polymerase chain reaction
SADR	serious adverse drug reactions
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SI	international system of units
SOC	standard of care
SOP	standard operating procedure
SSMT	Sponsor Safety Management Team
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAEs	treatment emergent adverse events
TNFα	tumor necrosis factor alpha
TYK	tyrosine kinase
UC	ulcerative colitis
UGT	uridine 5'-disphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
vs.	versus

WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

Inflammatory bowel disease (IBD) comprises 2 distinct pathologic entities, ulcerative colitis (UC) and Crohn's disease (CD).

1.1.1. 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}, whereas Europe has the highest reported prevalence at 505 per 100,000 persons for UC. The annual incidence of UC is 24.3 per 100,000 person-years in Europe and 6.3 per 100,000 person-years in Asia {Molodecky 2012}. The incidence and prevalence of UC appear to be increasing over time globally.

The hallmark symptoms of UC 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. UC 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 carries an increased risk of colorectal cancer{Ungaro 2016}. With poorly controlled disease, the rate of developing colorectal cancer increases with time. The incidence 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 an elevated 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 (TNFα) antagonist infusion or injection, such as infliximab (Remicade®), adalimumab (Humira®), or golimumab (Simponi®). Vedolizumab (Entyvio®), an injectable integrin α4β7 monoclonal antibody, and tofacitinib (Xeljanz®), a Janus kinase (JAK) 1/3 inhibitor, are indicated for adults with moderately to severely active UC. Ustekinumab (Stelara®, CNTO 1275; an interleukin (IL)-12 and IL-23 monoclonal antibody), upadacitinib (JAK inhibitor), etrolizumab (PRO145223; monoclonal antibody targeting the β7 subunit of the heterodimeric integrins α4β7 and αEβ7), risankizumab (IL-23 antibody) and ozanimod (RPC1063; selective S1P1 and S1P5 receptor agonist) are currently being tested in Phase 3 clinical trials. 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.

1.1.2. Crohn's Disease

CD is a form of IBD caused by inflammation of the luminal surface of the gastrointestinal tract that, in contrast to UC, can extend through the full thickness of the gastrointestinal wall to the serosal surface. Any segment of the gastrointestinal tract may be affected, and discontinuous regions of involvement may occur. CD is characterized by phenotype (inflammatory, stricturing, or penetrating subtypes) and by location and extent of involvement. The incidence and prevalence of CD have been increasing, with bimodal peaks affecting young adults (15 to 35 years of age) and older adults aged 50 to 70 years. The overall incidence of CD in the Northern Hemisphere ranges from 7 to 20 per 100,000 person years, with Europe having the highest reported prevalence at 322 per 100,000 persons. In the US and Europe, up to 1.5 million individuals may be affected, and CD incidence is rising in parts of Asia and the Middle East {Molodecky 2012}.

CD is a relapsing and remitting disorder characterized by diarrhea, abdominal pain, weight loss, and the passage of blood or mucus per rectum. Stricture formation can result in intestinal obstruction requiring surgical management. Over time, patients with repeated surgeries are at risk for developing short bowel syndrome and/or intestinal failure. Penetrating disease is characterized by fistula formation (bowel to bowel, bowel to skin, or bowel to adjacent organ such as bladder or vagina) that may also require surgical management. Penetrating disease can manifest with intra-abdominal abscess, a condition which can be life threatening if not treated early with systemic antibiotics. CD may affect other organ systems leading to rashes, joint pain and stiffness, fever, and weight loss {Baumgart 2012}. The cause of CD is poorly understood, however a complex interplay of genetic predisposition, aberrant immune activation, and early infection during childhood may be involved. The importance of environmental triggers is suggested by increasing incidence seen during industrialization and with improved domestic hygiene and sanitation. This "hygiene hypothesis" has also been implicated in various other autoimmune disorders {Ventham 2013}.

To assess disease severity in CD, a number of clinical scoring systems are utilized. The CDAI is a one such scoring tool with scores ranging from 0 to over 600 based upon a composite of symptoms (eg, abdominal pain), signs (eg, abdominal mass), laboratory values (ie, hematocrit), and complications (eg, arthritis/arthralgia), among other patient attributes. In this scoring system, patients with a score > 220 are defined as having moderately to severely active disease; these patients comprise the population with the greatest unmet medical need. The CDAI can also be used to determine how well a therapy is working, with therapeutic remission defined as a CDAI of < 150 points {Dignass 2010}.

The Simple Endoscopic Score for Crohn's Disease (SES-CD) was first validated in 2004 and has been used extensively in clinical trials. It measures presence and size of ulcers, proportion of surface affected with ulcers, proportion of surface affected by other lesions, and the presence and severity of stenotic lesions {Daperno 2004}. The bowel is divided into segments (ileum, right colon, transverse colon, left colon, and rectum) and each segment is scored individually, then the segment scores are summed for a total score (range: 0 to 60).

Over the last decade, therapeutic goals for CD have begun to extend beyond symptomatic control and to include long-term mucosal and endoscopic remission {Cheifetz 2013} in order to slow down or halt disease progression, avoiding surgeries and hospitalizations. Risk assessment and prediction by means of complex clinical, biochemical, and endoscopic markers have become the key to patient management, therapy optimization, and prediction of the therapeutic outcome and side effects. Currently available biologic therapies for CD focus on neutralizing cytokine activity or altering T-cell differentiation and homing. Three monoclonal antibodies which inhibit tumor necrosis factor alpha (TNFα), are currently marketed for the treatment of CD: infliximab (Remicade®), adalimumab (Humira® [approved in US and European Union {EU}]), and certolizumab pegol (Cimzia® [approved in US]). Vedolizumab (Entivyo®), a monoclonal antibody against $\alpha_4\beta_7$ integrin is also approved for moderately to severely active CD. Recently, ustekinumab (Stelara®), a monoclonal antibody directed against the p40 subunit of IL-23 and an antagonist for both IL-12 and IL-23 signaling, has been approved for the treatment of CD. Leukocytapheresis therapy may be used in Japan {Fukunaga 2012}. Other investigational treatment approaches include the administration of cytokines to stimulate innate immunity, the use of prebiotics to alter the gut flora, and blocking the IL-6 signaling pathway {Ito 2004, Korzenik 2016}. New treatments being tested in clinical trials include JAK inhibitors (eg, upadacitinib), and new biologic agents such as IL-23 p19 antagonists (eg, risankizumab) and a monoclonal antibody directed against β_7 integrin (eg, etrolizumab). While the introduction of biologic therapies has significantly improved response rates in patients with moderately to severely active CD, long-term or durable remission rates are still low at approximately 20%. Many patients receiving biologic therapies develop neutralizing antibodies with resulting loss of efficacy. These agents may be associated with specific safety issues including but not limited to anaphylaxis, increased risk of infection including progressive multifocal leukoencephalopathy, and liver injury. Safe and effective treatment options which may be conveniently administered in a chronic setting would provide a significant treatment advance for patients with moderately to severely active CD.

1.2. Filgotinib (GS-6034)

1.2.1. General Information

Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases (TYKs) that transduce cytokine signaling from membrane receptors through signal transducer and activator of transcription (STAT) to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine 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 subjects with RA and those with CD in Phase 2 studies.

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, carcinogenicity studies in rats and in transgenic (TgrasH2) mice, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study. A definitive juvenile toxicology study in rats is ongoing.

1.2.2.1. Nonclinical Pharmacology

In cellular assays, filgotinib inhibits JAK1 signaling with 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 (~70 receptors, ion channels, transporters and enzymes) did not reveal any off-target liabilities of the compound. Filgotinib demonstrated high potency in the rat collagen-induced arthritis (CIA) model as well as in the mouse dextran sulfate sodium (DSS)-induced colitis model, the latter of which is detailed below. The major human metabolite of filgotinib GS-829845 exhibits a similar JAK1 selectivity profile but is approximately 10-fold less potent as compared to parent filgotinib in vitro.

The efficacy of filgotinib was evaluated in a prophylactic setting of the chronic mouse DSS 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 TNFα (by RT-PCR) by filgotinib. Immunohistochemical analysis of the colon confirmed inhibition of the JAK-STAT pathway by filgotinib as evidenced by a reduction of DSS-induced STAT3 phosphorylation.

1.2.2.2. Safety Pharmacology

Filgotinib and GS-829845 had no relevant effects on cardiovascular parameters (human ether-a-go-go-related gene [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_{50}: 8.7 µM) and GS-829845 (IC_{50}: 67 µM). The clinical relevance of the IC_{50} values for inhibition of OCT2 will be further evaluated. MATE1 was also weakly inhibited by filgotinib (IC_{50}: 94 µM) and GS-829845 (IC_{50}: >100 µM). Filgotinib was found to be a substrate of P-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 general in the repeat-dose toxicity studies were generally similar to those of the parent filgotinib, however no testicular toxicity was noted following administration of GS-829845.

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

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

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

1.2.3. Clinical Trials of Filgotinib

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

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

A Phase 2, randomized, double-blind, placebo-controlled, multicenter study with filgotinib was performed in subjects with active CD with evidence of mucosal ulceration {Vermeire 2017}. In Part 1, a total of 174 subjects were randomized (3:1) to receive either filgotinib 200 mg once daily or placebo for 10 weeks. Based on their clinical response in Part 1, subjects in Part 2 either continued their current treatment or were reassigned to a different treatment for an additional 10 weeks.

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

The primary 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). 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.

1.2.3.2. Phase 2b/3 Studies in Ulcerative Colitis (GS-US-418-3898, SELECTION)

These are 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. Protocol GS-US-418-3898 consists of induction and maintenance studies, enrolling biologic-naïve and biologic-experienced subjects. The primary endpoint of the induction study for each cohort is the efficacy of filgotinib compared to placebo in establishing endoscopy/bleeding/stool remission at Week 10. The primary endpoint of the maintenance study for each cohort is the efficacy of filgotinib at establishing endoscopy/bleeding/stool remission at Week 58.

In May 2018, an independent Data Monitoring Committee (DMC) conducted an interim futility analysis after 350 subjects had completed the induction studies. The DMC recommended that the trial proceed as planned.

1.3. Rationale for this Study and Proposed IBD Population

Over the last decade, changes in IBD treatment strategies, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for subjects with IBD. Despite these developments, therapeutic challenges remain. A subset of patients respond to currently available biologic therapy while others lose response over

time or are intolerant over time. There is an unmet medical need for simple, orally administered therapies with novel and targeted mechanisms of action that can effectively improve the disease course while being safe and well tolerated. Filgotinib is an orally administered, small molecule inhibitor of JAK1, an intracellular tyrosine kinase dysregulated in subjects with inflammatory disorders including IBD. Filgotinib has demonstrated a favorable safety and tolerability profile in a Phase 2 study in subjects with moderately to severely active CD, where it was efficacious at inducing clinical remission at 10 weeks (Section 1.2.3.1). Filgotinib is presently being evaluated in Phase 3 studies in CD, UC, and RA. Filgotinib is also being evaluated in psoriatic arthritis, ankylosing spondylitis, Sjögrens syndrome, cutaneous lupus erythematosus, uveitis and lupus membranous nephritis.

While providing a treatment option for subjects with moderately to severely active UC or CD, the present study seeks to evaluate the impact, if any, of filgotinib on spermatogenesis in humans. The observed effects of filgotinib on the testes are consistent across the non-clinical species tested, with observations of histopathological changes in testes and epididymides, together with reductions in sperm counts and reduced fertility in the rat. A mechanistic study in the rat suggested a reversible direct impact on the genes involved in cell cycle. A dose of 200 mg once daily of filgotinib results in an estimated mean clinical AUC of 2.67 µg•h/mL in subjects with CD, which represents an exposure margin of 2.5, 1.9, and 3.6-fold when considering the mean AUC in male dogs at the no-observed-effect-levels (NOELs) in the 26-week and 39-week chronic toxicity studies, and 39-week targeted exposure toxicity study, respectively. The present study seeks to assess the impact on men of filgotinib at 200 mg, the highest proposed dose in the Phase 3 program, assessed by the proportion of subjects who experience a $\geq$ 50% decrease in sperm concentration from Baseline when compared with placebo after 13-weeks of therapy. The proposed study design and subject population for GS-US-418-4279 have been selected to generate clinical safety data which would be broadly applicable to patient populations with IBD and other chronic inflammatory diseases other than IBD.

The present study (Gilead Study Code GS-US-418-4279; Galapagos Study Code: GLPG0634-CL-228) has been designed in accordance with FDA's Guidance for Industry: Testicular toxicity: Evaluation During Drug Development (October 2018) and has also been guided by CHMP Scientific Advice EMEA/H/SA/2380/1/ FU/2/2016/III, 01 April 2016) and input received based on discussions with FDA and regulators in the EU. The study population will consist of subjects with either moderately to severely active UC (defined as a Mayo Clinic Score of $\geq$ 6, with endoscopic subscore $\geq$ 2 and Physician's Global Assessment $\geq$ 2) or moderately to severely active CD (defined as a CDAI score of $\geq$ 220 and SES-CD of $\geq$ 6 [or $\geq$ 4 in cases of CD limited to the ileum and/or right colon]). Subjects must have demonstrated a prior treatment failure/intolerance to UC or CD therapy, respectively but will be allowed to remain on permitted therapy, with the exception of sulfasalazine which will be prohibited due to known risks of oligospermia and infertility {Pharmacia & Upjohn Co 2014}. Subjects will be stratified by baseline sperm concentration and type of underlying IBD (ie, UC versus CD). In addition, subjects will also be stratified by use of methotrexate (MTX; yes or no) given its potential impact on spermatogenesis. There have been case reports of reversible oligospermia and azoospermia with treatment with MTX {Sussman 1980}, though a small case series in 26 men with psoriasis aged 33 to 52 treated with MTX at a dose of 25 mg

weekly did not reveal any impact of MTX on mean sperm count motility and morphology {El-Beheiry 1979}.

Subjects with mildly decreased testosterone will also be included in the study. The incidence of low testosterone increases with increasing age. The crude incidence of androgen deficiency in 1 large cohort (the Massachusetts Male Aging Study) was 12.3% overall, but increased with increasing age: 5.9% at 40 to 49 years, 11.2% at 50 to 59 years, and 23.3% at 60 to70 years {Araujo 2004}. One cohort demonstrated a prevalence of hypogonadism in men aged 45 and older (based on total testosterone < 300 ng/dL) of 38.7% {Mulligan 2006}. The present study will include men with testosterone levels at or above 80% of normal, given the expected incidence of hypogonadism in the upper age range of the study population.

1.3.1. Rationale for the Outcome Measures

While no single sperm parameter can predict fertility potential, sperm concentration may be considered the most reliably quantifiable parameter that has potential utility in providing information about male fertility{U. S. Department of Health and Human Services (DHHS) 2018}. Sperm concentration may also be considered the most important parameter of testicular dysfunction {Sikka 2016}. The present study will evaluate the reduction in sperm concentration of ≥ 50% or more from baseline at 13 weeks as the primary endpoint in accordance with the FDA draft guidance. Significant variations in sperm parameters are expected in men; a threshold of a ≥ 50% reduction, is considered the appropriate threshold to account for normal variability and is consistent with prior studies evaluating impact of potential testicular toxins {Hellstrom 2008, Hellstrom 2003, Jarvi 2008, Sikka 2014}. Substantial intra- and inter- subject variation can occur particularly in sperm count in patients with and without fertility issues; in one cohort, sperm counts ranged over an order of magnitude in a single healthy patient over time {Keel 2006}. Two semen samples will be collected for evaluation at each time point during this study, with controlled abstinence periods before each sample collection; longer or shorter abstinence periods may have an impact on quality of sample. Ejaculate volume and sperm number are markedly reduced during periods of high ejaculation frequency {Oldereid 1984}. Significant variability is noted even in healthy subjects {World Health Organization (WHO) 1999, World Health Organization (WHO) 2010}. Additional sperm parameters at 13 weeks will be evaluated as secondary endpoints in alignment with the FDA guidance.

