Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	Combined Phase 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 Crohn's Disease	
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium	
IND Number:	129646	
EudraCT Number:	2016-001367-36	
Clinical Trials.gov Identifier:	NCT02914561	
Indication:	Crohn's Disease	
Protocol ID:	GS-US-419-3895	
Galapagos Medical Leader:	Name:	PPD
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	Amendment 8.1:	04 September 2020 (Germany and Portugal)
	Amendment 9:	02 December 2021

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PROTOCOL SYNOPSIS

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Study Title:	Combined Phase 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 Crohn's Disease
IND Number: **EudraCT Number:** **Clinical Trials.gov Identifier:**	129646 2016-001367-36 NCT02914561
Study Centers Planned:	Approximately 500 sites globally
Objectives:	The overall objective of the study is to evaluate the effect of treatment with filgotinib on the induction and maintenance of clinical remission, as well as, endoscopic response in subjects with moderately to severely active Crohn's disease (CD). Subjects who are biologic-naïve or biologic-experienced will be enrolled in Cohort A and subjects who are biologic-experienced will be enrolled in Cohort B, respectively. Treatment assignments will be randomized within each Cohort. **Cohort A: Biologic-Naïve and Biologic-Experienced Subjects, Induction Study** The primary objectives of Cohort A Induction Study are: • To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by Crohn's Disease Activity Index (CDAI) at Week 10 • To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10 The key secondary objectives of Cohort A Induction Study are: • To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by Patient Reported Outcomes (PRO2) at Week 10 • To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives of Cohort A Induction Study are:

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

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- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
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Cohort A (European Union[EU]-Specific Objectives): Biologic-Naïve and Biologic-Experienced Subjects, Induction Study

The EU-specific primary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives of Cohort A Induction Study are:

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

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Cohort B: Biologic-Experienced Subjects, Induction Study

The primary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives of Cohort B Induction Study are:

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

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- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
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Cohort B (EU-Specific Objectives): Biologic-Experienced Subjects, Induction Study

The EU-specific primary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives of Cohort B Induction Study are:

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

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Maintenance Study

The primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by CDAI at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The other secondary objectives of the Maintenance Study are:

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

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- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
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Maintenance Study (EU-Specific Objectives)

The EU-specific primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The EU-specific key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The EU-specific other secondary objectives of the Maintenance Study are:

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

CCI [redacted]

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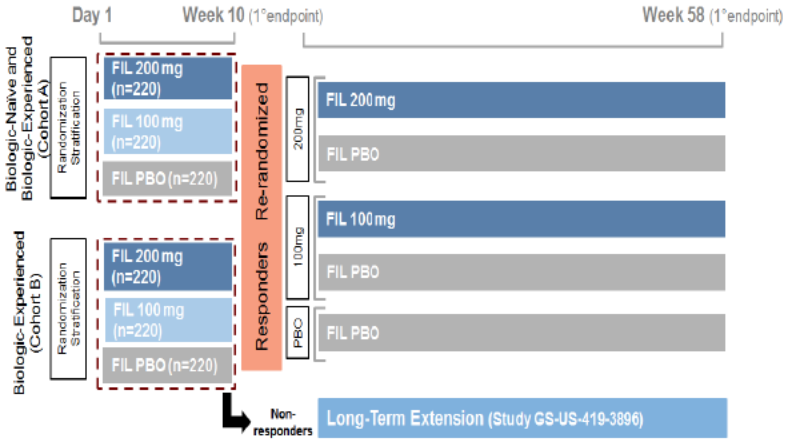
Study Design:

These are combined Phase 3 double-blind, randomized, placebo-controlled studies to evaluate the efficacy and safety of filgotinib in the induction and maintenance of clinical remission, as well as, endoscopic response in subjects with moderately to severely active CD.



These studies include:

- Screening (Days -30 to -1)
- Randomization (Day 1)
- Blinded Induction Studies (Day 1 to Week 11)
  - Cohorts A and B Week 10 efficacy assessments:
    - At Week 10, CDAI and PRO2 to assess clinical remission
    - At Week 10, Simple Endoscopic Score for Crohn's Disease (SES-CD) to assess endoscopic response
  - Blinded Bridge Phase (Week 10 to 11): Dosing will continue in a blinded fashion through the end of Week 10 until re-randomization at Week 11

- Re-randomization (Week 11)
  - Subjects in Cohorts A and B who complete the Induction Study and achieve either clinical remission by PRO2 or endoscopic response by SES-CD at Week 10 will be re-randomized into the Maintenance Study at Week 11
  - Subjects who do not achieve clinical remission by PRO2 or endoscopic response at Week 10 will have the option to enter a separate, Long-Term Extension (LTE) study (GS-US-419-3896; Galapagos Study ID GLPG0634-CL-310)
- Blinded Maintenance Study (Weeks 11 to 58)
- Post-Treatment (PTx) safety assessments
  - Subjects who opt out of the LTE study (GS-US-419-3896) will return 30 days after the last dose of study drug for PTx safety assessments
  - Subjects who complete all procedures per protocol, including the endoscopy, of the 58-week study will be offered the option to continue into the LTE study (GS-US-419-3896)
  - Subjects who are eligible and opt to participate in the LTE study (GS-US-419-3896) can continue into the study without PTx safety assessments.

Treatment Regimen (Cohorts A and B Induction Studies)

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

Treatment 1 (n = 220): filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily

Treatment 2 (n = 220): filgotinib 100 mg and PTM filgotinib 200 mg, once daily

Treatment 3 (n = 220): PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

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

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

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

- History of exposure to no biologic agent, one biologic agent, or more than one biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-mercaptopurine [6-MP], azathioprine, methotrexate [MTX]) at Day 1, (Yes or No)

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

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

Subjects from Cohort A or B who are eligible for the Maintenance study will be re-randomized to treatment as follows:

Treatment Assignment Induction Studies Cohorts A and B	Maintenance Study Re-randomization
Treatment 1, filgotinib 200 mg	Treatment 1, 200 mg
	Treatment 3, Placebo
Treatment 2, filgotinib100 mg	Treatment 2, 100 mg
	Treatment 3, Placebo
Treatment 3, Placebo	Continue Treatment 3, Placebo

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

Stratification Factors (Maintenance Study)

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

Substudies:	**Pharmacokinetic (PK) Substudy** An optional PK substudy will be performed in a subset of subjects (approximately 30 subjects each in Cohort A and Cohort B) who provide a separate informed consent. In the PK substudy, the daily dose of study drug should be administered under supervision in the clinic (at one visit between Week 2 and Week 10, inclusive), and PK samples should be collected predose and at 0.5, 1, 2, 3, 4, and 6 hours post dose. CCI [redacted]
Number of Subjects Planned:	Approximately 660 subjects for each Cohort for a total of 1320 subjects
Target Population:	Adult subjects with moderately to severely active CD as defined by: • CDAI total score between 220 and 450 (inclusive), AND • PRO2 abdominal pain score ≥ 2 (on a scale of 0 to 3) OR stool frequency ≥ 4 (refer to Appendix 4), AND • Evidence of active disease as measured by the SES-CD based on central reading — Total score ≥ 6, OR — If disease is limited to the ileum and/or right colon, a combined score ≥ 4 in these 2 segments
Duration of Treatment:	58 weeks
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Section 4. **Main Eligibility Criteria (Cohorts A & B):** All subjects must meet all of the following criteria to be eligible for participation in either the Cohort A or B Induction Study. • Males or non-pregnant, non-lactating females, ages 18 to 75 years, inclusive based on the date of the screening visit

- Documented diagnosis of CD with a minimum disease duration of 3 months with involvement of the ileum and/or colon at a minimum, documented by the following:
  a) Medical record documentation of, or an ileocolonoscopy (full colonoscopy with the intubation of terminal ileum) report dated ≥ 3 months before enrollment, which shows features consistent with CD, determined by the procedure performing physician, AND
  b) Medical record documentation of, or a histopathology report showing features consistent with CD, determined by the pathologist.
- Moderately to severely active CD determined by CDAI 220 to 450 (inclusive), AND PRO2 (abdominal pain score ≥ 2 [on a scale of 0 to 3] OR stool frequency ≥ 4), AND centrally read SES-CD score ≥ 6 (or ≥ 4 if disease is limited to the ileum and/or right colon)
- May be receiving the following drugs (subjects on these therapies must be willing to remain on stable doses for the noted time):
  a) Oral 5-aminosalicylate (5-ASA) compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization
  b) Azathioprine or 6-MP or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must remain stable for the first 10 weeks after randomization
  c) Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must remain stable for the first 14 weeks after randomization
  d) Antibiotics for the treatment of CD (eg, metronidazole, ciprofloxacin) provided the dose prescribed has been stable for 2 weeks prior to randomization. Dose must remain stable for the first 10 weeks after randomization. Subjects who are on cyclic therapy must continue their standard low-dose regimen without change for the first 10 weeks after randomization.

- Must not have the current following complications of CD:
  a) Symptomatic strictures, OR
  b) Severe (impassable) rectal/anal stenosis, OR
  c) Fistulae other than perianal fistulae, OR
  d) Short bowel syndrome, OR
  e) Any other manifestation that might require surgery, OR
  f) 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
- Must not have ulcerative colitis, indeterminate colitis, ischemic colitis, fulminant colitis, or toxic mega-colon
- Must not have active tuberculosis (TB) or history of latent TB that has not been treated (see inclusion criterion 7 for further information)
- Must not use any prohibited concomitant medications as described in Section 5.4.2

Cohort A (Biologic-Naïve and Biologic-Experienced) Induction Study

Main Eligibility Criteria, Cohort A ONLY

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

Biologic-Naïve Subjects

- 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 oral prednisone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, OR
     ii) Two failed attempts to taper steroids below a dose equivalent of 10 mg daily prednisone, OR
     iii) History of steroid intolerance including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, serious infections, depression, allergic reactions, mood disturbances, or any other condition that contributed to discontinuation of the agent

b) Immunomodulators

i) Active disease despite a history of at least a 12 week regimen of oral azathioprine (≥ 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

- No prior or current use of any TNFα antagonist including (but not limited to) infliximab, adalimumab, golimumab, certolizumab, or biosimilar agents at any time
- No prior or current use of vedolizumab at any time
- No prior or current use of ustekinumab at any time

Biologic-Experienced Subjects

- 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) or discontinuation of use of at least one of the following agents for reasons other than inadequate clinical response, loss of response, or intolerance:

  a) TNFα Antagonists

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

  - Infliximab: A 14-week induction regimen of 5 mg/kg IV at Weeks 0, 2, and 6 (6 week induction regimen with 2 doses at Weeks 0 and 2 in EU)
  - Adalimumab: A 4-week induction regimen consisting of 160 mg SC (four 40-mg injections in one day or two 40-mg injections per day for two consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg
  - Certolizumab: A 8 week induction regimen of 400 mg SC at Weeks 0, 2 and 4

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

b) Vedolizumab

i) Active disease despite a history of at least a 14-week induction regimen of vedolizumab consisting of 300 mg IV at Weeks 0, 2 and 6, OR

ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent

c) Ustekinumab

i) Active disease despite a history of a 8 week induction regimen with a single dose of ustekinumab IV per weight-based dosing (260mg for up to 55kg; 390mg for greater than 55 to 85kg; 520mg for greater than 85kg) at Week 0, OR

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

- Must not have used any TNFα antagonist or vedolizumab ≤ 8 weeks prior to screening, ustekinumab IV or SC ≤12 weeks prior to screening, or any other biologic agent ≤ 8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer. Subjects who have an undetectable serum level of a biologic agent since its last dose using a commercially available assay can undergo study screening without the above-mentioned waiting period.

Cohort B (Biologic-Experienced) Induction Study

Main Eligibility Criteria, Cohort B ONLY

- Previously demonstrated an inadequate clinical response, loss of response to, or intolerance of, at least *one* of the following agents (depending on current country treatment recommendations/guidelines):
  - a) TNFα Antagonists
    - i) Active disease despite a history of at least one induction regimen of infliximab, adalimumab, certolizumab or biosimilar as follows:
      - Infliximab: A 14-week induction regimen of 5 mg/kg IV at Weeks 0, 2, and 6 (6 week induction regimen with 2 doses at Weeks 0 and 2 in EU)
      - Adalimumab: A 4-week induction regimen consisting of 160 mg SC (four 40-mg injections in one day or two 40-mg injections per day for two consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg
      - Certolizumab: A 8 week induction regimen of 400 mg SC at Weeks 0, 2 and 4

      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
  - b) Vedolizumab
    - i) Active disease despite a history of at least a 14-week induction regimen of vedolizumab consisting of 300 mg IV at Weeks 0, 2 and 6, OR
    - ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent

c) Ustekinumab

i) Active disease despite a history of a 8 week induction regimen with a single dose of ustekinumab IV per weight-based dosing (260mg for up to 55kg; 390mg for greater than 55 to 85kg; 520mg for greater than 85kg) at Week 0, OR

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

- Must not have used any TNFα antagonist or vedolizumab ≤ 8 weeks prior to screening, ustekinumab IV or SC ≤12 weeks prior to screening, or any other biologic agent ≤ 8 weeks prior to screening or within 5 times the half-life of the biologic agent prior to screening, whichever is longer. Subjects who have an undetectable serum level of a biologic agent since its last dose using a commercially available assay can undergo study screening without the above-mentioned waiting period.

Maintenance Study

Main Eligibility Criteria:

- Completion of Cohort A or Cohort B Induction Study with either clinical remission by PRO2 or endoscopic response at Week 10

Study Procedures/ Frequency:

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

Non-responding subjects completing all Week 10 assessment will be eligible to enter the LTE study (GS-US-419-3896).

Subjects who opt out of the LTE study (GS-US-419-3896) will return 30 days after the last dose of study drug for PTx safety assessments.

Subjects who are eligible and opt to participate in the LTE study (GS-US-419-3896) can continue into the study without PTx safety assessments.

