Galápagos

CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Effect of Filgotinib on Semen Parameters in Adult Males with Active Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis or Non-radiographic Axial Spondyloarthritis.
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
EudraCT Number:	2018-003933-14
Clinical Trials.gov Identifier:	NCT03926195
Indication:	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or non-radiographical axial spondyloarthritis
Protocol ID:	GLPG0634-CL-227
Clinical Development Leader:	PPD
Medical Leader:	PPD
Protocol Version/Date:	Original: 05 Feb 2019 Amendment 1: 26 May 2020 Amendment 2: 09 Sep 2022

CLINICAL STUDY PROTOCOL HISTORY

Clinical study protocol (CSP) / Amendment #	Date	Main Rationale Generic / Country / Site Specific
CSP Version 1.0	05-Feb-2019	Initial CSP Version Generic
CSP Version 2.0 / Amendment #1	26-May-2020	CCI [redacted] request Generic
CSP Version 3.0 / Amendment #2	09-Sep-2022	Change in wording about blinding Generic

SUMMARY OF CHANGES

Amendment 2

The overall reason for this amendment:

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

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

The changes made to the clinical study protocol GLPG0634-CL-227 Version 2.0, 26-May-2020 are listed below, reflecting a brief rationale for each change and the applicable sections.

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

Applicable Sections: Synopsis

1.4 Risk/Benefit Assessment for the Study

8.8 Data Monitoring Committee/Sponsor Safety Management Team

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

Applicable Sections: Synopsis

5.1.1 Blinding

8.11 Unblinded Interim Analysis

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

Applicable Section: 3.7.1 Study Drug Interruption Considerations

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

Applicable Sections: Synopsis

8.10 Internal Independent Safety Review

Amendment 1

The overall reason for this amendment:

This amendment was initiated to address comments from the CCI [redacted]) related to new safety information suggesting an increased risk of thromboembolic events in patients treated with JAK inhibitors.

In addition, several sections were revised in line with the template update.

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

The changes made to the clinical study protocol GLPG0634-CL-227 Version 1.0, 05-Feb-2019 are listed below, reflecting a brief rationale for each change and the applicable sections.

Rationale: Text was revised to avoid confusion.

Applicable Section: Synopsis

4.2 Inclusion Criteria

5.3.1 Allowed Concomitant Medications

Rationale: Text was added per audit finding to clearly describe the end of the Double-blind Treatment Phase, when semen analysis results are available.

Applicable Sections: Synopsis

3.1 Double-blind Treatment Phase

6.4 Double-blind Treatment Phase

Appendix 2, Study Procedure Table – Double-blind Treatment Phase

Rationale: The revised text adds clarity to when subjects must perform yearly tuberculosis (TB) testing in the Extension Phase.

Applicable Sections: Section 3.2 Extension Phase

Appendix 2, Study Procedure Table - Extension phase

Rationale: Criterion for discontinuation for thromboembolism has been added to address comments of the CCI **Applicable Section:** 3.7.2 Study Drug Discontinuation Considerations
Rationale: Text was corrected. **Applicable Section:** 4.3 Exclusion Criteria
Rationale: New section was added to clarify blinding procedures in line with the protocol template update. **Applicable Section:** 5.1.1 Blinding
Rationale: Text was revised to describe that all unused and empty IMP supplies need to be returned to the warehouse and that local destruction is not allowed, and to align with the protocol template update, which removes Section 9.1.7 and incorporates the information in this section. **Applicable Section:** 5.5.1 Investigational Medicinal Product Return or Disposal
Rationale: Text was added to avoid confusion. **Applicable Section:** 6.8 Safety Follow-Up Visit 30 Days Post Dose (±5 Days)
Rationale: Text was added to address comments of the CCI. The language was added to guide the management of subjects who develop a thromboembolic event while under study, ensuring clinical management is addressed and clinical risk factors are captured. **Applicable Section:** 6.9.1 Thromboembolic Events
Rationale: Text was revised with a more general description to avoid confusion. **Applicable Section:** 6.11 Semen Collection Procedure
Rationale: Text was updated to align with the protocol template update. **Applicable Sections:** 7.7 Special Situations Reports 7.7.1 Definitions of Special Situations 7.7.2 Instructions for Reporting Special Situations
Rationale: A criterion to trigger an ad hoc DMC meeting related to a thromboembolic event was added to address comments of the CCI **Applicable Section:** 8.8 Data Monitoring Committee
Rationale: Text was added to describe a CVEAC that the Sponsor is establishing to address comments of the CCI **Applicable Section:** 8.9 Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

Rationale: Text was revised and added to align with the GS-US-418-4279 protocol. **Applicable Sections:** Synopsis 8.10 Internal Dependent Safety Review
Rationale: Text was removed to align with the protocol template update, which removes this section and incorporates the information in one place in Section 5.5.1. **Applicable Section:** 9.1.7 IMP Accountability and Return
Rationale: A footnote was added to provide more details on the Safety follow-up visit. **Applicable Section:** Appendix 2, Study Procedure Table – Double-blind Treatment Phase
Rationale: The 12-lead ECG assessment has been removed in (the last scheduled visit of) the Monitoring Phase since the patient is not on filgotinib anymore; therefore, this assessment is not needed for safety reasons. **Applicable Section:** Appendix 2, Study Procedure Table - Monitoring phase
Rationale: Footnotes have been updated for accurateness and to avoid confusion. **Applicable Section:** Appendix 2, Study Procedure Table - Extension phase
Rationale: Text was added to specify that in the Extension Phase ECG for safety assessment is only required for subjects on study drug (open-label filgotinib) and not for subjects on Standard of Care treatment. The ECG in subjects on Standard of Care treatment is seen as redundant and therefore removed to reduce the patient burden. **Applicable Section:** Appendix 2, Study Procedure Table - Extension phase

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PROTOCOL SYNOPSIS

Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium

Study Title:	A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Effect of Filgotinib on Semen Parameters in Adult Males with Active Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis or Non-radiographic Axial Spondyloarthritis.
EudraCT Number:	2018-003933-14
Clinical Trials.gov Identifier:	NCT03926195
Study Centers Planned:	Approximately 150 centers worldwide
Objectives:	The primary objective of this study is: • To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥50% decrease from Baseline in sperm concentration at Week 13 The secondary objectives of this study include: • To evaluate the effect of filgotinib on testicular function as defined by the proportion of subjects with a ≥50% decrease from Baseline in sperm concentration at Week 26 • To evaluate the effect of filgotinib on sperm total motility at Weeks 13 and 26 • To evaluate the effect of filgotinib on total sperm count at Weeks 13 and 26 • To evaluate the effect of filgotinib on the change from Baseline in sperm concentration at Weeks 13 and 26 • To evaluate the effect of filgotinib on ejaculate volume at Weeks 13 and 26 • To evaluate the effect of filgotinib on sperm morphology at Weeks 13 and 26

The exploratory objectives of this study include:

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

Study Design:

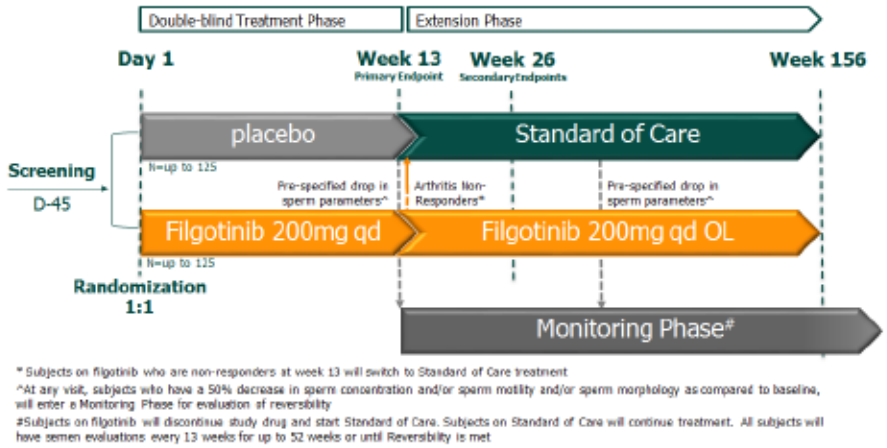
This is a randomized, double-blind, placebo-controlled, Phase 2 study in adult males with active rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) or non-radiographic axial spondyloarthritis (nrAxSpA) who have had an inadequate response to prior arthritis therapy as outlined in the inclusion criteria, an adverse prognosis of their condition per the investigator, and who may benefit from treatment with a Janus Kinase (JAK)-inhibitor.

Up to 250 males between the ages of 21 and 65 years (inclusive) at the time of consent will be randomized to receive filgotinib 200 mg or placebo once daily for 13 weeks, after which an Extension Phase will start.

Randomization will be stratified according to the type of rheumatic condition (RA or Spondyloarthritis [PsA, AS, nrAxSpA]), by concurrent use of methotrexate (MTX; yes or no), and by sperm concentration measured at Screening ("Baseline") according to the following strata:

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

Study Scheme



There are 3 distinct parts to the study:

1) Double–blind Treatment Phase (Day 1 through Week 13 Study Visit)
2) Extension Phase (After Week 13 Study Visit and up to Week 156)
3) Monitoring Phase (up to 52 weeks)

After fulfilling all selection criteria, subjects will be randomized to filgotinib or placebo (1:1) at Day 1 and enter the Double-blind Treatment Phase. Based on the outcomes of the Week 13 assessments (ie, individual subject's response of the underlying rheumatic condition to the assigned treatment and/or the observed changes in sperm parameters during the double blind treatment phase), subjects may enter the Extension or Monitoring Phase.

Double-blind Treatment Phase (Day 1 through Week 13 Study Visit) (Figure 3-2)

During the Double-blind Treatment Phase, all subjects will receive blinded study drug for 13 weeks starting from the Day 1/Randomization Study Visit. At the Week 13 study visit, sperm parameters (see "Semen Collection and Analysis") will be evaluated to determine whether they meet any of the pre-specified decrease thresholds (see Definition of Terms). In addition, arthritis response status (Arthritis Non-responder vs Arthritis Responder, see Definition of Terms) will be determined. As soon as Week 13 semen results are available to the investigator and have been evaluated, subjects are assigned to one of the following:

- Subjects whose sperm parameters meet any of the pre-specified decrease thresholds, regardless of arthritis response status, will discontinue study drug and enter the Monitoring Phase. These subjects will also have a safety follow-up visit 30 days after last study drug dose.

- Subjects who are Arthritis Non-responders and whose semen parameters do not meet any of the pre-specified decrease thresholds will discontinue blinded study drug and start Standard of Care treatment (see Definition of Terms) during the Extension Phase. These subjects will also have a safety follow-up visit 30 days after last study drug dose.
- Subjects who are Arthritis Responders and whose semen parameters do not meet any of the pre-specified decrease thresholds will be unblinded by the interactive web response system (IWRS) and enter the Extension Phase. Subjects on filgotinib will convert to open-label filgotinib and subjects receiving placebo will switch to Standard of Care treatment.

Extension Phase (After Week 13 through Week 156 Study Visit) (Figure 3-3)

In the Extension Phase, subjects will receive open-label treatment (filgotinib or Standard of Care) and have a study visit every 13 weeks that includes semen analysis. The first scheduled visit of the Extension Phase occurs at Week 26.

In case semen parameters at any visit (including Week 156) meet any of the pre-specified decrease thresholds, subjects will enter the Monitoring Phase.

During the Extension Phase, Standard of Care and background treatment concomitant to filgotinib may be optimized at the discretion of the investigator, taking into consideration the protocol restrictions (Sections 5.3 and 5.4).

In case a subject needs to be treated with a prohibited medication (see Table 5-1), for instance to control their rheumatic condition, the subject will discontinue the study and complete an Early Termination (ET) visit (including semen collection). For subjects on filgotinib, this will be followed by a safety follow-up visit 30 days after last study drug dose.

All subjects who did not enter the Monitoring Phase will continue the study until the Week 156 visit.

Monitoring Phase (up to 52 weeks) (Figure 3-4)

Subjects whose sperm parameters meet any of the pre-specified decrease thresholds will switch to the Monitoring Phase immediately. Subjects on double-blind treatment or open-label filgotinib who enter the Monitoring Phase will discontinue study drug and start Standard of Care. These subjects will also have a safety follow-up visit 30 days after last study drug dose. Subjects on Standard of Care will continue treatment.

All subjects who enter the Monitoring Phase will undergo semen evaluations every 13 weeks starting from their entry into the Monitoring Phase, for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first.

In case a subject needs to be treated with a prohibited medication (see Table 5-1), for instance to control their rheumatic condition, the subject will discontinue the study and complete an ET visit (including semen collection).

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

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

The DMC has monitored the study until the date of protocol amendment 2, including the data for the second unblinded interim analysis (IA2). As of amendment 2, the DMC will be decommissioned. The safety and progress of the remainder of the study will continue to be monitored by the Sponsor Medical Leader and Medical Monitor or designee, providing updates during regular Sponsor medical monitoring oversight meetings across the filgotinib program. If needed, safety issues will be escalated to the SSMT per internal standard procedures. The SSMT can consult external experts, if deemed necessary, and can review data in an unblinded fashion.

Internal Independent Safety Review Team

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

As of amendment 2, the Internal Independent Safety Review Team will be decommissioned. Safety reviews will be covered by the SSMT.

	Key Concomitant Medication Considerations: If using conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy prior to the study, subjects are permitted to continue the following drugs during the study, alone or in combination (with the exception of the MTX-leflunomide [LEF] combination) and must have been on a stable dose of the drug for at least 4 weeks prior to Screening and remain on a stable dose during the Double-blind Treatment Phase of the study (stable dose in all cases is defined as no change in prescription): a. MTX oral or parenteral up to 25 mg/week (plus concomitant use of folic or folinic acid supplementation as per local Standard of Care) b. Leflunomide (LEF) up to 20 mg/day orally c. Hydroxychloroquine up to 400 mg/day or chloroquine up to 250 mg/day d. Apremilast orally up to 30 mg twice daily Oral corticosteroids may be used at ≤10 mg/day (of prednisone or equivalent), provided that the prescription has been stable for at least 4 weeks prior to Day 1 and up to the Week 13 visit. For subjects continuing on open-label filgotinib after the Week 13 visit, the subject's steroid dose can be reduced based on investigator judgment (and may also be adjusted back up as needed), but should NOT exceed the stable dose prescribed at Baseline (Randomization/Day 1). For subjects continuing Standard of Care treatment, the dose of corticosteroids can also be reduced or increased but should not exceed 20 mg/day (of prednisone or equivalent). If a non-steroidal anti-inflammatory drug (NSAID) or cyclooxygenase-2 (COX-2) inhibitor is used, it must not exceed the maximum dose permitted as per local label and must have been used at a stable dose for at least 2 weeks prior to Day 1 and remain on a stable dose during the Double-blind Treatment Phase of the study. Subjects should not receive sulfasalazine at any time, beginning 26 weeks prior to Screening until the end of study. A list of permitted and prohibited medications is provided in the exclusion criteria and Section 5.3.
Number of Subjects Planned:	Up to 250 subjects to have 200 evaluable subjects
Target Population:	Males between the ages of 21 and 65 years (inclusive) with active RA, PsA, AS or nrAxSpA

Duration of Treatment:	The duration of blinded treatment is approximately 13 weeks, followed by an open-label Extension Phase of up to 143 weeks. Subjects entering the Monitoring Phase will be followed for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first.
Diagnosis and Main Eligibility Criteria:	For a complete list of study inclusion and exclusion criteria, please refer to Sections 4.2 and 4.3. Key inclusion criteria: • Males between the ages of 21 and 65 (inclusive) on the day of signing informed consent • Diagnosis of RA, PsA, AS, or nrAxSpA for at least 12 weeks prior to Screening, meeting the corresponding specific classification criteria: — RA, American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) 2010 — PsA, Classification criteria for Psoriatic Arthritis (CASPAR) criteria — AS or nrAxSpA, Assessment of Spondyloarthritis International Society (ASAS) criteria for axial spondyloarthritis • For RA, PsA, AS, or nrAxSpA, subject meets the following criteria: — RA ■ Inadequate response or intolerant to ≥12-weeks' course of csDMARD or biological DMARD (bDMARD) therapy for RA ■ Have an Clinical Disease Activity Index (CDAI) >10 at screening — PsA ■ Inadequate response or intolerant to ≥12-weeks' course of csDMARD or bDMARD therapy for PsA ■ Have a Disease Activity in Psoriatric Arthritis (DAPSA) score >14 at Screening — Axial Spondyloarthritis (applicable to those with diagnosis of AS or nrAxSpA) ■ Inadequate response or intolerant to at least 2 NSAIDs, which may include COX-2 inhibitors prescribed for a total period of ≥4 weeks OR to an ≥12 week course of csDMARD or biological disease modifying anti-rheumatic drug (bDMARD) therapy for spondyloarthritis

- Have a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 at Screening
- At Screening, subjects should have a high-sensitivity C-reactive protein (hsCRP) >0.3 mg/dL OR sacroiliitis according to the modified New York (NY) criteria OR a history of active inflammation on magnetic resonance imaging (MRI) consistent with sacroiliitis within 2 years of screening

- The mean of 2 separate semen samples collected at Screening must meet the following minimum criteria (in accordance with Section 6.11): semen volume ≥1.5 mL, total sperm/ejaculate ≥39 million, sperm concentration ≥15 million/mL, sperm total motility ≥40%, and normal sperm morphology ≥30%

Key Exclusion Criteria

- Previously or currently documented problems with male reproductive health including but not limited to primary hypogonadism, secondary hypogonadism, or reduced fertility
- Use of any prohibited concomitant medication(s) as described in Section 5.3 (and Table 5-1)
- Active tuberculosis (TB) or untreated latent TB (Section 4.2 Inclusion Criteria, 10)
- Infection with Hepatitis B, Hepatitis C or human immunodeficiency virus (HIV) (Section 4.3, Exclusion Criteria, #22-24)

Study Procedures/ Frequency:

After written informed consent is obtained, Screening procedures will commence, including but not limited to, evaluation of eligibility criteria, medical history, routine blood and urine collection for laboratory analyses and semen sample collection. All subjects meeting eligibility criteria will be randomized 1:1 to receive filgotinib 200 mg once daily or placebo once daily for 13 weeks, in a blinded fashion.