The primary endpoint at Week 13 will enable a direct assessment versus placebo in subjects with moderately to severely active UC or CD. Endpoints at 26 weeks of therapy have been chosen for secondary analyses to assess impact after 2 full spermatogenesis cycles in accordance with draft guidance, which recommends treatment for 26 weeks for drugs that are chronically dosed. The 26-week endpoint will also allow assessment of the impact of longer-term therapy on semen parameters, given the expectation for chronic dosing of therapy in the real world setting. Finally, in the present study, total motility, which is considered to be more consistently measured across observers, will remain as a secondary endpoint.

In this study the Mayo Clinic Score (MCS) will be utilized to define moderately to severely active UC for the purpose of eligibility. The minimum MCS of 6 (including endoscopic and physician global assessment scores of 2 or 3) ensures that subjects will have endoscopic evidence of disease (ie, active disease), have active symptoms (eg, blood in the stool or increased stool

frequency), and be determined by the provider to have moderately to severely active UC. After randomization, the partial MCS will be utilized to determine Responder, Non-responder, and Disease Worsening status for subjects with UC.

The CDAI score and SES-CD will be jointly used to define moderately to severely active CD, ensuring that subjects with CD will have active symptoms of the corresponding severity as well as endoscopic evidence of active disease for eligibility. After randomization, the CDAI score will be used to determine Responder, Non-responder, and Disease Worsening status for subjects with CD.

This study is based upon real-world outpatient clinical practice, where central endoscopy does not play a role in initiation of therapy, and where clinical signs/symptoms (and labs as applicable) and a provider's assessment are adequate to assess therapeutic response or non-response. This approach has been endorsed by the Toronto Consensus in 2015 {Bressler 2015}. Safety and tolerability will be assessed by the evaluation of adverse events (AEs), selected clinical laboratory parameters, vital signs, physical examinations, and ECGs all of which are standard safety evaluations in clinical development. All subjects who experience a $\geq$ 50% decrease in sperm concentration and/or total motility and/or morphology will be followed for one or more spermatogenesis cycles, up to 1 year as needed, to assess for sperm parameter reversibility.

1.3.2. Rationale for the Choice of Dose and Dosing Interval

The 200 mg once daily dose level of filgotinib is currently the highest clinical dose being evaluated in Phase 3 studies of RA, UC, and CD. 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). 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.

1.4. Risk/Benefit Assessment for the Study

Inflammatory bowel diseases are progressive and potentially life-threatening disorders 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 their 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. To assess this potential risk to male fertility, the male safety clinical study described herein is planned to examine the effect of filgotinib (if any) on sperm/ejaculate parameters. Male subjects who enroll will be appropriately consented via the ICF wherein risk language is highlighted. Impaired spermatogenesis is considered to be a potential risk for filgotinib. Refer to the IB for further information about nonclinical and clinical testicular findings.

Filgotinib has shown an increased risk in 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. As a result, highly effective contraception and male condoms will be required for male subjects with female partners of child bearing potential, which 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 treatment arms have increased incidences of infection versus placebo. In the present protocol, treatment interruption and discontinuation considerations surrounding infections are incorporated, and sites and investigators will be trained regarding such circumstances. All subjects will be screened for tuberculosis (TB), and subjects with active or untreated latent 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 surveillance in accordance with local guidelines, 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 the Phase 2 study (FITZROY) of subjects with CD. 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 high density lipoproteins (HDL) and no significant change in low density lipoproteins (LDL). Lipid and hemoglobin effects represent potential benefits in this population.

Overall clinical findings and laboratory changes reported with filgotinib are consistent with JAK 1 inhibition. Based on Phase 2 data the expected benefit of using filgotinib as proposed in this study is considered to outweigh any associated risks. In addition, the subject population in the present study will consent to a risk of potentially permanent infertility, thus individual male subjects in conjunction with the treating physician may evaluate the benefit-risk profile of filgotinib. A lack of response contingency from Week 13 onward in the current study, targeting Non-responders at Week 13 and any subject who experiences Disease Worsening thereafter, will enable early access to active drug or standard of care treatment when clinically indicated. This rescue approach, the provision of best supportive care, and the limited study duration, makes the use of placebo ethically acceptable for the specified duration.

An external multidisciplinary DMC, including an expert in male fertility, will be appointed to monitor the study.

The DMC has monitored the study until the date of protocol amendment 6, including the data for the second unblinded interim analysis (IA2). As of amendment 6, the DMC will be decommissioned. Details on the DMC's role have been described in a specific charter. The DMC's role will be transferred to the internal Sponsor Safety Management Team (SSMT). The SSMT is not involved in the conduct of the study and will evaluate safety data throughout the remainder of the study as part of continuous safety oversight across the filgotinib program.

Taking all of these considerations into account with respect to the filgotinib program, the early signals for efficacy demonstrated in a Phase 2 clinical trial in CD, as well as the beneficial findings in nonclinical models of disease and the overall safety, tolerability, and PK characteristics of filgotinib elucidated to date, there is a favorable benefit-risk profile for this agent in continued development as a treatment for UC and CD. The overall benefit-risk balance of this study is considered favorable.

For additional information about the risks of filgotinib, reference the latest version of the filgotinib IB.

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

- To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 13

The secondary objectives of this study include:

- To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 26
- To evaluate the effect of filgotinib on sperm total motility at Weeks 13 and 26
- To evaluate the effect of filgotinib on total sperm count at Weeks 13 and 26
- To evaluate the effect of filgotinib on the change from baseline in sperm concentration at Weeks 13 and 26
- To evaluate the effect of filgotinib on ejaculate volume at Weeks 13 and 26
- To evaluate the effect of filgotinib on sperm morphology at Weeks 13 and 26

The exploratory objectives of this study include:

- To evaluate the reversibility of observed effects of filgotinib on testicular function in subjects who experience a ≥ 50% decrease in sperm concentration, and/or motility and/or morphology
- To evaluate the effect of filgotinib on sex hormones, including luteinizing hormone (LH), follicle stimulating hormone (FSH), inhibin B, and total testosterone at Weeks 13 and 26
- To evaluate the safety and tolerability of filgotinib
- To characterize the plasma pharmacokinetics (PK) of filgotinib and its metabolite (GS-829845, formerly CCI)

3. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled Phase 2 study in adult males with moderately to severely active UC, or moderately to severely active CD, who may be on protocol-specified concomitant therapy.

Up to 250 males between the age of 21 and 65 years (inclusive) at the time of consent will be randomized to receive up to 26 weeks of filgotinib 200 mg or placebo-to-match (PTM) filgotinib 200 mg once daily, to ensure approximately 200 subjects are evaluable.

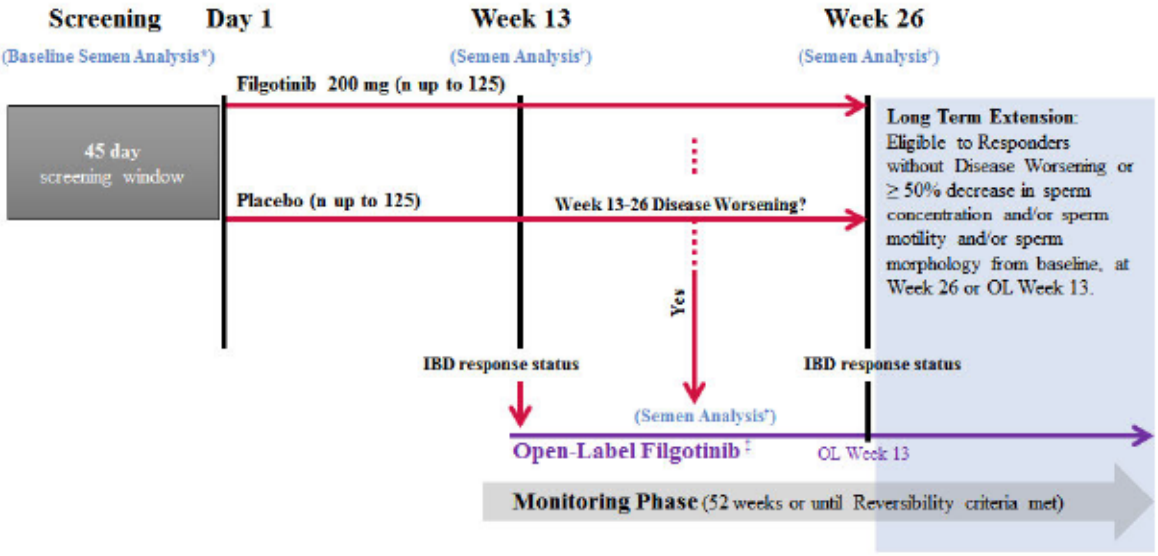
Randomization will be stratified according to the type of IBD (ie, UC versus CD), by concurrent use of MTX (yes or no), and by sperm concentration measured at Screening ("Baseline") according to the following strata:

- 15 to 25 million/mL
- > 25 to 50 million/mL
- > 50 million/mL

Male subjects with moderately to severely active IBD who provide written informed consent will be screened to determine eligibility as per the inclusion and exclusion criteria (see Section 4.2 and 4.3, respectively). The Screening period will be up to 45 days, and may be extended in consultation with the medical monitor.

The assessments to be performed at each visit are detailed in the study procedures table (Appendix 2). A schematic of the study design is provided below.

Figure 3-1. Study Schema



*A mean of 2 semen samples at Screening must meet the following minimum criteria: semen volume ≥ 1.5 mL, total sperm/ejaculate ≥ 39 million, sperm concentration ≥ 15 million/mL, sperm total motility ≥ 40%, and normal sperm morphology ≥ 30%
†All subjects with ≥ 50% decrease in sperm concentration and/or sperm motility and/or sperm morphology as compared to baseline will enter a Monitoring Phase (discontinue study drug and evaluate for Reversibility)
‡ At/after Week 13, protocol design allows a switch to open-label filgotinib for Non-responders or those with Disease Worsening; semen analysis is required to confirm that no pre-specified decrease threshold is met, prior to administration of open-label filgotinib

There are 5 distinct parts to the study which subjects may enter depending upon the individual response of the underlying IBD to assigned treatment and/or observed changes in semen parameters. The 5 parts which are described in the following sections comprise of the following:

1) Part A (Day 1 through Week 13 Study Visit)

2) Part B (After Week 13 through Week 26 Study Visit)

3) Open-Label Filgotinib Phase

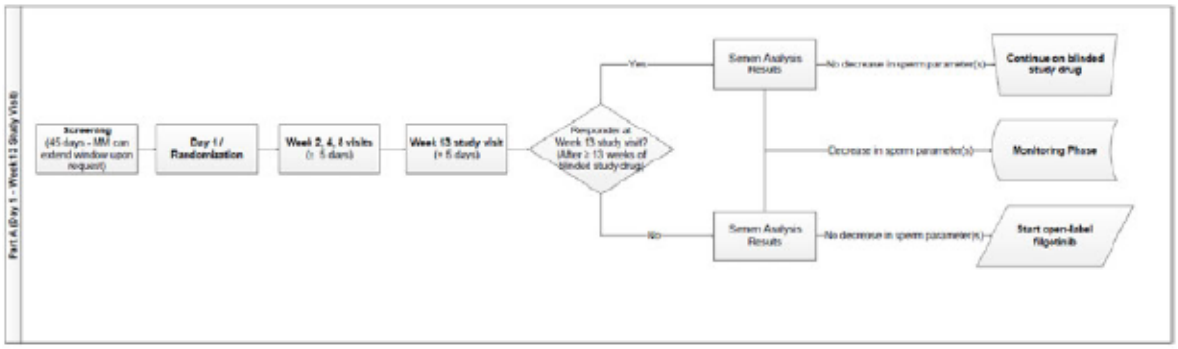
4) Monitoring Phase

5) Long Term Extension

The study parts are described in the following sections.

Subjects will visit the clinical study center to be evaluated for clinical and laboratory assessments at Screening, Day 1, Week 2, Week 4, Week 8, and Week 13, including semen sample collection during Week 13 visits. Subjects who continue on blinded treatment after the first 13 weeks of treatment will return for Week 20 and Week 26 assessments, including semen sample collection during Week 26 visits.

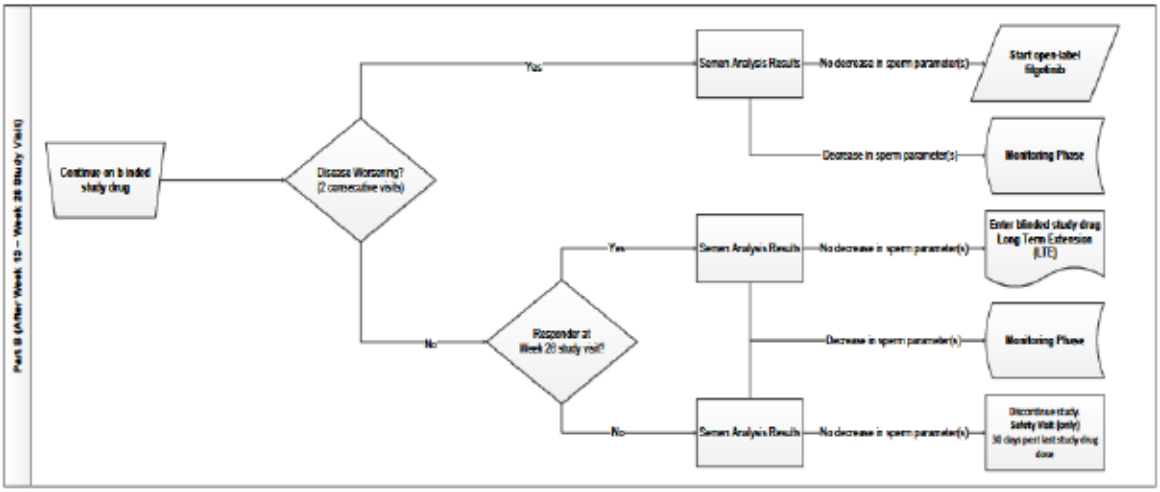
Figure 3-2. Part A (Day 1 through Week 13 Study Visit)



In Part A, all subjects will receive blinded study drug for the first 13 weeks, starting from the Day 1/Randomization Study Visit. At the Week 13 Study Visit, IBD response status (ie, Non-responder vs Responder, see Definition of Terms) will be determined based on the partial Mayo Clinic Score (partial MCS) for subjects with UC, or Crohn's Disease Activity Index (CDAI) for subjects with CD. In addition, sperm parameters (see Section 6.13 Semen Collection Procedure) will be evaluated to determine whether any of the pre-specified decrease thresholds (see Definition of Terms) have been met.

- Subjects who are Responders whose sperm parameters do not meet a pre-specified decrease threshold will continue blinded study drug in Part B.
- Subjects who are Non-responders whose sperm parameters do not meet a pre-specified decrease threshold will discontinue blinded study drug and commence open-label (OL) filgotinib.
- Subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of IBD response status, will discontinue blinded study drug and enter the Monitoring Phase.