Subjects who complete the Week 58 visit will have the option to continue study drug in a blinded fashion in the LTE study (GS-US-419-3896)

	Concomitant Crohn's Disease Medication Management: Subjects on permitted concomitant medications for CD that are described in the inclusion criteria (eg, 5-ASA, and immunomodulators) must remain on stable doses until Week 10. Steroids must remain stable to Week 14. Starting at Week 14, subjects who are on concomitant steroids must begin tapering steroid therapy. The dose should be reduced at a rate starting at 2.5 mg per week up to 5 mg per week (or equivalent taper if not prednisone). Subjects who are on budesonide should have their daily dose reduced by 3 mg every 3 weeks until they are completely off steroids. For subjects undergoing taper, steroids may be increased or restarted at doses up to and including their baseline dose if return of symptoms is apparent. These subjects will not be considered treatment failures. Subjects who need to restart or increase steroid treatment at a dose that exceeds their baseline dose of steroids (dose may not exceed 30 mg prednisone [or equivalent] or budesonide 9 mg/day) will be considered treatment failures for all clinical end points but will be permitted to remain in the study. • For additional prohibited CD medications, reference Table 5-1.
Test Product, Dose, and Mode of Administration:	• Filgotinib 200 mg oral tablet, once daily • Filgotinib 100 mg oral tablet, once daily
Reference Therapy, Dose, and Mode of Administration:	• PTM filgotinib 200 mg oral tablet, once daily • PTM filgotinib 100 mg oral tablet, once daily
Criteria for Evaluation:	
Safety:	Assessment of AEs and concomitant medications will continue throughout the duration of the study. Safety evaluations include documentation of AEs, PE (complete or symptom driven), vital signs, and clinical laboratory evaluations (hematology, chemistry, urinalysis). An ECG will be performed at screening, Week 10 (or at Early Termination (ET) if subject terminates prior to Week 10), Week 26 and Week 58. A data monitoring committee (DMC) will meet to evaluate all available safety data accumulated during the study. The initial meeting will occur after approximately 100 subjects reach Week 10 in Cohorts A and B combined. Following this, subsequent meetings will occur approximately once every 4 months or at a frequency determined by the DMC.

Efficacy:	Primary efficacy will be assessed by CDAI and SES-CD (co-primary): • Clinical remission by CDAI is defined as CDAI < 150 • Endoscopic response is defined as SES-CD score (based on central reading) reduction of ≥ 50% from baseline In the EU, primary efficacy will be assessed by PRO2 and SES-CD (co-primary): • Clinical remission by PRO2 is defined as abdominal pain score ≤ 1 (on a scale of 0 to 3) AND stool frequency ≤ 3. • Endoscopic response is defined as SES-CD score (based on central reading) reduction of ≥ 50% from baseline
Pharmacokinetics:	Plasma concentrations of filgotinib and its metabolite GS-829845 (formerly G254445) will be determined.
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Statistical Methods:

Induction Studies (Cohorts A and B)

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

The primary analysis will compare each filgotinib dose group to placebo on each co-primary end point (the proportion of subjects achieving clinical remission by CDAI at Week 10 and the proportion of subjects achieving endoscopic response at Week 10). In the EU, the primary analysis will compare each filgotinib dose group to placebo on each co-primary end point (the proportion of subjects achieving clinical remission by PRO2 at Week 10 and the proportion of subjects achieving endoscopic response at Week 10).

The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of the co-primary end points. Subjects who do not have sufficient measurements to determine efficacy end points will be considered failures (ie, non-responder imputation [NRI]).

The graphical approach {Bretz 2009} of sequentially rejective Beonferroni-based iterative multiple test procedures will be used to control a family-wise type I error rate (FWER) at 5% (ie, $\alpha = 0.05$) for hypothesis testing on co-primary and key secondary end points. See Section 8.5.3 for details and the significance level that will be used to declare a statistically significant treatment effect for each filgotinib dose group when compared to placebo.

Cohorts A and B End-of-Induction Analysis

Efficacy and safety data will be evaluated by the DMC after *all* subjects in Cohorts A and B complete Week 10 dosing (or prematurely discontinue study drug but complete PTx assessments). Data from Cohorts A and B (examined independently) will be used to evaluate the study overall for possible discontinuation (See Section 8.10 for details).

Maintenance Study

The primary analysis set for efficacy analyses is FAS, which includes all re-randomized subjects who met the protocol definition of clinical remission by PRO2 or endoscopic response at Week 10, and received at least 1 dose of study drug in the Maintenance Study (Weeks 11 to 58).

The primary analysis will compare each filgotinib dose group to placebo on each co-primary end point (the proportion of subjects achieving clinical remission by CDAI at Week 58 and the proportion of subjects achieving endoscopic response at Week 58). In the EU, the primary analysis will compare each filgotinib dose group to placebo on each co-primary end point (the proportion of subjects achieving clinical remission by PRO2 at Week 58 and the proportion of subjects achieving endoscopic response end points at Week 58). The CMH approach adjusting for stratification factors will be used for hypothesis testing of the co-primary end points. Subjects who do not have sufficient measurements to determine efficacy end points will be considered failures (ie, NRI).

The graphical approach {Bretz 2009} of sequentially rejective Beonferroni-based iterative multiple test procedures will be used to control a FWER at 5% (ie, $\alpha = 0.05$) for hypothesis testing on co-primary and key secondary end points. See Section 8.5.3 for details and the significance level that will be used to declare a statistically significant treatment effect for each filgotinib dose group when compared to placebo.

Pharmacokinetics:

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

Sample Size:

Induction Studies (Cohorts A and B)

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by CDAI at Week 10 and endoscopic response rate at Week 10 could be detected when comparing filgotinib 200 mg to placebo within each Induction Study.

A sample size of 220 subjects in each treatment group (n = 660 total) will provide an overall power of 97% for filgotinib 200 mg group comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 20% in clinical remission rate by CDAI at Week 10 (45% on filgotinib 200 mg and 25% on placebo) and a treatment difference of 15% in endoscopic response rate at Week 10 (25% on filgotinib 200 mg and 10% on placebo). Since each end point needs to achieve statistical significance, the overall power of 97% is calculated as the product of the two individual powers based on each end point.

For the EU, the sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by PRO2 at Week 10 and endoscopic response rate at Week 10 could be detected when comparing filgotinib 200 mg to placebo within each Induction Study.

A sample size of 220 subjects in each treatment group (n = 660 total) will provide an overall power of 93% for filgotinib 200 mg dose group comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 15% in clinical remission rate by PRO2 at Week 10 (30% on filgotinib 200 mg and 15% on placebo) and a treatment difference of 15% in endoscopic response rate at Week 10 (25% on filgotinib 200 mg and 10% on placebo). Since each end point needs to achieve statistical significance, the overall power of 93% is calculated as the product of the two individual powers based on each end point.

Maintenance Study

Assuming an induction response rate (ie, proportion of subjects achieving either clinical remission by PRO2 or endoscopic response at Week 10) of 40% among subjects receiving filgotinib 200 mg or filgotinib 100 mg treatment, approximately 176 subjects from each filgotinib dose group from Cohorts A and B Induction Studies combined would be eligible to be re-randomized into the Maintenance Study.

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by CDAI and endoscopic response rate at Week 58 could be detected when comparing filgotinib 200 mg to placebo in the Maintenance Study.

A sample size of 60 subjects in the placebo group and 120 subjects in the filgotinib group at the same dose level as the induction dose will provide an overall 94% power for filgotinib 200 mg comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 30% in maintenance clinical remission rate by CDAI at Week 58 and maintenance endoscopic response rate at Week 58 (50% on filgotinib 200 mg and 20% on placebo). Since each end point needs to achieve statistical significance, the overall power of 94% is calculated as the product of the two individual powers based on each end point.

For the EU, the sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by PRO2 and endoscopic response rate at Week 58 could be detected when comparing filgotinib 200 mg to placebo in the Maintenance Study.

A sample size of 60 subjects in the placebo group and 120 subjects in the filgotinib group at the same dose level as the induction dose will provide an overall 94% power for filgotinib 200 mg comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 30% in maintenance clinical remission rate by PRO2 at Week 58 and maintenance endoscopic response rate at Week 58 (50% on filgotinib 200 mg and 20% on placebo). Since each end point needs to achieve statistical significance, the overall power of 94% is calculated as the product of the two individual powers based on each end point.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

5-ASA	5-aminosalicylate
6-MP	6-mercaptopurine
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AP	abdominal pain
AST	aspartate aminotransferase
AUC	area under the plasma/serum/peripheral blood mononuclear cell concentration, drug versus time curve
CCI	[redacted]
BLQ	below the limit of quantitation
BMI	body mass index
C. diff	*Clostridium difficile*
CC&G	Cockcroft-Gault
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CES	Carboxylesterases
CFR	Code of Federal Regulations
CI	confidence interval
CIA	collagen-induced arthritis
CK	creatine kinase
C_{max}	the maximum observed serum/plasma/peripheral blood mononuclear (PBMC) concentration of drug
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CNS	central nervous system
CPK	creatine phosphokinase
CRF	case report form(s)
CRO	contract (or clinical) research organization
CCI	[redacted]
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	Cardiovascular Safety Endpoint Adjudication Committee
CYP	Cytochrome P450
DAI	disease activity index
DMC	data monitoring committee
DNA	deoxyribonucleic acid

DSS	dextran sodium sulfate
E.coli	*Escherichia coli*
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form(s)
EDC	Electronic Data Capture
e-Diary	electronic diary
EMA	European Medicines Agency
CCI	[redacted]
eSAE system	electronic SAE system
ET	early termination
EU	European Union
EudraCT	European clinical trials database
FAS	Full Analysis Set
FDA	(United States) Food and Drug Administration
FWER	family-wise type I error rate
GCP	Good Clinical Practice (Guidelines)
CCI	[redacted]
GI	gastrointestinal
HBcAB	Hepatitis B Virus core antibody
HBsAB	Hepatitis B Virus surface antibody
HBsAG	Hepatitis B Virus surface antigen
HBV	Hepatitis B virus
CCI	[redacted]
HCV	Hepatitis C virus
HDL	high-density lipoprotein
HDPE	high density polyethylene
hERG	human ether-a-gogo
HIV	Human Immunodeficiency Virus
HLGT	High-Level Group Term
HLT	High-Level Term
CCI	[redacted]
IB	investigator brochure
IBD	inflammatory bowel disease
CCI	[redacted]
IC_{50}	concentration of an inhibitor that is required for 50-percent inhibition
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee

IL	Interleukin
IM	intramuscularly
IMP	investigational medicinal product
IND	Investigational new drug
INR	International Normalized Ratio
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
IWRS	interactive web response system
JAK	Janus Kinase
JAK-STAT	Janus Kinase (JAK)-Signal Transducer and Activator of Transcription (STAT)
LAM	lactational amenorrhea method
LDL	low-density lipoprotein
LLOQ	Lower limit of quantitation
LLT	Lower-Level Term
LOCF	Last Observation Carried Forward
LTE	long-term extension
mAb	monoclonal antibody
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
CCI	[redacted]
MPO	myeloperoxidase
MTX	Methotrexate
NOEL	no-observed-effect-levels
NRI	non-responder imputation
CCI	[redacted]
NSAID	Nonsteroidal Anti-inflammatory Drugs
O&P	ova and parasites test
OAT	organic anion transporters
PBMC	peripheral blood mononuclear cell
PCP	pneumocystis
PD	pharmacodynamics
PE	physical examination
PEG	polyethylene glycol
P-gp	p-glycoprotein
PI	principal investigator
PK	Pharmacokinetic
PRO2	patient reported outcomes consisting of 2 items: abdominal pain severity and liquid stool frequency

PT	Preferred Term
PTM	Placebo-to-match
PTx	Post-Treatment
Q1	1st quartile
Q3	3rd quartile
RA	rheumatoid arthritis
CCI	[redacted]
RNA	ribonucleic acid
ROC	receiver operating characteristic
RT-PCR	reverse transcription polymerase chain reaction
SADR	serious adverse drug reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	standard deviation
SES-CD	Simple Endoscopic Score for Crohn's Disease
SF	stool frequency
CCI	[redacted]
SI	international system of units
SOC	system organ class
SOP	standard operating procedure
spp	Species
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TgrasH2	transgenic
TNFα	tumor necrosis factor-alpha
TPMT	thiopurine methyltransferase
TYK	Tyrosine kinase
UC	ulcerative colitis
UGT	uridine 5' diphosphate glucuronosyltransferase
ULN	upper limit of the normal range
US	United States
CCI	[redacted]
WBC	white blood cell
CCI	[redacted]

DEFINITION OF TERMS

Clinical Remission by CDAI	CDAI score < 150 points
Clinical Response by CDAI	Reduction in CDAI from Induction baseline by at least 100 points or CDAI score < 150
Clinical Remission by PRO2	Abdominal pain score [a] ≤ 1 (on a scale of 0 to 3) and liquid or very soft stool (Bristol stool scale type 6 or 7) frequency[a] ≤ 3
CCI	[redacted]
Corticosteroid-Free Remission	Clinical remission by CDAI or PRO2 (EU-specific) with no corticosteroid use for at least 6 months prior to Week 58 among subjects who are on corticosteroid at baseline
Disease Worsening	A ≥ 100 point increase in CDAI score from the Week 10 value and CDAI score ≥ 220 points at 2 consecutive visits
CCI	[redacted]
Endoscopic Response	≥ 50% reduction from Induction baseline in SES-CD score based on central reading
Non-responder	Subject who achieves neither clinical remission by PRO2 nor endoscopic response at Week 10
Sustained Clinical Remission by CDAI	Achieving clinical remission by CDAI at Weeks 10 and 58
Sustained Clinical Remission by PRO2	Achieving clinical remission by PRO2 at Weeks 10 and 58

a Each PRO2 subscore will be rounded to the nearest integer for determination of eligibility and calculation of end points.