All subjects will return to the clinical study center to be evaluated for clinical and laboratory assessments at Week 2, Week 4, Week 8 and Week 13, including semen sample collection during Week 13 visit.

Subjects entering the Extension Phase (on open-label filgotinib or on Standard of Care) will undergo scheduled visits for safety assessments (including semen analysis) every 13 weeks up to Week 156.

Subjects entering the Monitoring Phase (on Standard of Care) will undergo scheduled visits for safety assessments every 13 weeks up to Week 52 or until Reversibility is met.

	Sparse Plasma PK Sample Collection Sparse plasma PK samples will be collected from all subjects at least 30 minutes post dose at the Week 2 visit, at any time at the Week 4 visit and prior to study drug dosing at the Week 13 visit. At the Week 26 visit, only subjects on open-label filgotinib will provide a PK sample prior to study drug administration. **Semen Collection and Analysis:** At each of the following time points, subjects will provide 2 semen samples collected within a 14-day period. Each semen sample must be collected with an ejaculation free period of ≥48 hours and ≤7 days (Section 6.11): • Screening (Baseline) • After the Double-blind Treatment Phase (Week 13 study visit) • Every 13 weeks during the Extension Phase • Every 13 weeks during the Monitoring Phase • At the Early Termination Visit In select instances where the semen sample with questioned value(s) is found to be non-assessable or invalid (eg, collection without adherence to ejaculation-free period; intercurrent illness or dehydration at time of collection; incomplete capture of semen sample; and/or sample processing or semen analysis that deviates from standardized procedure), a third semen sample, when indicated, must be collected within 14 days of the prior sample, with an ejaculation free period of ≥48 hours and ≤7 days. All decisions on retesting any semen/sperm parameter (ie, obtaining a third semen sample at any of the above time points) must be approved by the Sponsor Medical Leader or designee before the retest.
Test Product, Dose, and Mode of Administration:	200-mg filgotinib tablet orally once daily
Reference Therapy, Dose, and Mode of Administration:	Placebo-to-match tablet orally once daily
Required Background Medication:	Permitted medication as described in the concomitant medications section

Criteria for Evaluation:	
Safety:	Semen samples will be collected as outlined in Section 6.11. Sex hormones including LH, FSH, inhibin B and total testosterone will be measured at various time points during this study. Other aspects of safety will be assessed by the reporting of adverse events (AEs), clinical laboratory evaluations (hematology, chemistry, and urinalysis), physical examination, vital signs and at various time points during the study. Concomitant medication usage will also be assessed throughout the study
PK:	Plasma concentrations of filgotinib and its metabolite (GS-829845) will be analyzed.
Statistical Methods:	The primary endpoint is the proportion of subjects with a ≥50% decrease in sperm concentration from Baseline at Week 13. A cumulative distribution plot for the percent change from Baseline in sperm concentration at Week 13 for each treatment group will be constructed. The x-axis will display percent changes from Baseline sperm concentration ranging from 100% decrease (ie, -100% or azoospermia) to the maximal observed increase. The y-axis will display the proportion of subjects who experienced a percentage change in sperm concentration equal to or less than the corresponding x-axis value at Week 13. This method is suggested in Food and Drug Administration's (FDA) Guidance for Industry: Testicular toxicity: Evaluation During Drug Development" (October 2018). The proportion of subjects experiencing at least a 50% decrease in sperm concentration from Baseline will be calculated together with the associated 95% confidence interval for the difference between the filgotinib and placebo groups. Additional assessments of semen parameters may be conducted. All continuous endpoints will be summarized using an 8-number summary (n, mean, standard deviation [SD], median, 1st quartile [Q1], 3rd quartile [Q3], minimum, maximum) by treatment group. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition. Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, SD, median, Q1, Q3, minimum, maximum) for continuous data by dosing group. A sample size of 100 evaluable subjects per group, where evaluable is defined as subjects in the Semen Analysis Set (Section 8.2.1.2), is adequate for the purposes of estimating cumulative distribution curves

and producing a 95% confidence interval width that is reasonably narrow for the percentage of subjects in each group who experience a ≥50% decrease in sperm concentration compared to Baseline. Assuming a 20% rate of non-evaluable subjects at Week 13, up to 125 subjects per arm may be enrolled.

Results of this study may be pooled with the results of a separate study being conducted in subjects with inflammatory bowel disease (Protocol GS-US-418-4279) with the same objective. The total planned number of subjects in both studies combined will be approximately 250 subjects.

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

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

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

DEFINITION OF TERMS

Monitoring Phase	A subject who experiences a ≥50% decrease in sperm concentration, and/or motility, and/or morphology at any time after 13 weeks will start the Monitoring Phase. Semen samples will be collected every 13 weeks starting from their entry into the Monitoring Phase, for up to 52 weeks or until Reversibility is met, whichever is achieved first.
Arthritis Responder	For RA, PsA, AS or nrAxSpA - improvement in physician's global assessment (PhGADA) of at least 20% compared to Baseline (Day 1) at the specified assessment time
Arthritis Non-responder	For RA, PsA, AS or nrAxSpA, a subject who does not fulfill the definition of Arthritis Responder at the specified assessment time point (refer to Appendix 2)
Pre-specified decrease threshold	A ≥50% decrease in sperm concentration, and/or motility, and/or morphology in comparison to Baseline (Screening). The mean of values for each of the sperm parameters (measured from 2 separate semen samples) will be used in all analyses. Samples will be collected within a 14-day period and with an ejaculation-free period of ≥48 hours and ≤7 days.
Reversibility	Reversibility is met when all semen parameter(s) qualifying the subject to enter into the Monitoring Phase return(s) to greater than 50% of Baseline (ie, to greater than [0.50 x mean of 2 sperm collections collected at the Screening visit (ie, Baseline)]).
Week 13	The Week 13 Study Visit occurs once a subject completes 13 weeks of blinded study drug, and is inclusive of all study assessments performed at the clinic visit and the semen sample collection visits associated with this time point.
Week 26	The Week 26 Study Visit occurs once a subject completes 13 weeks of open-label filgotinib or Standard of Care treatment during the Extension Phase, and is inclusive of all study assessments performed at the clinic visit and the semen sample collection visits associated with this time point.
Standard of Care	Locally approved treatment, accepted by medical experts as a proper treatment for rheumatic conditions, prescribed according to best clinical practice, with no known testicular toxicity. Standard of Care will be reimbursed by the sponsor until the Week 156 visit of the Extension Phase or until a subject completes the Monitoring Phase.
Study Drug	Study drug is defined as blinded filgotinib or placebo during the Double-blind Treatment Phase and open-label filgotinib during the Extension Phase.
First unblinded interim analysis (IA1)	Unblinded Week 26 analysis to be performed after at least 200 evaluable subjects pooled across studies GS-US-418-4279 (GLPG0634-CL-228) and GLPG0634-CL-227 complete Week 13 and evaluable subjects from Study GLPG0634-CL-227 complete Week 26 or permanently discontinue from study drug. Referred to as 'Week 26 Analysis' in the SAP.
Second unblinded interim analysis (IA2)	Unblinded Week 26 analysis to be performed after all subjects reach Week 26 and all subjects with a ≥ 50% decrease in sperm concentration, and/or motility, and/or morphology up to Week 26 enter the Monitoring Phase and either meet reversibility criteria or are followed off-treatment for 52 weeks, whichever occurs first. Referred to as 'Week 26 and Reversibility Analysis for Pre-specified Sperm Decreases Up to Week 26' in the SAP.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

Ab	antibody
ACR (20/50/70)	American College of Rheumatology (20/50/70% improvement)
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration-time curve
BASDAI	Bath Ankylosing Spondylitis Disease Activity
bDMARD	biological disease-modifying antirheumatic drug
BLQ	below the limit of quantitation
BUN	blood urea nitrogen
CASPAR	Classification criteria for Psoriatic Arthritis
CC&G	Cockcroft-Gault
CD	Crohn's disease
CDAI	Clinical Disease Activity Index
CES	carboxylesterases
CI	confidence interval
C_{max}	maximum observed plasma concentration
CMV	cytomegalovirus
CNS	central nervous system
CrCl	creatinine clearance
CRO	contract research organization
CRP	C-reactive protein
COX-2	cyclooxygenase-2
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CVEAC	Cardiovascular Safety Endpoint Adjudication Committee
CXR	chest x-ray
CYP	cytochrome P450

DAPSA	Disease Activity in Psoriatric Arthritis
DAS28	Disease Activity Score 28 joints
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ERAP	endoplasmic reticulum aminopeptidase
ET	early termination
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Galapagos, NV
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HDL	high density lipoprotein
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HLGT	high level group term
HLT	high level term
hsCRP	high sensitivity C-reactive protein
IA1/2	first/second unblinded interim analysis
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization (of Technical Requirements for Pharmaceuticals for Human Use)
IEC	Independent Ethics Committee

IFN	interferon
IFNγ	interferon gamma
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
IND	Investigational new drug
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
JAK	Janus kinase
LDL	low density lipoprotein
LEF	leflunomide
LH	luteinizing hormone
LLOQ	lower limit of quantitation
LLT	low level term
LTBR	lymphotoxin beta receptor
MACE	major adverse cardiovascular events
MATE1	multidrug and toxin extrusion protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MCP	monocyte chemoattractant protein
MCV	mean corpuscular volume
MHC	major histocompatibility complex
MMP	matrix metallopeptidase
MRI	magnetic resonance imaging
MTX	methotrexate
NOAEL	no observed adverse effect level
NOEL	no observed effect level
nrAxSpA	non-radiographical axial spondyloarthritis
NSAID	non-steroidal anti-inflammatory drug
NY	New York
OAT	organic anion transporter
OCT	organic cation transporter
PCP	pneumocystis pneumonia
PE	physical examination
PEG	polyethylene glycol
P-gp	P-glycoprotein

PhGADA	Physician Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
pSTAT	phospho signal transducer and activator of transcription
PT	preferred term
PtGADA	Patient Global Assessment of Disease Activity
PTT	partial thromboplastin time
Q1	1st quartile
Q3	3rd quartile
RA	rheumatoid arthritis
SADR	serious adverse drug reactions
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SDAI	Simplified Disease Activity Index
SJC28	swollen joint count 28 joints
SJC66	swollen joint count 66 joints
SOP	standard operating procedure
SpA	spondyloarthritis
SSMT	Sponsor Safety Management Team
SSZ	sulfalazine
STAT	signal transducer and activator of transcription
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TIMP	tissue inhibitor of metallopeptidase
TJC28	tender joint count 28
TJC68	tender joint count 68
TMF	trial master file
TNFα	tumor necrosis factor alpha
TNFi	tumor necrosis factor inhibitor
TNFRSF1A	tumor necrosis factor receptor superfamily member 1A
TSH	thyroid stimulating hormone
TYK	tyrosine kinase
UC	ulcerative colitis

UGT	uridine 5'-disphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

1.1. Background

1.1.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease that affects approximately 1.3 million adults in the United States (US). RA manifests principally as an attack on peripheral joints and may lead to marked destruction and deformity of joints, with considerable disability and impact on quality of life. It is characterized by the production of autoantibodies, synovial inflammation with formation of pannus tissue, and erosion of underlying cartilage and bone. Although people of any age can be affected, the onset of RA is most frequent between the ages of 40 and 50 years, and women are affected 3 times more often than men. While the cause of RA is still not completely understood, aberrant B-cell activation, T-cell co-stimulation, osteoclast differentiation, and cytokine release all have been implicated in its pathogenesis.

Treatment of RA is dependent on severity, the patient's co-morbidities and initial response to therapy. Methotrexate (MTX) is a conventional systemic disease-modifying antirheumatic drug (csDMARD) and continues to be the cornerstone of RA therapy. Patients with an inadequate response to csDMARD(s) are often treated with biologic therapies such as tumor necrosis factor inhibitors (TNFi) as an initial second line therapy. However, approximately 28% to 58% of patients with RA with inadequate response to MTX fail TNFi as reviewed in (Redlich, et al., 2003). In this setting, treatment guidelines recommend either switching to another TNFi, alternate biologic, or to a small molecule drug. Despite significant advances in disease management in recent years, there remains a need for new treatments, since not all patients respond adequately to current therapies, have co-morbidities and some patients experience toxicities and/or intolerance that limit the use of approved therapies.

In November 2012, tofacitinib (Xeljanz®) became the first Janus Kinase (JAK) inhibitor to receive Food and Drug Administration (FDA) approval for the treatment of adult patients with RA. The drug proved to be efficacious in treating the signs and symptoms of RA. However, the observed side effects and risk profile of tofacitinib are similar to those of several existing antirheumatic agents with cytopenias, elevated levels of liver function enzymes, increased total cholesterol levels, with increases in low density lipoprotein (LDL) typically exceeding those for high density lipoprotein (HDL), and increased risk for infections including serious and opportunistic infections. At higher doses, tofacitinib treatment was associated with anemia, which is thought to be linked to inhibition of JAK 2. While the pan JAK inhibitor tofacitinib has shown an early onset of action and long term efficacy in RA as mono therapy and in combination with background csDMARD therapy, dose levels were limited by side effects potentially mediated by its effect on JAK 2 and JAK 3. Another JAK inhibitor, baracitinib (Olumiant®) has been approved in the European Union (EU) in February 2017 as a second-line therapy for moderate to severe active rheumatoid arthritis in adults, either alone or in combination with methotrexate (with the exception of the MTX-leflunomide [LEF] combination). This was followed, in May 2018, by the FDA approval for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies. Baricitinib is a selective and reversible inhibitor of JAK1 and JAK2 and thereby acts by reducing the phosphorylation and activation of signal transducers and activators

of transcription (STATs). Observed side effects and risk profile of baracitinib is consistent with unselective JAK/STAT pathway inhibition. Elevated levels of liver function enzymes, increased total cholesterol levels, increased risk for infections including serious and opportunistic infections. JAK2 inhibition specific haematological side effects such as anemia, neutropenia, lymphocytopenia and thrombocytosis with increased risk for deep vein thrombosis/pulmonary embolism have also been reported.

This highlights the need for more selective and targeted therapies with improved immunomodulatory and hematologic effects. JAK1 is thought to be an integral part of RA pathogenesis due its role in transmitting inflammatory cytokine signaling. Hence, targeted inhibition of JAK1 has great potential for the treatment of RA with an improved safety and side effect profile.