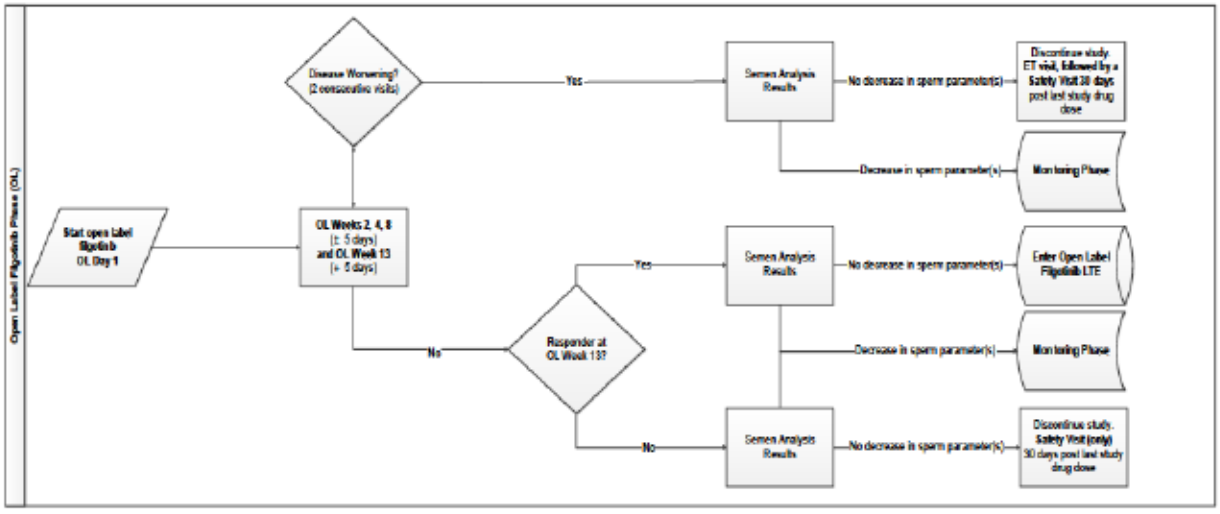
Figure 3-3. Part B (After Week 13 through Week 26 Study Visit)



In Part B, all subjects will continue on blinded study drug for up to an additional 13 weeks. Subjects may experience Disease Worsening (see Definition of Terms) of their underlying IBD at any time during blinded study drug treatment (after Week 13 through Week 26). If Disease Worsening is confirmed, sperm parameters will be evaluated to determine whether a pre-specified decrease threshold has been met prior to a study drug change (changing from blinded study drug to OL filgotinib). Based upon the sperm parameters at this time point, subjects may follow one of the following pathways:

- All subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of IBD response status, will discontinue blinded study drug, complete a safety follow-up visit 30 days after last study drug dose, and enter the Monitoring Phase.
- Subjects who experience Disease Worsening after Week 13 and prior to Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold will discontinue blinded study drug and commence OL filgotinib.
- Subjects who do not experience Disease Worsening, are Responders at Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold, will continue blinded study drug as part of the Long Term Extension (LTE).
- Subjects who do not experience Disease Worsening, but are Non-responders at Week 26, and whose sperm parameters do not meet a pre-specified decrease threshold, will discontinue blinded study drug and complete a safety follow-up visit 30 days after last study drug dose.

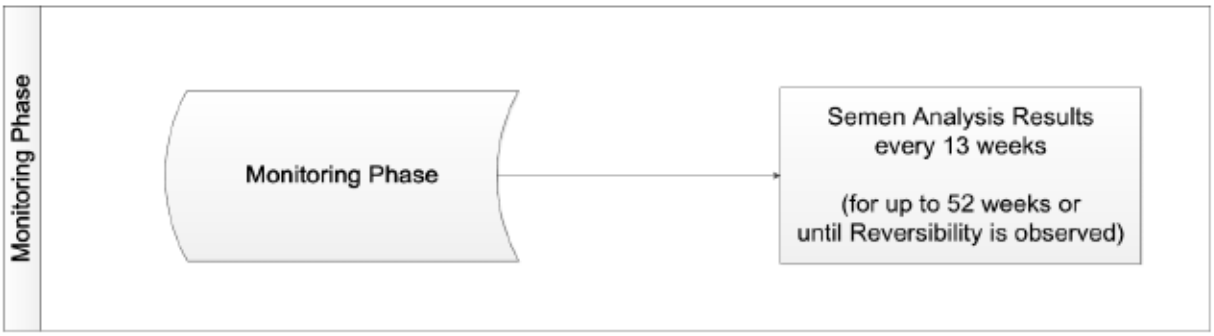
Figure 3-4. Open-Label Filgotinib Phase (Open-Label Day 1 through Open-Label Week 13 Study Visit)



As above, after the first 13 weeks of exposure to blinded study drug those subjects who are deemed Non-responders at Week 13 or those who meet Disease Worsening criteria after Week 13 and prior to Week 26 may qualify for entry into the OL Filgotinib Phase and return for study assessments at OL Day 1, OL Week 2, OL Week 4, OL Week 8, and OL Week 13. After exposure to 13 weeks of OL filgotinib in the OL Filgotinib Phase, the subject's IBD response status will again be determined using the partial MCS (in the case of UC) or CDAI score (in the case of CD), and sperm parameters will be evaluated to determine whether a pre-specified decrease threshold has been met:

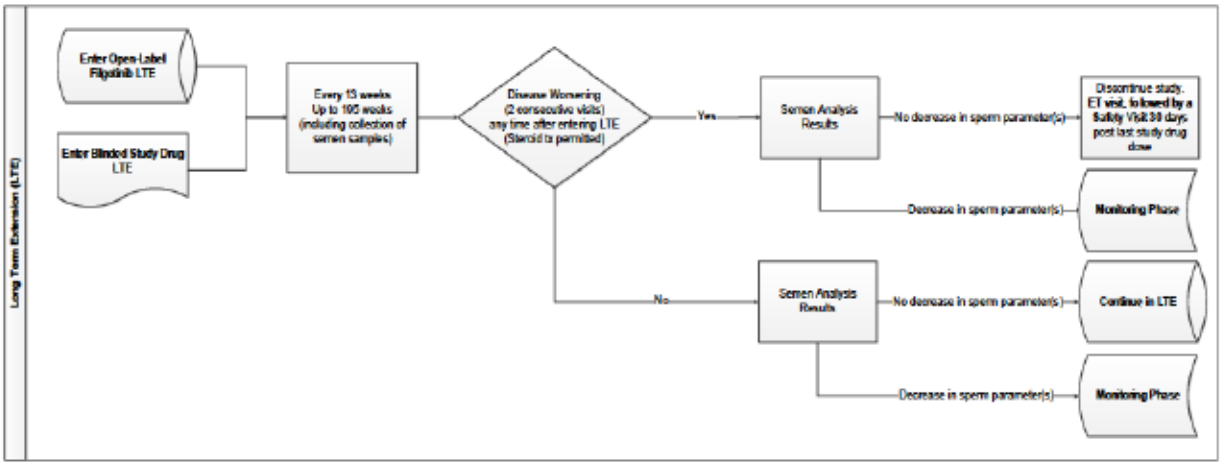
- All subjects whose sperm parameters meet a pre-specified decrease threshold, regardless of Responder status, will discontinue OL filgotinib, complete a safety follow-up visit 30 days after last study drug dose, and enter the Monitoring Phase.
- Subjects who experience Disease Worsening during OL filgotinib treatment and whose sperm parameters do not meet a pre-specified decrease threshold will discontinue OL filgotinib, complete Early Termination (ET) and a safety follow-up visit 30 days after last study drug dose.
- Subjects who do not experience Disease Worsening, and are Responders at OL Week 13 after exposure to 13 weeks of OL filgotinib, and whose sperm parameters do not meet a pre-specified decrease threshold, will continue receiving OL filgotinib as part of the LTE.
- Subjects who do not experience Disease Worsening, but are Non-responders after exposure to 13 weeks of OL filgotinib, and whose sperm parameters do not meet a pre-specified decrease threshold, will discontinue OL filgotinib and complete a safety follow-up visit 30 days after last study drug dose.

Figure 3-5. Monitoring Phase (up to 52 weeks)



All subjects who enter the Monitoring Phase will undergo semen evaluations every 13 weeks from the day of study drug discontinuation, for up to 52 weeks or until Reversibility is met, whichever is achieved first. Subjects will be offered locally approved SOC therapy during the Monitoring Phase.

Figure 3-6. Long Term Extension (up to 195 weeks)



Subjects continuing on to the LTE will undergo scheduled visits for safety assessments every 13 weeks up to 195 weeks, and semen monitoring will be collected every 13 weeks until the Week 13 primary study results are analyzed. All subjects who enter the LTE will receive either OL filgotinib or blinded study drug based on the individual's response criteria described above. If a subject experiences Disease Worsening during the LTE, the treatment (either OL filgotinib or blinded study drug) will be discontinued, and the subject will receive locally approved SOC therapy as determined by the primary investigator. Subject will complete an ET visit, followed by a safety follow-up visit 30 days after last study drug dose.

Sparse plasma PK Sample Collection:

In Parts A and B, sparse plasma PK samples will be collected at least 30 minutes post dose at the Week 2 visit, anytime at the Week 4 visit, and predose during visits at Weeks 13 and 26. In the OL Filgotinib Phase, sparse plasma PK samples will be collected at least 30 minutes post dose at the OL Week 2 visit, anytime at the OL Week 4 visit, and predose during visits at OL Week 13.

Semen Collection and Analysis:

At each of the following time points, subjects will provide 2 separate semen samples collected within a 14-day period. Each semen sample must be collected with an ejaculation free period of $\geq$ 48 hours and $\leq$ 7 days (Section 6.13).

- Screening (Baseline)
- After Part A (Week 13 Study Visit)
- After Part B (Week 26 Study Visit)

  OR

  For Subjects who experience confirmed Disease Worsening between Weeks 13-26 in Part B, prior to beginning OL Filgotinib Phase and at the OL Week 13 Study Visit

- Every 13 weeks during the Monitoring Phase (if applicable)
- Every 13 weeks during the LTE

In select instances where the semen sample with questioned value(s) is found to be non-assessable or invalid (eg, collection without adherence to ejaculation-free periods; intercurrent illness or dehydration at time of collection; incomplete capture of semen sample; and/or sample processing or semen analysis that deviates from standardized procedure), a third semen sample, when indicated, must be collected within 14 days of the prior sample, with an ejaculation free period of ≥ 48 hours and ≤ 7 days. All decisions of retesting any semen/sperm parameter (ie, obtaining a third semen sample at any of the above time points) must be confirmed by the Sponsor Medical Monitor or designee before the retest.

3.1. Study Treatments

Up to 250 subjects will be randomized in a 1:1 ratio (within strata) to receive filgotinib 200 mg once daily or PTM filgotinib 200 mg once daily.

3.2. Duration of Treatment

The duration of treatment is approximately up to 26 weeks of blinded study drug and up to 13 weeks of OL filgotinib (if eligible). Subsequently, for subjects qualifying, this will be followed by an LTE lasting up to 195 weeks. Subjects whose sperm parameters meet a pre-specified decrease threshold at any time during the study will discontinue study drug and should be managed with allowed standard of care therapy. These subjects will be followed in the Monitoring Phase of the study, for up to 52 weeks or until Reversibility (see Definition of Terms) of all parameters meeting sperm decrease threshold is met, whichever is achieved first.

3.3. Criteria for Interruption or Discontinuation of Study Treatment

3.3.1. Study Drug Interruption Considerations

The medical monitor or designee should be consulted prior to study drug interruption, when medically feasible. Study drug interruption should be considered in the following circumstances:

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

- After becoming aware of a laboratory change representing moderate renal failure (estimated creatinine clearance [CrCl] ≥35 mL/min and <60 mL/min per Cockcroft-Gault [CC&G] formula) at any time during the study, the following actions should be taken and documented:
  - Establish possible underlying condition and initiate appropriate action to resolve.
  - Retest CrCl within 8 weeks.
  - Carefully consider individual benefit/risk of continuation of filgotinib 200 mg once daily in relation to the observation.
  - If continuation of filgotinib 200 mg once daily is not considered appropriate, interrupt treatment until retest confirms CrCl ≥60 mL/min.
  - The principal investigator/deputy should assess individual patient benefit/risk with regards to re-initiation of treatment after repeat or prolonged interruptions, or if re-initiation is not considered appropriate. Consultation with the Sponsor medical monitor or designee is preferred in these situations.

During the time of study drug interruption, subjects are to continue with Study Visit participation and complete study procedures and assessments, deemed medically appropriate by the investigator.

After study drug interruption, prior to resumption of study drug, the investigator should discuss the case with the medical monitor or designee.

The medical monitor should consult the medical leader as needed.

3.3.2. Study Drug Discontinuation Considerations

The medical monitor or designee should be consulted prior to study drug discontinuation, when medically feasible.

Study drug should be permanently discontinued in the following instances:

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

- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin < 7.5 g/dL, or if transfusion is indicated regardless of hemoglobin value
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active HCV during the study, as evidenced by HCV RNA positivity
- Evidence of active HBV during the study, as evidenced by HBV DNA positivity
- Any thromboembolic event that meets SAE reporting criteria
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- A ≥ 50% decrease from Baseline (based on the mean of 2 separate semen samples collected at the Screening visit) in sperm concentration, and/or motility and/or morphology
- Subject request to discontinue for any reason
- Subject noncompliance to the protocol
- Discontinuation of the study at the request of the Sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subject's use of prohibited concurrent therapy *may* trigger study discontinuation; consultation should be made with the medical monitor or designee
- Worsening of UC or CD requiring intensification of therapy beyond what is allowed in the protocol or requiring the use of a prohibited medication
- Subjects with newly positive (converted) QuantiFERON® [or centrally reported equivalent assay] TB test and any subject with active TB should be discontinued from study drug.
- Any of the below described abnormal laboratory changes occurring at any one time, and confirmed by repeat testing (refer to guidelines detailed in Appendix 8):
  - 2 sequential neutrophil counts < 0.75×10^9 cells/L (750 neutrophils/mm^3)
  - 2 sequential platelet counts < 75.0×10^9 cells/L (75,000 platelets/mm^3)

- 2 sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations > 3x the upper limit of normal (ULN) and at least 1 of the following confirmed values: a) total bilirubin > 2x ULN, b) international normalized ratio (INR) > 1.5, or c) 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 elevations > 5x ULN

- 2 sequential values for estimated CrCl < 35 mL/min based on the CC&G formula

Subjects who permanently stop blinded study drug due to Non-response at Week 13 or Disease Worsening after Week 13 through Week 26, will be offered OL 200 mg once daily filgotinib, and those subjects should be encouraged to continue on study, if deemed medically appropriate by the investigator. Subjects who permanently stop study drug due to meeting a pre-specified decrease threshold in sperm parameters (Section 3.4) will be offered locally approved standard of care therapy as part of the Monitoring Phase.

Subjects withdrawing from the study should complete an ET visit, followed by a safety follow-up visit 30 days after last dose of study drug.

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

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 drug or the company occur, that makes further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

The medical monitor should consult the medical leader as needed.

3.4. Disease Worsening Criteria

Subjects meeting the following Disease Worsening criteria, evaluated after Week 13 through Week 26, must be discontinued from blinded treatment. These subjects will be offered the option to commence OL filgotinib 200 mg once daily, as long as they have not experienced a decrease of ≥ 50% from baseline in sperm concentration, and/or motility, and/or morphology.

Upon confirmation of Disease Worsening and before switching to the OL Filgotinib Phase, 2 semen samples will be collected. Disease Worsening is confirmed at the time of the second consecutive visit. If the second Disease Worsening visit occurs during the 14-day semen

collection window for the Week 13 or Week 26 Study Visit, the routine Week 13 or Week 26 semen collection will suffice.

Disease Worsening assessments will be driven by the patient history, physical and laboratory examinations and are based on the following criteria:

For subjects with UC, Disease Worsening is defined by a partial MCS after Week 13 consisting of:

- An increase of ≥ 3 points to at least 5 points from the Week 13 value on 2 consecutive visits, OR
- An increase to 9 points from the Week 13 value on 2 consecutive visits, if the Week 13 value was > 6 points

For subjects with CD, Disease Worsening is defined by a total CDAI score after Week 13 consisting of:

- A score ≥ 220 on 2 consecutive visits, AND
- An increase of ≥ 100 points from the Week 13 value on 2 consecutive visits

For all subjects, Disease Worsening is further defined by:

- Disease Worsening to the extent that the subject requires medications prohibited by the study (at investigator's discretion, with discussion with the medical monitor or designee if feasible); these subjects do not qualify to receive OL filgotinib 200 mg once daily.

Disease Worsening visits may include Unscheduled Visits (eg, a Study Visit followed by an Unscheduled Visit, or 2 sequential Unscheduled Visits after Week 13).