1. INTRODUCTION

1.1. Background

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

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

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

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

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

The Simple Endoscopic Score for Crohn's Disease (SES-CD) was first validated in 2004 and has been used extensively in clinical trials to demonstrate endoscopic improvement in disease activity following interventions. 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). A 50% or higher reduction in the overall SES-CD score is generally used as a sign of treatment response {Ferrante 2013}.

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

Currently available biologic therapies focus on neutralizing cytokine activity or altering T-cell differentiation and homing. Three monoclonal antibodies which inhibit tumor necrosis factor-alpha (TNFα), are currently marketed for the treatment of CD: infliximab (Remicade®), adalimumab (Humira® [approved in US and European Union {EU}]) and certolizumab pegol (Cimzia® [approved in US]). Vedolizumab (Entivyo®), a monoclonal antibody against $\alpha_4\beta_7$ 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 therefore an antagonist for both IL-12 and IL-23 signaling, has been approved for the treatment of CD. Leukocytapheresis therapy may be used in Japan {Fukunaga 2012}.Other investigational treatment approaches still in development include the administration of cytokines to stimulate innate immunity, the use of prebiotics to alter the gut flora, and blocking the IL-6 signaling pathway {Ito 2004, Korzenik 2016}. New treatments being tested in clinical trials include janus kinase (JAK) inhibitors (eg, upadacitinib), and new biologic agents such as IL-23 p19 antagonists (eg, risankizumab) and a monoclonal antibody directed against β_7 integrin (eg, etrolizumab).

While the introduction of biologic therapies has significantly improved response rates in patients with moderately to severely active CD, long-term or durable remission rates are still low at approximately 20%. Many patients receiving biologic therapies develop neutralizing antibodies with resulting loss of efficacy. These agents may be associated with specific safety issues including but not limited to anaphylaxis, increased risk of infection including progressive multifocal leukoencephalopathy, and liver injury. Safe and effective treatment options which may be conveniently administered in a chronic setting would provide a significant treatment advance for patients with moderately to severely active CD.

1.2. Filgotinib (GS-6034)

1.2.1. General Information

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

Filgotinib (GS-6034, formerly known as GLPG0634) is a potent and selective inhibitor of JAK1. Filgotinib is approved in the European Union (EU), Japan, and Great Britain for treatment of moderate to severe active RA in adult patients. It is also approved for the treatment of moderately to severely active ulcerative colitis (UC) in adults in the EU, and is currently under regulatory review for the treatment of UC in Japan and Great Britain. The compound has shown good preliminary efficacy in CD patients in Phase 2 studies.

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

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

1.2.2. Preclinical Pharmacology and Toxicology

Filgotinib and its metabolite, GS-829845 have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1; efficacy studies in rats and mice; repeat-dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), in vitro and in vivo safety pharmacology and genetic toxicology studies, and reproductive toxicology studies in rats and rabbits.

Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive juvenile toxicity study. A definitive juvenile toxicology study in rats is ongoing.

1.2.2.1. Nonclinical Pharmacology

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

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

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

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

1.2.2.2. Safety Pharmacology

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

1.2.2.3. Key Nonclinical Distribution, Metabolism, and Excretion Data

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

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

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

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

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

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'- diphosphate - glucuronosyltransferase (UGTs), and no relevant inhibition of key drug transporters, including organic anion transporters (OATs), by filgotinib or GS-829845. OCT2 was inhibited by both filgotinib (IC_{50}: 8.7 μM) and GS-829845 (IC_{50}: 67 μM). The clinical relevance of the IC_{50} values for inhibition of OCT2 will be further evaluated. MATE1 was also weakly inhibited by filgotinib (IC_{50}: 94 μM) and GS-829845 (IC_{50}: >100 μM). Filgotinib was found to be a substrate of P-glycoprotein (P-gp).

1.2.2.4. Nonclinical Toxicology

In repeat oral dose toxicity studies in both rats and dogs, the primary target tissues identified for filgotinib were the lymphoid tissues which are expected based on the pharmacology of JAK inhibition. Additional filgotinib-related findings were observed in the male reproductive organs of both species, and in the incisor teeth of rats only. Effects on the lymphoid system were fully reversible. Testicular toxicity demonstrated partial reversibility; however, sperm counts remained low. When using the mean exposure (AUC) at the NOAELs for the most sensitive species (the dog), the exposure margins compared to a 200 mg once daily dose of filgotinib in CD subjects are 2.5, 1.9, and 3.6-fold for the 26-week and 39-week chronic toxicity studies and the 39-week targeted exposure toxicity study, respectively.

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

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

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

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

1.2.3. Clinical Trials of Filgotinib

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

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

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

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

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

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

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

1.3. Rationale for This Study

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

This is a double-blind, placebo controlled trial (GS-US-419-3895; Galapagos Study ID GLPG0634-CL-309) comparing the efficacy of filgotinib versus placebo in the induction and maintenance of clinical remission and endoscopic response in subjects with moderately to severely active CD. A previous Phase 2 study with filgotinib demonstrated the efficacy of filgotinib 200 mg in inducing clinical remission in 10 weeks. Thus the onset of response is expected to occur early in the course of treatment.

The use of placebo in this type of design has an important value, as "placebo response" is widely known to occur during clinical studies conducted in CD. The addition of a placebo arm is important, as this enables a control for potential influences derived from the natural course of CD and other effects that are inherent to overall medical care. Therefore the inclusion of a placebo arm in this study is necessary to prove efficacy of filgotinib. However, exposure to placebo has been kept as minimal as possible.

1.3.1. Rationale for Endpoint and Timing

The co-primary end points for this study are assessed by the CDAI and SES-CD. In the EU, based on the Committee for Medicinal Products for Human Use Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease, the co-primary end points are assessed by PRO2 and SES-CD.

Part 1 of Study GLPG0634-CL-211 supports the efficacy of filgotinib in CD at Week 10. The study assessed for clinical remission, defined by CDAI < 150 as the primary end point.

Week 10 CDAI and un-weighted stool frequency (SF) and abdominal pain (AP) data from Study GLPG0634-CL-211 in the subset of subjects with available data was evaluated to determine a PRO2 responder (clinical remission by PRO2) definition corresponding to achieving clinical remission as assessed by a CDAI score < 150. A receiver operating characteristic (ROC) curve analysis was conducted to find the optimal cutoffs for SF and AP corresponding to CDAI score < 150. The optimal cutoffs (specificity, sensitivity) for SF and AP are 3.071 (0.803, 0.755) and 0.929 (0.902, 0.755), respectively. A responder definition of 3 or less daily stools (SF score ≤ 3) AND mild or no abdominal pain (AP score ≤ 1) is well reflective of the state of minimal to mild disease activity equivalent to clinical remission. Based on the Phase 2 CDAI data, a clinical remission by PRO2 response definition of achieving 3 or less liquid stools and a maximum abdominal pain score of 1 (based upon CDAI scale of 0 to 3 in which 1 represents mild abdominal pain) will be used to define clinical response as co-primary end points.

The rationale for the change in the clinical co-primary end point from PRO2 to CDAI is that the US Food and Drug Administration (FDA) informed the Sponsor, in 2019, that it had recently accepted proposals from other sponsors to define the co-primary end points in CD studies as clinical remission using a CDAI score of < 150 and CCI [redacted] or response using the SES-CD score. The rationale provided by the FDA for this recommendation was the paucity of available prospective data validating the best cutoffs for PRO-based scoring that define either eligibility or clinical remission. Therefore, the Study GS-US-419-3895 protocol was revised in Amendment 8 to align with this recommendation. CDAI remission is a well-established clinical primary end point that has been evaluated in clinical trials for products approved for the treatment of moderate to severely active CD in the US, the EU, and other regions.

Endoscopic response will be another co-primary end point assessed by SES-CD. Use of centrally read endoscopy will further reduce bias in assessment of CCI [redacted]. Maintenance and durability of response and remission will be explored in the 48-week maintenance phase using a traditional model of induction-maintenance design.

1.3.2. Rationale for Dose

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

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

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

1.4. Risk/Benefit Assessment for the Study

Crohn's disease is a progressive and potentially life-threatening disease with few treatment options, many of which result in primary or secondary nonresponse. Inflammatory bowel disease may lead to increased risk of gastrointestinal malignancies, impairment in quality of life, and ultimate need for life-altering surgery. Current treatment options are limited in ability to establish mucosal healing and clinical remission and have significant safety and efficacy limitations; for example, biologics have significant immunogenic risks and steroids are associated with increased morbidity and mortality. Remission rates are generally low when compared to placebo rates across most therapies for IBD. There remains substantial unmet need in IBD, particularly in moderate to severe disease. The lifelong nature of IBD increases the probability that subjects have cycled through various therapies, leaving few approved options.

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

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

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

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

An independent and experienced data monitoring committee (DMC) appointed to monitor the study will provide an additional level of risk mitigation. The DMC may advise to continue the study unchanged, to modify the study, or to discontinue the study. The initial meeting will occur after approximately 100 subjects reach Week 10 in Cohorts A and B combined. Following this, subsequent meetings will occur approximately once every 4 months or at a frequency determined by the DMC.

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

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

1.5. Compliance

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

2. OBJECTIVES

2.1. Cohort A Induction Study

The primary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The key secondary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives of Cohort A Induction Study are:

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

CCI

- CCI
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI
- CCI
- CCI

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

2.1.1. EU-Specific Objectives for Cohort A Induction Study

The EU-specific primary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort A Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives of Cohort A Induction Study are:

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

CCI

[redacted]

2.2. Cohort B Induction Study

The primary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives of Cohort B Induction Study are:

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

CCI

- CCI
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 score and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

2.2.1. EU-Specific Objectives for the Cohort B Induction Study

The EU-specific primary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort B Induction Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 score and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives of Cohort B Induction Study are:

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

CCI

[redacted]

2.3. Maintenance Study

The primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by CDAI at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The other secondary objectives of the Maintenance Study are:

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

CCI [redacted]

- CCI [redacted]
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

2.3.1. EU-Specific Objectives for the Maintenance Study

The EU-specific primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The EU-specific key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The EU-specific other secondary objectives of the Maintenance Study are:

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

CCI

3. STUDY DESIGN

3.1. Endpoints

3.1.1. Cohort A Induction Study

The primary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

The key secondary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving clinical response by CDAI at Week 10

The other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI

- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI

- CCI
- CCI
- CCI

3.1.1.1. EU-Specific Endpoints for the Cohort A Induction Study

The EU-specific primary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

The EU-specific key secondary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI

3.1.2. Cohort B Induction Study

The primary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

The key secondary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving clinical response by CDAI at Week 10

The other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI

- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI 0
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

3.1.2.1. EU-Specific Endpoints for the Cohort B Induction Study

The EU-specific primary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

The EU-specific key secondary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI

3.1.3. Maintenance Study

The primary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 58
- The proportion of subjects achieving endoscopic response at Week 58

The key secondary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 58
- The proportion of subjects achieving clinical response by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by CDAI at Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by PRO2 at Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by PRO2 at Week 58

The other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI

- CCI
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- CCI
- CCI
- CCI

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

3.1.3.1. EU-Specific Endpoints for the Maintenance Study

The EU-specific primary end points are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 58
- The proportion of subjects achieving endoscopic response at Week 58

The EU-specific key secondary end points are:

- The proportion of subjects achieving clinical remission by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by PRO2 at Weeks 10 and 58
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by PRO2 at Week 58

The EU-specific other secondary end point is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI [redacted]

[redacted]

[redacted]

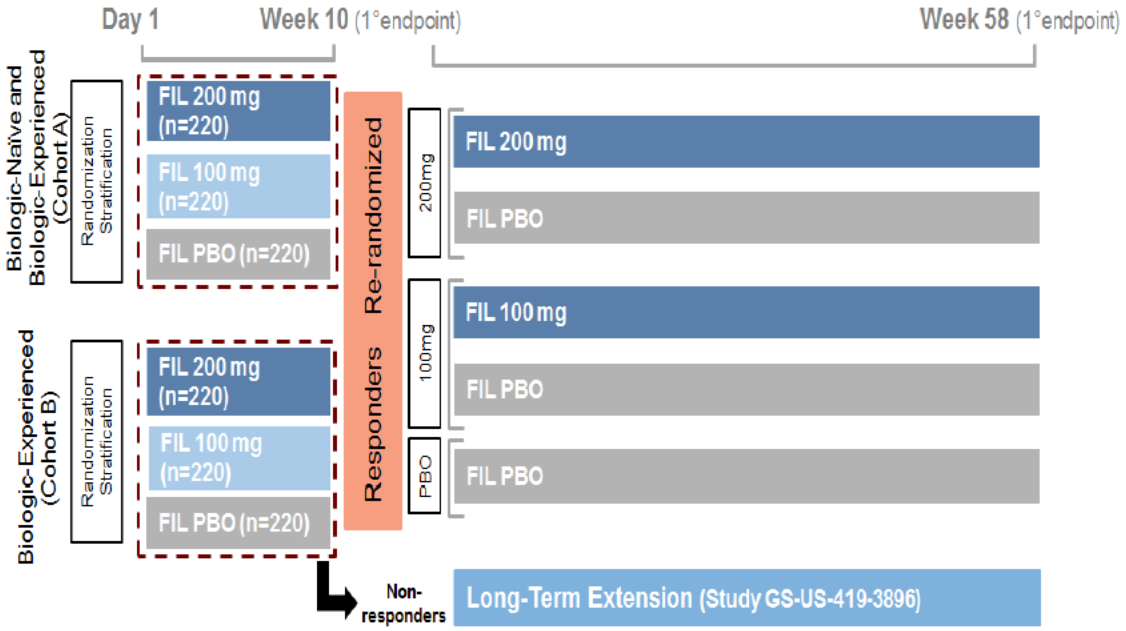
- CCI

[redacted]

3.2. Study Design

These are combined Phase 3 double-blind, randomized, placebo-controlled studies to evaluate the efficacy and safety of filgotinib in the induction and maintenance of clinical remission, as well as, endoscopic response in subjects with moderately to severely active CD. A schematic of this study is provided in Figure 3-1.