1.1.2. Psoriatic Arthritis

Psoriatic arthritis (PsA) is an inflammatory joint disease associated with psoriasis and characterized by heterogeneous musculoskeletal phenotypes that involve multiple domains including the peripheral joints, axial skeleton, tendon and ligament insertion sites (enthesitis), and digits (dactylitis). PsA occurs in approximately 30% of psoriasis patients. In the majority of cases (75%) psoriasis precedes joint disease, but in some cases (15%) the onset is synchronous and in 10% arthritis precedes psoriasis.

PsA occurs just as frequently in males and females. The arthritis in PsA commonly involves distal joints and has the tendency to distribute in a ray pattern, so that all the same joints of a single digit are more likely to be affected (dactylitis). The degree of erythema over the affected joints, the presence of asymmetrical spinal involvement, the presence of enthesitis and a lower level of tenderness are also typical features of PsA. PsA belongs to the group of spondyloarthropathies because of the presence of spondylitis in up to 40% of patients. The extra-articular features observed in PsA are similar to other spondyloarthropathies including mucous membrane lesions, iritis, urethritis, diarrhea and aortic root dilatation, and association with human leukocyte antigen B27 (HLA-B27).

First-line treatment traditionally consists of non-steroidal anti-inflammatory drugs (NSAIDs) and csDMARDs such as sulfalazine (SSZ), MTX, and leflunomide (LEF). These drugs remain a mainstay of therapy where there is limited access to biological agents. The arrival of TNFi agents over a decade ago dramatically increased the treatment armamentarium for PsA leading to much improved outcomes for both skin and joint disease. Nevertheless, TNFi agents do not work in all patients and may lose response over time, partly because of immunogenicity. Agents with different mechanism of actions that target the interleukin (IL)-23/IL-17 pathways that promote skin and joint inflammation have become available and more are currently under evaluation in clinical studies. These agents include the IL-12/IL-23 inhibitors ustekinumab; the IL-23 inhibitors guselkumab, tildrakizumab, and risankizumab; the IL-17 receptor A inhibitors such as secukinumab and ixekizumab; the IL-17 receptor A/F inhibitor bimekizumab; and the phosphodiesterase E4 inhibitor apremilast. The therapeutic response of these new agents is most evident in psoriasis, resulting in marked plaque clearance; the results in PsA for these agents are similar to those observed with TNFi agents. IL-17 blockade is also effective for axial disease and inhibits radiographic progression. The oral agent apremilast offers a modest response in the skin

and joints, with few safety signals and is not indicated in patients who demonstrate radiographic damage or axial involvement.

Several key cytokines in the IL-23/IL-17 pathways promote skin and joint inflammation signal through the JAK family of receptor-associated tyrosine kinases (TYKs). Activated JAKs recruit and activate STATs which in turn drive gene transcription. The specific JAK-STAT activation depends on the cytokine signal which includes interferon (IFN) and its related cytokines, the common γ-chain cytokines and the IL-6 type cytokines. Studies have demonstrated increased phosphoSTAT3 (pSTAT3) and pSTAT1 expression in psoriasis skin and have shown that interferon gamma (IFNγ), IL-6 and IL-22 can induce pSTAT1 or pSTAT3 in keratinocytes. Tofacitinib, an orally administered JAK1/JAK3 inhibitor, is registered in US and Europe for the treatment of moderate to severe psoriatic arthritis. It has been shown to decrease pSTAT3, pSTAT1, NF-κB, p65, and induce SOCS3 and PIAS3 expression in PsA synovial fibroblasts. In PsA synovial biopsy cultures, tofacitinib significantly decreased spontaneous secretion of IL-6, IL-8, monocyte chemoattractant protein 1 (MCP-1), matrix metallopeptidase (MMP)9/MMP2/MMP3 and decreased the MMP3/tissue inhibitor of metalloproteinase (TIMP)3 ratio. Results from a proof of concept study with the JAK1 selective inhibitor filgotinib have demonstrated the efficacy of the compound in psoriatic arthritis. Upadacitinib, a JAK1/JAK3 I, inhibitor is currently being tested in Phase 3.

1.1.3. Ankylosing Spondylitis

Ankylosing spondylitis (AS) is a chronic, inflammatory autoimmune disease, which belongs to a group of conditions known as spondyloarthropathies. AS is mainly characterized by inflammation of the sacroiliac joints and axial skeleton. Extra-axial involvement can occur in up to half of patients and manifest as peripheral arthritis, enthesitis, and dactylitis. Acute anterior uveitis is the most common extra-articular manifestation, with lifetime prevalence of 30-40%. Psoriasis occurs in about 10% and inflammatory bowel disease (IBD), more commonly Crohn's disease (CD), has been reported in 5-10% of AS patients; however, microscopic inflammatory lesions from the colon or distal ileum biopsies have been reported more commonly. Osteoporosis of the spine and peripheral bones is frequently present, leading to increased spinal fracture rates in these patients.

First symptoms indicative of AS tend to develop in adolescents, aged 20-30 years. The disease occurs 3 times more often in young men compared to young women, with a prevalence of 0.15-0.8% in the general population. Although the exact cause of AS is unknown, a strong genetic predisposition is known, with >90% of the disease risk determined genetically. The strongest and most established association has been found with the HLA-B27 gene. More recent whole genome association studies have identified further loci in non-major histocompatibility complex (MHC) genes or genetic regions that influence susceptibility to AS; these loci confer endoplasmic reticulum aminopeptidase 1 (ERAP-1), IL-23R, lymphotoxin beta receptor (LTBR), and tumor necrosis factor receptor superfamily member 1A (TNFRSF1A).

The primary goals of AS treatment are to reduce symptoms, improve and maintain spinal flexibility and normal posture, reduce functional limitation with the aim to maintain the ability to work, and decrease long-term complications associated with AS. The first-line treatment of mild

AS are NSAIDs, providing a substantial relief of back pain and stiffness in approximately 70-80% of AS patients.

In case NSAID treatment does not adequately control symptoms sufficiently, treatment with corticosteroids can be considered, which however could increase the risk of spinal osteoporosis. While used widely in RA treatment, csDMARDs are generally ineffective for treatment of AS, although peripheral joint symptoms may effectively be treated with SSZ.

TNFi treatment has been a major progress in treatment options for poorly controlled AS, improving disease activity, spinal mobility, physical function, and pain. TNFi include the monoclonal antibodies infliximab, adalimumab, certolizumab pegol and golimumab, as well as the TNF alpha (TNFα) binding recombinant receptor etanercept. However, serious infections such as tuberculosis (TB), allergic reactions and autoimmune reactions can result from treatment. Additionally, TNFi agents are only effective in about 40% of patients and patients may lose response over time because of immunogenicity.

Recent studies suggest that IL-23/IL-17 pathways may have a role in the pathogenesis of AS. New compounds that target these pathways have become available and additional compounds are currently under evaluation in clinical studies. These agents include the, the IL-23 inhibitor tildrakizumab; the IL-17 A inhibitors such as secukinumab and ixekizumab; the IL17 A and F inhibitor bimekizumab; several key cytokines in the IL-23/IL-17 pathways signal through the JAK family of receptor-associated TYKs.

Several key cytokines in the IL-23/IL-17 pathways signal through the JAK family of receptor-associated TYKs, therefore inhibition of JAK signaling may be efficacious in the treatment of these diseases.

1.1.4. Non-radiographical Axial Spondyloarthritis

The term non-radiographic axial spondyloarthritis (nrAxSpA) is recently being introduced to identify patients suffering from the early phase of AS, where the standard diagnosis, historically based on the presence of sacroiliitis on X-ray, is impossible due to the absence of radiographic changes.

A study demonstrated that the frequency of radiographic sacroiliitis increases in parallel with disease duration and approximately 60% of patients will require at least 10 or more years of active disease to demonstrate its radiographic features seen in “classical” AS (Sahid-Nahal, Miceli-Richard, & Berthelot, 2000).

Therefore today, patients presenting with a clinical picture of AS but without its radiological hallmark, will be diagnosed with nrAxSpA.

This distinction is important as agents effective in alleviating clinical symptoms and signs of AS could be used much earlier in the course of the disease and therefore may prevent structural damage and complications (Rudwaleit, et al., 2009).

1.2. Filgotinib (GS-6034)

1.2.1. General Information

JAKs are intracellular cytoplasmic TYKs that transduce cytokine signaling from membrane receptors through STAT to the nucleus of cells. JAK inhibitors block the signaling of various cytokines, growth factors, and hormones, including the pro-inflammatory cytokine IL-6. Four different types of JAKs are known, JAK1, JAK2, JAK3, and TYK2 which interact with different sets of membrane receptors. Inhibition of JAKs is a promising therapeutic option for a range of inflammatory conditions including RA and CD. Filgotinib (GS-6034, formerly known as GLPG0634) is a potent and selective inhibitor of JAK1. The compound has shown good preliminary efficacy in subjects with RA and those with CD in Phase 2 studies.

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

1.2.2. Preclinical Pharmacology and Toxicology

Filgotinib and its metabolite, GS-829845, have been extensively characterized in nonclinical studies. This program includes cellular assays demonstrating potency and selectivity of the compound against JAK1; efficacy studies in rats and mice; repeat dose toxicity studies (up to 26 weeks in the rat and 39 weeks in the dog), in vitro and in vivo safety pharmacology and genetic toxicology studies, carcinogenicity studies in rats and in transgenic (TgrasH2) mice, and reproductive toxicology studies in rats and rabbits. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in support of a definitive rat juvenile toxicity study. A definitive juvenile toxicology study in rats is ongoing.

1.2.2.1. Nonclinical Pharmacology

In cellular assays, filgotinib inhibits JAK1 signaling with half maximum inhibitory concentration (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.

1.2.2.2. Safety Pharmacology

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

1.2.2.3. Key Nonclinical Distribution, Metabolism, and Excretion Data

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

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

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

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

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

In vitro experiments have shown that drug-drug interactions with filgotinib and GS-829845 are unlikely. There is no inhibition or induction of CYPs or uridine 5'-diphospho-glucuronosyltransferase (UGTs), and no relevant inhibition of key drug transporters, including organic anion transporters (OATs), by filgotinib or GS-829845. Organic cation transporter 2 (OCT2) was inhibited by both filgotinib (IC_{50}: 8.7 µM) and GS-829845 (IC_{50}: 67 µM). The clinical relevance of the IC_{50} values for inhibition of OCT2 will be further evaluated. Multidrug and toxin extrusion protein 1 (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 (area under the plasma drug concentration-time curve [AUC]) at the no observed adverse effect levels (NOAELs) for the most sensitive species (the dog), the exposure margins compared to a 200 mg once daily dose of filgotinib in CD subjects are 2.5, 1.9, and 3.6-fold for the 26-week and 39-week chronic toxicity studies and the 39-week targeted exposure toxicity study, respectively.

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

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

In embryofetal development studies, filgotinib and GS-829845 caused embryolethality and teratogenicity in rats and rabbits. Teratogenicity was observed at exposures slightly higher or similar to the human exposure at 200 mg once daily of filgotinib in subjects with RA. 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 Studies of Filgotinib

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

In two 24-week, Phase 2b, randomized, double-blind, placebo-controlled studies in 594 (Study GLPG0634-CL-203) and 283 subjects (Study GLPG0634-CL-204) with moderately to severely active RA who had insufficient response to MTX, filgotinib added to a stable dose of background MTX or administered as monotherapy was efficacious in a dose-dependent manner in treating the signs and symptoms of active RA (Westhovens, et al., 2016; Kavanaugh, et al., 2017). In Study GLPG0634-CL-203, an American College of Rheumatology 20 (ACR20) response was achieved by a statistically significantly higher percentage of subjects in the 100-mg once daily, 200-mg once-daily, and 100-mg filgotinib twice daily groups (63.5%, 68.6%, and 78.6%, respectively) compared with placebo (44.2%) ($p = 0.0435$, 0.0068, and <0.0001, respectively). In Study GLPG0634-CL-204, an ACR20 response at Week 12 was achieved by a statistically significantly higher percentage of subjects in all filgotinib dose groups compared with placebo (66.7%, 65.7%, and 72.5% in the 50-mg once-daily, 100-mg once-daily, and 200-mg filgotinib once-daily groups, respectively, compared with 29.2% on placebo) ($p <0.0001$ for all comparisons). In both studies, the ACR20 appeared to plateau at Week 8 and was maintained through Week 24. In addition, at Week 12, filgotinib showed a beneficial effect across the following secondary efficacy parameters: ACR50, ACR70, ACR-N, Disease Activity Score 28 joints (DAS28) (C-reactive protein [CRP]), Clinical Disease Activity Index (CDAI), and Simplified Disease Activity Index (SDAI). A dose-dependent fast onset of efficacy was reported, and the responses were maintained or continued to improve through 24 weeks. No significant difference in efficacy was observed between 100-mg and 200-mg once daily dosing regimens.

Safety in the proof of concept studies in PsA and AS was in line with the safety profile reported from previous studies with filgotinib in RA and no unexpected safety signals were identified.

1.3. Rationale for this Study and Proposed Study Population

Over the last decade, changes in treatment strategies for rheumatic diseases, accompanied by advances in drug development and the addition of targeted biological therapies, have greatly improved the outcomes for patients. Despite these developments, therapeutic challenges remain. Only a subset of patients responds to currently available biologic therapy while others lose response over time or become intolerant over time. There is an unmet medical need for simple, orally administered therapies with novel and targeted mechanisms of action that can effectively improve the disease course while being safe and well tolerated. Filgotinib is an orally administered, small molecule inhibitor of JAK1, an intracellular tyrosine kinase dysregulated in subjects with inflammatory disorders including RA, PsA, AS and nrAxSpA. Filgotinib has demonstrated a favorable safety and tolerability profile in a Phase 2 study in subjects with moderately to severely active RA. Filgotinib is presently being evaluated in Phase 3 studies in CD, ulcerative colitis (UC), and RA. Filgotinib is also being evaluated in, Sjögrens syndrome, cutaneous lupus erythematosus, noninfectious uveitis and lupus membranous nephritis.

While providing a treatment option for subjects with RA, PsA, AS and nrAxSpA, the present study seeks to evaluate the impact, if any, of filgotinib on spermatogenesis in humans. The observed effects of filgotinib on the testes are consistent across the nonclinical species tested, with observations of histopathological changes in testes and epididymides, together with reductions in sperm counts and reduced fertility in the rat. A mechanistic study in the rat suggested a reversible direct impact on the genes involved in cell cycle. A dose of 200 mg once daily of filgotinib results in an estimated mean clinical AUC of 2.8 µg·h/mL in subjects with RA, which represents an exposure margin of 2.3, 1.8, and 3.4-fold when considering the mean AUC in male dogs at the no observed effect levels (NOELs) in the 26-week and 39-week chronic toxicity studies, and 39-week targeted exposure toxicity study, respectively. The present study seeks to assess the impact of filgotinib at 200 mg, the highest proposed dose in the Phase 3 program, assessed by the proportion of male subjects who experience a ≥50% decrease in sperm concentration from Baseline when compared with placebo after 13 weeks of therapy. The proposed study design and subject population for GLPG0634-CL-227 have been selected to generate clinical safety data which would be broadly applicable to patient populations treated with filgotinib.

The present study has been designed in accordance with FDA Guidance for Industry: Testicular Toxicity: Evaluation During Drug Development (October 2018).

The study population will consist of males with active RA (defined as a CDAI score >10), active PsA (defined as DAPSA score >14) or active AS or nrAxSpA (defined as Bath Ankylosing Spondylitis Disease Activity [BASDAI] ≥4). Subjects must have demonstrated a prior treatment failure/intolerance to disease specific therapies but will be allowed to remain on permitted therapy, with the exception of SSZ which will be prohibited due to known risks of oligospermia and infertility {Pharmacia & Upjohn Co 2014}. Subjects will be stratified by Baseline sperm concentration and type of underlying rheumatic disease (RA or spondyloarhritis). In addition, subjects will also be stratified by use of MTX (yes or no) given its potential impact on

spermatogenesis. There have been case reports of reversible oligospermia and azoospermia with treatment with MTX {Sussman 1980}, though a small case series in 26 men with psoriasis aged 33 to 52 treated with MTX at a dose of 25 mg weekly did not reveal any impact of MTX on mean sperm count motility and morphology {El-Beheiry 1979}.