In the LTE, subjects who meet Disease Worsening criteria (per above criteria), or have Disease Worsening per investigator judgment, should be discontinued from study drug. These subjects should complete an ET visit (which includes semen collection), followed by a routine safety follow-up visit 30 days after the last dose of study drug.

3.5. End of Study

End of Study is reached when the last subject completes the LTE Week 195 visit, or when the last subject completes his last visit, whichever is sooner.

3.6. Post-Study Care

Upon completion of study participation, the long-term care of subjects will remain the responsibility of their primary treating physician.

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 250 subjects with moderately to severely active UC or CD will be enrolled in the study to ensure approximately 200 subjects are evaluable at Week 13. Enrollment will be evaluated during the course of the study, and may be expanded if the dropout rate is higher than expected.

4.2. Inclusion Criteria

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

1) Able to understand and willing to sign the informed consent as approved by the IRB/IEC. Written consent must be provided before initiating any Screening evaluations. Subjects must have read and understood the informed consent form (ICF), must fully understand the requirements of the study, and must be willing to comply with all study visits and assessments; subjects who cannot read or understand the ICF may not be enrolled in the study by a guardian or any other individual.

2) Males between the age of 21 and 65 (inclusive) on the day of signing informed consent

3) Body mass index (kg/m^2) of $\geq$ 18.5 to $\leq$ 40 at Screening, with no evidence of malnutrition as determined by the investigator

4) Documented diagnosis of UC or CD of at least 4 months duration. Documentation must include endoscopic and histopathologic documentation, as follows:

   a) UC

      i) Medical record documentation of, or an endoscopy report dated $\geq$ 4 months before randomization, which shows features consistent with UC, determined by the procedure performing physician, AND

      ii) Medical record documentation of, or a histopathology report indicating features consistent with UC as determined by the pathologist, AND

      Note: Subject also needs to have minimum disease extent of 15 cm from the anal verge

b) CD

i) Medical record documentation of, or an ileocolonoscopy (full colonoscopy with intubation of terminal ileum) reported dated ≥ 4 months before randomization, which shows features consistent with CD, determined by the procedure performing physician, AND

ii) Medical record documentation of, or a histopathology report indicating features consistent with, CD as determined by the pathologist

5) Moderately to severely active UC, or moderately to severely active CD, assessed locally and defined by:

a) UC

i) Mayo Clinic Score (MCS; Appendix 3) ≥ 6, Physician Global Assessment (PGA) of 2 or 3, and endoscopic subscore ≥ 2, at Screening or in the prior 90 days

b) CD

i) CDAI total score (Appendix 9) ≥ 220, AND

ii) Evidence of active inflammation, with a total score of ≥ 6 by the Simple Endoscopic Activity Score in Crohn's Disease (SES-CD; Appendix 10), OR if disease is limited to the ileum and/or right colon, a combined SES-CD score ≥ 4 in these 2 segments, at Screening or in the prior 90 days

6) 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) Corticosteroids

i) Active disease despite a history of at least an induction regimen of a dose equivalent to prednisone ≥20 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 (≥ 2 mg/kg/day) or 6 MP (≥ 1 mg/kg/day), or MTX (25 mg subcutaneously [SC] or intramuscularly [IM] per week for induction and ≥ 15 mg IM per week for maintenance), OR

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

c) TNFα antagonists

   i) Active disease despite an induction regimen with a TNFα antagonists (infliximab, adalimumab, golimumab [UC only], or certolizumab [CD only]), or corresponding biosimilar prescribed at a dose and duration consistent with the approved product labeling, OR

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

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

d) Vedolizumab

   i) Active disease despite an induction regimen prescribed in accordance with the approved product labeling, OR

   ii) Recurrence of symptoms during maintenance therapy with vedolizumab, OR

   iii) 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

e) Ustekinumab [criterion applicable only to subjects with CD]

   i) Active disease despite an induction regimen prescribed in accordance with the approved product labeling, OR

   ii) Recurrence of symptoms during maintenance therapy with ustekinumab, OR

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

7) May be receiving 1 or more of the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted times):

   a) 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 13 weeks after randomization

   b) Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose of MTX must remain stable for 26 weeks, and dose of AZA/6-MP must remain stable for the first 13 weeks, but can be adjusted if indicated between 13 and 26 weeks.

   c) Corticosteroid therapy (prednisone prescribed at a stable dose ≤ 20 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day); dose should not be changed during the first 13 weeks. A steroid taper should only commence after Week 13.

8) The mean of 2 separate semen samples collected at the Screening visit must meet the following minimum criteria (in accordance with Section 6.13 and Figure 6-1): semen volume ≥ 1.5 mL, total sperm per ejaculate ≥ 39 million, sperm concentration ≥ 15 million per mL, sperm total motility ≥ 40%, and normal sperm morphology ≥ 30%

9) LH, FSH, inhibin B, and total testosterone values within 20% of laboratory reference ranges at Screening

10) Subjects who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 5, including use of condoms during the study and for 90 days after the last dose of study drug

11) Willingness to refrain from receiving live attenuated vaccines within 30 days of Day 1, throughout the study, and for 12 weeks after the last dose of study drug (Section 5.4, Vaccine Guidelines).

12) Meet one of the following 3 tuberculosis (TB) Screening criteria:

   a) No evidence of active or latent TB:

      — A negative QuantiFERON® TB-Gold Plus In-Tube test at Screening, AND

      — 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

      — No history of either untreated or inadequately treated latent TB infection

b) Previously treated for TB:

— A subject who 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 alternative regimen according to local country guidelines) or active TB (acceptable multi-drug regimen). In these cases, no QuantiFERON® TB-Gold Plus In-Tube test (or a centrally reported equivalent assay) needs to be obtained

— A chest radiograph must be obtained if not done 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:

— A subject who has a newly identified positive diagnostic TB test result (defined as a positive QuantiFERON® TB Gold Plus In-Tube test or equivalent assay), in which active TB has been ruled out and for which appropriate ongoing treatment for latent TB has been initiated for at least 4 weeks prior to the first administration of study drug.

— Adequate treatment for latent TB is defined according to local country guidelines for immunocompromised patients.

Cases falling under category "b" and "c" must be approved by the Gilead medical monitor or designee prior to enrollment in the study. No subject with currently active TB or untreated latent TB may be enrolled in the study. If a subject had a QuantiFERON® TB-Gold Plus In-Tube test for the purposes of clinical care or for the purpose of Screening for another Gilead-sponsored study within 60 days, the prior result may be used to assess eligibility.

13) Laboratory parameters need to be met as per below

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

b) Estimated CrCl ≥ 40 mL/min as calculated by the CC&G equation

c) Hemoglobin ≥ 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

14) Be up to date on colorectal cancer surveillance (per local guidelines) prior to Screening.

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study. [Note: "Screening" refers to the first day of Screening]

1) Previously documented problems with male reproductive health including, but not limited to, known hypothalamic-pituitary disorders (eg, pituitary macroadenomas, pituitary infarction, hyperprolactinemia, panhypopituitarism), primary hypogonadism (eg, cryptorchidism, Klinefelter's syndrome)

2) Prior diagnosis of male infertility (including reduced fertility), or history of anti-sperm antibodies

3) Clinically significant (per judgment of investigator) varicocele or spermatocele

4) History of radiation to the testicles

5) History of clinically significant trauma to, or surgery on, the testicles, including vasectomy

6) Current treatment with antiandrogen therapy (including but not limited to spironolactone or oral ketoconazole), or treatment within 4 weeks of Screening

7) Current treatment with testosterone replacement therapy, or treatment within 12 weeks of Screening

8) Current treatment with 5-α reductase inhibitors (including but not limited to finasteride and dutasteride)

9) Current treatment with alpha-1 blockers (including but not limited to tamsulosin, doxazosin, prazosin)

10) Current use of sulfasalazine or use of sulfasalazine within 26 weeks of Screening; sulfasalazine is not permitted at any point during the study

11) Current use of alkylating agents or any recognized testicular toxin within 26 weeks of Screening (may be discussed with Gilead medical monitor or designee)

12) Treatment with cyclosporine or other calcineurin inhibitors within 30 days of Screening

13) Use of any TNFα antagonist or vedolizumab within 8 weeks prior to Screening, ustekinumab within 12 weeks prior to Screening, or any other biologic agent within 8 weeks prior to Screening or within 5 times the half-life of the biologic agent prior to Screening, whichever is longer

14) Use of any prohibited concomitant medication(s) as described in Section 5.3

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

16) Presence of disorders of sperm transport including, but not limited to, retrograde ejaculation and immotile cilia syndrome

17) Clinically significant urinary tract infection, prostatitis, epididymitis, including sexually transmitted infection within 4 weeks of Screening

18) Positive urine test for amphetamines or cocaine; positive test to opioids without a prescription, or heavy tobacco use (current use of $\geq$ 2 packs per day equivalent)

19) Uncontrolled thyroid dysfunction (eg, untreated hypothyroidism or hyperthyroidism)

20) Any sexual dysfunction of a nature that would prevent sperm collection in accordance with protocol guidance (phosphodiesterase inhibitors, however, are permitted during the study)

21) History of major surgery or trauma within 30 days prior to Screening, or anticipated need for major surgery during the study

22) History of total colectomy, subtotal colectomy, partial or hemi-colectomy, ileostomy, colostomy, or anticipated need for any of these interventions during the study

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

    a) Symptomatic strictures, OR

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

    c) Fistulae, OR

    d) Short bowel syndrome, OR

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

24) Have any current or prior abscesses, unless they have been drained and treated at least 6 weeks prior to Day 1, and are not anticipated to require surgery during the study

25) Indeterminate colitis, ischemic colitis, fulminant colitis, isolated ulcerative proctitis, or toxic mega-colon

26) Dependence on parenteral nutrition

27) History or evidence of incompletely resected colonic mucosal dysplasia

28) Screening stool sample positive for *Clostridium difficile* (*C. difficile*) toxin, pathogenic *Escherichia coli* (*E. coli*), *Salmonella* species (spp), *Shigella* spp, *Campylobacter* spp or *Yersinia* spp, or ova and parasites (O&P), unless approved by the Gilead medical monitor or designee

29) Current use of steroids at a dose > 20 mg/day of prednisone equivalents at randomization

30) Administration of a live attenuated vaccine within 30 days of Randomization (see also Section 5.4, Vaccine Guidelines)

31) A positive test result for HIV-1 or HIV-2 (See Appendix 6)

32) Evidence of active HCV infection. Subjects with positive HCV antibody (Ab) at Screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA at Screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment. Subjects with active HCV during the study, as evidenced by HCV RNA positivity will be discontinued from study drug as outlined in the protocol.

33) Evidence of active HBV infection. Subjects with positive Hepatitis B surface antigen (HBsAg) at Screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at Screening will be excluded. Subjects with positive HBV core Ab and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months. Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol.

34) Presence of Child-Pugh Class C hepatic impairment

35) History of malignancy within the past 5 years prior to Screening, (exception will be made for adequately treated basal cell carcinoma or non-metastatic squamous cell carcinoma of the skin, with no evidence of recurrence)

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

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

38) History of leukocytapheresis ≤ 6 months prior to Screening

39) 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, would make the subject unsuitable for the study or would prevent compliance with the study protocol procedures

40) 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)

41) History of opportunistic infection or immunodeficiency syndrome

42) Currently on any systemic (oral or intravenous) anti-infective therapy for chronic infection (such as pneumocystis pneumonia (PCP), cytomegalovirus (CMV), herpes zoster, atypical mycobacteria)

43) History of disseminated *Staphylococcus aureus* infection

44) 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

45) Participation in any clinical study of an investigational device within 30 days, investigational non-biologic drug within 30 days, or investigational biologic drug within 8 weeks (or 5 half-lives, whichever is longer), prior to Screening.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

An Interactive Web Response System (IWRS) will be employed to manage subject randomization and treatment assignments. It is the responsibility of the investigator to ensure that the subject is eligible for the study prior to enrollment. Subjects will be assigned a Screening number at the time of consent.

5.1.1. Randomization

Subjects who meet randomization eligibility criteria will be randomized in a 1:1 ratio to Filgotinib 200 mg or PTM filgotinib 200 mg starting on Day 1, and assigned a subject number. Randomization will be stratified by type of IBD (UC versus CD), concurrent use of MTX (yes or no), and sperm concentration (15-25 million/mL; >25 to 50 million/mL; or > 50 million/mL) based on the mean of 2 eligible semen samples collected at Screening.

5.1.2. Blinding

During the randomized phase, subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between the Sponsor and vendors, will remain unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS system for purposes of study drug inventory management will remain unblinded. Individuals responsible for safety signal detection, investigational new drug (IND) safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case data and/or group level summaries. External (ie, Contract Research Organizations [CROs]) Biostatisticians and Programmers will be unblinded to produce tables, figures, and listings for unblinded review at DMC meetings, and the external biostatistician will serve as the external statistician to the DMC. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

For ongoing subjects, the study teams and study staff at the sites and all other staff directly involved in the conduct of the study will remain blinded to the treatment assignments until the final analysis when the database has been locked. Publication of the IA2 data is planned by the Sponsor. This publication will contain group level data for the entire study population, but will unblind the study teams and staff directly involved in the conduct of the study to the individual baseline treatment assignment of subjects who completed the study before IA2.

5.1.3. 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 the individual subject treatment assignment directly from the IWRS system. The Sponsor recommends, but does not require, that the investigator contact the medical monitor or designee before breaking the blind. Treatment assignments should remain blinded unless that knowledge is necessary to determine emergency medical care for the subject. The rationale for unblinding must be clearly explained in source documentation and on the electronic case report form (eCRF), along with the date on which the treatment assignment was unblinded. The investigator is requested to contact the medical monitor or designee promptly in case of any treatment unblinding.

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

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

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

5.2.1. Formulation

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

Placebo-to-match (PTM) filgotinib 200 mg tablets are identical in appearance to the active tablets. Placebo-to-match (PTM) filgotinib 200 mg tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, macrogol/polyethylene glycol (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 and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice - Annex 13 (Investigational Medicinal Products) and/or other local regulations, as applicable.

5.2.3. Storage and Handling

Filgotinib and PTM filgotinib tablets, should be stored at controlled room temperature of 25 °C (77 °F). Temperature variability between 15 °C and 30 °C (59 °F to 86 °F) are permitted and are not considered excursions. Storage conditions are specified on the label.

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

5.2.4. Dosage and Administration of Filgotinib

Filgotinib and PTM filgotinib tablets will be administered once daily, with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For missed dose(s) of study medication, subjects should be instructed to take the missed dose of study medication as soon as possible during the same day. Subjects should not take the missed dose with the next day's dose (ie, double dose). Missed dose(s) or unused study drug should not be discarded.

5.3. Prior and Concomitant Medications

All medications taken up to 30 days prior to the Screening visit through the end of subject's participation in the study need to be recorded in the source documents and on the eCRF. There should be no variation in dose or regimen during the study, if possible. At each study visit, the study center will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription, non-prescription medications, dietary supplements, and minerals.

Effective current therapies should not be discontinued for the sole purpose of participating in this study. Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the Investigator or the subject's physician. Should subjects have a need to initiate treatment with any excluded concomitant medication, the medical monitor or designee must 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 must notify the Sponsor as soon as he/she is aware of the use of the excluded medication.

5.3.1. Allowed Concomitant Medications

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

The allowed medications for UC and for CD are as follows:

- Oral 5-ASA compounds, provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for the first 13 weeks after randomization.
- Azathioprine, 6-MP, or MTX, provided the dose prescribed has been stable for 4 weeks prior to randomization; dose of MTX must remain stable for 26 weeks, and dose of AZA/6-MP must remain stable for the first 13 weeks, but can be adjusted if indicated between 13 and 26 weeks.
- Corticosteroid therapy (prednisone prescribed at a stable dose $\leq$ 20 mg/day or budesonide prescribed at a stable dose of $\leq$ 9 mg/day); dose should not be changed during the first 13 weeks. A steroid taper should only commence after Week 13.