Figure 3-1. Study Design Schematic



FIL = filgotinib; PBO = placebo; mg = milligram.
Non-responders are subjects who achieve neither clinical remission (PRO2) nor endoscopic response (SES-CD) at Week 10.
Subjects in the Maintenance Study that meet disease worsening criteria (see Section 3.6) will be offered open-label filgotinib.

These studies include:

- Screening (Days -30 to -1)
- Randomization (Day 1)
- Blinded Induction Studies (Day 1 – Week 11)
  - Cohorts A and B Week 10 efficacy assessments:
    - At Week 10, CDAI and PRO2 to assess clinical remission
    - At Week 10, SES-CD to assess endoscopic response
  - Blinded Bridge Phase (Week 10 to 11): dosing will continue in a blinded fashion through the end of Week 10 until re-randomization at Week 11
- Re-randomization (Week 11)
  - Subjects in Cohort A and B who complete the Induction Study and achieve either clinical remission by PRO2 or endoscopic response by SES-CD at Week 10 will be re-randomized into the Maintenance Study at Week 11
  - Subjects who achieve neither clinical remission by PRO2 nor endoscopic response at Week 10 will have the option to enter a separate Long-Term Extension (LTE) study (GS-US-419-3896 [Galapagos Study ID GLPG0634-CL-310])
- Blinded Maintenance Study (Weeks 11 to 58)
- Post-Treatment (PTx) safety assessments:
  - Subjects who opt out of the LTE study (GS-US-419-3896) will return 30 days after the last dose of study drug for PTx safety assessments
  - Subjects who complete all procedures per protocol, including the endoscopy, of the 58 week study will be offered the option to continue into the LTE study (GS-US-419-3896)
  - Subjects who are eligible and opt to participate in the LTE study (GS-419-3896) can continue into the study without PTx safety assessments

3.3. Study Treatments

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

Treatment 1 (n = 220): filgotinib 200 mg and placebo-to-match (PTM) filgotinib 100 mg, once daily

Treatment 2 (n = 220): filgotinib 100 mg and PTM filgotinib 200 mg, once daily

Treatment 3 (n = 220): PTM filgotinib 200 mg and PTM filgotinib 100 mg, once daily

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

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

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

- History of exposure to no biologic agent, one biologic agent, or more than one biologic agent
- Concomitant use of oral, systemically absorbed corticosteroids (eg, prednisone) at Day 1, (Yes or No)
- Concomitant use of immunomodulators (eg, 6-mercaptopurine [6-MP], azathioprine, MTX) at Day 1, (Yes or No)

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

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

Subjects from Cohorts A and B who are eligible for the Maintenance Study will be re-randomized to treatment as follows:

Table 3-1. Re-Randomization of Induction Cohorts A and B to Maintenance Study

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

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

Stratification Factors (Maintenance Study)

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

3.4. Duration of Treatment

Randomized subjects will receive a maximum of 58 weeks of study drug. Subjects who are non-responders based on the results of the Week 10 assessments will be offered the option to receive open-label filgotinib by entering into the LTE study (GS-US-419-3896).

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

Subjects who complete all procedures per protocol, including the endoscopy of the Week 58 visit, will have the option to continue study drug in a blinded fashion in the LTE study.

3.5. Criteria for Study Drug Interruption or Discontinuation

3.5.1. Study Drug Interruption Considerations

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

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

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

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

The medical monitor should consult the medical leader as needed.

3.5.2. Study Drug Discontinuation Considerations

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

Study drug must be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria.
- Febrile neutropenia (temperature > 38.3°C or a sustained temperature of > 38°C for more than one hour) with absolute neutrophil count of < 1,000/mm^3
- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin < 7.5 g/dL, or if transfusion is indicated regardless of hemoglobin value
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active HCV during the study, as evidenced by HCV RNA positivity
- Evidence of active HBV during the study, as evidenced by HBV DNA positivity
- Any thromboembolic event that meets SAE reporting criteria
- Unacceptable toxicity, or toxicity that, in the judgment of the investigator, compromises the subject's ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Subject noncompliance
- Pregnancy during the study; refer to Section 7.7.2.1
- Discontinuation of the study at the request of the Sponsor, a regulatory agency or an institutional review board or independent ethics committee (IRB/IEC)
- Subject use of prohibited concurrent therapy may trigger study drug discontinuation; consultation should be made with the medical monitor.

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

  — 2 sequential neutrophil counts < 750 neutrophils/mm^3 (international system units [SI]: < $0.75x10^9$ cells/L)

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

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

    ■ total bilirubin > 2x ULN

    ■ international normalized ratio (INR) > 1.5

    ■ or accompanied by symptoms consistent with hepatic injury

    For any subject with an **initial** AST or ALT elevation > 3x the upper limit of normal (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 > 5x ULN

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

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

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

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

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

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

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

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

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

The medical monitor should consult the medical leader as needed.

3.6. Disease Worsening Criteria

Subjects meeting the following disease worsening criteria evaluated after Week 11 must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib by entering into the separate LTE study (GS-US-419-3896).

- Increase in CDAI score ≥ 100 points from the Week 10 value and CDAI score ≥ 220 points at 2 consecutive visits.
  - The disease worsening visits may include unscheduled visits (eg, a study visit followed by an unscheduled visit, or 2 sequential unscheduled visits anytime subsequent to the Week 11 visit).
- If a subject experiences significant worsening of underlying CD, which requires any of the prohibited medications (refer to Section 5.4.2), or surgical intervention at any point during the study, treatment discontinuation should be considered at investigator's discretion, in consultation with medical monitor if feasible (refer to Section 3.5.2); these subjects do not qualify for LTE study.

3.7. End of Study

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

3.8. Post Study Care

All subjects completing all study related procedures, including endoscopy at Week 58, will be offered an opportunity to participate in the LTE study (GS-US-419-3896). For those subjects who do not participate in the LTE study, after the subject has completed their study participation, the long-term care of the participant will remain the responsibility of their primary treating physicians.

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CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Cohort A Induction Study

Approximately 660 subjects who meet the eligibility criteria at screening will be randomized in a blinded fashion in a 1:1:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or matching placebo.

Cohort B Induction Study

Approximately 660 subjects who meet the eligibility criteria at screening will be randomized in a blinded fashion in a 1:1:1 ratio to filgotinib 200 mg, filgotinib 100 mg, or matching placebo.

Maintenance Study

Subjects from Cohorts A and B who achieve either clinical remission by PRO2 or endoscopic response at Week 10 will be re-randomized at Week 11 in a blinded fashion in a 2:1 ratio to either the same dose of filgotinib or placebo. Refer to Section 3.3, Table 3-1.

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

4.2. Induction Study (Cohorts A and B)

4.2.1. Inclusion Criteria

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

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

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

3) Females of childbearing potential (as defined in Appendix 7) must have a negative serum pregnancy test at screening and a negative urine pregnancy test at baseline

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

5) Documented diagnosis of CD with a minimum disease duration of 3 months with involvement of the ileum and/or colon at a minimum, documented by the following:

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

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

6) Moderately or severely active CD as defined by:

   a) CDAI total score between 220 and 450 inclusive (refer to Appendix 4), AND

   b) PRO2 score consisting of abdominal pain ≥ 2 (on CDAI scale of 0 to 3) OR daily stool frequency ≥ 4 (refer to Appendix 4), AND

   c) Evidence of active disease as measured by SES-CD (refer to Appendix 5) based on central reading:

      i) Total score ≥ 6, OR

      ii) If disease is limited to the ileum and/or right colon, a combined score ≥ 4 in these two segments

7) Meet one of the following TB screening criteria:

   a) No evidence of active or latent TB ie,

      i) A negative QuantiFERON® TB-Gold In-Tube test (or centrally reported equivalent assay) at screening, AND

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

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

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

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

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

8) Laboratory parameters (subjects who fail to meet below reference laboratory tests may be re-tested once at discretion of investigator prior to being considered a screen failure):

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

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

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

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

   e) Platelets ≥ 100×10^9/L

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

   g) Absolute lymphocyte count >750/mm^3

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

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

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

   c) Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must remain stable for the first 14 weeks after randomization

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

10) Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose.

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

4.2.2. Exclusion Criteria

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

1) Pregnant or lactating females

2) Males and females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined by Appendix 7

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

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

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

6) Currently have any of the following complications of CD:

   a) Symptomatic strictures, OR

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

   c) Fistulae other than perianal 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

7) 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

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

9) Presence of UC, indeterminate colitis, ischemic colitis, fulminant colitis, or toxic mega-colon

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

11) Dependence on parenteral nutrition

12) History or evidence of incompletely resected colonic mucosal dysplasia

13) Stool sample positive for Clostridium difficile (C. diff) toxin, pathogenic Escherichia coli (E. coli), Salmonella species (spp), Shigella spp, Campylobacter spp, or Yersinia spp

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

15) Active clinically significant infection or any infection requiring hospitalization or treatment with intravenous anti-infectives within 30 days of screening (or 8 weeks of Day 1); or any infection requiring oral anti-infective therapy within 2 weeks of screening (or 6 weeks of Day 1)

16) Infection with HIV, hepatitis B, or hepatitis C

17) Presence of Child-Pugh Class C hepatic impairment

18) Active TB or history of latent TB that has not been treated (See inclusion criterion 7 for further information)

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

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

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

22) History of cytapheresis ≤ 2 months prior to screening

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

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

25) Administration of a live or attenuated vaccine within 30 days of randomization

26) History of opportunistic infection or immunodeficiency syndrome

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

28) History of disseminated Staphylococcus aureus

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

4.3. Cohort A (Biologic-Naïve and Biologic-Experienced) Induction Study

4.3.1. Inclusion Criteria for Biologic-Naïve Subjects Enrolled in Cohort A

Biologic-Naïve subjects must meet all of the additional inclusion criteria to be eligible for Cohort A.

1) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to 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 oral prednisone 30 mg daily for 2 weeks or intravenously (IV) for 1 week, OR

        ii) Two failed attempts to taper steroids below a dose equivalent of 10 mg daily prednisone, OR

        iii) History of steroid intolerance including, but not limited to, Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, serious infections, depression, allergic reactions, mood disturbances, or any other condition that contributed to discontinuation of the agent

    b) Immunomodulators

        i) Active disease despite a history of at least a 12 week regimen of oral azathioprine (≥ 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 ≥ 15mg 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

4.3.2. Exclusion Criteria for Biologic-Naïve Subjects Enrolled in Cohort A

Biologic-Naïve subjects who meet *any* of the following exclusion criteria are not eligible for Cohort A.

1) Prior or current use of TNFα antagonist, including (but not limited to) infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent

2) Prior or current use of vedolizumab at any time

3) Prior or current use of ustekinumab at any time

4.3.3. Inclusion Criteria for Biologic-Experienced Subjects Enrolled in Cohort A

Biologic-Experienced subjects must meet all of the additional inclusion criteria to be eligible for Cohort A.

1) Previously demonstrated an inadequate clinical response, loss of response to, or intolerance to at least *one* of the following agents (depending on current country treatment recommendations/guidelines) or discontinuation of use of at least one of the following agents for reasons other than inadequate clinical response, loss of response, or intolerance:

   a) TNFα Antagonists

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

         - Infliximab: A 14 week induction regimen of 5 mg/kg IV at Weeks 0, 2, and 6 (6 week induction regimen with 2 doses at Weeks 0 and 2 in EU)
         - Adalimumab: A 4 week induction regimen consisting of 160 mg SC (four 40-mg injections in one day or two 40-mg injections per day for two consecutive days) on Day 1, followed by a second dose 2 weeks later (Day 15) of 80 mg
         - Certolizumab: A 8 week induction regimen of 400 mg SC at Weeks 0, 2, and 4

   OR

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

      ii) 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

   b) Vedolizumab

      i) Active disease despite a history of at least a 14 week induction regimen of vedolizumab consisting of 300 mg IV at Weeks 0, 2, and 6, OR

      ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent

   c) Ustekinumab

      i) Active disease despite a history of a 8 week induction regimen with a single dose of ustekinumab IV per weight-based dosing (260 mg for up to 55 kg; 390 mg for greater than 55 to 85 kg; 520 mg for greater than 85 kg) at Week 0, OR

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

4.3.4. Exclusion Criteria for Biologic-Experienced Subjects Enrolled in Cohort A

Biologic-Experienced subjects who meet the following exclusion criterion are not eligible for Cohort A.

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

4.4. Cohort B (Biologic-Experienced) Induction Study

4.4.1. Inclusion Criteria, Cohort B ONLY

Subjects must meet all of the additional inclusion criteria to be eligible for participation in Cohort B induction study.

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

    a) TNFα Antagonists

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

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

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

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

    OR

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

        ii) 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

b) Vedolizumab

i) Active disease despite a history of at least a 14 week induction regimen of vedolizumab consisting of 300 mg IV at Weeks 0, 2, and 6, OR

ii) History of intolerance to vedolizumab including, but not limited to, serious infections, hepatotoxicity, cytopenia, allergic reactions, or any other condition that contributed to discontinuation of the agent

c) Ustekinumab

i) Active disease despite a history of a 8 week induction regimen with a single dose of ustekinumab IV per weight-based dosing (260mg for up to 55kg; 390mg for greater than 55 to 85kg; 520mg for greater than 85kg) at Week 0, OR

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

4.4.2. Exclusion Criteria, Cohort B ONLY

Subjects who meet the following exclusion criterion are not to be enrolled in Cohort B induction study.