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

1.3.1. Rationale for the Outcome Measures

While no single sperm parameter can predict fertility potential, sperm concentration may be considered the most reliably quantifiable parameter that has potential utility in providing information about male fertility (FDA Guidance on Testicular Toxicity; October 2018). Sperm concentration may also be considered the most important parameter of testicular dysfunction (Sikka & Hellstrom, Current updates on laboratory techniques for the diagnosis of male reproductive failure., 2016). The present study will evaluate the reduction in sperm concentration of ≥50% or more from Baseline at 13 weeks as the primary endpoint in accordance with the FDA guidance. Significant variations in sperm parameters are expected in men; a threshold of a ≥50% reduction is considered the appropriate threshold to account for normal variability and is consistent with prior studies evaluating impact of potential testicular toxins (Sikka, et al., 2014; Hellstrom, et al., 2008; Hellstrom, et al., 2003; Jarvi, et al., 2008). Substantial intra- and inter-subject variation can occur particularly in sperm count in patients with and without fertility issues; in one cohort, sperm counts ranged over an order of magnitude in a single healthy patient over time (Keel, 2006). Two semen samples will be collected for evaluation at each time point during this study, with controlled abstinence periods before each sample collection; longer or shorter abstinence periods may have an impact on quality of sample. Ejaculate volume and sperm count are markedly reduced during periods of high ejaculation frequency (Oldereid, Gordeladze, Kirkhus, & Purvis, 1984). Significant variability is noted even in healthy subjects (World Health Organization (WHO), Laboratory Manual for the examination of human semen and sperm-cervical mucus interaction. Fourth Edition., 1999; World Health Organization (WHO), Laboratory manual for the Examination and processing of human semen. Fifth Edition., 2010). Additional sperm parameters at 13 weeks will be evaluated as secondary endpoints in alignment with the FDA Guidance on Testicular Toxicity (October 2018).

The primary endpoint at Week 13 will enable a direct assessment versus placebo in subjects with RA, PsA, AS, and nrAxSpA. Endpoints at 26 weeks of therapy have been chosen for secondary and exploratory analyses to assess impact after 2 full spermatogenesis cycles in accordance with The FDA Guidance on Testicular Toxicity (October 2018), which recommends treatment for 26 weeks for drugs that are chronically dosed. The 26-week endpoint will also allow assessment of the impact of longer-term therapy on semen parameters, given the expectation for chronic dosing of therapy in the real world setting. Finally, in the present study, total motility, which is

considered to be more consistently measured across observers, will remain as a secondary endpoint.

In this study the ACR/EULAR (2010) criteria will be used to define a diagnosis of RA, the CASPAR criteria will be used to define a diagnosis of PsA, and the Assessment of Spondyloarthritis International Society (ASAS) criteria for will be used to define a diagnosis of axial spondyloarthritis (AS or non-radiographical axial spondyloarthritis [nrAxSpA]) for the purpose of eligibility.

Subjects with RA and PsA will be required to have an inadequate response or intolerance to at least a 12-week course of csDMARD or biological DMARD (bDMARD) therapy for their arthritis. Subjects with AS and nrAxSpA will be required to have an inadequate response or intolerant to at least 2 NSAIDs (see Section 4.2).

At the Week 13 Visit, Physician Global Assessment of Disease Activity (PhGADA) will be used to determine arthritis Responder, and arthritis Non-responder status. During the Extension Phase, individual subject response to treatment has to be evaluated at each visit in accordance with good rheumatology practice.

This study is based upon real world outpatient clinical practice, where clinical signs/symptoms (and labs as applicable) and a provider's assessment are adequate to assess therapeutic response or non-response. Safety and tolerability will be assessed by the evaluation of adverse events (AEs), selected clinical laboratory parameters, vital signs, physical examinations, and ECGs all of which are standard safety evaluations in clinical development. All subjects who experience a ≥50% decrease in sperm concentration and/or total motility and/or normal morphology will be followed for one or more spermatogenesis cycles, up to 52 weeks as needed, to assess for sperm parameter reversibility.

1.3.2. Rationale for the Choice of Dose and Dosing Interval

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

1.4. Risk/Benefit Assessment for the Study

Over the last decade, changes in RA and PsA treatment strategies, accompanied by advances in drug development and the addition of targeted therapies, have improved patient outcomes. Despite these developments, therapeutic challenges remain. Current csDMARDs and bDMARDs may produce only partial responses in some patients and may be associated with significant safety and tolerability concerns. There is an ongoing need for orally administered therapies with novel and targeted mechanisms of action that can more effectively improve the disease course.

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 RA. To assess this potential risk to male fertility, the male safety clinical study described herein is planned to examine the effect of filgotinib (if any) on sperm/ejaculate parameters. Male subjects who enroll will be appropriately consented via the informed consent form (ICF) wherein risk language is highlighted. Impaired spermatogenesis is considered to be a potential risk for filgotinib. Refer to the IB for further information about nonclinical and clinical testicular findings.

Filgotinib has shown an increased risk in embryofetal malformations in rats and rabbits at exposures similar to, or slightly higher than, exposures associated with a 200 mg once daily dose in subjects with RA. As a result, highly effective contraception and male condoms will be required for male subjects with female partners of childbearing potential, which is expected to mitigate this risk.

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

The potential benefits of JAK inhibition include improvement in clinical symptoms. JAK inhibition may be efficacious in the treatment of RA, PsA, AS and nrAxSpA based on results from the Phase 2 studies of subjects with PsA, and AS. Filgotinib is currently in Phase 3 studies for RA.

Overall, clinical findings and laboratory changes associated with filgotinib are consistent with JAK 1 inhibition. Based on Phase 2 and Phase 3 data the expected benefit of using filgotinib as proposed in this study is considered to outweigh any associated risks. In addition, the subject population in the present study will consent to a risk of potentially permanent infertility, thus individual male subjects in conjunction with the treating physician may evaluate the benefit-risk profile of filgotinib. A lack of response contingency from Week 13 onward in the current study, targeting arthritis Non-responders at Week 13, will enable early access to active drug or Standard of Care treatment when clinically indicated. This rescue approach, the provision of best supportive care during the extension phase, and the limited study duration, makes the use of placebo ethically acceptable for the specified duration.

An external multidisciplinary Data Monitoring Committee (DMC), including an expert in male fertility, will be appointed to monitor the study.

The DMC has monitored the study until the date of protocol amendment 2, including the data for the second unblinded interim analysis (IA2). As of amendment 2, the DMC will be

decommissioned. Details on the DMC's role have been described in a specific charter. The DMC's role will be transferred to the internal Sponsor Safety Management Team (SSMT). The SSMT is not involved in the conduct of the study and will evaluate safety data throughout the remainder of the study as part of continuous safety oversight across the filgotinib program.

Taking all of these considerations into account with respect to the filgotinib program, the early signals for efficacy demonstrated in Phase 2 and Phase 3 clinical studies of RA, AS and PsA, as well as the beneficial findings in nonclinical models of disease and the overall safety, tolerability, and PK characteristics of filgotinib elucidated to date, there is a favorable benefit-risk profile for this agent in continued development as a treatment for RA, PsA, AS, and nrAxSpA. The overall benefit-risk balance of this study is considered favorable.

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

1.5. Compliance

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

2. OBJECTIVES

The primary objective of this study is:

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

The secondary objectives of this study include:

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

The exploratory objectives of this study include:

- To evaluate the reversibility of observed effects of filgotinib on testicular function in subjects who experience a $\geq$ 50% decrease in sperm concentration, and/or motility, and/or morphology

- To evaluate the effect of filgotinib on sex hormones, including luteinizing hormone (LH), follicle stimulating hormone (FSH), inhibin B, and total testosterone at Weeks 13 and 26

- To evaluate the safety and tolerability of filgotinib

- To characterize the plasma PK of filgotinib and its metabolite (GS-829845, formerly CCI

3. STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, Phase 2 study in adult males with active RA, PsA, AS or nrAxSpA who have had an inadequate response to prior arthritis therapy as outlined in the inclusion criteria, an adverse prognosis of their condition per the investigator and may benefit from treatment with a JAK inhibitor.

Up to 250 males between the ages of 21 and 65 years (inclusive) at the time of consent will be randomized to receive filgotinib 200 mg or placebo once daily for 13 weeks.

Randomization will be stratified according to the type of rheumatic condition (RA or Spondyloarthritis [PsA, AS, nrAxSpA]), by concurrent use of MTX (yes or no), and by sperm concentration measured at Screening ("Baseline") according to the following strata:

- 15 to 25 million/mL

- > 25 to 50 million/mL

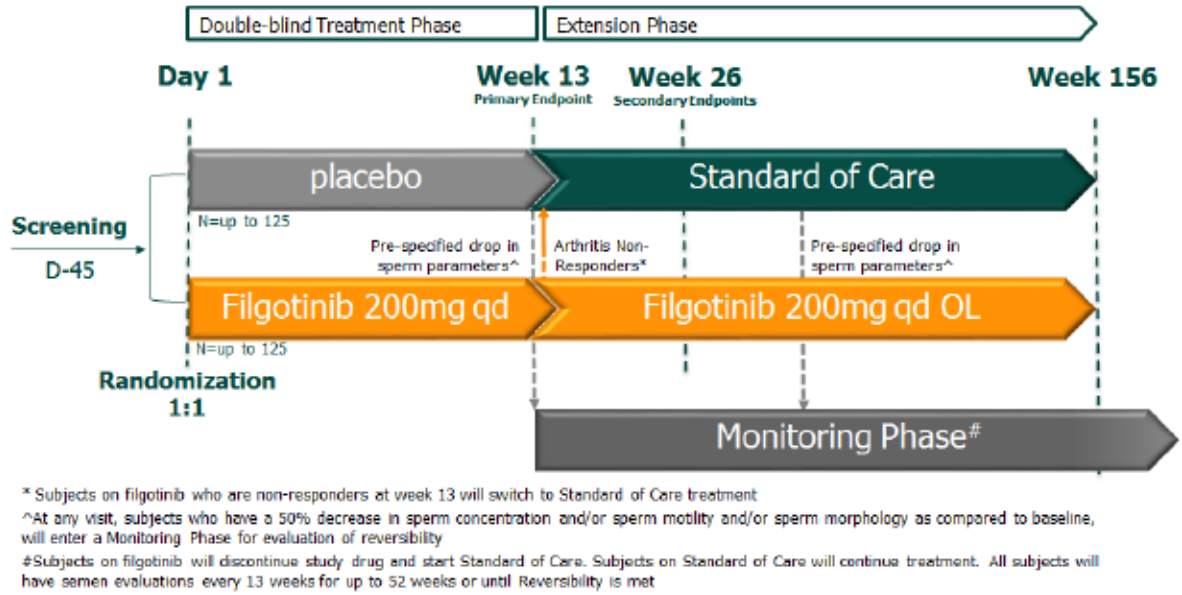
- > 50 million/mL

Male subjects with RA, PsA, AS or nrAxSpA who provide written informed consent will be screened to determine eligibility as per the inclusion and exclusion criteria (see Section 4.2 and 4.3, respectively).

The Screening period will be up to 45 days and may be extended in consultation with the Sponsor Medical Monitor. During the Screening period, subjects will provide 2 semen samples within a 14-day period as detailed in Section 6.11 (ie, the Screening ["Baseline"] sample).

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

Figure 3-1. Study Scheme



* Subjects on filgotinib who are non-responders at week 13 will switch to Standard of Care treatment

^At any visit, subjects who have a 50% decrease in sperm concentration and/or sperm motility and/or sperm morphology as compared to baseline, will enter a Monitoring Phase for evaluation of reversibility

#Subjects on filgotinib will discontinue study drug and start Standard of Care. Subjects on Standard of Care will continue treatment. All subjects will have semen evaluations every 13 weeks for up to 52 weeks or until Reversibility is met

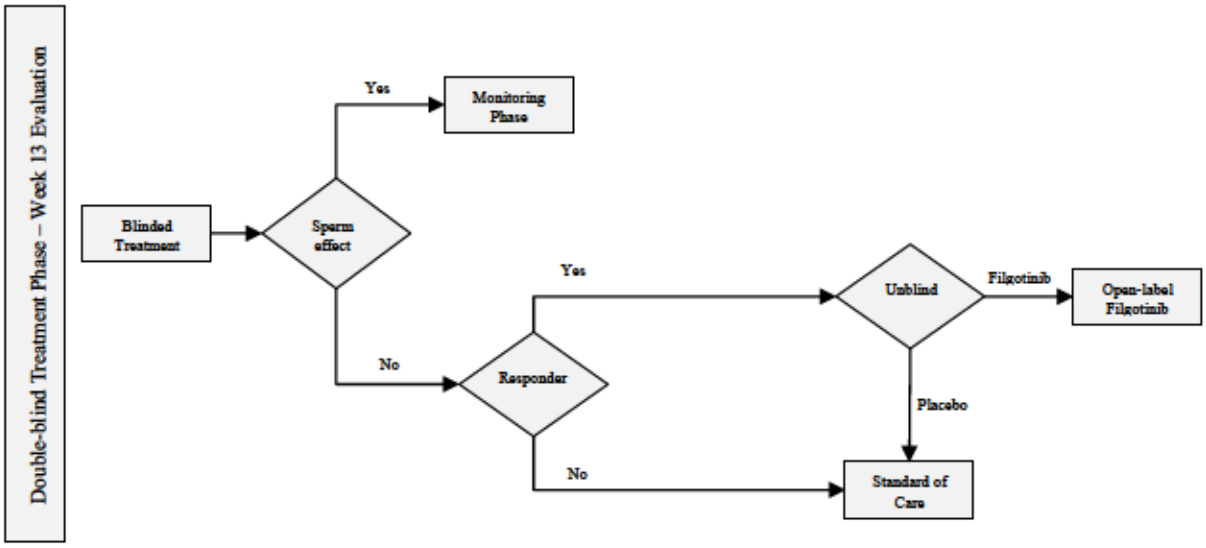
There are 3 distinct parts to the study:

1) Double–blind Treatment Phase (Day 1 through Week 13 Study Visit)
2) Extension Phase (After Week 13 Study Visit and up to Week 156)
3) Monitoring Phase (up to 52 weeks)

After fulfilling all selection criteria, subjects will be randomized to filgotinib or placebo (1:1) at Day 1 and enter the Double-blind Treatment Phase. Based on the outcomes of the Week 13 assessments (ie, individual subject's response of the underlying rheumatic condition to the assigned treatment and/or the observed changes in sperm parameters during the double-blind treatment phase), subjects may enter the Extension or Monitoring Phase.

3.1. Double-blind Treatment Phase (Day 1 through Week 13 Study Visit)

Figure 3-2. Double-blind Treatment Phase – Week 13 Evaluation

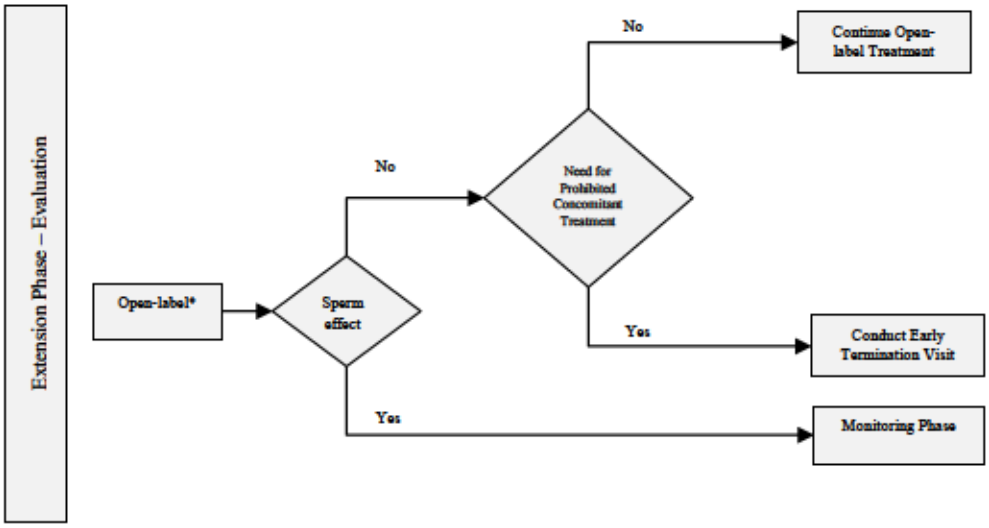


During the Double-blind Treatment Phase, all subjects will receive blinded study drug for 13 weeks starting from the Day 1/Randomization Study Visit. Subjects will visit the clinical study center to be evaluated for clinical and laboratory assessments at Day 1, Week 2, Week 4, Week 8, and Week 13. At the Week 13 study visit, sperm parameters (see Semen collection and Analysis) will be evaluated to determine whether they meet any of the pre-specified decrease thresholds (see Definition of Terms). In addition, arthritis response status (Arthritis Non-responder vs Arthritis Responder, see Definition of Terms) will be determined. As soon as the Week 13 semen results are available to the investigator and have been evaluated, subjects are assigned to one of the following:

- Subjects whose semen parameters meet any of the pre-specified decrease thresholds, regardless of arthritis response status, will discontinue blinded study drug and enter the Monitoring Phase. These subjects will also have a safety follow-up visit 30 days after last study drug dose.
- Subjects who are arthritis Non-responders and whose sperm parameters do not meet any of the pre-specified decrease thresholds will discontinue blinded study drug and start Standard of Care treatment (see Definition of Terms) during the Extension Phase. These subjects will also have a safety follow-up visit 30 days after last study drug dose.
- Subjects who are Arthritis Responders and whose sperm parameters do not meet any of the pre-specified decrease thresholds will be unblinded by the IWRS system and enter the Extension Phase. Subjects on filgotinib will convert to open-label filgotinib and subjects receiving placebo will switch to Standard of Care treatment.