Concomitant Steroid Management:

Starting at Week 13, subjects who are on concomitant steroids may begin tapering steroid therapy at the discretion of the investigator. Steroids may be increased or restarted if return of symptoms is apparent (but dose may not exceed 20 mg prednisone equivalent).

5.3.2. Prohibited Concomitant Medications

The prohibited medications while on study are as follows:

Table 5-1. Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Prohibited Period
Strong P-gp Inducers[a]		
Anticonvulsants	Phenobarbital, phenytoin, and carbamazepine	21 days prior to Screening through the end of the study
Antimycobacterials	Rifabutin, rifapentine, and rifampin	
Herbal/Natural Supplements	St. John's wort and danshen (Salvia Miltiorrhiza)	
Prohibited IBD Medications[d]		
Corticosteroids	Dose equivalent to > 20 mg/day of prednisone	Randomization through the end of the study (unless in Monitoring Phase)
TNFα antagonist	Infliximab, adalimumab, golimumab, certolizumab, and biosimilar agents	8 weeks prior to Screening through the end of the study (unless in Monitoring Phase)
Integrin antagonist	Vedolizumab and natalizumab	8 weeks prior to Screening through the end of the study (unless in Monitoring Phase)
Interleukin antagonist	Ustekinumab	12 weeks prior to Screening through the end of the study (unless in Monitoring Phase)
JAK inhibitor	Any JAK inhibitor other than filgotinib	90 days prior to Screening through the end of the study (unless in Monitoring Phase)
	Filgotinib	Any time prior to Randomization in this study
Other (non-biologic)	Cyclosporine, thalidomide, tacrolimus, leflunomide, and any investigational agent	30 days prior to Screening through the end of the study
Other (biologic)[c]	Any investigational biologic agent	8 weeks (or 5 half-lives, whichever is longer) prior to Screening through the end of the study
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
Sulfa drugs	Sulfasalazine	Current use of sulfasalazine or use of sulfasalazine within 26 weeks of Screening. Sulfasalazine is not permitted at any point during the study
Other Prohibited Medications		
Chronic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)[b]	Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, COX-2 inhibitors	From Screening through the end of the study

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_{max} by 64% and AUC_{inf} by 45% and had no effect on the major, active metabolite GS-829845.

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

c Other approved biologics (eg, antibody based or other systemic biologics) may be allowed with the approval of the medical monitor or designee who will also specify the corresponding prohibited period

d Subjects who discontinue study drug and enter the Monitoring Phase, will be offered locally approved SOC therapy; in this case, concomitant medications in the above table may be permitted upon discussion with the medical monitor or designee

5.4. 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 attenuated vaccines (including, but not limited to, varicella and intranasal influenza vaccines) 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 live attenuated (oral) typhoid vaccines – avoid contact for 4 weeks following household contact vaccination
  - Live attenuated (oral) polio vaccine – avoid contact for 6 weeks following household contact vaccination
  - Live attenuated rotavirus vaccine – avoid contact for 10 days following household contact vaccination
  - Live attenuated (intranasal) influenza vaccine – avoid contact for 1 week following household contact vaccination
- Inactivated vaccines (such as inactivated influenza 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.

5.5. Accountability for Study Drugs

The investigator is responsible for ensuring adequate accountability of all used and unused study drugs. This includes acknowledgement of receipt of each shipment of study drugs (quantity and condition). All used and unused study drugs 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, the investigational medicinal product (IMP) number dispensed
- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information
- Dispensing records will include the initials of the person dispensing the study drug or supplies

5.5.1. Investigational Medicinal Product Return or Disposal

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

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

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

For both disposal options listed above, the study monitor must first perform drug accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

The study assessments as described below will be performed at the time points specified in the Study Procedures Table (Appendix 2).

The investigator must document any deviation from protocol procedures and notify the sponsor or CRO.

6.1. Subject Enrollment and Treatment Assignment

Subject eligibility will be established at the conclusion of the Screening evaluations. The subject ID will be assigned for each subject by IWRS.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before randomization and the start of treatment. A subject will be considered enrolled once they have been randomized.

Subjects who meet protocol criteria will be randomized to filgotinib 200 mg or PTM filgotinib 200 mg once daily.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

Subjects will be screened within 45 days before randomization to determine eligibility for participation in the study. The 45 day Screening period may be extended in consultation with the medical monitor. Refer to the Study Procedure Tables in Appendix 2 *for a complete list of assessments to be performed and documented at Screening:*

- Obtain written informed consent
- Obtain demographics and medical history (including onset of IBD, prior number of children fathered, disease characteristics, smoking habits, average weekly alcohol consumption, and family history of premature coronary heart disease)
- Review Inclusion / Exclusion Criteria
- Complete Physical Exam (PE) as detailed in Appendix 7
- Vital signs, weight and height
- Perform standard 12-Lead ECG

- QuantiFERON® test and Chest X-ray (CXR) (if applicable). QuantiFERON® 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 TB or newly identified latent TB during Screening require sponsor approval (See Inclusion Criterion No. 12 for details). Subjects who are diagnosed with latent TB at Screening must initiate an adequate course of prophylaxis according to local country guidelines for immunocompromised patients for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the medical monitor or designee. If a subject had a QuantiFERON® test for the purposes of clinical care or Screening for another Gilead-sponsored study within 60 days, the prior Gilead result may be used to assess eligibility with permission of the medical monitor or designee.
- Urinalysis, including a urine drug screen
- Obtain blood samples for:
  - Hematology and Serum Chemistry
  - Serology
  - Quantitative Ig subclasses
  - Endocrine tests: Thyroid stimulating hormone (TSH), HbA1c
  - Sex hormones, including LH, FSH, inhibin B, and total testosterone to be collected between 07:00 – 11:00 in the morning, if possible
- Stool Collection for:
  - *C. difficile* toxin, *E. coli, Salmonella spp, Shigella spp, Campylobacter spp* and *Yersinia spp* testing
  - Ova & Parasites (O&P)
- Review and collection of concomitant medications
- Record all serious adverse events (SAEs) and any AEs related to protocol-mandated procedures occurring after signing of the consent form
- Semen collection (2 separate collections in accordance with Section 6.13) and record date and time of last ejaculation prior to sample. Semen collection should be collected to coincide with baseline visit as much as possible.

- For subjects with UC, collect the variables to calculate baseline MCS (Definition of Terms and Appendix 3), including performing flexible sigmoidoscopy unless performed in the 90 days prior to Screening. The MCS is composed of sub-scores from endoscopy, rectal bleeding, stool frequency, and PGA. Subject recall of the last 24 hours will be used for the patient reported components of the MCS. For the complete MCS, PGA will be evaluated after reviewing the endoscopy.

- For subjects with CD, collect the variables to calculate baseline total CDAI score (Definition of Terms and Appendix 9) and to calculate baseline SES-CD (Definition of Terms and Appendix 10), including performing ileocolonoscopy unless performed in the 90 days prior to Screening. Subject recall of the last 7 days will be used for the patient reported components of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.

A single retest of any exclusionary screening lab (non-semen samples) is permitted:

- at the discretion of the investigator, if the initial exclusionary value is invalid due to a documented error in sample collection or laboratory processing, OR

- upon the approval of the Sponsor Medical Monitor or designee, if there is an extenuating circumstance around the exclusionary value.

Retesting of exclusionary parameters in Screening semen samples is discussed in Section 6.13

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic after Screening, for randomization into the study.

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

6.2.1.1. Rescreening

Subjects who do not meet the eligibility criteria will not be randomized, but may be considered for a single rescreening after consultation with, and approval by, the Sponsor Medical Monitor or designee. Subjects who are rescreened do not need to have a repeat QuantiFERON® and/or CXR, if these were performed within 90 days of written consent for rescreening, unless a repeat is deemed appropriate by the investigator.

6.2.2. Day 1 Assessments

On Day 1, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive filgotinib 200 mg or PTM filgotinib 200 mg once daily. Study drug will be dispensed as assigned by the IWRS system. The subject will take the first dose in clinic. Invasive study procedures such as blood draws should be done at the end of the Study Visit. The following will be performed and documented at Day 1 prior to dosing:

- Review Inclusion / Exclusion Criteria
- Symptom-driven physical examination, as needed
- Vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Weight (without shoes)
- Physician's Global Assessment [applied only to subjects with UC]
- Obtain blood samples for:
  - Hematology and Serum Chemistry
  - Lipid profile (fasting) [Total cholesterol and subfractions]
  - Sex hormones, including LH, FSH, inhibin B, and total Testosterone to be collected between 07:00 – 11:00 in the morning, if possible
- Urinalysis
- Review concomitant medications
- Record any adverse events related to protocol mandated procedures and all serious adverse events (SAEs) occurring after signing of the consent form.

6.3. Randomization

Subjects will be randomly allocated to dosing group according to a pre-specified randomization scheme prepared by an independent statistician. Once confirmed eligible for the study, subjects will be randomized using a computerized IWRS system to filgotinib 200 mg or PTM filgotinib 200 mg in a 1:1 ratio, within strata.

Randomization will be stratified according to the type of IBD (UC versus CD), concurrent use of MTX (yes or no), and sperm concentration measured at Screening ("Baseline") according to the following strata:

- 15 to 25 million/mL
- > 25 to 50 million/mL
- > 50 million/mL

6.4. Part A (Day 1 through Week 13 Study Visit)

All subjects will receive blinded study drug for the first 13 weeks.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2) and Figure 3-2.

Invasive study procedures such as blood draws should be done at the end of a Study Visit, as much as possible.

6.5. Part B (After Week 13 through Week 26 Study Visit)

Subjects who are Responders at Week 13 and whose sperm parameters do not meet a pre-specified decrease threshold will continue blinded study drug in Part B.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2) and Figure 3-3.

Invasive study procedures such as blood draws should be done at the end of a Study Visit, as much as possible.

6.6. Open-Label Filgotinib Phase (Open-Label Day 1 through Open-Label Week 13 Study Visit)

Subjects who are Non-Responders at Week 13 in Part A, or have Disease Worsening after Week 13 and before reaching Week 26 in Part B, will discontinue blinded study drug and commence OL filgotinib in the OL Filgotinib Phase, if subjects' sperm parameters do not meet a pre-specified decrease threshold. Two separate semen samples will be collected and analyzed before switching a subject to OL filgotinib.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2) and Figure 3-4.

6.7. Monitoring Phase

Subjects whose sperm parameters meet a pre-specified decrease threshold during the study will discontinue study drug, complete a safety follow-up visit 30 days after last dose of study drug, and enter the Monitoring Phase. Subjects will be offered SOC therapy as part of the Monitoring Phase, and undergo sperm evaluations every 13 weeks (2 separate samples at each time point) from the day of study drug discontinuation, for up to 52 weeks or until Reversibility is met (see Definition of Terms), whichever is achieved first.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2) and Figure 3-5.

6.8. Early Termination

If a subject discontinues study participation for any reason prior to Week 26, OL Week 13, reaching Reversibility or Monitoring Phase Week 52 (whichever occurs first), or LTE Week 195, ET visit assessments will be completed as specified in the Study Procedures Table (Appendix 2).

Subjects who are Responders at Week 26 and at OL Week 13 and choose not to continue to the LTE will also complete ET visit assessments.

6.9. Safety Follow-Up Visit 30 Days Post Last Dose (±5 days)

Any time a subject discontinues study drug, a safety follow-up visit, 30 days after the last dose of study drug is required, even if the subject is entering the Monitoring Phase.

Study assessments will be completed as specified in the Study Procedures Table (Appendix 2).

6.10. Long Term Extension

Subjects who are Responders at either Week 26 (Part B) or OL Week 13 (OL Phase), and whose sperm parameters do not meet a pre-specified decrease threshold, will enter the LTE and continue on the same drug they were responding to (ie, OL filgotinib or blinded study drug). As specified in the Study Procedures Table (Appendix 2) and Figure 3-6, subjects continuing on to the LTE will undergo scheduled visits for safety assessments every 13 weeks, up to 195 weeks, and semen monitoring will be collected every 13 weeks until the Week 13 primary study results are analyzed.

Subjects in the LTE who meet Disease Worsening criteria as described in Section 3.4 or have Disease Worsening per investigator judgment should be discontinued from study drug. These subjects should complete ET and the safety follow-up visit 30 days after the last dose of study drug.

6.11. Safety and Tolerability

AEs, PE, vital signs, and laboratory assessments (standard hematology, serum/plasma chemistry, and urinalysis) will be collected. Semen samples will be collected in accordance with Section 6.13.

6.12. Clinical Laboratory Evaluations

The hematology and serum chemistry laboratory 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 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. Subjects only need to be fasted on days where lipid profiling is scheduled.

Please refer to Appendix 6 for table of clinical laboratory tests.

The 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 indicated and 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 withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) after the investigator has consulted with the medical monitor or designee. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section 3.3 for additional information).

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

6.13. Semen Collection Procedure

Each subject will provide 2 separate semen samples collected within a 14-day period and with an ejaculation-free period of ≥ 48 hours and ≤ 7 days, at the following time points:

- Screening (Baseline)
- After Part A (Week 13 Study Visit)
- After Part B (Week 26 Study Visit)

  OR

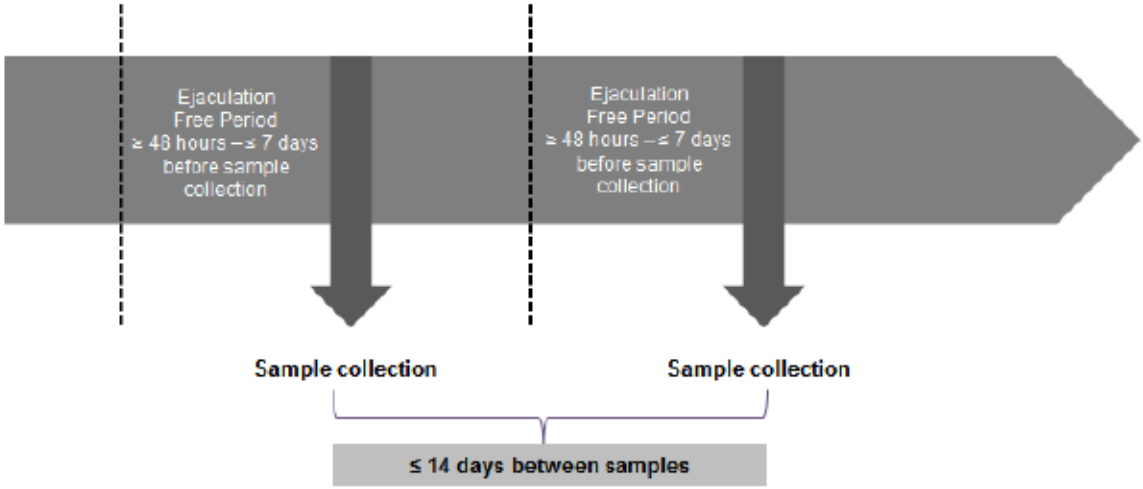
  For Subjects who experience confirmed Disease Worsening between Weeks 13-26 in Part B, prior to beginning OL Filgotinib and at the OL Week 13 Study Visit

- Every 13 weeks during the Monitoring Phase (if applicable)
- Every 13 weeks during the LTE

All decisions of retesting any semen/sperm parameter (ie, obtaining a third semen sample at any of the above time points), must be approved by the Sponsor Medical Monitor or designee before the retest. Such inquiries will only be considered in select instances where the semen sample with the questioned value(s) is found to be non-assessable or invalid (eg, collection without adherence to ejaculation-free periods; intercurrent illness or dehydration at time of collection; incomplete capture of semen sample; and/or sample processing or semen analysis that deviates from standardized procedure). The third semen sample, when indicated, must be collected within 14 days of the prior sample and with an ejaculation-free period of ≥ 48 hours and ≤ 7 days (See Figure 6-1).