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

4.5. Maintenance Study

4.5.1. Inclusion Criteria

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

1) Completion of Cohort A or B induction study with either clinical remission by PRO2 or endoscopic response at Week 10

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

3) May be on oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30 mg/day or budesonide at a dose of ≤ 9 mg/day); dose must remain stable to Week 14

4.5.2. Exclusion Criteria

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

1) Males and females of reproductive potential who are unwilling to abide by protocol-specified contraceptive methods as defined by Appendix 7

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

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

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

5.1.1. Procedures for Breaking Treatment Codes

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

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

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

5.1.2. 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 and Labeling or Clinical Supply Management who have an unblinded inventory manager role in the interactive voice/web response system for purposes of study drug inventory management will remain unblinded. Individuals responsible for safety signal detection, investigational new drug safety reporting and/or expedited reporting of SUSARs may be unblinded to individual case data and/or group level summaries. External (ie, contract research organizations) biostatisticians and programmers will be unblinded to support data monitoring committee data review and PK/PD data merge. Regulatory quality and compliance personnel in Research and Development may also be unblinded for purposes of supporting quality assurance activities and/or regulatory agency inspections.

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

5.2.1. Formulation

Filgotinib is available as 200 mg and 100 mg strength tablets. Filgotinib tablets, 200 mg and 100 mg are beige, debossed with "GSI" on one side and "200" or "100" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg or 100 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

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

5.2.2. Packaging and Labeling

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

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

5.2.3. Storage and Handling

Filgotinib and PTM filgotinib tablets should be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to authorized site personnel.

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

5.3. Dosage and Administration

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

The following treatments will be evaluated:

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

Subjects who are non-responders based on the results of the Week 10 assessments will be offered the option to receive open-label filgotinib by entering into the LTE study (GS-US-419-3896). Subjects meeting disease worsening criteria after Week 11 must be discontinued from blinded treatment and will be offered the option to receive open-label filgotinib 200 mg (See Section 3.6, Disease Worsening Criteria), except for US and Korea males who will be offered filgotinib 100 mg unless they have failed at least 2 other biologic therapies (any TNFα antagonist and vedolizumab). Subjects who complete the Week 58 visit will have the option to continue study drug in a blinded fashion in the LTE study.

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

5.4. Prior and Concomitant Medications

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

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

5.4.1. Allowed Concomitant Medications

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

The allowed medications for CD are as follows:

- Oral 5-ASA compounds provided the dose prescribed has been stable for at least 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization
- Azathioprine, 6-MP, or MTX provided the dose prescribed has been stable for 4 weeks prior to randomization; dose must be stable for the first 10 weeks after randomization
- Oral corticosteroid therapy (prednisone prescribed at a stable dose ≤ 30 mg/day or budesonide prescribed at a stable dose of ≤ 9 mg/day) provided the dose prescribed has been stable for 2 weeks prior to randomization; dose must be stable for the first 14 weeks after randomization
- Antibiotics for the treatment of CD (eg, metronidazole, ciprofloxacin) provided the dose prescribed has been stable for 2 weeks prior to randomization. Dose must remain stable for the first 10 weeks after randomization. Subjects who are on cyclic therapy must continue their standard low-dose regimen without change for the first 10 weeks after randomization.
- Antidiarrheals for chronic diarrhea are allowed throughout the study as necessary for control of chronic diarrhea; stable doses are encouraged

5.4.2. Prohibited Concomitant Medications

The prohibited medications are as follows:

Table 5-1. Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Prohibited Period
Strong P-gp Inducers[a]		
Anticonvulsants	Phenobarbital, phenytoin, carbamazepine,	30 days prior to screening through the end of the study
Antimycobacterials	Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort, danshen (Salvia Miltiorrhiza)	
Prohibited IBD Medications		
Corticosteroids	Dose equivalent to > 30 mg/day of prednisone	30 days prior to screening through the end of the study
TNFα antagonist	Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agent	8 weeks prior to screening[d] through the end of the study
Integrin antagonist	Vedolizumab and natalizumab	8 weeks prior to screening[d] through the end of the study
Interleukin antagonist	Ustekinumab	12 weeks prior to screening[d] through the end of the study
Other (non-biologic)	Cyclosporine, thalidomide, tacrolimus, leflunomide, and any investigational agent	30 days prior to screening through the end of the study
	Any JAK inhibitor	Any time before and through the end of the study
Investigational biologics	Any investigational biologic agent	8 weeks prior to screening through the end of the study (or at least 5 half lives)
Lymphocyte-depleting therapies	Alemtuzumab, cyclophosphamide, total lymphoid irradiation, rituximab, and any other lymphocyte depleting therapy	Any time before and through the end of the study
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
Other biologics[c]	Antibody based or other systemic biologics, eg, denosumab, trastuzumab	Requires medical monitor consultation

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

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

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

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

d Subjects who have an undetectable serum level of a biologic agent since its last dose using a commercially available assay can undergo study screening without the above-mentioned waiting period.

5.4.3. Corticosteroid Tapering

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

5.5. Vaccine Guidelines

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

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

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

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

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

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

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

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

5.6. Accountability for Study Drug

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

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

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

5.6.1. Investigational Medicinal Product Return or Disposal

Please refer to Section 9.1.7.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment and Treatment Assignment

Subjects who meet the protocol criteria will be assigned to the respective cohort and subsequently randomized in a blinded fashion in a 1:1:1 ratio to filgotinib, or matching placebo.

- **Treatment 1 (n = 220)** : filgotinib 200 mg and PTM filgotinib 100 mg, once daily
- **Treatment 2 (n = 220)** : filgotinib100 mg and PTM filgotinib 200 mg, once daily
- **Treatment 3 (n = 220)**: PTM filgotinib 200 mg and PTM filgotinib100 mg, once daily

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

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

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

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

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

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

Stratification Factors (Maintenance Study)

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

Refer to Section 3.3, Table 3-1 for re-randomization in the Maintenance Study.

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent
  - Additional consent will be required from subjects participating in the PK substudy , CCI and left-over samples for future research
- Review inclusion/exclusion criteria and other protocol restrictions (Section 4)
- Obtain medical history and concomitant medications, including CD history and treatment
- CCI
- Ask Anchor Questions for abdominal pain and stool frequency
- Complete physical examination (PE) including, vital signs, body weight, and height
- Perform 12-Lead ECG
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the informed consent form.
- Instruct subjects to maintain concomitant medication at a stable dose
- Provide subject with the electronic diary (e-Diary) and instructions for daily documentation of stool frequency, abdominal pain and general well-being
  - Subjects should be instructed that all stools in the same toilet visit should be counted as one stool. If they pass more than one stool during a toilet visit, they will still count as one

- Conduct phone call approximately 4 days after screening visit to encourage compliance with daily documentation of abdominal pain, stool frequency and general well-being
- Collect the variables to calculate baseline CDAI score (reference Appendix 4)
  - Site enters patient assessments from screening visit
  - CDAI score calculated centrally after all components have been captured electronically
- Baseline PRO2 (Appendix 4) – centrally calculated using the patient reported symptoms of stool frequency and abdominal pain captured in the e-Diary
- TB Assessment – Must have negative QuantiFERON® test (or centrally reported equivalent assay) during screening, and negative chest x- ray within 3 months of or during screening for those with no evidence or history of TB. Positive or negative results must not be repeated. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Two sequential indeterminate results is considered a positive result for the purpose of the study. Subjects with previously treated latent or active TB requires sponsor approval (See inclusion criterion 7 for details). Subjects who are diagnosed with latent TB at screening must initiate an adequate course of prophylaxis as per local standard of care for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the medical monitor.
- Obtain blood samples (reference Study Procedures Table [Appendix 2])
  - **HCV Screening Guidelines**
    - Subjects with positive HCV antibody at Screening require reflex testing for HCV RNA. Subjects with HCV RNA ≥ lower limit of quantification (LLOQ) at Screening will be excluded. Subjects with positive HCV antibody but HCV RNA < LLOQ are eligible.
  - **HBV Screening and Surveillance Guidelines**
    - Subjects with positive HBV surface antigen (HBsAg) at Screening are excluded.
    - Subjects who are positive for HBV surface antibody (HBsAb), but negative for **both** HBsAg and HBV core antibody (HBcAb) at Screening are eligible.
    - Subjects with positive HBcAb require reflex testing for HBV DNA. Subjects with HBV DNA ≥ LLOQ at Screening will be excluded. Subjects with positive HBcAb and HBV DNA < LLOQ are eligible, but will require ongoing HBV DNA monitoring every 3 months during this study. These subjects may require prophylactic treatment per investigator discretion in accordance with local guidelines/standard of care.

- In Japan and where required by local guidelines, subjects with positive HBcAb and/or positive HBsAb will require reflex testing for HBV DNA at Screening. Subjects with positive HBcAb and/or HBsAb but with HBV DNA < LLOQ at Screening are eligible for the study. These subjects will require ongoing HBV DNA monitoring every 4 weeks in accordance with local guidelines during this study.
- Any subject who has HBV DNA ≥ LLOQ during the study will be discontinued (reference Section 3.5.2).

— **HIV Screening Guidelines**

- Subjects who have HIV infection, regardless of virologic status, are excluded from the study.

- Obtain blood samples for serum pregnancy test (for females of childbearing potential only)
- Obtain stool sample (reference Study Procedures Table [Appendix 2])
  - A stool sample will be obtained for culture for pathogenic bacteria, ova and parasite evaluation, and *C. difficile* toxin assay during screening for the purposes of determining eligibility.
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
- Obtain urine sample for urine drug screen (reference Study Procedures Table [Appendix 2])
- Review subject eligibility criteria (centrally calculated CDAI, PRO2 and labs), prior to performing a full video ileocolonoscopy with biopsies within 14 days prior to baseline visit: Biopsy samples will be collected and sent to central laboratory for storage and then to specialty laboratories for subsequent analysis.
  - Record local endoscopic assessment
- Baseline SES-CD scoring and calculation performed by central reader (Appendix 5).

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

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic within 30 days after screening for randomization into the study. Subjects may be randomized more than 30 days after screening if they receive permission from the medical monitor. If the subject does not begin the treatment within this 30-day window, specific screening evaluation procedures may need to be repeated at the direction of the medical monitor. No more than one repeat screening visit is allowed for each subject, unless prior written approval has been provided by the Sponsor. All screening procedures will need to be repeated during the repeat screening visit except for the ileocolonoscopy procedures. Ileocolonoscopy procedures from the previous screening attempt that fall within the specified timeframe (i.e, ileocolonoscopy with biopsies within 14 days prior to Day 1 visit) do not need to be repeated.

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

6.2.2. Day 1

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

- Review inclusion/exclusion criteria and other protocol restrictions
- Symptom directed PE
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse, and temperature)
- Fistula assessment, if applicable
- Review AEs and concomitant medications
- Review e-Diary for compliance and scores – remind subjects of diary instructions at every visit
- CCI [redacted]
- Have subject complete the Patient Global Impression – Severity (PGI-S) questionnaire
- CCI [redacted]
- CCI [redacted]
- Obtain fasting blood samples (reference Study Procedures Table [Appendix 2])
- Obtain blood sample for CCI [redacted] and leukocyte subsets (US and Canadian sites only)
- CCI [redacted]
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
  - Sample will be used for urinalysis and pregnancy test (for females of childbearing potential only)

6.3. Randomization

Please refer to Section 6.1.

6.3.1. Randomization and Study Drug Administration

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

6.4. Study Assessments

Please refer to the Study Procedure Table in Appendix 2 for all procedures and time points to be conducted after randomization.

6.4.1. Priority of Assessments

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

6.4.2. Efficacy

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

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

The Crohn's Disease Activity Index or CDAI is a tool used to assess the disease activity of Crohn's disease. Refer to Appendix 4. The PRO2 is 2 patient reported outcomes of liquid or very soft stool and abdominal pain which are components of the CDAI.

6.4.2.2. Patient Global Impression – Severity (PGI-S) and Patient Global Impression - Change (PGI-C)

The Patient Global Impression of Severity (PGI-S) is a global index that is used to rate the severity of Crohn's disease by patients (a single-state scale). The Patient Global Impression of Change (PGI-C) is a scale that aims at evaluating all aspects of patients' health related to Crohn's disease and determining if there has been an improvement or not. The patient has to select the one response from the response options that gives the most accurate description of his/her state of health (overall status).

[redacted]

6.4.3. Safety

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

6.4.3.1. Clinical Laboratory Evaluations

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

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

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

Refer to Appendix 8 for table of clinical laboratory tests.

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

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

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

6.4.3.2. Pregnancy Testing (for females of childbearing potential)

All females meeting the childbearing potential criteria (Appendix 7) must have a serum pregnancy testing at screening and an in-clinic urine pregnancy test must be completed every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic that will be centrally reported.

6.4.3.3. Vital Signs

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

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

6.4.3.4. Physical Examination

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

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

6.4.3.5. 12-lead Electrocardiogram

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

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

6.4.3.6. 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).

6.4.4. Pharmacokinetics Assessments

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

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

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

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

[redacted]

6.5. Post-Treatment Assessments

All subjects must complete the PTx assessments 30 days after the last dose of study drug. Subjects who enter into the LTE study (GS-US-419-3896) will not complete PTx assessments associated with this protocol.

The following will be performed and documented:

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

6.6. Early Termination Assessments

The following will be performed and documented:

- Symptom-directed PE
- Obtain body weight and vital signs (resting blood pressure, respiratory rate, pulse and temperature)
- Perform 12-Lead ECG (for subjects who terminate prior to Week 10)
- Review AEs and concomitant medications
- CCI
- Collect the variables to calculate CDAI score (reference Appendix 4)
  - Site collects patient assessments at each visit
  - CDAI score calculated centrally after all components have been captured electronically
- PRO2 score calculated centrally
- Obtain fasting blood samples (reference Study Procedures Table (Appendix 2)
- Obtain urine sample (reference Study Procedures Table [Appendix 2])
  - Pregnancy test (for females of child bearing potential only)

6.7. End of Study

Please refer to Section 3.7

6.8. Post Study Care

Please refer to Section 3.8

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

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

An AE does not include the following:

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

7.1.2. Serious Adverse Events

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

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

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

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified 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 investigational medicinal product (IMP) therapy using clinical judgment and the following considerations:

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

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

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

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

7.2.2. Assessment of Severity

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

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1 and Appendix 6.

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 medication, the following types of events should be reported on the eCRF: all SAEs and adverse events related to protocol mandated procedures.