3.2. Extension Phase

Figure 3-3. Extension Phase – Evaluation



*Open-label treatment with filgotinib or Standard of Care. Adjustment of background treatment with non-prohibited medication allowed at any time during the Extension Phase

In the Extension Phase, subjects will receive open-label treatment (filgotinib or Standard of Care) and have a study visit every 13 weeks that includes semen analysis. The first scheduled visit of the Extension Phase occurs at Week 26.

In case sperm parameters at any visit (including Week 156) meet any of the pre-specified decrease thresholds, subjects will enter the Monitoring Phase.

During the Extension phase, Standard of Care and background treatment concomitant to filgotinib may be optimized at the discretion of the investigator, taking into consideration the protocol restrictions.

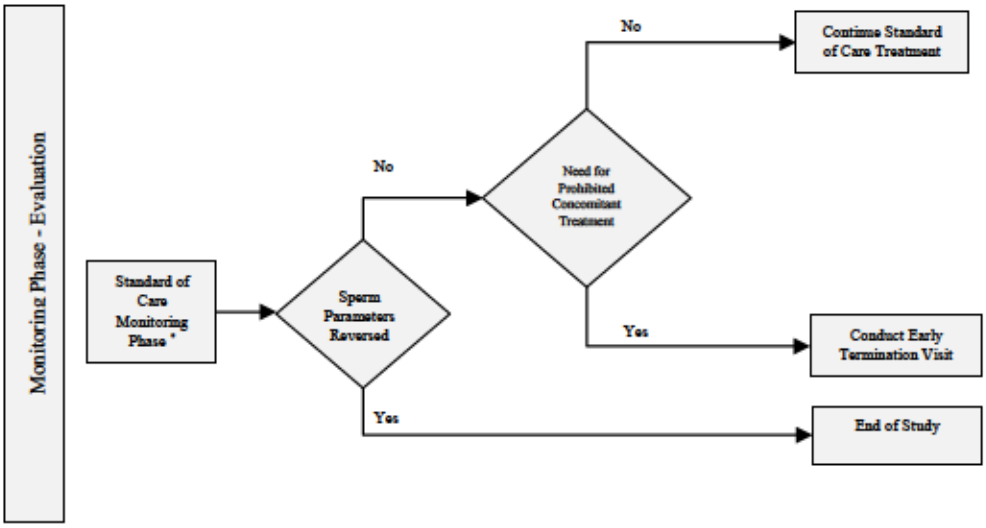
In case a subject needs to be treated with a prohibited medication (see Table 5-1), for instance to control their rheumatic condition, the subject will discontinue the study and complete an Early Termination (ET) visit (including semen collection). For subjects on filgotinib, this will be followed by a safety follow-up visit 30 days after last study drug dose.

All subjects who did not enter the Monitoring Phase will continue the study until the Week 156 visit.

In the Extension Phase, subjects must have yearly Quantiferon® testing. Yearly TB testing begins 1 year from the screening TB test date. If yearly TB testing falls between study visits, the yearly TB testing should be performed at the visit prior to 1 year from the screening TB test date. Subjects with newly positive (converted) Quantiferon® (or centrally reported equivalent assay) TB test should be discontinued from the study. Subjects who were previously treated for TB with a complete and adequate course of therapy as per local Standard of Care and as verified by the investigator do not need to have yearly tests.

3.3. Monitoring Phase (up to 52 weeks)

Figure 3-4. Monitoring Phase - Evaluation



*Adjustment of background treatment with non-prohibited medication allowed at any time during the Monitoring Phase

Subjects whose sperm parameters meet any of the pre-specified decrease thresholds will switch to the Monitoring Phase immediately. Subjects on double-blinded treatment or open-label filgotinib who enter the Monitoring Phase will discontinue study drug and start Standard of Care. These subjects will also have a safety follow-up visit 30 days after last study drug dose. Subjects on Standard of Care will continue treatment.

All subjects who enter the Monitoring Phase will undergo semen evaluations every 13 weeks starting from their entry into the Monitoring Phase, for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first.

In case a subject needs to be treated with a prohibited medication (see Table 5-1), for instance to control their rheumatic condition, the subject will discontinue the study and complete an ET visit (including semen collection).

3.4. Semen Collection and analysis:

At each of the following time points, subjects will provide 2 separate semen samples collected within a 14-day period. Each semen sample must be collected with a ≥48 hours and ≤7 days ejaculation free period (Section 6.11) at the following time points.

- Screening (Baseline)
- After the Double-blind Treatment Phase (Week 13 study visit)
- Every 13 weeks during the Extension Phase
- Every 13 weeks during the Monitoring Phase
- At the Early Termination Visit

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

3.5. Study Treatments

Up to 250 subjects will be randomized in a 1:1 ratio to receive filgotinib 200 mg once daily or placebo once daily.

3.6. Duration of Treatment

The duration of blinded treatment is approximately 13 weeks followed by an open-label Extension Phase of up to 143 weeks. Subjects entering the Monitoring Phase will be followed for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first.

3.7. Criteria for Interruption or Discontinuation of Study Treatment

3.7.1. Study Drug Interruption Considerations

The Sponsor Medical Leader or designee should be consulted prior to study drug interruption when medically feasible. Study drug interruption should be considered in the following circumstances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
- Subject is scheduled for elective or emergency surgery (excluding minor skin procedures under local or no anesthesia); timing of study drug interruption should be determined in consultation with the Sponsor Medical Leader or designee.
- Any subject who develops a new infection during the study should undergo prompt and complete diagnostic testing appropriate for an immunocompromised individual, and the subject should be closely monitored.
- After becoming aware of a laboratory change representing moderate renal failure (estimated creatinine clearance [CrCl] ≥35 mL/min and <60 mL/min per Cockcroft-Gault [CC&G] formula) at any time during the study, the following actions should be taken and documented:
  - Establish possible underlying condition and initiate appropriate action to resolve.
  - Retest CrCl within 8 weeks.

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

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

- The principal investigator/deputy should assess individual patient benefit/risk with regards to re-initiation of treatment after repeat or prolonged interruptions, or if re-initiation is not considered appropriate. Consultation with the Sponsor medical monitor or designee is preferred in these situations.

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

After study drug interruption, prior to resumption of study drug, the investigator should discuss the case with the Sponsor Medical Leader or designee.

3.7.2. Study Drug Discontinuation Considerations:

The Sponsor Medical Leader or designee should be consulted prior to study drug discontinuation when medically feasible.

Study drug should be permanently discontinued in the following instances:

- Any opportunistic infection
- Any **serious** infection that requires parenteral/intravenous antimicrobial therapy or hospitalization, or any infection that meets serious adverse event (SAE) reporting criteria.
- Febrile neutropenia (temperature >38.3°C or a sustained temperature of >38°C for more than 1 hour) with absolute neutrophil count of <1,000/mm^3
- Symptomatic anemia (eg, signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with hemoglobin <7.5 g/dL, or if transfusion is indicated regardless of hemoglobin value
- Complicated herpes zoster infection (with multi-dermatomal, disseminated, ophthalmic, or CNS involvement)
- Evidence of active Hepatitis C virus (HCV) during the study, as evidenced by HCV RNA positivity
- Evidence of active Hepatitis B virus (HBV) during the study, as evidenced by HBV deoxyribonucleic acid (DNA) positivity
- Any thromboembolic event that meets SAE reporting criteria

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

- A ≥50% decrease from Baseline (based on the mean of 2 separate semen samples collected at the Screening Visit) in sperm concentration and/or motility and/or morphology

- Subject request to discontinue for any reason

- Subject noncompliance to the protocol

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

- Subject's use of prohibited concurrent therapy will trigger study discontinuation; consultation should be made with the Sponsor Medical Leader or designee

- Subjects with newly positive (converted) QuantiFERON® TB test (or centrally reported equivalent assay) and/or any subject with active TB

- Any of the below described abnormal laboratory changes occurring at any one time, and confirmed by repeat testing (Appendix 11):

  — 2 sequential neutrophil counts $<0.75 \times 10^9$ cells/L (750 neutrophils/mm^3)

  — 2 sequential platelet counts $<75.0 \times 10^9$ cells/L (75,000 platelets/mm^3)

  — 2 sequential aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations >3x the upper limit of normal (ULN) and at least 1 of the following confirmed values: a) total bilirubin >2x ULN, b) international normalized ratio (INR) >1.5, or c) accompanied by symptoms consistent with hepatic injury. For any subject with an initial AST or ALT elevation > 3x the ULN, at the time of the second confirmatory draw, an INR, prothrombin time (PT) and partial thromboplastin time (PTT) must also be drawn.

  — 2 sequential AST or ALT elevations > 5xULN

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

- Subjects who permanently stop study drug due to pre-specified decrease in sperm parameters (Section 6.11) will be offered standard of care as part of the Monitoring Phase.

- Subjects who are unblinded prior to Week 13.

3.7.3. Study Discontinuation

Subjects withdrawing from the study should make every effort to complete an ET visit; for subjects on blinded treatment or on filgotinib, this will be followed by a safety follow-up visit 30 days after last dose of study drug.

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

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

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

3.8. End of Study

End of Study is reached when the last scheduled study visit occurred. This can be a Week 156 visit, a Follow-up visit, or the last visit of a Monitoring Phase.

3.9. Post-Study Care

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

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 250 subjects with active RA, PsA, AS or nrAxSpA will be randomized in the study to ensure 200 subjects are evaluable at Week 13. Enrollment may be expanded if the dropout rate is higher than expected and will be evaluated during the course of the study.

4.2. Inclusion Criteria

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

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

2) Male between the ages of 21 and 65 (inclusive) on the day of signing informed consent

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

4) Diagnosis of RA, PsA, AS, or nrAxSpA for at least 12 weeks prior to Screening, meeting the corresponding specific classification criteria:

    a) RA, ACR/ European League Against Rheumatism (EULAR) 2010

    b) PsA, Classification criteria for Psoriatic Arthritis (CASPAR) criteria

    c) AS or nrAxSpA, Assessment of Spondyloarthritis International Society (ASAS) criteria for axial spondyloarthritis

5) For RA, PsA, AS, or nrAxSpA, meets the following criteria:

    a) RA

        i. Inadequate response or intolerant to an ≥12-weeks' course of csDMARD or bDMARD therapy for RA

        ii. Have an CDAI >10 at Screening

    b) PsA

        i. Inadequate response or intolerant ≥12-weeks' course of csDMARD or bDMARD therapy for PsA

        ii. Have a Disease Activity in Psoriatric Arthritis (DAPSA) score >14 at Screening

    c) Axial Spondyloarthritis (applicable to those with diagnosis of AS or nrAxSpA)

        i. Inadequate response or intolerant to at least 2 NSAIDs, which may include cyclooxygenase-2 (COX-2 inhibitors) prescribed for a total period of ≥4 weeks OR to an at least 12-weeks' course of csDMARD or bDMARD therapy for spondyloarthritis

        ii. Have a BASDAI ≥4 at Screening

        iii. At Screening, subjects should have a high-sensitivity C-reactive protein (hsCRP) >0.3 mg/dL OR sacroiliitis according to the modified New York (NY) criteria OR a history of active inflammation on magnetic resonance imaging (MRI) consistent with sacroiliitis within 2 years of screening

6) If using csDMARD therapy, subjects are permitted to use one of the following drugs, alone or in combination (with the exception of the MTX-LEF combination) and must have been on a stable dose of the drug for at least 4 weeks prior to Screening and remain on a stable dose during the Double-blind Treatment Phase of the study (stable dose in all cases is defined as no change in prescription):

a) MTX oral or parenteral up to 25 mg/week (plus concomitant use of folic or folinic acid supplementation as per local Standard of Care)

b) Leflunomide (LEF) up to 20 mg/day orally

c) Hydroxychloroquine up to 400 mg/day or chloroquine up to 250 mg/day orally

d) Apremilast orally up to 30 mg twice daily

Note that SSZ is not permitted at any time, beginning 26 weeks prior to Screening until the end of the study, and cannot be included in the Standard of Care arthritis regimen, due to its potential impact on semen parameters.

7) The mean of 2 separate semen samples collected at Screening must meet the following minimum criteria (in accordance with Section 6.11): semen volume ≥1.5 mL, total sperm per ejaculate ≥39 million, sperm concentration ≥15 million per mL, sperm total motility ≥40% and normal sperm morphology ≥30%

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

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

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

11) Meet one of the following 3 TB Screening criteria:

a) No evidence of active or latent TB:

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

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

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

b) Previously treated for TB:

— A subject who has previously received an adequate course of therapy as per local standard of care for either latent TB (e.g. 9 months of isoniazid in a location where rates of primary multi-drug resistant TB infections are <5%, or an alternative regimen according to local country guidelines) or active TB (acceptable multi-drug regimen).

In these cases, no QuantiFERON® TB-Gold PLus In-Tube test (or a centrally reported equivalent assay) needs to be obtained.

— A chest radiograph must be obtained if not done within 3 months prior to Screening (with the report or films available for investigator review).

— It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation.

c) Newly identified latent TB during Screening:

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

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

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

12) Laboratory parameters need to be met as per below:

a) Hepatic panel (AST, ALT, total bilirubin) $\leq$ 2 X the ULN

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

c) Hemoglobin $\geq$8 g/dL

d) Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L (1,500/mm3)

e) Platelets $\geq 100 \times 10^9$/L

f) White blood cells (WBC) $\geq 3.0 \times 10^9$/L

g) Absolute Lymphocyte count >750/mm^3

4.3. Exclusion Criteria

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

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

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

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

4) History of radiation to the testicles

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

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

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

8) Current treatment with 5-α reductase inhibitors (including but not limited to finasteride and dutasteride), or treatment within 4 weeks of Screening

9) Current treatment with alpha-1 blockers (including but not limited to tamsulosin, doxazosin, prazosin), or treatment within 4 weeks of Screening

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

11) Current use of with alkylating agents or any recognized testicular toxin, or treatment within 26 weeks prior to Screening (may be discussed with Sponsor Medical Leader or designee)

12) Current treatment with TNFα antagonist (including but not limited to infliximab, adalimumabn etanercept, golimumab, certolizumab, and biosimilar agents), or treatment within 4 weeks of Screening

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

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

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

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

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

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

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

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

21) Vaccination with live attenuated vaccine(s) within 30 days of Day 1 (see also Section 5.4, Vaccine Guidelines)

22) A positive test result for human immunodeficiency virus (HIV)-1 or HIV-2 (See Appendix 12)

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

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

25) Presence of Child-Pugh Class C hepatic impairment

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

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

28) History of leukocytapheresis ≤6 months prior to Screening

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

30) 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)

31) History of opportunistic infection or immunodeficiency syndrome

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

33) History of disseminated *Staphylococcus aureus* infection

34) 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 CNS zoster

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

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Randomization, Blinding and Treatment Codes

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

5.1.1. Blinding

During the randomized Double-blind Treatment Phase, subjects and all personnel directly involved in the conduct of the study will be blinded to treatment assignment. Specified personnel not directly involved in the study conduct may be unblinded based on their study role. Study drug will be dispensed by the study pharmacist, or designee, in a blinded fashion to the subjects. The Pharmacokinetics File Administrator, or designee, in Bioanalytical Operations and/or Clinical Data Management, who facilitates the data transfer of PK files between the Sponsor and vendors, will remain unblinded. Individuals in Clinical Packaging & Labeling or Clinical Supply Management who have an Unblinded Inventory Manager role in the IWRS system for purposes of study drug inventory management will remain unblinded. Individuals responsible for safety signal detection, Investigational New Drug (IND) safety reporting and/or expedited reporting of suspected unexpected serious adverse reactions (SUSARs) may be unblinded to individual case

data and/or group level summaries. External (ie, contract research organizations [CROs]) biostatisticians and programmers will be unblinded to produce tables, figures, and listings for unblinded review at DMC meetings, and the external biostatistician will serve as the external statistician to the DMC. Regulatory Quality and Compliance personnel in Research and Development may also be unblinded for purposes of supporting Quality Assurance activities and/or Regulatory Agency inspections.