At each time point, the mean of 2 separate semen samples for each parameter will be used for the assessment of study eligibility, entry into the Monitoring Phase, and exit from the Monitoring Phase.

Figure 6-1. Semen Collection Schema



A standardized procedure for semen collection and analysis will be provided to sites in a separate manual. Semen will be assessed locally for all parameters (motility, concentration, count, and volume), except morphology, which will be assessed centrally.

6.14. 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 for 5 minutes (please refer to Appendix 7 for details) and will include heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body temperature.

6.15. Physical Examination

A physical examination will be performed at the time points indicated in the Study Procedures Table (Appendix 2).

Any changes from Baseline will be recorded. Height will be measured at Screening only. Weight without shoes is measured at all visits.

A complete physical examination, as detailed in Appendix 7, will be performed at Screening, only. Symptom-directed physical exams will be performed at all other visits, as needed.

6.16. Pharmacokinetic Assessments

In Parts A and B, blood samples for PK analysis will be collected at least 30 minutes post study drug dosing at the Week 2 visit, anytime at the Week 4 visit, and prior to study drug dosing at the Week 13 and 26 visits. In the OL Filgotinib Phase, blood samples for PK analysis will be collected at least 30 minutes post study drug dosing at the OL Week 2 visit, anytime at the OL Week 4 visit, and prior to study drug dosing at the OL Week 13 visit. Subjects should be instructed not to take their study drug on these visit days (except for the Week 4 visit) and bring it with them to the clinic, instead.

Subjects will be instructed when to take their dose during their scheduled visit at the study site.

Plasma concentrations of filgotinib and its metabolite, GS-829845, will be analyzed.

6.17. Thromboembolic Events

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

6.18. Mayo Clinic Score and Partial Mayo Clinic Score

MCS and partial MCS will be assessed at the time points indicated in the Study Procedures Table (Appendix 2). The MCS (Appendix 3) is allowed to have been performed within the 90 days prior to Screening and is composed of sub-scores from endoscopy, rectal bleeding, stool frequency, and PGA. The partial MCS includes the rectal bleeding, stool frequency, and PGA sub-scores. Subject recall of the last 24 hours will be used for the patient reported components of the MCS and partial MCS. For the complete MCS, PGA will be evaluated after reviewing the endoscopy, which will be locally read.

6.19. Simple Endoscopic Score for Crohn's Disease

SES-CD will be assessed at the time points indicated in the Study Procedures Table (Appendix 2). The SES-CD (Appendix 10) is allowed to have been performed within the 90 days prior to Screening and is a composite score of mucosal inflammation consisting of four endoscopic variables (ulcer presence and size; luminal surface covered by ulcers; luminal surface with disease involvement; and stenosis presence and severity). The bowel is divided into segments (ileum, right colon, transverse colon, left colon, and rectum) and each segment is scored individually, then the segment scores are summed for a total score (range: 0 to 60). The SES-CD will be locally read.

6.20. Crohn's Disease Activity Index

CDAI will be assessed at the time points indicated in the Study Procedures Tables (Appendix 2). The CDAI (Appendix 9) is a composite score of CD activity consisting of gastrointestinal symptoms (eg, abdominal pain), signs (eg, abdominal mass), laboratory values (ie, hematocrit), and complications (eg, arthritis/arthralgia), among other attributes. Subject recall for the last 7 days will be used for the patient reported components of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.

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. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an 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 CRF.

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

- **No**: Evidence exists that the adverse event has an etiology other than the study drug. 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 Event (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 4.

Table 7-1. Grading of Adverse Event Severity

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

* Activities of Daily Living (ADL) Instrumental ADL refer to opening preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

Requirements for collection prior to study drug initiation:

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

Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study drug(s) must be reported to the CRF/eCRF database as instructed.

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

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 CRF/eCRF database and the Sponsor as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur during any portion of the study or after study discontinuation but within 30-days of the last dose of study IMP, regardless of causality, should also be reported.

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

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

Requirements for collection in the Monitoring Phase:

During the Monitoring Phase, all AEs ***related*** to protocol-mandated procedures, and all SAEs (regardless of relatedness) should be reported on the case report form (CRF/eCRF).

Electronic Serious Adverse Event (eSAE) Reporting Process

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

Email: MANTA_safety@glpg.com

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.
- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.
- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.
- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by 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 CRF/eCRF and the event description section of the SAE form.

7.4. Sponsor Reporting Requirements

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

Assessment of expectedness for filgotinib SAEs will be determined by the Sponsor or designee using reference safety information specified in the IB. Methotrexate may be used as standard of care therapies in this study; consequently, any SAEs that are attributed to methotrexate by the investigator will be forwarded to its marketing authorization holder.

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

7.5. Clinical Laboratory Abnormalities

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, electrocardiogram, 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 Common Terminology Criteria for Adverse Events (CTCAE).

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 8 and as outlined below.

Refer to Section 3.3, Criteria for Study Drug Interruption or Discontinuation, for additional specific discontinuation criteria. Specific toxicity discontinuation criteria in Section 3.3 supersede below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The medical monitor or designee 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.

- For study specific interruption and stopping criteria, please refer to Section 3.3 (Criteria for Interruption or Discontinuation of Study Treatment)
- For Grades 1 and 2 Laboratory Abnormality or Clinical Event not specified in Section 3.3, continue study drug at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.3 (Criteria for Interruption or Discontinuation of Study Treatment)
- For Grades 3 Laboratory Abnormality or Clinical Event not specified in Section 3.3, the following toxicity management guidelines apply:
  - For Grade 3 clinically significant laboratory abnormality or clinical event, investigational medicinal product may be continued if the event is considered to be unrelated to investigational medicinal product.
  - For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to investigational medicinal product, investigational medicinal product should be withheld until the toxicity returns to $\leq$ Grade 2.

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

7.6.3. Grades 4 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.3 (Criteria for Interruption or Discontinuation of Study Treatment).
- For Grade 4 Laboratory Abnormality or Clinical Events not specified in Section 3.3, the following toxicity management guidelines apply:
  - For a Grade 4 clinical event or clinically significant Grade 4 laboratory abnormality confirmed by repeat testing that is considered related to investigational medicinal product, investigational medicinal product should be permanently discontinued and the subject managed according to local clinical 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 CK after strenuous exercise or triglyceride elevation that is nonfasting or that can be medically managed) or a clinical event considered unrelated to investigational medicinal product.

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

Any questions regarding toxicity management should be directed to the medical monitor or designee. The medical monitor should consult the medical leader as needed.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

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

Abuse is defined as persistent or sporadic intentional excessive use of a 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 is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

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

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

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

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

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Partner Pregnancies

Pregnancies of female partners of male study subjects exposed to the Sponsor's or other study drugs must be reported and relevant information should be submitted to MANTA_safety@glpg.com using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to MANTA_safety@glpg.com.

Refer to Appendix 5 for Pregnancy Precautions, Definition of Females 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 MANTA_safety@glpg.com within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to concomitant medications.

Special situations involving concomitant medications do not need to be reported on the special situations report form; however, for special situations that result in AEs due to a 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 CRF/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 CRF/eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

- To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 13

The secondary objectives of this study are:

- To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 26
- To evaluate the effect of filgotinib on sperm total motility at Weeks 13 and 26
- To evaluate the effect of filgotinib on total sperm count at Weeks 13 and 26
- To evaluate the effect of filgotinib on the change from baseline in sperm concentration at Weeks 13 and 26
- To evaluate the effect of filgotinib on ejaculate volume at Weeks 13 and 26
- To evaluate the effect of filgotinib on sperm morphology at Weeks 13 and 26

The exploratory objectives of this study are:

- To evaluate the reversibility of observed effects of filgotinib on testicular function in subjects who experience a ≥ 50% decrease in sperm concentration, and/or motility, and/or morphology
- To evaluate the effect of filgotinib on sex hormones, including luteinizing hormone (LH), follicle stimulating hormone (FSH), inhibin B, and total testosterone at Weeks 13 and 26
- To evaluate the safety and tolerability of filgotinib
- To characterize the plasma pharmacokinetics (PK) of filgotinib and its metabolite (GS-829845, formerly CCI)

8.1.2. Primary Endpoint

The primary endpoint is the proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 13.

8.1.3. Secondary Endpoints

The secondary endpoints are:

- The proportion of subjects with a ≥ 50% decrease from baseline in sperm concentration at Week 26
- Change from baseline in percent motile sperm at Weeks 13 and 26
- Change from baseline in total sperm count at Weeks 13 and 26
- Change from baseline in sperm concentration at Weeks 13 and 26
- Change from baseline in ejaculate volume at Weeks 13 and 26
- Change from baseline in percent normal sperm morphology at Weeks 13 and 26

8.1.4. Exploratory Endpoints

The exploratory endpoints are:

- Percent of subjects who achieve reversibility among subjects who experience a ≥ 50% decrease in sperm concentration, and/or motility, and/or morphology
- Change from baseline in sex hormones, including LH, FSH, inhibin B, and total testosterone at Weeks 13 and 26
- PK characteristics for filgotinib and its metabolite GS-829845

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized Set

The All Randomized Set includes all subjects who were randomized.

8.2.1.2. Semen Analysis Set

The Semen Analysis Set includes all randomized subjects who have baseline and at least one post-baseline semen sample. This is the primary analysis set for semen-related parameters.

8.2.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least one dose of study drug. This is the primary analysis set for safety endpoints.

8.2.1.4. Pharmacokinetic (PK) Analysis Set

The PK analysis set includes all subjects in the Safety Analysis Set who have at least 1 nonmissing postdose concentration value for filgotinib and/or its metabolite GS-829845. This is the primary analysis set for all PK analyses.

8.3. Data Handling Conventions

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

In general, missing data will not be imputed unless methods for handling missing data are specified. To assess missing semen data patterns, missingness by treatment arm, randomization stratum and baseline demographic characteristics will be summarized. Details on handling missing data and sensitivity analyses will be provided in the statistical analysis plan (SAP).

8.4. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group using standard descriptive statistics including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables and numbers and percentages for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics may include sperm concentration, ejaculate volume, total sperm per ejaculate, and other variables of interest.

8.5. Statistical Analysis

8.5.1. Primary Analysis

The primary endpoint is the proportion of subjects with a $\geq$ 50% decrease from baseline in sperm concentration at Week 13. A cumulative distribution plot for the percent change from baseline in sperm concentration at Week 13 for each treatment group will be constructed. The x-axis will display percent changes from baseline in sperm concentration ranging from 100% decrease (ie, -100 % or azoospermia) to the maximal observed increase. The y-axis will display the proportion of subjects who experienced a percentage change in sperm concentration equal to or less than the corresponding x-axis value at Week 13. This method is suggested in FDA's Guidance for Industry (October 2018): "Testicular toxicity: Evaluation During Drug Development". The proportion of subjects experiencing at least a 50% decrease in sperm concentration from baseline will be calculated for each treatment group. The difference between the filgotinib and placebo groups will be calculated together with the associated 95% confidence interval (CI).

Subjects who have 2 samples available at Week 13 will be included in the primary analysis. Sensitivity analyses will be performed to evaluate the impact of different missing data patterns on the primary analysis. Details of the sensitivity analyses will be provided in the SAP.

8.5.2. Secondary Analyses

The secondary endpoints include the proportion of subjects with a $\geq$ 50% decrease from baseline in sperm concentration at Week 26, and changes from baseline at Weeks 13 and 26 in sperm concentration, total sperm count, ejaculate volume, percent motile sperm, and percent normal sperm morphology.

The continuous endpoints will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group at Weeks 13 and 26 along with corresponding change from Baseline and 95% CIs.

An analysis of covariance (ANCOVA) model adjusting for baseline value and stratification factors will be used to estimate treatment differences (95% CI) for the continuous endpoints. The categorical endpoint at Week 26 will be summarized descriptively.

8.5.3. Exploratory Analyses

The exploratory analyses of sex hormones will use the same analysis methods used for the continuous secondary endpoints. For reversibility, the number and percentage and cumulative number and percentage of subjects who achieve reversibility will be displayed by sperm parameter and monitoring phase visit for those subjects with a $\geq$ 50% decrease in the sperm parameter(s) qualifying them for entry into the monitoring phase.

8.5.4. Other Safety Analysis

All other safety analyses will be performed using the safety analysis set.

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.

All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug, unless specified otherwise, will be summarized by treatment group according to the study drug received.

8.5.5. Extent of Exposure

A subject's extent of exposure to study drug will be generated from the study drug administration page of the eCRF. Exposure data will be summarized by treatment group.

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment group.

8.5.6. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class, 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:

- Any AEs with an onset date on or after the study drug start date and no later than 30 days after permanent discontinuation of study drug or
- 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.

8.5.7. Laboratory Evaluations

Selected laboratory data will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group and Study Visit along with corresponding change from Baseline. The incidence of treatment-emergent graded laboratory abnormalities will be summarized similarly.

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale in Appendix 4.

8.6. Pharmacokinetic Analysis

Plasma concentrations of filgotinib and its metabolite (GS-829845) will be listed and summarized for all subjects using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation (SD), median, minimum, and maximum). Plasma concentrations of the filgotinib and GS-829845 over time may be plotted in semi logarithmic and linear formats as mean ± standard deviation.

Exposure-response analyses may be performed.

8.7. Sample Size

A sample size of approximately 100 evaluable subjects per group, where evaluable is defined as subjects in the Semen Analysis Set, is adequate for the purposes of estimating cumulative distribution curves and producing a 95% confidence interval width that is reasonably narrow for the percentage of subjects in each group who experience a ≥ 50% decrease in sperm concentration compared to baseline. This sample size is suggested in FDA's guidance on testicular toxicity studies {U. S. Department of Health and Human Services (DHHS) 2018}. Assuming a 20% rate of non-evaluable subjects at Week 13, up to 125 subjects per arm may be enrolled.

Results of this study may be pooled with the results of a separate study being conducted in subjects with rheumatic diseases (GLPG0634-CL-227) with the same objective. The total planned number of enrolled subjects in both studies combined will be up to approximately 250 subjects.

8.8. Data Monitoring Committee/Sponsor Safety Management Team

An external DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to the Sponsor 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 is planned to occur after approximately the first 50 subjects reach Week 13. Following this, subsequent meetings will occur approximately every 4 months (if enrollment supports the need). Additional DMC meetings may be scheduled as needed.

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

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

An ad hoc DMC meeting may be triggered by the following conditions or based upon review of emerging semen data:

- ≥ 2 subjects develop the same (by preferred term) related, Grade 4, unexpected adverse event (AE) in the infections and infestations system organ class;
- ≥ 2 subjects develop any related, Grade 4, thromboembolic event that has been positively adjudicated by the adjudication committee (See Section 8.9);
- 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.

The DMC has monitored the study until the date of protocol amendment 6, including the data for IA2. As of amendment 6, the DMC will be decommissioned. The safety and progress of the remainder of the study will continue to be monitored by the Sponsor medical leader and medical monitor, or designee, providing updates during regular Sponsor medical monitoring oversight meetings across the filgotinib program. If needed, safety issues will be escalated to the SSMT per internal standard procedures, including the organization of ad hoc meetings if required. The SSMT can consult external experts, if deemed necessary, and can review data in an unblinded fashion.

8.9. Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

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

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

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

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

Further details will be specified in the CVEAC Charter.

8.10. Internal Independent Safety Review

A Gilead internal unblinded team, independent of the blinded study team, will be assembled. The Gilead internal unblinded team may be granted the access to blinded and unblinded clinical data including treatment assignment to closely monitor semen parameters in real-time. This internal team will be supported by an external expert in male fertility. To mitigate the risk of inadvertently releasing treatment assignment to sites and subjects, the internal team will keep the unblinded information confidential and will not communicate any information to the blinded study team, site staff or subjects. Data unblinding due to medical emergency will follow standard Gilead procedures. Prior to any unblinding of the committee, the Internal Independent Safety Review committee's specific activities will be defined by a mutually agreed upon charter, which will define the committee membership, conduct, and meeting schedule.