7.3.1. Adverse Events

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

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

7.3.2. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post-treatment follow-up period, must be reported to the eCRF database and 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 after the post-treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

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

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

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

Electronic Serious Adverse Event Reporting Process

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

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

  Email: DIVERSITY_safety@glpg.com

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

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

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

- Additional information may be requested to ensure the timely completion of accurate safety reports.
- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

7.4. Sponsor Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by the Sponsor or designee using reference safety information specified in the investigator's brochure (IB) or relevant local label as applicable.

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

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

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

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

Severity should be recorded and graded according to the CTCAE Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 6). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

7.6. Toxicity Management

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

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

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

7.6.2. Grade 3 Laboratory Abnormality or Clinical Event

- For a Grade 3 clinically significant laboratory abnormality or clinical event, IMP may be continued if the event is considered to be unrelated to IMP.
- For a Grade 3 clinical event, or clinically significant laboratory abnormality confirmed by repeat testing, that is considered to be related to IMP, IMP should be withheld until the toxicity returns to ≤ Grade 2.
- If a laboratory abnormality recurs to ≥ Grade 3 following re-challenge with IMP and is considered related to IMP, then IMP should be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation.

7.6.3. Grade 4 Laboratory Abnormality or Clinical Event

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

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

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

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

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

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

Medication error is any unintentional error in the prescribing, dispensing, preparation for administration, or administration of an investigational product while the medication is in the control of 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 an investigational product by a subject.

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

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

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

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

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

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

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

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

7.7.2. Instructions for Reporting Special Situations

7.7.2.1. Instructions for Reporting Pregnancies

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

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

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

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

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to DIVERSITY_safety@glpg.com.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to DIVERSITY_safety@glpg.com using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to DIVERSITY_safety@glpg.com.

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

Refer to Appendix 7 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to DIVERSITY_safety@glpg.com within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to concomitant medications.

Special situations involving concomitant medications do not need to be reported on the special situations report form; however, special situations that result in AEs due to a concomitant medication must be reported as an AE.

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

Cohort A Induction Study

The primary objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The key secondary objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives of Cohort A are:

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

CCI [redacted]

- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 score and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

8.1.1.1.1. EU-Specific Objectives for the Cohort A Induction Study

The EU-specific primary objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort A are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives of Cohort A are:

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

CCI

[redacted]

8.1.1.2. Cohort B Induction Study

The primary objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The key secondary objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 10

The other secondary objectives are:

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

CCI

- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 score and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

8.1.1.2.1. EU-Specific Objectives for the Cohort B Induction Study

The EU-specific primary objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 10

The EU-specific key secondary objectives of Cohort B are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 10
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary objectives are:

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

CCI

[redacted]

8.1.1.3. Maintenance Study

The primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical response by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by CDAI at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The other secondary objectives of the Maintenance Study are:

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

CCI [redacted]

[redacted]

- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

8.1.1.3.1. EU-Specific Objectives for the Maintenance Study

The EU-specific primary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by PRO2 at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing endoscopic response at Week 58

The EU-specific key secondary objectives of the Maintenance Study are:

- To evaluate the efficacy of filgotinib as compared to placebo in establishing clinical remission by CDAI at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing sustained clinical remission by PRO2 at Weeks 10 and 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- To evaluate the efficacy of filgotinib as compared to placebo in establishing 6-month corticosteroid-free remission by PRO2 at Week 58

The EU-specific other secondary objectives of the Maintenance Study are:

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

CCI

[redacted]

8.1.2. Primary Endpoints

8.1.2.1. Cohort A Induction Study

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

8.1.2.1.1. EU-Specific Primary End points for the Cohort A Induction Study

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

8.1.2.2. Cohort B Induction Study

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

8.1.2.2.1. EU-Specific Primary Endpoints for the Cohort B Induction Study

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving endoscopic response at Week 10

8.1.2.3. Maintenance Study

- The proportion of subjects achieving clinical remission by CDAI at Week 58
- The proportion of subjects achieving endoscopic response at Week 58

8.1.2.3.1. EU-Specific Primary Endpoints for the Maintenance Study

- The proportion of subjects achieving clinical remission by PRO2 at Week 58
- The proportion of subjects achieving endoscopic response at Week 58

8.1.3. Secondary Endpoints

8.1.3.1. Cohort A Induction Study

The key secondary end points of Cohort A are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving clinical response by CDAI at Week 10

The other secondary end point of Cohort A is:

- PK characteristics for filgotinib and its metabolite GS-829845

8.1.3.1.1. EU-Specific Secondary Endpoints for the Cohort A Induction Study

The EU-specific key secondary end points of Cohort A are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary end point of Cohort A is:

- PK characteristics for filgotinib and its metabolite GS-829845

8.1.3.2. Cohort B Induction Study

The key secondary end points of Cohort B are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 10
- The proportion of subjects achieving clinical response by CDAI at Week 10

The other secondary end point of Cohort B is:

- PK characteristics for filgotinib and its metabolite GS-829845

8.1.3.2.1. EU-Specific Secondary Endpoints for the Cohort B Induction Study

The EU-specific key secondary end points of Cohort B are:

- The proportion of subjects achieving clinical remission by CDAI at Week 10
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10

The EU-specific other secondary end point of Cohort B is:

- PK characteristics for filgotinib and its metabolite GS-829845

8.1.3.3. Maintenance Study

The key secondary end points of the Maintenance Study are:

- The proportion of subjects achieving clinical remission by PRO2 at Week 58
- The proportion of subjects achieving clinical response by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by CDAI at Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by PRO2 at Weeks 10 and 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by PRO2 at Week 58

The other secondary end point of the Maintenance Study is:

- PK characteristics for filgotinib and its metabolite GS-829845

8.1.3.3.1. EU-Specific Secondary Endpoints for the Maintenance Study

The EU-specific key secondary end points of the Maintenance Study are:

- The proportion of subjects achieving clinical remission by CDAI at Week 58
- The proportion of subjects achieving sustained clinical remission by PRO2 at Weeks 10 and 58
- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- The proportion of subjects achieving 6-month corticosteroid-free remission by PRO2 at Week 58

The EU-specific other secondary end point of the Maintenance Study is:

- PK characteristics for filgotinib and its metabolite GS-829845

CCI [redacted]

8.1.4.1. Cohort A Induction Study

CCI [redacted]

[redacted]

- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

- CCI
- CCI
- CCI

CCI

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.4.2. Cohort B Induction Study

CCI

[redacted]

- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 10
- CCI

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

CCI [redacted]

[redacted]

8.1.4.3. Maintenance Study

CCI

- The proportion of subjects achieving both clinical remission by PRO2 and endoscopic response (combined into a single end point on a patient level) at Week 58
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

CCI

[redacted]

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Efficacy

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

- The FAS for each Induction Study (Cohorts A and B) includes all randomized subjects who received at least one dose of study drug in the corresponding Induction Study (Day 1 to Week 10).
- The FAS for the Maintenance Study includes all re-randomized subjects who met the protocol definition of clinical remission by PRO2 or endoscopic response at Week 10, and received at least one dose of study drug in the Maintenance Study (Weeks 11 to 58).

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

8.2.1.2. Safety

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

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

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

8.2.1.3. Pharmacokinetics

8.2.1.3.1. Pharmacokinetic Substudy Analysis Set

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

8.2.1.3.2. Pharmacokinetic Analysis Set

The primary analysis set for general PK analyses will be defined separately for each individual study (Cohort A Induction Study, Cohort B Induction Study, and Maintenance Study). For each study, the PK analysis set includes all subjects in the corresponding Safety Analysis Set who have at least 1 non-missing plasma concentration data for filgotinib and/or its metabolite GS-829845.

CCI [redacted]

[redacted]

8.3. Data Handling Conventions

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

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

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

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

Procedures for handling missing data for CDAI, PRO2 and SES-CD (and components) will be described in the statistical analysis plan (SAP).

8.4. Demographic Data and Baseline Characteristics

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

Demographic summaries will include age, sex, race and ethnicity. Baseline characteristics may include height, weight, body mass index (BMI), SES-CD score, CDAI score, PRO2 score, number of years since diagnosis of CD, concomitant use of oral corticosteroids, concomitant use of immunomodulators, CCI [redacted], and other variables of interest.

8.5. Efficacy Analysis

8.5.1. Primary Analyses

For each Induction Study (Cohort A and Cohort B), the primary analysis will compare a filgotinib dose group to placebo on the proportion of subjects achieving clinical remission by CDAI at Week 10 and the proportion of subjects achieving endoscopic response at Week 10. In the EU, for each Induction Study (Cohort A and Cohort B), the primary analysis will compare a filgotinib dose group to placebo on the proportion of subjects achieving clinical remission by PRO2 at Week 10 and the proportion of subjects achieving endoscopic response at Week 10. Similarly, for the Maintenance Study, the primary analysis will compare a filgotinib dose group to placebo on the proportion of subjects achieving clinical remission by CDAI at Week 58 and the proportion of subjects achieving endoscopic response at Week 58. In the EU, for the Maintenance Study, the primary analysis will compare a filgotinib dose group to placebo on the proportion of subjects achieving clinical remission by PRO2 at Week 58 and the proportion of subjects achieving endoscopic response at Week 58. For a dose group to demonstrate significant treatment effect over placebo, statistical significance needs to be achieved on both clinical remission by CDAI and endoscopic response end points at significance level that is specified in Section 8.5.3. In the EU, for a dose group to demonstrate significant treatment effect over placebo, statistical significance needs to be achieved on both clinical remission by PRO2 and endoscopic response end points at significance level that is specified in Section 8.5.3.

The Cochran-Mantel-Haenszel (CMH) approach adjusting for stratification factors will be used for hypothesis testing of each primary end point within each study. For calculation of reduction from baseline in SES-CD score in the endoscopic response, SES-CD score at screening will be used as baseline value. For calculation of CDAI and PRO2 scores, refer to Appendix 4.

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

8.5.2. Secondary Analyses

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

8.5.3. Multiplicity Adjustments

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

8.5.3.1. Induction Studies (Cohorts A and B)

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

The primary null hypotheses to be tested:

- H_{11}: The clinical remission by CDAI rate in the filgotinib 200 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 10
- H_{12}: The endoscopic response rate in the filgotinib 200 mg group is equal to the endoscopic response rate in the placebo group at Week 10
- H_{21}: The clinical remission by CDAI rate in the filgotinib 100 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 10
- H_{22}: The endoscopic response rate in the filgotinib 100 mg group is equal to the endoscopic response rate in the placebo group at Week 10

The key secondary null hypotheses to be tested:

- H_{13}: The clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 10
- H_{14}: The clinical response by CDAI rate in the filgotinib 200 mg group is equal to the clinical response by CDAI rate in the placebo group at Week 10
- H_{23}: The clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 10
- H_{24}: The clinical response by CDAI rate in the filgotinib 100 mg group is equal to the clinical response by CDAI rate in the placebo group at Week 10

Each co-primary endpoint for filgotinib 200 mg compared with placebo will be tested at 2-sided 0.05 significance level first. If it fails to reject the null hypothesis for at least one co-primary end point, then no further formal testings will be performed. If the null hypotheses for both co-primary endpoints are rejected, testing will proceed in two sequences as describe below:

- Key secondary end points for filgotinib 200 mg compared with placebo at 2-sided 0.025 significance level in a sequential order
- Each co-primary end point for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level. If the null hypotheses for both co-primary end points are rejected, then the key secondary end points for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level will be tested in a sequential order

If all the null hypotheses within the same sequence are rejected, then the respective alpha can be passed on to the other sequence. If an end point fails to reach statistical significance within the sequence, then formal testing will stop, and only nominal significance will be reported for the remaining end points.

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

8.5.3.1.1. EU-Specific Multiplicity Adjustments for the Induction Studies (Cohorts A and B)

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

The EU-specific primary null hypotheses to be tested:

- H_{11}: The clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 10

- H_{12}: The endoscopic response rate in the filgotinib 200 mg group is equal to the endoscopic response rate in the placebo group at Week 10

- H_{21}: The clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 10

- H_{22}: The endoscopic response rate in the filgotinib 100 mg group is equal to the endoscopic response rate in the placebo group at Week 10

The EU-specific key secondary null hypotheses to be tested:

- H_{13}: The clinical remission by CDAI rate in the filgotinib 200 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 10

- H_{14}: The clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the filgotinib 200 mg group is equal to the clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the placebo group at Week 10

- H_{23}: The clinical remission by CDAI rate in the filgotinib 100 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 10

- H_{24}: The clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the filgotinib 100 mg group is equal to the clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the placebo group at Week 10

Each co-primary end point for filgotinib 200 mg compared with placebo will be tested at 2-sided 0.05 significance level first. If it fails to reject the null hypothesis for at least one co-primary end point, then no further formal testings will be performed. If the null hypotheses for both co-primary end points are rejected, testing will proceed in two sequences as describe below:

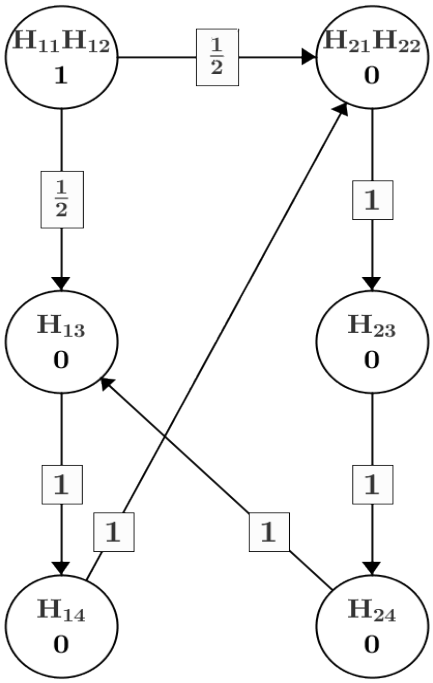
- Key secondary end points for filgotinib 200 mg compared with placebo at 2-sided 0.025 significance level in a sequential order

- Each co-primary end point for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level. If the null hypotheses for both co-primary end points are rejected, then the key secondary end points for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level will be tested in a sequential order

If all the null hypotheses within the same sequence are rejected, then the respective alpha can be passed on to the other sequence. If an end point fails to reach statistical significance within the sequence, then formal testing will stop, and only nominal significance will be reported for the remaining end points.