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

5.1.2. Procedures for Breaking Treatment Codes

After Week 13 of the Double-blind Treatment Phase, subjects who are Arthritis Responders and whose sperm parameters do not meet any of the pre-specified decrease thresholds will be unblinded by the IWRS system and enter the Extension Phase.

Blinding of study treatment until the Week 13 visit is critical to the integrity of this clinical study. Therefore, treatment assignments should remain blinded until the semen analysis results related to the Week 13 visit are known, unless that knowledge is necessary to determine emergency medical care for the subject. In the event of a medical emergency where breaking the blind prior to completion of the Week 13 visit procedures is required to provide medical care to the subject, the investigator may obtain the individual subject treatment assignment directly from the IWRS system. The Sponsor recommends, but does not require, that the investigator contacts the Sponsor Medical Leader or designee before breaking the blind.

The investigator however must contact the Sponsor Medical Leader or designee promptly after unblinding prior to the Week 13 visit. 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 unblinded. If a subject's treatment assignment is disclosed to the investigator, the subject will have study drug discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

The Sponsor may independently unblind cases prior to the Week 13 visit for expedited reporting of SUSARs to Regulatory Authorities.

5.2. Description and Handling of Filgotinib and Placebo

5.2.1. Formulation

Filgotinib is available as 200 mg strength tablets. Filgotinib 200 mg tablets are beige, debossed with "GSI" on one side and "200" on the other, capsule-shaped, biconvex, film-coated tablets for clinical use. Each tablet contains the equivalent of 200 mg filgotinib free base in the form of filgotinib maleate. In addition to the active ingredient, filgotinib tablets contain the following

inactive ingredients: microcrystalline cellulose, lactose monohydrate, fumaric acid, pregelatinized starch, silicon dioxide, magnesium stearate, macrogol/polyethylene glycol (PEG) 3350, polyvinyl alcohol, talc, titanium dioxide, iron oxide yellow, and iron oxide red.

Placebo to match tablets are identical in appearance to the active tablets. Placebo 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 200 mg and placebo 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 participating countries shall be labeled to meet applicable requirements of the 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 200 mg and placebo tablets, should be stored at controlled room temperature of 25°C (77°F). Temperature variability between 15°C and 30°C (59°F to 86°F) are permitted and are not considered excursions. Storage conditions are specified on the label.

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

5.2.4. Dosage and Administration of Filgotinib and Placebo

Filgotinib 200 mg tablets or placebo will be administered once daily with or without food. Each subject must be given instructions to maintain approximately the same daily dosing interval between study drug doses.

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

5.3. Prior and Concomitant Medications

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

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

5.3.1. Allowed Concomitant Medications

If using csDMARD therapy prior to the study, subjects are permitted to continue one of the following drugs during the study, alone or in combination (with the exception of the MTX-LEF combination), and must have been on a stable dose of the drug for at least 4 weeks prior to Screening and remain on a stable dose during the Double-blind Treatment Phase of the study (stable dose in all cases is defined as no change in prescription):

a) MTX oral or parenteral up to 25 mg/week (plus concomitant use of folic or folinic acid supplementation as per local Standard of Care)

b) Leflunomide up to 20 mg/day orally

c) Hydroxychloroquine up to 400 mg/day or chloroquine up to 250 mg/day

d) Apremilast orally up to 30 mg twice daily

Oral corticosteroids may be used at ≤10 mg/day (of prednisone or equivalent), provided that the prescription has been stable for at least 4 weeks prior to Day 1 and up to the Week 13 visit. For subjects continuing on open-label filgotinib after the Week 13 visit, the subject's steroid dose can be reduced based on investigator judgment (and may also be adjusted back up as needed), but should NOT exceed the stable dose identified at Baseline (Randomization/Day 1). For subjects continuing Standard of Care treatment, the dose of corticosteroids can also be reduced or increased but should not exceed 20 mg/day (of prednisone or equivalent; the prednisone conversion table is provided in Appendix 13).

If an NSAID or COX-2 inhibitor is used, it must not exceed the maximum dose permitted as per local label and must have been used at a stable dose for at least 2 weeks prior to Day 1 and up to the Week 13 visit.

5.3.2. Prohibited Concomitant Medications

The prohibited medications while on study are as follows:

Table 5-1. Prohibited Concomitant Medications

Drug Class	Agents Disallowed	Prohibited Period
Strong P-gp Inducers[a]		
Anticonvulsants	Including, but not limited to Phenobarbital, phenytoin, carbamazepine	21 days prior to Screening through the end of the Double-blind Treatment Phase of the study and through the end of the Extension Phase for subjects on open-label filgotinib
Antimycobacterials	Including, but not limited to Rifabutin, rifapentine, rifampin	
Herbal/Natural Supplements	St. John's wort and danshen (Salvia Miltiorrhiza)	
Prohibited Medications for Rheumatic Conditions		
Corticosteroids	Dose equivalent to >10 mg/day of prednisone or equivalent (oral) For subjects on Standard of Care treatment: dose equivalent to >20 mg/day of prednisone or equivalent (oral) All parenteral corticosteroids are prohibited During the Extension and Monitoring Phase, subjects may receive a maximum of 3 intra-articular injections of corticosteroid every 12 months; The dose of corticosteroid injected should not exceed the equivalent dose of triamcinolone 40-mg suspension; The dose and volume should be adjusted downward as appropriate to the size of the joint	Randomization through the end of the study
TNFα antagonist	Including, but not limited to: infliximab, adalimumab, etanercept, golimumab, certolizumab, and biosimilar agents	4 weeks prior to Screening through the end of the Double-Blind Treatment Phase of the study and through the end of the Extension Phase for subjects on open-label filgotinib
Interleukin antagonists	Including, but not limited to: ustekinumab, tocilizumab, secukinumab, anakinara,	12 weeks prior to Screening through the end of the Double-Blind Treatment Phase of the study and through the end of the Extension Phase for subjects on open-label filgotinib
JAK inhibitor	Any JAK inhibitor other than filgotinib	90 days prior to Screening through the end of the Double-Blind Treatment Phase of the study and through the end of the Extension Phase for subjects on open-label filgotinib

Drug Class	Agents Disallowed	Prohibited Period
	Filgotinib	Any time prior to Randomization in this study
Other (non-biologic) DMARDs	Including, but not limited to: cyclosporine (and other calcineurin inhibitors), thalidomide, tacrolimus, mycophenolate, azathioprine, gold salts, (NOTE: apremilast is permitted during the study)	4 weeks prior to Screening through the end of the Double-Blind Treatment Phase of the study and through the end of the extension phase for subjects on open-label filgotinib
Other (biologic)	Any investigational biologic agent	8 weeks prior to Screening (or 5 half-lives, whichever is longer) through the end of the study
Lymphocyte-depleting therapies	Including, but not limited to: alemtuzumab, cyclophosphamide, total lymphoid irradiation, and any other lymphocyte-depleting therapy	Any time before and through the end of the study
Other Lymphocyte-depleting therapies	Rituximab	12 months prior to screening and through the end of the study
Sulfa drugs	Sulfasalazine	Current use of sulfasalazine or use of sulfasalazine within 26 weeks of Screening. Sulfasalazine is not permitted at any point during the study
Alkylating agents or any recognized testicular toxin		Within 26 weeks of Screening and through the end of the study (may be discussed with Sponsor Medical Leader or designee)
Prohibited Medications for Other Indications		
Other biologics[b]	Antibody based or other systemic biologics, e.g. denosumab, trastuzumab	Requires Sponsor Medical Leader consultation
Alpha-1 blockers	Including but not limited to tamsulosin, doxazosin, prazosin	4 weeks prior to Screening and through the end of the study
5-α reductase inhibitors	Including, but not limited to, finasteride and dutasteride	4 weeks prior to Screening and through the end of the study
Antiandrogen therapy	Including but not limited to: spironolactone or oral ketoconazole, cyproterone acetate	4 weeks prior to Screening and through the end of the study
Testosterone replacement therapy		12 weeks prior to Screening and through the end of the study

a May decrease study drug exposure and are excluded to avoid potential reduction in study drug activity.
PK results indicate filgotinib is a P-gp substrate, as a single dose of 200 mg itraconazole (a potent P-gp inhibitor) increased filgotinib C_{max} by 64% and AUC_{inf} by 45% and had no effect on the major, active metabolite GS-829845.
b Other approved biologics (e.g. antibody based or other systemic biologics) may be allowed with the approval of the Sponsor Medical Leader or designee who will also specify the corresponding prohibited period.

5.4. Vaccine Guidelines

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

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

  It should be noted that the investigator must remind the subject at the Follow-up Visit that vaccination with live components are not allowed until 12 weeks after the last dose of study medication.

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

  — Varicella or live attenuated (oral) typhoid vaccines – avoid contact for 4 weeks following household contact vaccination

  — Live attenuated (oral) polio vaccine – avoid contact for 6 weeks following household contact vaccination

  — Live attenuated rotavirus vaccine – avoid contact for 10 days following household contact vaccination

  — Live attenuated (intranasal) influenza vaccine – avoid contact for 1 week following household contact vaccination

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

5.5. Accountability for Study Drugs

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

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

- Record the date received and quantity of study drug

- Record the date, subject number, the investigational medicinal product (IMP) number dispensed

- Record the date, quantity of used and unused IMP returned, along with the initials of the person recording the information

- Dispensing records will include the initials of the person dispensing the study drug or supplies

5.5.1. Investigational Medicinal Product Return or Disposal

Used and unused IMP supplies must be returned to the designated disposal facility for destruction. The study monitor will provide instructions for return. Drug destruction at the site is not allowed.

IMP may be returned on an ongoing basis during the study if appropriate. At the end of the study, following final IMP inventory reconciliation by the study monitor, the study site will return all unused IMP supplies, including empty containers, according to these procedures. Upon study completion, copies of the IMP accountability reports 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. The study monitor must first perform IMP accountability during an on-site monitoring visit.

6. STUDY PROCEDURES

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

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

6.1. Subject Enrollment and Treatment Assignment

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

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

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

6.2. Pretreatment Assessments

6.2.1. Screening Visit

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

- Obtain written informed consent

- Obtain demographics and medical history (including RA/PsA/AS/nrAxSpA history), prior number of children fathered, disease characteristics (relevant for disease classification and disease severity), smoking habits, average weekly alcohol consumption, and family history of premature coronary heart disease)

- Review Inclusion / Exclusion Criteria

- Complete physical examination (PE) as detailed in Appendix 12

- Vital signs, weight, and height

- Perform standard 12-Lead ECG

- QuantiFERON test and chest X-ray (CXR) (if applicable). QuantiFERON positive or negative results must not be repeated. An indeterminate result should be repeated once and the second result (if positive or negative) will be accepted. Two sequential indeterminate results constitute a screen failure. Subjects with previously treated TB or newly diagnosed latent TB during Screening require sponsor approval (See Inclusion Criterion #10 for details). Subjects who are diagnosed with latent TB at Screening must initiate an adequate course of prophylaxis according to local country guidelines for immunocompromised patients for a minimum of 4 weeks prior to randomization. Subject may initiate study drug dosing only after consultation with the Sponsor Medical Leader or designee. If a subject had a QuantiFERON test for the purposes of clinical care or Screening for another Galapagos- or Gilead-sponsored study within 60 days, the prior result may be used to assess eligibility with permission of Sponsor Medical Leader or designee.

- Chest X-ray

- Urinalysis, including a urine drug screen

- Obtain blood samples for:

  — Hematology and serum chemistry

  — Serology

  — Serum hsCRP

  — Endocrine tests: thyroid stimulating hormone (TSH), HbA1c

  — Sex hormones, including LH, FSH, inhibin B, and total testosterone to be collected between 07:00 – 11:00 in the morning if possible

- Review and collection of concomitant medications

- Record all SAEs and any AEs related to protocol-mandated procedures occurring after signing of the ICF

- Semen collection (2 separate collections in accordance with Section 6.11) and record date and time of last ejaculation prior to sample. Semen collection should be collected to coincide with Day 1 (Baseline visit) as much as possible.

- Disease Specific scales and questionnaires

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

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

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

Retesting of exclusionary parameters in Screening semen samples is discussed in Section 6.11.

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

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

6.2.1.1. Rescreening

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

6.2.2. Day 1 Assessments

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

- Review inclusion / exclusion Criteria

- Symptom-driven PE, as needed

- Vital signs (resting blood pressure, respiratory rate, pulse and temperature)

- Weight (without shoes)

- Obtain blood samples for:
  - Hematology and serum chemistry
  - Lipid profile (fasting) [total cholesterol and subfractions]
  - Serum hsCRP
  - Sex hormones, including LH, FSH, inhibin B, and total testosterone to be collected between 07:00 – 11:00 in the morning if possible
- Urinalysis
- Disease Specific scales and questionnaires
- Review concomitant medications
- Record any AEs related to protocol-mandated procedures and all SAEs occurring after signing of the consent form.

6.3. Randomization

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

Randomization will be stratified according to the type of rheumatic condition (RA or Spondylarthritis [PsA, AS, nrAxSpA]), concurrent use of MTX (yes or no) and sperm concentration measured at Screening ("Baseline") according to the following strata:

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

6.4. Double-blind Treatment Phase (Day 1 Through Week 13 Study Visit)

All subjects will receive blinded study drug until completion of all Week 13 assessments.

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

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

The end of the Double-Blind Treatment Phase is when the Week 13 semen results are available to the investigator and have been evaluated. Based on this evaluation, subjects are assigned to enter the Monitoring Phase or the Extension Phase.

6.5. Extension Phase

In the Extension Phase, subjects will receive open-label treatment (filgotinib or Standard of Care) and have a study visit every 13 weeks that includes semen analysis. The first scheduled visit of the Extension Phase occurs at Week 26.

In case sperm parameters at any visit (including Week 156) meet any of the pre-specified decrease thresholds, subjects will enter the Monitoring Phase.

During the Extension phase, Standard of Care and concomitant treatment may be optimized at the discretion of the investigator taking into consideration the protocol restrictions (see Section 5.3).

In case a subject needs to be treated with a prohibited medication to control their rheumatic condition (see Table 5-1), the subject will discontinue the study and complete an ET visit (including semen collection). For subjects on filgotinib, this will be followed by a safety follow-up visit 30 days after last study drug dose.

All subjects who did not enter the Monitoring Phase will continue the study until the Week 156 visit.

Subjects with newly positive (converted) QuantiFERON® [or centrally reported equivalent assay] TB test should be discontinued from study drug. Subjects who were previously treated for TB with a complete and adequate course of therapy as per local standard of care and as verified by the investigator do not need to have yearly QuantiFERON® tests. Subjects previously treated for TB should be screened at least yearly for signs and symptoms consistent with reactivation of TB. Any subject with active TB should be discontinued from the study.

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

6.6. Monitoring Phase

Subjects on filgotinib who enter the Monitoring Phase will discontinue study drug and start Standard of Care. Subjects on Standard of Care will continue treatment.