As of amendment 6, the Internal Independent Safety Review Team will be decommissioned. Safety reviews will be covered by the SSMT.

8.11. Unblinded Interim Analysis

Unblinded interim analyses of the clinical trial data will be performed by the Sponsor for regulatory submissions when 200 subjects (eg, pooled data from GS-US-418-4279 and GLPG0634-CL-227), and/or when some defined subset(s) of subjects, have completed the Week 13 and Week 26 (or OL Week 13) assessments (first unblinded interim analysis [IA1]), and when complete reversibility data for all subjects who entered the Monitoring Phase at these time points is available (IA2; see Definition of Terms). A Data Integrity and Communication

Plan for the interim analysis will be developed prior to unblinding. The analyses will be conducted primarily to evaluate the testicular safety and further details will be described in the SAP.

For ongoing subjects, the study teams and study staff at the sites and all other staff directly involved in the conduct of the study will remain blinded to the treatment assignments until the final analysis when the database has been locked. Publication of the IA2 data is planned by the Sponsor. This publication will contain group level data for the entire study population, but will unblind the study teams and staff directly involved in the conduct of the study to the individual baseline treatment assignment of subjects who completed the study before IA2.

8.12. Integrated Semen Analysis

As part of the male safety assessment of filgotinib, integrated analyses may be performed in which data from the present study, GS-US-418-4279, will be combined with similar data from a separate study being conducted in subjects with rheumatic disease. The analyses will be conducted primarily to evaluate the testicular safety. Further details of the integrated analysis will be described in the Integrated Semen and Hormone SAP.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with the Sponsor, 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 the Sponsor of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, 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.

Initial submission and substantial amendment(s) should be approved by the national competent authorities before starting of enrollment and/or implementation of changes.

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 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, and their right to receive clinically relevant genomic analysis results.

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. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

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

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all adverse events 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, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with the Sponsor. The investigator must notify the Sponsor before destroying any clinical study records.

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

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

9.1.6. 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 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 Study Procedures Table (Appendix 2). System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or data management staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, the Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Inspections

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

9.1.8. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

The monitor is responsible for routine review of the CRF/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 CRF/eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Sponsor and Investigator Signature Page

GALAPAGOS NV
GENERAAL DE WITTELAAN L11 A3
2800 MECHELEN, BELGIUM

STUDY ACKNOWLEDGEMENT

A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Testicular Safety of Filgotinib in Adult Males with Moderately to Severely Active Inflammatory Bowel Disease

GS-US-418-4279, Amendment #6, 09 September 2022

This protocol has been approved by Galapagos NV. The following signature documents this approval.

An electronic signature of the sponsor's responsible person is provided at the end of the document.

PPD (Clinical Development Leader) in absence of PPD (Medical Leader)

Signature

Date

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Tables

Study Procedure	Screening[a]	Part A (Section 6.4)					Part B (Section 6.5)		Open-Label Filgotinib Phase (Section 6.6)						Long Term Extension (Section 6.10)	30 Day Safety Follow-up[e]	ET[f]
		Day 1	Wk 2	Wk 4	Wk 8	Wk 13[a]	Wk 20	Wk 26[a]	Sperm Parameter Eligibility Confirmation[b]	OL Day 1	OL Wk 2	OL Wk 4	OL Wk 8	OL Wk 13[c]	LTE Week 13 through LTE Week 195[d]		
	45 days		±5 days	±5 days	±5 days	+ 5 days	±5 days	+ 5 days			±5 days	±5 days	±5 days	+ 5 days	±10 days	±5 days	
Informed Consent	X																
Medical History, Number of times subject impregnated women, IBD History, and Demographics	X																
Inclusion/exclusion criteria review	X	X															
Complete Physical Exam[g]	X																
Symptom-directed Physical Exam, as needed		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Vital Signs[g] and Weight	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Height	X																
12-lead ECG[g]	X							X						X	X[h]		X
Flexible Sigmoidoscopy[i]	X																
Ileocolonoscopy[i]	X																
Complete Mayo Clinic Score (complete MCS)[j]	X																
Partial Mayo Clinic Score (partial MCS)[j]		X	X	X	X	X	X	X		X	X	X	X	X	X		X

Study Procedure	Screening[g]	Part A (Section 6.4)					Part B (Section 6.5)		Open-Label Filgotinib Phase (Section 6.6)						Long Term Extension (Section 6.10)	30 Day Safety Follow-up[e]	ET[f]
		Day 1	Wk 2	Wk 4	Wk 8	Wk 13[a]	Wk 20	Wk 26[a]	Sperm Parameter Eligibility Confirmation[b]	OL Day 1	OL Wk 2	OL Wk 4	OL Wk 8	OL Wk 13[c]	LTE Week 13 through LTE Week 195[d]		
	45 days		±5 days	±5 days	±5 days	+ 5 days	±5 days	+ 5 days			±5 days	±5 days	±5 days	+ 5 days	±10 days	±5 days	
Simple Endoscopic Score for Crohn's Disease (SES-CD)	X																
Crohn's Disease Activity Index (CDAI)[k]	X	X	X	X	X	X	X	X		X	X	X	X	X	X		X
TB (QuantiFERON®) Test	X[l]														X[m]		
Chest X-ray[n]	X																
Urinalysis[o]	X	X				X		X		X				X	X		X
Urine drug screen[o]	X																
Hematology and Chemistry[o]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Lipid profile (fasting)[o]		X				X		X		X				X	X[p]		
Serum Immunoglobulin[o]	X					X		X						X	X		
Endocrine: TSH, HbA1c[o]	X																
LH, FSH, inhibin B, total Testosterone[o] collection time between 07:00-11:00 in the morning	X	X		X		X		X		X		X		X	X	X	X
Stool[o]	X																
Concomitant Medications	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Assessment of Adverse Events	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X

Study Procedure	Screening[g]	Part A (Section 6.4)					Part B (Section 6.5)		Open-Label Filgotinib Phase (Section 6.6)						Long Term Extension (Section 6.10)	30 Day Safety Follow-up[e]	ET[f]
		Day 1	Wk 2	Wk 4	Wk 8	Wk 13[a]	Wk 20	Wk 26[a]	Sperm Parameter Eligibility Confirmation[b]	OL Day 1	OL Wk 2	OL Wk 4	OL Wk 8	OL Wk 13[c]	LTE Week 13 through LTE Week 195[d]		
	45 days		±5 days	±5 days	±5 days	+ 5 days	±5 days	+ 5 days			±5 days	±5 days	±5 days	+ 5 days	±10 days	±5 days	
Semen Collection (2 samples as per collection instructions in Section 6.13)[q]	X[r]					X		X	X[s]					X[t]	X		X
Date and time of most recent ejaculation[u]	X					X		X	X					X	X		X
HIV, Hepatitis B, and Hepatitis C[v]	X																
HBV DNA[w]						X		X						X	X		
Randomization		X															
Study Drug Accountability				X	X	X	X	X		X		X	X	X	X		X
Study Drug Dispensation		X		X	X	X	X	X		X		X	X	X	X		
PK collection (sparse)			X[x]	X[y]		X[z]		X[z]			X[x]	X[y]		X[z]			
In-Clinic Dosing[aa]		X	X			X		X			X			X			

a Weeks 13 and 26 must occur after 13 weeks and 26 weeks of drug exposure, respectively. Therefore, visit window for these visits are +5 days

b Subjects on blinded study drug meeting criteria as a non-responder (Week 13) or for Disease Worsening (after Week 13 through 26), and not meeting the pre-specified decrease threshold in sperm parameters, are eligible for open-label filgotinib (refer Appendix 11 and Section 3). For definitions of IBD response status, Disease Worsening, and/or pre-specified decrease threshold in sperm parameters please refer to Definition of Terms and Section 3.4.

c OL Week 13 must occur after 13 weeks of starting open-label filgotinib. Therefore, visit window is +5 days.

d Subjects in the LTE will undergo scheduled visits for safety assessments and semen sample collection every 13 weeks, starting with LTE Week 13. Semen monitoring will be collected until the Week 13 primary study results are analyzed.

e Any time a subject discontinues study drug, a safety follow-up visit, 30 days (± 5 days) after the last dose of study drug is required, even if the subject is entering the Monitoring Phase

f Any time a subject discontinues participation in the study prior to Week 26, OL Week 13, reaching reversibility or Monitoring Phase Week 52 (whichever occurs first), or LTE Week 195, an ET Visit is required. Subjects who are Responders at Week 26 or at OL Week 13 and choose not to continue in the LTE are also required to complete ET visit assessments.

g As detailed in Appendix 7

h 12-Lead ECG will be performed at LTE Week 195 or ET, whichever occurs sooner
i Flexible Sigmoidoscopy (UC patients) or ileocolonoscopy (CD patients) is only required if it has not been done in the last 90 days.
j Partial MCS includes all parts of the complete MCS except endoscopy. For definitions of IBD response status, please refer to Definition of Terms; for definitions of Disease Worsening, please refer to Section 3.4 and Definition of Terms. Subject recall for the last 24 hours will be used for the patient reported components of the complete MCS and partial MCS. Subjects on blinded study drug meeting criteria for Non-Responder at Week 13 or Disease Worsening after Week 13 through Week 26 (and not meeting the pre-specified decrease threshold in sperm parameters) will be eligible for open-label filgotinib (see Section 3). MCS and partial MCS will be collected for UC patients. Physician Global Assessment is a component of MCS and partial MCS.
k CDAI will be collected for CD patients. Subject recall for the last 7 days will be used for the patient reported outcomes of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.
l 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 or designee.
m In the LTE subjects must have yearly QuantiFERON® testing. Yearly TB testing begins 1 year from the screening TB test date. If yearly TB testing falls between study visits, the yearly TB testing should be performed at the visit prior to 1 year from the screening TB test date. Subjects with newly positive (converted) QuantiFERON® [or centrally reported equivalent assay] TB test should be discontinued from study drug. Subjects who were previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator do not need to have yearly QuantiFERON® tests. Subjects previously treated for TB should be screened at least yearly for signs and symptoms consistent with reactivation of TB. Any subject with active TB should be discontinued from study.
n 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
o As detailed in Appendix 6. For visits that require fasting, subjects should not have any food or drink (except water) for at least 8 hours before the visit.
p Lipid profile should be performed every 26 weeks
q Semen samples will be collected on the visit day and/or after the visit. Those meeting the pre-specified decrease threshold in sperm parameters (as defined in the Definition of Terms) must enter the Monitoring Phase (see schedule below).
r The screening semen sample collection should coincide with the Day 1 (baseline) visit as much as possible.
s At time of confirmation of Non-responder status/Disease Worsening and prior to initiation of open-label filgotinib, Semen Analysis must confirm subject did not meet the pre-specified decrease threshold in sperm parameters.
t At time of confirmation of Non-responder status/Disease Worsening and prior to entry into the LTE, Semen Analysis must confirm subject did not meet the pre-specified decrease threshold in sperm parameters.
u This question will be asked prior to each semen collection.
v An HIV-1/HIV-2 antigen/antibody test, a Hepatitis C virus antibody test, a Hepatitis B surface antigen, a Hepatitis B surface antibody and a Hepatitis core antibody test will be conducted on all subjects; Subjects with positive Hepatitis B surface antigen (HBsAg) at Screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at Screening will be excluded. Subjects with positive HBV core Ab and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months. Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol. Subjects with positive HCV antibody (Ab) at Screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA at Screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment.
w Subjects with positive HBV core Ab and negative HBV DNA at Screening require ongoing monitoring with blood tests for HBV DNA every 3 months
x Sparse plasma PK samples are collected at least 30 minutes post-dose.
y Sparse plasma PK samples can be collected at any time without regard to dosing.
z Sparse plasma PK samples are collected pre-dose.
aa The subject will take the first dose (Day 1) in the clinical study center. For PK collection purposes, at Weeks 2, 13, and 26, and OL Weeks 2 and 13, subjects should be instructed **not** to take their study drug, but rather to bring it with them to the clinic. Subjects will be instructed to take their dose during their scheduled visit, as detailed in Section 6.16.

Study Procedure	Monitoring Phase (Section 6.7) Visits occur every 13 weeks (±5 days) for up to 52 weeks or until Reversibility is met, whichever is sooner	ET[a]
Symptom-directed Physical Exam, as needed	X	X
Vital Signs[b] and Weight	X	X
12-lead ECG		X
Partial Mayo Clinic Score (partial MCS)[c]		X
Crohn's Disease Activity Index (CDAI)[d]		X
Urinalysis[e]	X	X
Hematology and Chemistry[e]	X	X
LH, FSH, inhibin B, total Testosterone[e] collection time between 07:00-11:00 in the morning	X	X
Concomitant Medications	X	X
Assessment of Adverse Events[f]	X	X
Semen Collection (2 samples as per collection instructions in Section 6.13)[g]	X	
Date and time of most recent ejaculation[h]	X	

a Not required if Reversibility is met or if subject completes Week 52
b As detailed in Appendix 7
c Partial MCS includes all parts of the complete MCS except endoscopy. For definitions of IBD response status, please refer to Definition of Terms; for definitions of Disease Worsening, please refer to Section 3.4 and Definition of Terms. Subject recall for the last 24 hours will be used for the patient reported components of the complete MCS and partial MCS. MCS and partial MCS will be collected for UC patients. Physician Global Assessment is a component of MCS and partial MCS.
d CDAI will be collected for CD patients. Subject recall for the last 7 days will be used for the patient reported outcomes of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.
e As detailed in Appendix 6
f As detailed in Section 7.3
g Semen samples will be collected on the visit day and/or after the visit
h This question will be asked prior to each semen collection

Appendix 3. Mayo Scoring System* for Assessment of Ulcerative Colitis Activity

Stool Frequency** – *Each subject serves as his or her own control to establish the degree of abnormality of the stool frequency*	☐ 0 Normal number of stools for subject ☐ 1 1 to 2 stools per day more than normal ☐ 2 3 to 4 stools more than normal ☐ 3 ≥ 5 stools more than normal
Rectal Bleeding** – *The daily bleeding score represents the most severe bleeding of the day.*	☐ 0 No blood seen ☐ 1 Streaks of blood with stool less than half the time ☐ 2 Obvious blood with stool half or more than half of the time ☐ 3 Blood alone passes
Endoscopic findings – Assessed by Local Reader (include only for MCS assessment*)	☐ 0 Normal or inactive disease ☐ 1 Mild Disease *(erythema, decreased vascular pattern)* ☐ 2 Moderate Disease *(marked erythema, lack of vascular pattern, friability, erosions)* ☐ 3 Severe Disease *(spontaneous bleeding, ulceration)*
Physician's Global Assessment – *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.*	☐ 0 Normal ☐ 1 Mild disease ☐ 2 Moderate disease ☐ 3 Severe disease

* The partial Mayo Clinic Score (partial MCS; range: 0 - 9) uses the 3 non-invasive sub-scores from, and omits the endoscopic sub-score of, the full Mayo Clinic Score (range: 0 - 12)

** Subject recall for the last 24 hours will be used for the patient reported components of the complete MCS and partial MCS

Appendix 4. 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:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/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 5. 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, men must agree to use condoms during the study and for 90 days after the last dose of study drug. Female sexual partners of childbearing potential, defined below, should also consider use of highly effective contraception as outlined below.

1) Definitions

a. Definition of Childbearing Potential (for female sexual partners of male subjects)

For the purposes of this study, a female-born partner 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 are considered to be in a postmenopausal state when they are ≥ 54 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause.

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

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.

2) Contraception for Female Sexual Partners of Male 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 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 Sexual Partners of Childbearing Potential

Male subjects in this study with female sexual partners of childbearing potential must agree to use a condom. Male subjects must share the following information with female sexual partners regarding which contraceptive methods are recommended, starting at the time of Screening until 90 days following the last dose of study drug in the male subject.