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

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



8.5.3.2. Maintenance Study

The hypotheses to be tested for the Maintenance Study are outlined below.

The primary null hypotheses to be tested:

- H_{11}: The clinical remission by CDAI rate in the filgotinib 200 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 58
- H_{12}: The endoscopic response rate in the filgotinib 200 mg group is equal to the endoscopic response rate in the placebo group at Week 58
- H_{21}: The clinical remission by CDAI rate in the filgotinib 100 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 58
- H_{22}: The endoscopic response rate in the filgotinib 100 mg group is equal to the endoscopic response rate in the placebo group at Week 58

The key secondary null hypotheses to be tested:

- H_{13}: The clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 58
- H_{14}: The clinical response by CDAI rate in the filgotinib 200 mg group is equal to the clinical response by CDAI rate in the placebo group at Week 58
- H_{15}: The sustained clinical remission by CDAI rate in the filgotinib 200 mg group is equal to sustained clinical remission by CDAI rate in the placebo group at Weeks 10 and 58
- H_{16}: The 6-month corticosteroid-free remission by CDAI rate in the filgotinib 200 mg group is equal to the 6-month corticosteroid-free remission by CDAI rate in the placebo group at Week 58
- H_{17}: The sustained clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to the sustained clinical remission by PRO2 rate in the placebo group at Weeks 10 and 58
- H_{18}: The 6-month corticosteroid-free remission by PRO2 rate in the filgotinib 200 mg group is equal to 6-month corticosteroid-free remission by PRO2 rate in the placebo group at Week 58
- H_{23}: The clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 58
- H_{24}: The clinical response by CDAI rate in the filgotinib 100 mg group is equal to the clinical response by CDAI rate in the placebo group at Week 58
- H_{25}: The sustained clinical remission by CDAI rate in the filgotinib 100 mg group is equal to sustained clinical remission by CDAI rate in the placebo group at Weeks 10 and 58
- H_{26}: The 6-month corticosteroid-free remission by CDAI rate in the filgotinib 100 mg group is equal to the 6-month corticosteroid-free remission by CDAI rate in the placebo group at Week 58
- H_{27}: The sustained clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to the sustained clinical remission by PRO2 rate in the placebo group at Weeks 10 and 58
- H_{28}: The 6-month corticosteroid-free remission by PRO2 rate in the filgotinib 100 mg group is equal to 6-month corticosteroid-free remission by PRO2 rate in the placebo group at Week 58

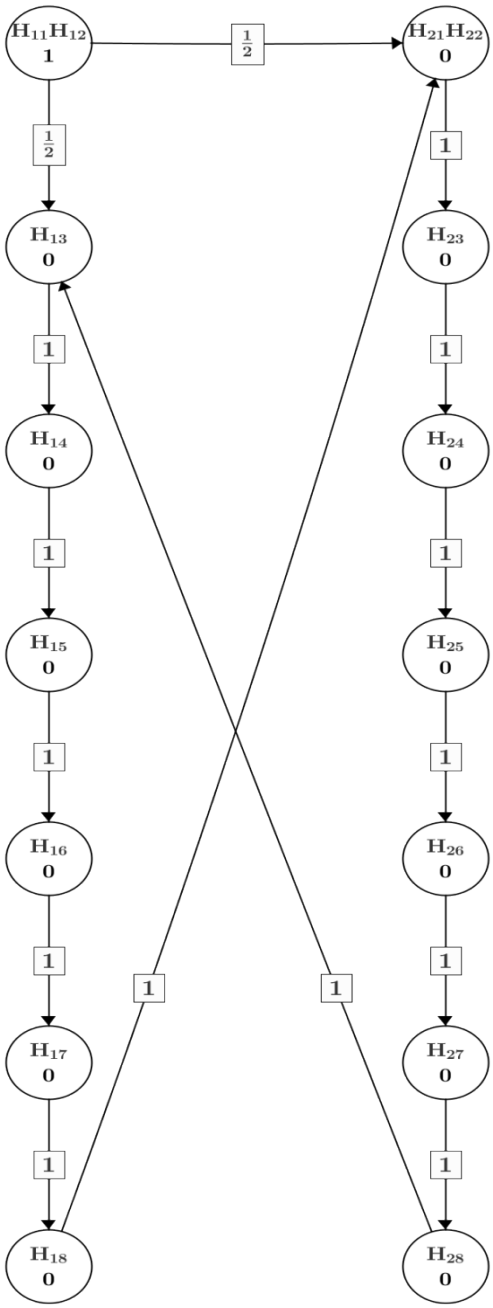
Each co-primary end point for filgotinib 200 mg compared with placebo will be tested at 2-sided 0.05 significance level first. If it fails to reject the null hypothesis for at least one co-primary end point, then no further formal testings will be performed. If the null hypotheses for both co-primary end points are rejected, testing will proceed in two sequences as describe below:

- Key secondary end points for filgotinib 200 mg compared with placebo at 2-sided 0.025 significance level in a sequential order
- Each co-primary end point for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level. If the null hypotheses for both co-primary end points are rejected, then the key secondary end points for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level will be tested in a sequential order

If all the null hypotheses within the same sequence are rejected, then the respective alpha can be passed on to the other sequence. If an end point fails to reach statistical significance within the sequence, then formal testing will stop and only nominal significance will be reported for the remaining endp oints.

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

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



8.5.3.2.1. EU-Specific Multiplicity Adjustments for the Maintenance Study

The EU-specific hypotheses to be tested for the Maintenance Study are outlined below.

The EU-specific primary null hypotheses to be tested:

- H_{11}: The clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 58
- H_{12}: The endoscopic response rate in the filgotinib 200 mg group is equal to the endoscopic response rate in the placebo group at Week 58
- H_{21}: The clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to the clinical remission by PRO2 rate in the placebo group at Week 58
- H_{22}: The endoscopic response rate in the filgotinib 100 mg group is equal to the endoscopic response rate in the placebo group at Week 58

The EU-specific key secondary null hypotheses to be tested:

- H_{13}: The clinical remission by CDAI rate in the filgotinib 200 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 58
- H_{14}: The sustained clinical remission by PRO2 rate in the filgotinib 200 mg group is equal to sustained clinical remission by PRO2 rate in the placebo group at Weeks 10 and 58
- H_{15}: The clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the filgotinib 200 mg group is equal to the clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the placebo group at Week 58
- H_{16}: The 6-month corticosteroid-free remission by PRO2 rate in the filgotinib 200 mg group is equal to the 6-month corticosteroid-free remission by PRO2 rate in the placebo group at Week 58
- H_{23}: The clinical remission by CDAI rate in the filgotinib 100 mg group is equal to the clinical remission by CDAI rate in the placebo group at Week 58
- H_{24}: The sustained clinical remission by PRO2 rate in the filgotinib 100 mg group is equal to sustained clinical remission by PRO2 rate in the placebo group at Weeks 10 and 58
- H_{25}: The clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the filgotinib 100 mg group is equal to the clinical remission by PRO2 and endoscopic response rate (combined into a single end point at patient level) in the placebo group at Week 58
- H_{26}: The 6-month corticosteroid-free remission by PRO2 rate in the filgotinib 100 mg group is equal to the 6-month corticosteroid-free remission by PRO2 rate in the placebo group at Week 58

Each co-primary end point for filgotinib 200 mg compared with placebo will be tested at 2-sided 0.05 significance level first. If it fails to reject the null hypothesis for at least one co-primary end point, then no further formal testings will be performed. If the null hypotheses for both co-primary end points are rejected, testing will proceed in two sequences as describe below:

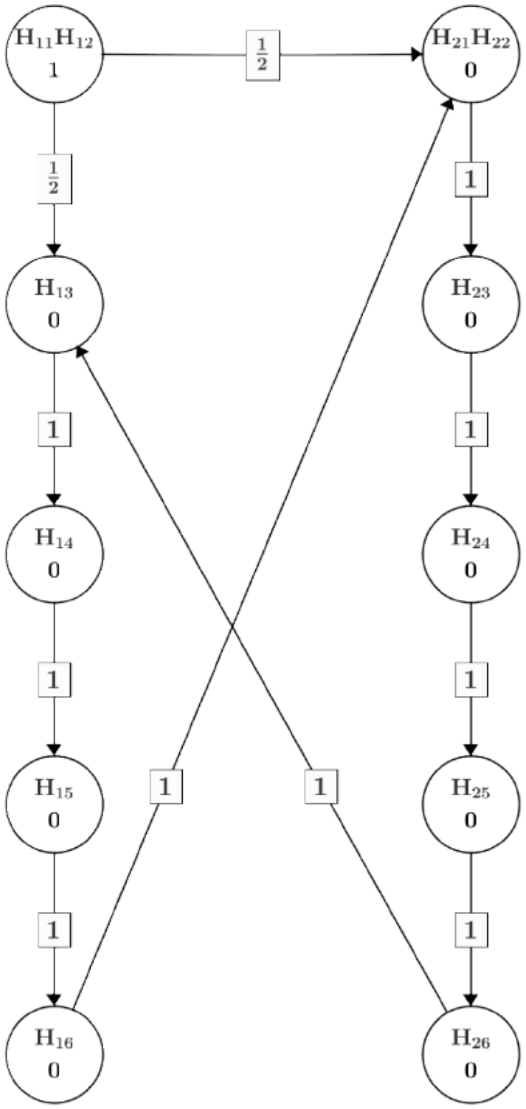
- Key secondary end points for filgotinib 200 mg compared with placebo at 2-sided 0.025 significance level in a sequential order

- Each co-primary end point for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level. If the null hypotheses for both co-primary end points are rejected, then the key secondary end points for filgotinib 100 mg compared with placebo at 2-sided 0.025 significance level will be tested in a sequential order

If all the null hypotheses within the same sequence are rejected, then the respective alpha can be passed on to the other sequence. If an end point fails to reach statistical significance within the sequence, then formal testing will stop and only nominal significance will be reported for the remaining end points.

Graphical illustrations for the testing strategies for the EU-specific primary and key secondary hypotheses in the Maintenance Study are shown in Figure 8-3.

Figure 8-3. Maintenance Study: EU-Specific Testing Strategy for the Primary and Key Secondary Hypotheses



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8.6. Safety Analysis

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

Induction Studies (Cohorts A and B)

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

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

Maintenance Study

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

Overall (Induction and Maintenance)

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

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

8.6.1. Extent of Exposure

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

8.6.2. Adverse Events

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

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

Induction Studies (Cohorts A and B)

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

Maintenance Study

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

Overall (Induction and Maintenance)

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

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

8.6.3. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using the grading scheme defined in the CTCAE in Appendix 6.

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

8.6.4. Other Safety Evaluations

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

8.7. Pharmacokinetic Analysis

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

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

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

CCI [redacted]

[redacted]

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8.9. Sample Size

8.9.1. Induction Studies (Cohorts A and B)

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by CDAI at Week 10 and endoscopic response rate at Week 10 could be detected when comparing filgotinib 200 mg to placebo within each Induction Study.

A sample size of 220 subjects in each treatment group (n = 660 total) will provide an overall power of 97% for a filgotinib 200 mg group comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 20% in clinical remission rate by CDAI at Week 10 (45% on filgotinib 200 mg and 25% on placebo) and a treatment difference of 15% in endoscopic response rate at Week 10 (25% on filgotinib 200 mg and 10% on placebo). Since each end point needs to achieve statistical significance, the overall power of 97% is calculated as the product of the two individual powers based on each end point.

8.9.1.1. EU-Specific Sample Size for the Induction Studies (Cohorts A and B)

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by PRO2 at Week 10 and endoscopic response rate at Week 10 could be detected when comparing filgotinib 200 mg to placebo within each Induction Study.

A sample size of 220 subjects in each treatment group (n = 660 total) will provide an overall power of 93% for a filgotinib 200 mg group comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 15% in clinical remission rate by PRO2 at Week 10 (30% on filgotinib 200 mg and 15% on placebo) and a treatment difference of 15% in endoscopic response rate at Week 10 (25% on filgotinib 200 mg and 10% on placebo). Since each end point needs to achieve statistical significance, the overall power of 93% is calculated as the product of the two individual powers based on each end point.

8.9.2. Maintenance Study

Assuming an Induction response rate (ie, proportion of subjects achieving clinical remission by PRO2 or endoscopic response at Week 10) of 40% among subjects receiving filgotinib 200 mg or filgotinib 100 mg treatment, approximately 176 subjects from each filgotinib dose group from Cohorts A and B Induction Studies combined would be eligible to be re-randomized into the Maintenance Study.

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by CDAI and endoscopic response rate at Week 58 could be detected when comparing filgotinib 200 mg to placebo in the Maintenance Study.

A sample size of 60 subjects in the placebo group and 120 subjects in the filgotinib group at the same dose level as the induction dose will provide an overall 94% power for a filgotinib 200 mg comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 30% in maintenance clinical remission rate by CDAI at Week 58 and maintenance endoscopic response rate at Week 58 (50% on filgotinib 200 mg and 20% on placebo). Since each end point needs to achieve statistical significance, the overall power of 94% is calculated as the product of the two individual powers based on each end point.

8.9.2.1. EU-Specific Sample Size for the Maintenance Study

The sample size was chosen to ensure that a clinically meaningful difference in both clinical remission rate by PRO2 at Week 58 and endoscopic response rate at Week 58 could be detected when comparing filgotinib 200 mg to placebo in the Maintenance Study.