All subjects who enter the Monitoring Phase will undergo semen evaluations every 13 weeks starting from their entry into the Monitoring Phase, for up to 52 weeks or until Reversibility (see Definition of Terms) is met, whichever is achieved first.

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

6.7. Early Termination

Subjects who discontinue study participation for any reason prior to Week 156 in the Extension Phase, prior to reaching Reversibility or Week 52 in the Monitoring Phase (whichever occurs first) will complete an ET Visit. Subjects on blinded study drug or open-label filgotinib will also undergo a routine safety follow-up visit 30 days (±5 days) after the last dose of study drug.

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

All subjects will complete a safety follow-up visit 30 days after the last dose of study drug (blinded [filgotinib or placebo] or open-label [filgotinib]).

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

6.9. Safety and Tolerability

AEs, PE, vital signs, ECGs, and laboratory assessments (standard hematology, serum/plasma chemistry, and urinalysis) will be collected. Semen samples will be collected in accordance with Section 6.11.

6.9.1. Thromboembolic Events

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

6.10. Clinical Laboratory Evaluations

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

Blood samples will be collected by venipuncture in the arm at the time points indicated in the Study Procedures Table (Appendix 2). In addition, urine samples for the clinical laboratory assessments will be collected. Subjects only need to be fasted on days where lipid profiling is scheduled.

Please refer to Appendix 11 for table of clinical laboratory tests.

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

Note that in the case where clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting of the affected parameter(s) should be prompt (within 3 to 7 days) after the investigator has consulted with the Sponsor Medical Leader or designee. A decision regarding subject discontinuation should be made after the results from the retest are available (see Section 3.7 for additional information).

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

6.11. Semen Collection Procedure

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

- Screening (Baseline)
- After the Double-blind Treatment Phase (Week 13 study visit)
- Every 13 weeks during the Extension Phase
- Every 13 weeks during the Monitoring Phase
- At the Early Termination Visit

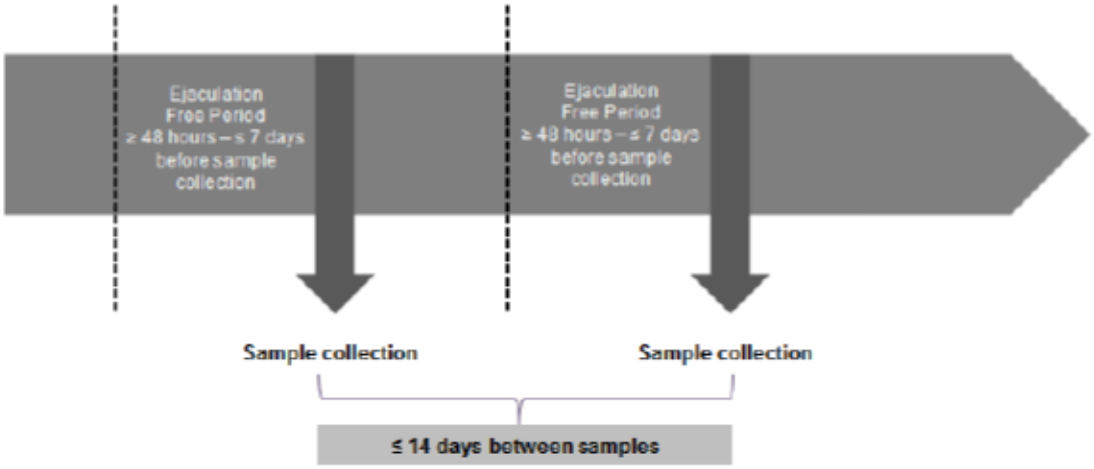
The 2 time-points for the semen sample collection will be scheduled in agreement with the investigator on the study visit day and/or as soon as possible after the visit day.

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

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

The results of the semen analysis will be evaluated and discussed with the subject and he will be informed about the appropriate next steps to be taken in the study.

Figure 6-1. Semen Collection Schema



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

6.12. Vital Signs

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

Vital signs should be taken after the subject has been resting for 5 minutes (please refer to Appendix 12 for details) and will include heart rate, respiratory rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body temperature.

6.13. Physical Examination

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

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

A complete PE, as detailed in Appendix 12, will be performed at Screening only. Symptom-directed physical exams should be performed at all other visits, as needed.

6.14. Pharmacokinetic Assessments

Blood samples for PK analysis will be collected at least 30 minutes post-study drug dosing at the Week 2 visit, anytime at the Week 4 visit, and prior to study drug dosing at the Week 13 and 26 (only for subjects on open-label filgotinib in the Extension Phase) visits. Subjects should be instructed not to take their study drug on these visit days (except for the Week 4 visit) and bring it with them to the clinic instead.

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

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

6.15. High Sensitivity Serum C-Reactive Protein

The subject's serum CRP will be measured using a hsCRP test at the time points indicated in the study activities table (Appendix 2).

Post-Baseline CRP results will be blinded up to and including Week 13 to the investigator until database lock.

6.16. 66/68-Joint Count (PsA) and 28-Joint Count (RA) (used for DAPSA and CDAI)

For subjects enrolled with PsA, the 66/68 joint count will be used to calculate the DAPSA score. For subjects enrolled with RA, the 28 joint count will be used to calculate the CDAI score.

Each of 66/28 joints will be evaluated for swelling (swollen joint count 66/28 joints [SJC66/SJC28]) and each of 68/28 joints will be evaluated for tenderness (tender joint count 68 /28 joints [TJC68/TJC28]) (Appendix 3) at time points described in the Study Procedures Table (Appendix 2).

The 68/28 tender joint count should be performed by scoring the presence or absence of tenderness as assessed by pressure and joint manipulation.

The 66/28 swollen joint count should be performed by scoring the presence or absence of synovial fluid and/or soft tissue swelling (but not bony overgrowth) as assessed by pressure and joint manipulation.

6.17. Physician Global Assessment of Disease Activity (PhGADA)

Global assessment of the subject's disease activity will be performed by drawing a perpendicular line on the visual analogue scale (VAS), and measuring the distance between the "no disease activity" anchor and the mark on the 10-cm line in mm.

The PhGADA will be recorded at the time points indicated in the Study Procedures Table (Appendix 2) and is provided in Appendix 4.

6.18. Patient Global Assessment of Disease Activity (PtGADA) (used for CDAI and DAPSA)

For subjects with RA and PsA, the patient's global assessment of their arthritis disease activity will be recorded on a 0 to 100 mm VAS. A perpendicular line will be drawn on the VAS, and with a ruler, the distance between the beginning of the line and the mark on the 10-cm line in mm will be the score from 0-100. A score of 0 indicates "very well" and 100 indicates "very poor" to the question "Considering all the ways psoriatic arthritis affects you, please draw a

vertical mark (|) on the horizontal line below for how well you have been doing over the last week.

The PtGADA will be recorded at the time points indicated in the Study Procedures Table (Appendix 2) and is provided Appendix 5.

6.19. Patient's Global Assessment of Pain Intensity (PPAIN) (used for DAPSA)

For subjects with PsA, the patient's assessment of pain is a set of 2 questions on pain on the numerical rating scale.

The Patient's Global Assessment of Pain Intensity as related to arthritis will be recorded at the time points indicated in the Study Procedures Table (Appendix 2) and is provided in Appendix 6.

6.20. BASDAI

For subjects with AS or nrAxSpA, the patient-reported arthritis activity will be measured at Screening using BASDAI. This is a 6-item index (fatigue, spinal pain, peripheral arthritis, enthesitis, intensity and duration of morning stiffness) in which the items will be recorded on a 0 to 10 numerical rating scale. The total score will range from 0-10.

The BASDAI will be assessed at the time points indicated in the Study Procedures Table (Appendix 2) and is provided in Appendix 7.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing 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 (e.g. hospitalization for elective surgery, social and/or convenience admissions)

- Overdose without clinical sequelae (see Section 7.7.1)

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

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

- Death

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

- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity

- A congenital anomaly/birth defect

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

7.2. Assessment of Adverse Events and Serious Adverse Events

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

7.2.1. Assessment of Causality for Study Drugs and Procedures

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

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

Yes: There is reasonable possibility that the event may have been caused by the IMP.

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 9.

Table 7-1. Grading of Adverse Event Severity

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

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

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

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study drug, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and AEs related to protocol-mandated procedures. All SAE's should also be reported via the paper SAE forms.

Adverse Events

Following initiation of study drug, collect all AEs, regardless of cause or relationship, until the last study visit must be reported to the CRF/eCRF database as instructed.

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

Serious Adverse Events

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

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

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

All AEs and SAEs will be recorded in the CRF/eCRF database and all SAE's should also be reported via the paper SAE form within the timelines outlined in the CRF/eCRF completion guideline.

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

Serious Adverse Event Paper Reporting Process

In case of a serious adverse event (SAE) the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the SAE to:

E-mail: CCI [redacted]

or

CCI Medical Affairs SAE Fax #: CCI [redacted]

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

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

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

After the last Study Drug intake, and for all patients under Standard of Care, the investigator is highly encouraged to report any AE/SAE considered as related to the Standard of Care medication directly to the marketing authorization holder and/or its National Competent Authority.

In order to avoid duplication in the reporting of such events, the Sponsor will not report these events simultaneously.

7.4. Sponsor Reporting Requirements

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

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

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

7.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments

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

Severity should be recorded and graded according to the CTCAE.

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

7.6. Toxicity Management

All clinical and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 14 and as outlined below.

Refer to Section 3.7, Criteria for Study Drug Interruption or Discontinuation, for additional specific discontinuation criteria. Specific toxicity discontinuation criteria in Section 3.7 supersede below general toxicity guidelines, and in general, where discrepancy is present, the more conservative criteria apply. The Sponsor Medical Leader or designee should be consulted prior to study drug discontinuation when medically feasible.

7.6.1. Grades 1 and 2 Laboratory Abnormality or Clinical Event

Continue study drug at the discretion of the investigator.

- For study specific interruption and stopping criteria, please refer to Section 3.7 (Criteria for Interruption or Discontinuation of Study Treatment)
- For Grades 1 and 2 Laboratory Abnormality or Clinical Event not specified in Section 3.7, continue study drug at the discretion of the investigator.

7.6.2. Grades 3 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.7 (Criteria for Interruption or Discontinuation of Study Treatment)
- For Grades 3 Laboratory Abnormality or Clinical Event not specified in Section 3.7, the following toxicity management guidelines apply:

- For 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 clinical practice. Recurrence of laboratory abnormalities considered unrelated to IMP may not require permanent discontinuation.

7.6.3. Grades 4 Laboratory Abnormality or Clinical Event

- For study specific interruption and stopping criteria, please refer to Section 3.7 (Criteria for Interruption or Discontinuation of Study Treatment).

- For Grade 4 Laboratory Abnormality or Clinical Events not specified in Section 3.7, the following toxicity management guidelines apply:

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

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

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

Any questions regarding toxicity management should be directed to the Sponsor Medical Leader or designee.

7.7. Special Situations Reports

7.7.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, product complaints, occupational exposure, drug interactions, unexpected benefit, transmission of

infectious agents via the product, counterfeit or falsified medicine, exposure via breastfeeding, and partner pregnancy reports regardless of an associated AE.

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

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

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

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

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

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

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

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

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

Counterfeit or falsified medicine: Any 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 Partner Pregnancies

Pregnancies of female partners of male study subjects exposed to study drug must be reported until 90 days after the last study drug intake and relevant information should be submitted to the Sponsor using the pregnancy and pregnancy outcome forms within 24 hours. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to:

E-mail: CCI [redacted]

or

CCI Medical Affairs SAE Fax #: CCI [redacted]

After 90 days from the last Study Drug intake, and if the patient is under Standard of Care treatment, the investigator is highly encouraged to report any Pregnancy considered as related to this Standard of Care treatment directly to the marketing authorization holder and/or its National Competent Authority.

In order to avoid duplication in the reporting of such events, the sponsor will not report these Pregnancies simultaneously.

Refer to Appendix 10 for Pregnancy Precautions, Definition of Females of Childbearing Potential and Contraceptive Requirements.

7.7.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to the Sponsor within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP.

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

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

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

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

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective of this study is:

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

The secondary objectives of this study include:

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

The exploratory objectives of this study include:

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

8.1.2. Primary Endpoint

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

8.1.3. Secondary Endpoints

The secondary endpoints are:

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

- Change from Baseline in ejaculate volume at Weeks 13 and 26
- Change from Baseline in percent normal sperm morphology at Weeks 13 and 26

8.1.4. Exploratory Endpoints

The exploratory endpoints are:

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

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. All Randomized Set

The All Randomized Set includes all subjects who were randomized.

8.2.1.2. Semen Analysis Set

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

8.2.1.3. Safety Analysis Set

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

8.2.1.4. Pharmacokinetic Analysis Set

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

8.3. Data Handling Conventions

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

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

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

8.4. Demographic Data and Baseline Characteristics

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

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

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

8.5. Statistical Analysis

8.5.1. Primary Analysis

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

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

8.5.2. Secondary Analyses

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

The continuous endpoints will be summarized (n, mean, SD, median, Q1, Q3, minimum, and maximum) by treatment group at Weeks 13 and 26 along with corresponding change from Baseline and 95% CIs. All categorical endpoints will be summarized by the number and percentage of subjects who meet the endpoint definition.

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

8.5.3. Exploratory Analyses

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

8.5.4. Other Safety Analysis

All other safety analyses will be performed using the Safety Analysis Set.

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

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

8.5.5. Extent of Exposure

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

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

8.5.6. Adverse Events

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

TEAEs are:

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

- Any AEs leading to premature discontinuation of study drug.

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

8.5.7. Laboratory Evaluations

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

Graded laboratory abnormalities will be defined using CTCAE 4.03 grading scale in Appendix 9.

8.6. Pharmacokinetic Analysis

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

Exposure-response analyses may be performed.

8.7. Sample Size

A sample size of approximately 100 evaluable subjects per group, where evaluable is defined as subjects in the Semen Analysis Set, is adequate for the purposes of estimating cumulative distribution curves and producing a 95% CI width that is reasonably narrow for the percentage of subjects in each group who experience a ≥50% decrease in sperm concentration compared to Baseline. This sample size is suggested in FDA Guidance on Testicular Toxicity (October 2018). Assuming a 20% rate of non-evaluable subjects at Week 13, up to 125 subjects per arm may be enrolled.

Results of this study may be pooled with the results of a separate study being conducted in subjects with IBD (Protocol GS-US-418-4279) with the same objective. The total planned number of subjects in both studies combined will be up to approximately 250 subjects.

8.8. Data Monitoring Committee/Sponsor Safety Management Team

An external DMC will review the progress of the study and perform interim reviews of safety data and provide recommendation to the Sponsor whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the participants, whether the study should continue as planned, or the study should continue with modifications. The initial meeting is planned to occur after approximately the first 50 subjects reach Week 13. Following this, subsequent meetings will occur

approximately every 4 months (if enrollment supports the need). Additional DMC meetings may be scheduled as needed.

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

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

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

- ≥2 subjects develop the same (by preferred term) related, Grade 4, unexpected AE in the infections and infestations System Organ Class;
- ≥2 subjects develop any related, Grade 4, thromboembolic event that has been positively adjudicated by the adjudication committee (see Section 8.9);
- any subject develops a Grade 5, related, unexpected AE. The definition of an unexpected AE will be based on the Reference Safety Information that is on file at the time the event occurs.

The DMC has monitored the study until the date of protocol amendment 2, including the data for IA2. As of amendment 2, the DMC will be decommissioned. The safety and progress of the remainder of the study will continue to be monitored by the Sponsor Medical Leader and Medical Monitor, or designee, providing updates during regular Sponsor medical monitoring oversight meetings across the filgotinib program. If needed, safety issues will be escalated to the SSMT per internal standard procedures, including the organization of ad hoc meetings if required. The SSMT can consult external experts, if deemed necessary, and can review data in an unblinded fashion.

8.9. Cardiovascular Safety Endpoint Adjudication Committee (CVEAC)

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

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

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

- Cardiovascular death
- Myocardial infarction
- Stroke

- Arterial thromboembolism
- Venous thromboembolism (eg, deep venous thrombosis, pulmonary embolism)

Further details will be specified in the CVEAC Charter.