Contraceptive Methods include:

Complete abstinence from sexual intercourse of reproductive potential with the male subject. Abstinence is an acceptable method of contraception only when it is in line with the female sexual partner and male 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)
- Hormonal methods (each method *must* be used with a condom in the male partner)
  - — Oral contraceptives (either combined or progesterone only)
  - — Injectable progesterone
  - — Implants of levonorgestrel
  - — Transdermal contraceptive patch
  - — Contraceptive vaginal ring

All female sexual partners of male subjects should refrain from in vitro fertilization with exposed male's sperm during male subject study participation and until at least 90 days after the last dose of study drug in the male partner.

3) Contraception 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 last 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 in a Female Sexual Partner

Subjects will be instructed to notify the investigator if their female partner becomes pregnant at any time during the study, or if she becomes pregnant within 90 days of his last study drug dose. Subjects who have sexual partners who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator.

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

Appendix 6. Clinical Laboratory Assessment Table

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count Differentials (absolute and percentage), including: Lymphocytes Monocytes Neutrophils Eosinophils Basophils Reticulocyte count Mean corpuscular volume (MCV)	Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Total bilirubin Direct and indirect bilirubin Total protein Albumin Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Serum creatinine Creatinine clearance (CrCl) Glucose Phosphorus Magnesium Potassium Sodium Creatine phosphokinase (CPK)	Appearance: Blood Color Glucose Leukocyte esterase pH Protein Urobilinogen Ketones Bilirubin Nitrite Specific Gravity Microscopic	Urine drug screen for: Amphetamines Cocaine Barbiturates Opiates Benzodiazepines QuantiFERON® TB – Gold Plus In-Tube Analysis (when required, per inclusion criteria) Fecal (stool) Bacterial Stool Culture C-Diff Toxin Ova and Parasites (O&P) Pharmacokinetics (PK) Serum Immunoglobulin Prothrombin Time (PT) Partial thromboplastin time (PTT) International Normalized Ratio (INR)
Endocrine (at Screening Only)		**Serology**	
HbA1c TSH		Hepatitis B Surface Ag Hepatitis B Surface Ab Hepatitis B Core Ab Hepatitis C Ab HIV Ag/Ab Reflex hepatitis B DNA (when indicated) Reflex hepatitis C RNA (when indicated)	
Sex Hormones		**Fasting Lipids**	
Luteinizing hormone (LH) Follicle stimulating hormone (FSH) Testosterone (total) Inhibin B		Triglycerides Cholesterol and its subfractions (high-density lipoprotein [HDL] and low density lipoprotein [LDL])	

Appendix 7. Procedures and Specifications

Complete Physical Examination

A complete physical examination should 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.

Vital Signs

Assessment of vital signs should include measurement of resting blood pressure, pulse, respiratory rate, and temperature.

Blood pressure should be measured using the following standardized process:

- Subject should be resting for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;
- Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

Creatinine Clearance

Creatinine clearance is calculated by the Cockcroft-Gault equation {Cockcroft 1976} using actual body weight (BW).

$$\text{Male:} \quad \text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{BW(kg)}}{72 \times S_{cr}}$$

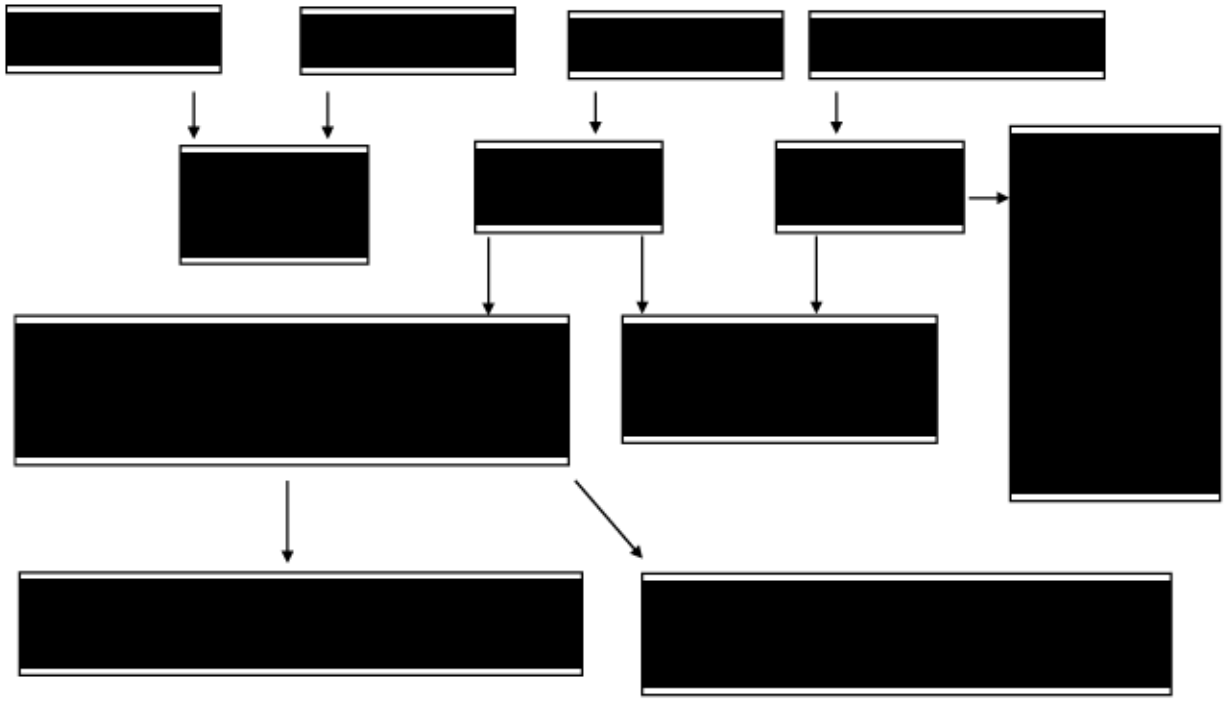
S_{cr} = serum creatinine (mg/dL)

12-Lead ECG

Subjects should rest in a supine position for ≥ 5 minutes prior to making a recording.

The investigator (or qualified designee) should review the ECG traces recorded in real time for clinically significant abnormalities.

Appendix 8. Management of Clinical and Laboratory Adverse Events



NOTE: Repeat labs should occur within 3 to 7 days of the initial abnormal lab value (except for creatinine clearance, which should be repeated within 7 to 14 days of the initial abnormal value). An unscheduled visit (ie, sequential visit) should be utilized to obtain the repeat lab values.

Appendix 9. Crohn's Disease Activity Index (CDAI)

The CDAI will be calculated as follows:

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

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

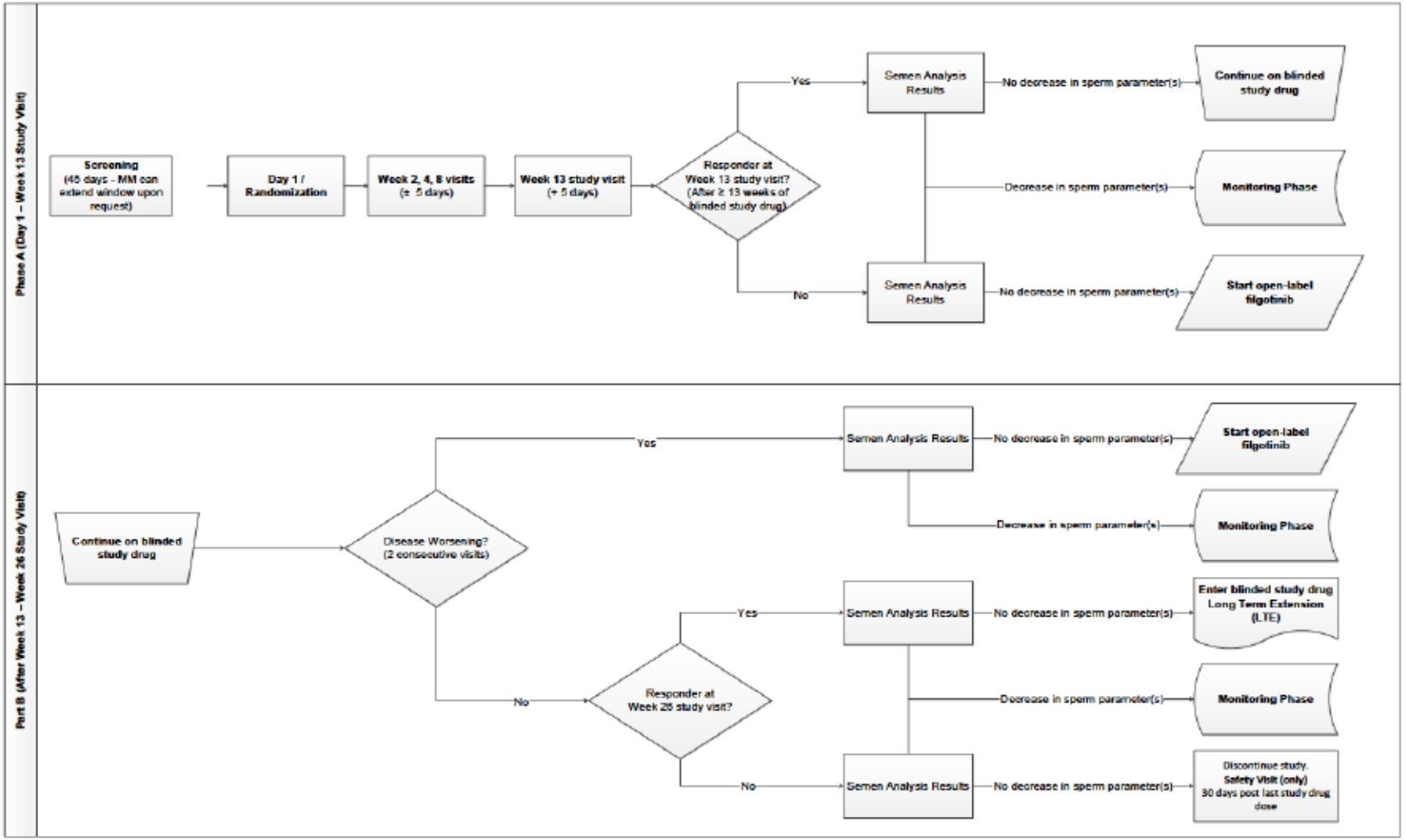
* Subject recall for the last 7 days will be used for the patient reported components of the CDAI. The CDAI score calculations should not be inclusive of days that involve an endoscopy procedure or preparation for that procedure.

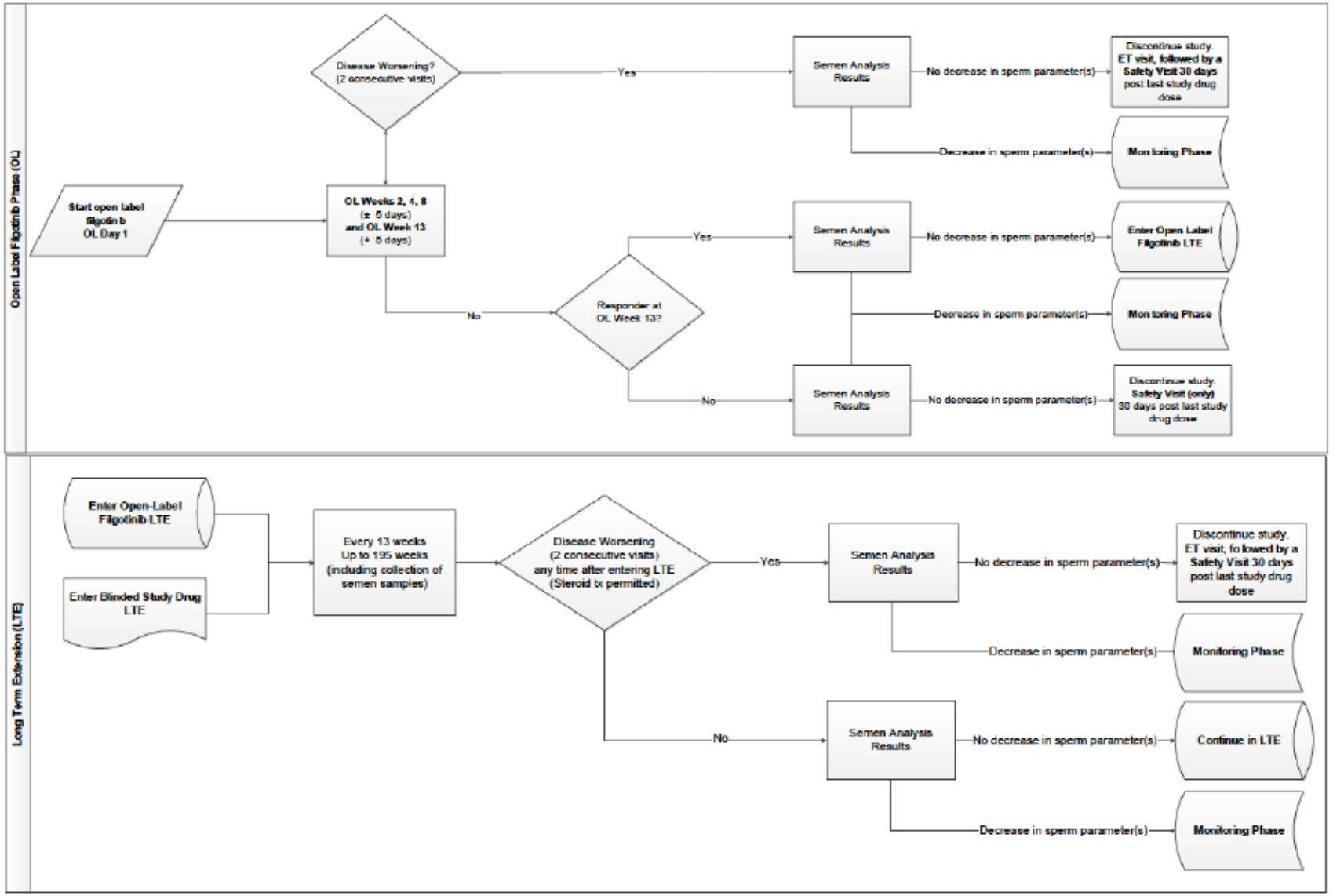
Appendix 10. Simple Endoscopic Score for Crohn's Disease (SES-CD)

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

Total SES-CD (range: 0-60): sum of the values of the 4 variables for the 5 bowel segments. Values are given to each variable and for every examined bowel segment (eg, rectum, left colon, transverse colon, right colon, and ileum) {Daperno 2004}

Appendix 11. Study Flow




Open Label Filgotinib Phase (OL)
Start open label filgotinib OL Day 1
OL Weeks 2, 4, 8 (± 5 days) and OL Week 13 (+ 5 days)
Disease Worsening? (2 consecutive visits)
Yes
Semen Analysis Results
No decrease in sperm parameter(s)
Discontinue study. ET visit, followed by a Safety Visit 30 days post last study drug dose
Decrease in sperm parameter(s)
Monitoring Phase
No
Responder at OL Week 13?
Yes
Semen Analysis Results
No decrease in sperm parameter(s)
Enter Open Label Filgotinib LTE
Decrease in sperm parameter(s)
Monitoring Phase
No
Semen Analysis Results
No decrease in sperm parameter(s)
Discontinue study. Safety Visit (only) 30 days post last study drug dose
Long Term Extension (LTE)
Enter Open-Label Filgotinib LTE
Enter Blinded Study Drug LTE
Every 13 weeks Up to 195 weeks (including collection of semen samples)
Disease Worsening (2 consecutive visits) any time after entering LTE (Steroid tx permitted)
Yes
Semen Analysis Results
No decrease in sperm parameter(s)
Discontinue study. ET visit, followed by a Safety Visit 30 days post last study drug dose
Decrease in sperm parameter(s)
Monitoring Phase
No
Semen Analysis Results
No decrease in sperm parameter(s)
Continue in LTE
Decrease in sperm parameter(s)
Monitoring Phase

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Approval	PPD opment Leader Clinical Development 09-Sep-2022 12:26:26 GMT+0000

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