A sample size of 60 subjects in the placebo group and 120 subjects in the filgotinib group at the same dose level as the induction dose will provide an overall 94% power for filgotinib 200 mg comparison to placebo at a 2-sided 0.05 significance level to detect a treatment difference of 30% in maintenance clinical remission rate by PRO2 at Week 58 and maintenance endoscopic response rate at Week 58 (50% on filgotinib 200 mg and 20% on placebo). Since each end point needs to achieve statistical significance, the overall power of 94% is calculated as the product of the two individual powers based on each end point.

8.10. Data Monitoring Committee

An external DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to 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 will occur after approximately 100 subjects reach Week 10 in Cohorts A and B combined. Following this, subsequent meetings will occur approximately once every 4 months or at a frequency determined by the DMC.

The DMC's specific activities will be defined by a mutually agreed 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. If the DMC recommends stopping the study for lack of efficacy, the Sponsor's Executive team will be unblinded to confirm the DMC recommendation.

Cohorts A and B End-of-Induction Analysis

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

Both cohorts will be examined independently.

Taking into account data in Cohort A and Cohort B, if ALL the following 4 criteria are met for BOTH cohorts, the DMC may recommend overall study discontinuation.

- 2-sided p-value for filgotinib 200 mg vs placebo comparison is larger than 0.05 on clinical remission by CDAI at Week 10
- 2-sided p-value for filgotinib 100 mg vs placebo comparison is larger than 0.05 on clinical remission by CDAI at Week 10
- 2-sided p-value for filgotinib 200 mg vs placebo comparison is larger than 0.05 on endoscopic response at Week 10
- 2-sided p-value for filgotinib 100 mg vs placebo comparison is larger than 0.05 on endoscopic response at Week 10

If any of the above criteria is not met from either cohort, the DMC may recommend that the study continue without modification.

Ad-hoc DMC Meetings

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

- ≥ 2 subjects develop the same (by preferred term) related, Grade 4, unexpected 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 8.11)
- Any subject develops a Grade 5, related, unexpected AE. The definition of an unexpected AE will be based on the Reference Safety Information that is on file at the time the event occurs

8.11. Cardiovascular Safety Endpoint Adjudication Committee

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

The Cardiovascular Safety End point Adjudication Committee (CVEAC)'s specific activities will be governed by a mutually agreed charter, which will define the CVEAC's membership, conduct, and meeting schedule.

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

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

Further details will be specified in the CVEAC Charter.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

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

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

The investigator and all applicable 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/Independent Ethics Committee Review and Approval

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

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

9.1.3. Informed Consent

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

9.1.4. Confidentiality

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

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

9.1.5. Study Files and Retention of Records

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

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

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

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

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

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. The eCRF should be completed on the day of the subject visit to enable the Sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the electronic data capture (EDC) system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF captures the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or the data management staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, the Sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

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

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

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

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

9.1.8. Inspections

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

9.1.9. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

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

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Investigator Signature Page

GALAPAGOS NV
GENERAAL DE WITTELAAN L11 A3
2800 MECHELEN
BELGIUM

STUDY ACKNOWLEDGEMENT

Combined Phase 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 Crohn's Disease

GS-US-419-3895, Amendment 9, 02 December 2021

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

PPD
PPD

Medical Leader

PPD
Date

PPD
Signature

INVESTIGATOR STATEMENT

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

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

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

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

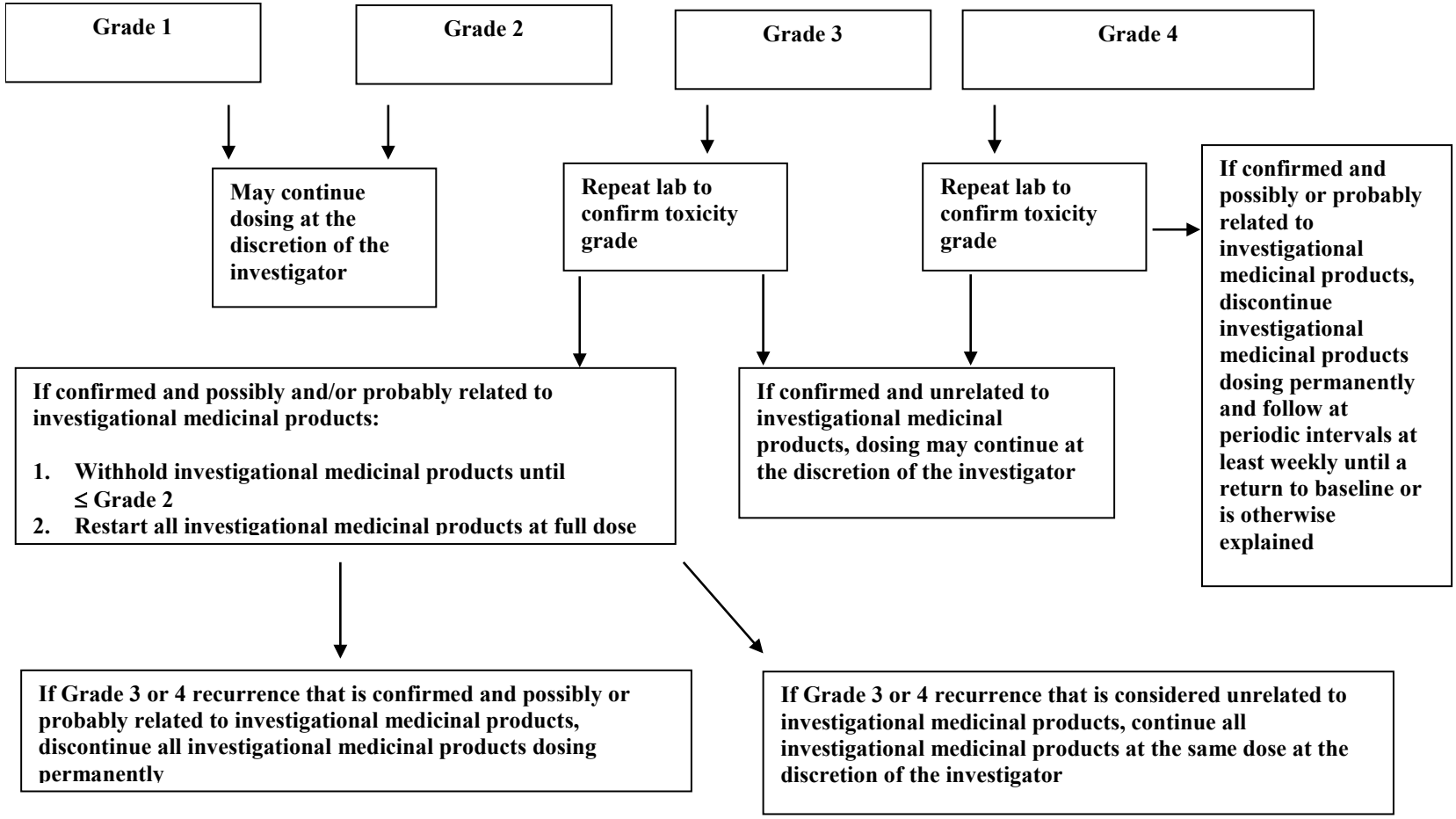
Period	Screen	Treatment																			Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**PTx[a]**	**ET**
Week		**0**	**2**	**4**	**6**	**10**	**11**	**14**	**17**	**20**	**23**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**		
Study Day	**-30 to -1**	**1**	**15**	**29**	**43**	**71**	**78**	**99**	**120**	**141**	**162**	**183**	**211**	**239**	**267**	**295**	**323**	**351**	**379**	**407**		
Visit Window (±)			**±3**	**±3**	**±3**	**±2**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±3**	**±3**	
Study Drug Dispensing		X		X			X	X		X		X		X		X		X				
Ileocolonoscopy (with Biopsies)[d]	X					X														X		
Local Endoscopic Assessment[e]	X					X														X		
SES-CD	X					X														X		
CDAI[f]	X		X	X	X	X		X		X		X		X		X		X		X		X
PRO2[f]	X		X	X	X	X		X		X		X		X		X		X		X		X
Abdominal pain assessment[g]	X	X	X	X	X	X		X		X		X		X		X		X		X		X
Anchor Questions	X																					
Patient Global Impression Scales[h]		X				X														X		
eDiary instruction & review[i]	X	X	X	X	X	X	X	X		X		X		X		X		X		X		
Stool for *C. diff* toxin, pathogenic *E. coli*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp or *Yersinia* spp testing [j]	X																					
Stool O&P [j]	X																					

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

Period	Screen	Treatment																			Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**PTx[a]**	**ET**
Week		**0**	**2**	**4**	**6**	**10**	**11**	**14**	**17**	**20**	**23**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**		
Study Day	**-30 to -1**	**1**	**15**	**29**	**43**	**71**	**78**	**99**	**120**	**141**	**162**	**183**	**211**	**239**	**267**	**295**	**323**	**351**	**379**	**407**		
Visit Window (±)			**±3**	**±3**	**±3**	**±2**	**±3**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±3**	**±3**	
Blood TCR/BCR repertoire sample[r]		X		X		X						X								X		
CCI																						
PK collection (sparse) [s]				X		X						X								X		
CCI																						
PK substudy[u]			X																			
CCI																						

a The Post-Treatment (PTx) visit should occur 30 days after the last dose of study drug. Only subjects who roll over into the LTE study (GS-US-419-3896) will not complete PTx assessments.
b For subjects who terminate prior to Week 10.
c A complete physical examination (PE) including, vital signs, body weight, and height will be performed at screening. A symptom directed PE may be done at other time points.
d Once a subject meets all other eligibility criteria (centrally calculated CDAI, PRO2 and labs), perform the screening full video ileocolonoscopy with biopsies within 14 days prior to Day 1 visit.
e The investigator (ie local endoscopist) may enter endoscopic assessment data based on the SES-CD in the eCRF (Appendix 5). The locally read SES-CD score may not be used for eligibility or assessing endoscopic response for primary efficacy analysis, and it is not a substitute for the centrally read score, CCI [redacted]
f The screening CDAI will be used as the Day 1 measurement. The CDAI patient reported outcomes of stool frequency and abdominal pain will be used to derive the PRO2 score.
g CCI [redacted]
h Patient global impression change (PGI-C) should be assessed at Weeks 10 and 58 only. Patient global impression of severity (PGI-S) should be assessed at Day 1, Weeks 10 and 58.
i Subjects should begin filling out the e-Diary the day of their initial screening visit and continue to fill it out throughout the remainder of the study.
j Stool samples should be collected to rule out infectious causes when disease worsens.
k Positive cocaine test disqualifies subject; positive amphetamines, barbiturates, benzodiazepines, and opioids require medical monitor review.
l All females meeting the childbearing potential criteria must have a serum pregnancy testing at screening and a urine pregnancy test must be completed in clinic every 4 weeks at a minimum. If any pregnancy test is positive, study drug should be immediately interrupted and the subject should have a serum pregnancy test in clinic.
m 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.
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 Hepatitis B surface Ag, surface Ab and core Ab, reflex HBV DNA, Hepatitis C Ab, reflex HCV RNA, HIV Ag/Ab, reflex HIV 1/2 Ab at Screening (Section 6.2.1).
p In Japan, subjects with negative HBsAg, positive HBcAb and/or positive HBsAb at Screening require HBV DNA monitoring every 4 weeks in accordance with local guidelines (Section 6.2.1). In other regions, subjects with negative HBsAg and positive HBcAb require HBV DNA monitoring every 3 months in accordance with local guidelines (Section 6.2.1)
q Fasting means no food or drink, except water, for 8 hours
r TCR: T-cell receptor; BCR: B-cell receptor.
s This PK sample at Weeks 10 and 58 are collected at pre-dose (within 2 hours prior to dosing). The PK sample at Week 4 is collected post-dose dose (at least 30 minutes and up to 3 hours after study drug dosing . For this visit, it is preferred that study drug dosing is in clinic. The PK sample at Week 26 can be collected at any time without regard to dosing. For these visits, the time of dose taken on the day of and the dose taken prior to the PK sample being drawn will be noted in the eCRF.
t CCI [redacted]
u Subjects who consent to optional PK substudy will have an additional plasma PK sample at any single visit from Week 2 to 10, collected pre-dose and at 0.5, 1, 2, 3, 4 and 6 hours after supervised dosing in the clinic. For all visits with PK sampling, the time of dose taken prior to and on the day of visit will be noted in the eCRF
v CCI [redacted]
w CCI [redacted]
x CCI [redacted]

Appendix 3. Management of Clinical and Laboratory Adverse Events



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

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

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

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

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

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

{Daperno 2004}
Each PRO2 score will be rounded to the nearest integer for determination of eligibility and calculation of end points.

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

Variables	Score			
	0	**1**	**2**	**3**
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-.05)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter > 2)
Ulcerated Surface (%)	None	< 10	10-30	> 30
Affected surface (%)	Unaffected segment	< 50	50-75	> 75
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

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

{Daperno 2004}

Appendix 6. CTCAE Grading Scale for Severity of Adverse Events

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

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

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

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

CTCAE V4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE V4.03 AE Term Definition
Upper respiratory infection	Mild symptoms; symptomatic relief (eg, cough suppressant, decongestant)	Moderate symptoms; oral intervention indicated (eg, antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).

Appendix 7. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

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

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

1) Definitions

a. Definition of Childbearing Potential

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

Women are considered to be in a postmenopausal state when they are ≥ 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. Bilateral tubal ligation is not considered permanent sterilization.

b. Definition of Male Fertility

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

2) Contraception for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

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

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

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

b. Contraception for Female Subjects of Childbearing Potential

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

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

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

Or

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

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

- Hormonal methods (each method *must* be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined estrogen/progestin or progesterone only)
  - Injectable progesterone
  - Implants of levonorgestrel
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring
- Barrier methods (each method *must* be used with a hormonal method)
  - Male or female condom with or without spermicide
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

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

3) Contraception Requirements for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy

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

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

Pregnancy Testing

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

Appendix 8. Clinical Laboratory Assessment Table

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

* CCI and Leukocyte subsets in North America only