8.10. Internal Independent Safety Review

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

As of amendment 2, the Internal Independent Safety Review Team will be decommissioned. Safety reviews will be covered by the SSMT.

8.11. Unblinded Interim Analysis

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

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

8.12. Integrated Semen Analysis

As part of the male safety assessment of filgotinib, integrated analyses may be performed in which data from the present study, will be combined with similar data from a separate study GS-US-418-4279 being conducted in males with inflammatory bowel disease. The analyses will

be conducted primarily to evaluate the testicular safety. Further details of the integrated analysis will be described in the Integrated Semen and Hormone SAP.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonization (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. IRB/IEC Review and Approval

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

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

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

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The

investigator must use the most current IRB/IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject and the person conducting the consent discussion, and also by an impartial witness if required by IRB/ IEC or local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB/IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a Screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the study. 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 investigator brochure, this protocol, CRF/eCRF, the IMP, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

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

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

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

- Subject identification (name, date of birth, gender)
- Documentation that subject meets eligibility criteria, ie, history, 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, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with the sponsor. The investigator must notify the sponsor before destroying any clinical study records.

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

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

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. 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 system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately

reflect the information in the source documents. The eCRF captures the data required per the protocol Study Procedures Table (Appendix 2). System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal sponsor 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 study, the sponsor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Inspections

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

9.1.8. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

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

9.2.2. Study Report and Publications

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

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

- The results of the study in their entirety have been publicly disclosed by or with the consent of the sponsor in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years
- The investigator will submit to the sponsor any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

- No such communication, presentation, or publication will include the sponsor's confidential information (see Section 9.1.4).

- The investigator will comply with the sponsor's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

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

9.3.2. Access to Information for Monitoring

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

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

9.3.3. Access to Information for Auditing or Inspections

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

9.3.4. Study Discontinuation

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

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11. APPENDICES

Appendix 1. Sponsor and Investigator Signature Page

GALAPAGOS NV GENERAAL DE WITTELAAN L11 A3 2800 MECHELEN, BELGIUM

STUDY ACKNOWLEDGEMENT

A Randomized, Double-blind, Placebo-controlled Phase 2 Study to Evaluate the Effect of Filgotinib on Semen Parameters in Adult Males with active Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis or Non-radiographic Axial Spondyloarthritis

Amendment 2, Final 09 Sep 2022

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

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

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

Signature

Date

INVESTIGATOR STATEMENT

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

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by the sponsor. 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 – Double-blind Treatment Phase (Section 6.4)

EVENT								Safety follow-up[c]
Study days (D)/weeks (W)[a]	Screening	Day 1	W2 (±5 days)	W4 (±5 days)	W8 (±5 days)	W13** (+5 days)	ET[b]	30 Days after last dose of study drug (±5 days)
Informed Consent	X							
Demographics and Medical History(Disease Characteristics, RA/PsA/AS/nrAxSpA History, Number of Children Fathered, Smoking Habits, Average Weekly Alcohol Consumption, and Family History of Coronary Heart Disease)	X							
Inclusion/exclusion criteria review	X	X						
Complete Physical Exam[c]	X						X	X
Symptom-directed Physical Exam, as needed		X	X	X	X	X		
Vital Signs[c] and Weight	X	X	X	X	X	X	X	X
Height	X							
12-lead ECG	X					X	X	
Tender Joint Count 28 (TJC28) (for RA subjects only)	X							
Swollen Joint Count 28 (SJC28) (for RA subjects only)	X							
Tender Joint Count 68 (TJC68) (for PsA subjects only)	X							
Swollen Joint Count 66 (SJC66) (for PsA subjects only)	X							

EVENT								Safety follow-up[c]
Study days (D)/weeks (W)[a]	Screening	Day 1	W2 (±5 days)	W4 (±5 days)	W8 (±5 days)	W13** (+5 days)	ET[b]	30 Days after last dose of study drug (±5 days)
Patient Global Assessment of Disease Activity (PtGADA) (for RA and PsA subjects only)	X							
Physician's Global Assessment of Disease Activity (PhGADA)[d] (for all subjects)	X	X				X		
Patient's Global Assessment of Pain Intensity (PPain) (for PsA subjects only)	X							
Bath Ankylosing Spondyloarthritis Disease Activity Index (BASDAI) (for AS/nrAXSpA subjects only)	X							
TB (Quantiferon ®)Test[e]	X							
Chest X-ray[f]	X							
Urinalysis[g]	X	X				X	X	X
Urine drug screen[g]	X							
Hematology and Serum Chemistry[g]	X	X	X	X	X	X	X	X
Lipid profile (fasting) (Total cholesterol and subfractions)[g]		X				X		
Serum hsCRP	X	X	X	X	X	X		
Endocrine: TSH, HbA1c[g]	X							

EVENT								Safety follow-up[c]
Study days (D)/weeks (W)[a]	Screening	Day 1	W2 (±5 days)	W4 (±5 days)	W8 (±5 days)	W13** (+5 days)	ET[b]	30 Days after last dose of study drug (±5 days)
LH, FSH, inhibin B, total Testosterone collection time between 07:00-11:00 in the morning[g]	X	X		X		X	X	X
PK collection (sparse)[h]			X	X		X		
Concomitant Medications	X	X	X	X	X	X	X	X
Assessment of Adverse Events	X	X	X	X	X	X	X	X
Semen Collection (2 samples as per collection instructions in Section 6.11)[i]	X					X	X[j]	
Date and time of most recent ejaculation[k]	X					X	X	
HIV, Hepatitis B, and Hepatitis C[l]	X							
HBV DNA[l, m]						X		
Randomization		X						

EVENT								Safety follow-up[c]
Study days (D)/weeks (W)[a]	Screening	Day 1	W2 (±5 days)	W4 (±5 days)	W8 (±5 days)	W13** (+5 days)	ET[b]	30 Days after last dose of study drug (±5 days)
Study Drug Accountability				X	X	X	X	
Study Drug Dispensation[n]		X		X	X	X[o]		
In-clinic Dosing[n]		X	X			X		

a Visits correlate with the number of days/weeks on drug.
b Any time a subject discontinues participation in the study prior to Week 13 an Early Termination (ET) Visit is required. Subjects who are Responders at Week 13 and choose not to continue in the Extension Phase are also required to complete ET visit assessments.
c All subjects will have a 30-day safety follow-up visit after discontinuing blinded study drug, except Arthritis Responders at Week 13 who are continuing in the Extension Phase of the study.
c As detailed in Appendix 12.
d For definitions of Arthritis Responder/Non-responder status please refer to Definition of Terms.
e Proof of no active or untreated latent tuberculosis (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 Sponsor Medical Leader or designee.
f 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.
g As detailed in Appendix 11. For visits that require fasting, subjects should not have any food or drink (except water) for at least 8 hours before the visit.
h Sparse plasma pharmacokinetic (PK) samples at Week 2 are collected at 30 minutes post dose. The PK sample at Week 4 can be collected at any time without regard to dosing. The PK sample at Week 13 is collected prior to study drug administration. Please refer to Section 6.14 for details on study drug administration.
i The Screening semen sample collection should coincide with the Day 1 (Baseline) visit as much as possible. Semen samples will be collected on the visit day and/or as soon as possible after the visit day.
j Semen collection will be completed at ET visit only if previous semen samples were not collected within 2 weeks of ET.
k This question will be asked prior to each semen collection.
l An HIV-1/HIV-2 antigen/antibody test, a Hepatitis C virus antibody test, a Hepatitis B surface antigen, a Hepatitis B surface antibody and a Hepatitis core antibody test will be conducted on all subjects; Subjects with positive Hepatitis B surface antigen (HBsAg) at Screening are excluded from the study. Subjects with positive HBV core Ab and negative HBsAg, require reflex testing for HBV DNA. Subjects with positive HBV DNA at Screening will be excluded. Subjects with positive HBV core Ab and negative HBV DNA are eligible per investigator judgment, but may require prophylactic treatment in accordance with HBV treatment guidelines/local standard of care and require ongoing monitoring with blood tests for HBV DNA every 3 months. Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol. Subjects with positive HCV antibody (Ab) at Screening, require reflex testing for HCV RNA. Subjects with positive HCV RNA at Screening will be excluded. Subjects with positive HCV Ab, but negative HCV RNA are eligible per investigator judgment.
m Subjects with positive HBV core Ab and negative HBV DNA at Screening require ongoing monitoring with blood tests for HBV DNA every 3 months.
n The subject will take the first dose (Day 1) in the clinical study center. For PK collection purposes, at Weeks 2 and 13, subjects should be instructed not to take their study drug, but rather to bring it with them to the clinic. Subjects will be instructed to take their dose during their scheduled visit, as detailed in Section 6.14.
o Only for subjects continuing on open-label filgotinib in the Extension Phase.
** Week 13 visit must occur after 13 weeks of drug exposure. Therefore, visit window for this visit is +5 days. The end of the Double-Blind Treatment Phase is when the Week 13 semen results are available to the investigator and have been evaluated. Based on this evaluation, subjects are assigned to enter the Monitoring Phase or the Extension Phase.

Monitoring Phase (Section 6.6)

EVENT	Monitoring Phase (±5 days)	ET
Study days (D)/weeks (W)	Visits occur every 13 weeks starting from their entry into the Monitoring Phase (for up to 52 weeks or until Reversibility is met, whichever is sooner)	
Symptom-directed Physical Exam, as needed	X	X
Vital Signs[a] and Weight	X	X
Urinalysis[a]	X	X
Hematology and Chemistry[a]	X	X
Serum hsCRP	X	
LH, FSH, inhibin B, total Testosterone[a] collection time between 07:00-11:00 in the morning	X	X
Concomitant Medications	X	X
Assessment of Adverse Events[b]	X	X
Semen Collection[c] (2 samples as per collection instructions in Section 6.11)	X	X[e]
Date and time of most recent ejaculation[d]	X	

a As detailed in Appendix 12.
b As detailed in Section 7.3.
c Semen samples will be collected every 13 weeks from the day of study drug discontinuation, for up to 52 weeks or until Reversibility is met, whichever is achieved sooner. Reversibility is met when all sperm parameter(s) qualifying the subject to enter the Monitoring Phase return(s) to greater than 50% of Baseline (ie, to greater than [0.50 x Baseline]).
d This question will be asked prior to semen collection not at the site visit.
e Semen collection will be completed at ET visit only if previous semen samples were not collected within 2 weeks of ET.

Extension Phase (Section 6.5)

EVENT	Extension Phase		Safety follow-up
Study days (D)/weeks (W)	Week 26 up to 156 weeks[a] (±10 days)	ET[b]	30 Days after last dose of study drug (±5 days)
Symptom-directed Physical Exam, as needed	X	X	X
Vital Signs and Weight	X	X	X
TB QuantiFERON[c]	X		
Urinalysis[d]	X	X	X
Hematology and Chemistry[d]	X	X	X
Lipid profile (fasting) [Total cholesterol and subfractions][d,e]	X		
Serum hsCRP	X		
LH, FSH, inhibin B, total Testosterone[d] collection time between 07:00-11:00 in the morning	X		
Concomitant Medications	X	X	X
Assessment of Adverse Events	X	X	X
Semen Collection (2 samples as per collection instructions in Section 6.11)	X	X[l]	
Date and time of most recent ejaculation[f]	X		
Study Drug Accountability[g]	X	X	
Study Drug Dispensation[g]	X		
12-lead ECG[h]	X	X	
PK collection (sparse)	X[i]		
HBV DNA[j,k]	X		
In-clinic dosing	X (Week 26)		

a Subjects in the Extension Phase (EP) will complete EP Week 26 visit and every 13 weeks thereafter up to 156 weeks.

b Any time a subject discontinues participation in the study prior to Week 156 in the Extension Phase, an Early Termination (ET) Visit is required.

c In the EP subjects must have yearly QuantiFERON testing. Yearly TB testing begins 1 year from the screening TB test date. If yearly TB testing falls between study visits, the yearly TB testing should be performed at the visit prior to 1 year from the screening TB test date. Subjects with newly positive (converted) QuantiFERON® [or centrally reported equivalent assay] TB test should be discontinued from study drug. Subjects who were previously treated for TB with a complete and adequate course of therapy as per local Standard of Care and as verified by the investigator do not need to have yearly QuantiFERON® tests. Subjects previously treated for TB should be screened at least yearly for signs and symptoms consistent with reactivation of TB. Any subject with active TB should be discontinued from study.

d As detailed in Appendix 12. For visits that require fasting, subjects should not have any food or drink (except water) for at least 8 hours before the visit.

e Lipid profile should be performed at Weeks 26, 39, 65, 91, 117 and 143.

f This question will be asked prior to semen collection not at the site visit.

g Only applicable for subjects on filgotinib.

h ECG will be performed at Week 156 or ET (for subjects on open-label filgotinib only).

i A sparse plasma PK sample is collected at Week 26 prior to study drug administration (for subjects on open label filgotinib only). Please refer to Section 6.14 for details on study drug administration.

j An HIV-1/HIV-2 antigen/antibody test, a Hepatitis C virus antibody test, a Hepatitis B surface antigen, a Hepatitis B surface antibody and a Hepatitis core antibody test will be conducted on all subjects; Subjects with evidence of active Hepatitis B during the study, as evidenced by HBV DNA positivity, will be discontinued from study drug as outlined in the protocol.

k Subjects with positive HBV core Ab and negative HBV DNA at Screening require ongoing monitoring with blood tests for HBV DNA every 3 months.

l Semen collection will be completed at ET visit only if previous semen samples were not collected within 2 weeks of ET.

Appendix 3.66/68-joint Count (SJC66/TJC68)

An overview of the joints to be assessed is provided below (subject's left and right):

- Temporomandibular
- Sternoclavicular
- Acromioclavicular
- Shoulder (*)
- Elbow (*)
- Wrist (*)
- Metacarpophalangeal: first, second, third, fourth, fifth (*)
- Proximal interphalangeal: first, second, third, fourth, fifth (*)
- Distal interphalangeal: second, third, fourth, fifth
- Hip (assessed for tenderness only, not included in SJC)
- Knee (*)
- Ankle
- Tarsus
- Metatarsophalangeal: first, second, third, fourth, fifth
- Proximal interphalangeal: first, second, third, fourth, fifth

Replaced (or otherwise not assessable) joints should be documented at Screening and omitted from further evaluation during the study. Parenteral corticosteroids are not routinely permitted during the study; if the subject requires a joint injection for AE of arthritis flare, the injected joint should be marked as "non-assessable" for the remainder of the study.

Joints flagged with an (*) are used in the 28-joint counts (TJC28/SJC28).

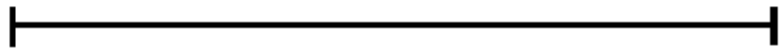
Note: The TJC68/TJC28 and SJC66/SJC28 are used to derive the DAPSA and CDAI.

Appendix 4.Physician's Global Assessment of Disease Activity (PhGADA)

The PhGADA will be recorded on a 0-100 mm VAS, with 0 indicating "no disease activity" and 100 indicating "extreme disease activity" as relates to the subject's arthritis. The evaluating physician and the subject should complete the global assessments independently of each other, as much as possible.

Instructions are provided below.

Considering all the ways arthritis affects your patient, draw a line on the scale for how well his or her condition is today.



0 100

No Disease Activity Extreme Disease Activity

Note: The VAS scale must be 100 mm long.

Appendix 5.Patient's Global Assessment of Disease Activity (PtGADA)

In RA and PsA, the PtGADA will be recorded on a 0-100 mm VAS, with 0 indicating "very well" and 100 indicating "very poor". The evaluating physician and the subject should complete the global assessments independently of each other.

Instructions:

Considering all the ways arthritis affects you, please draw a vertical mark (|) on the horizontal line below for how well you have been doing over the last week.

0 100

Very Well Very Poor

Note: The VAS scale must be 100 mm long.

Note: The PtGADA is part of the DAPSA and CDAI.

– Source: ASAS Handbook (Sieper, et al., 2009)

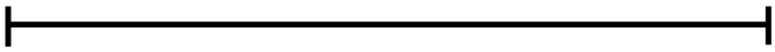
Appendix 6.Patient's Global Assessment of Pain Intensity

In PsA: (PPain)

The Patient's Global Assessment of Pain Intensity will be recorded on a 0-100 mm VAS, with 0 indicating "no pain" and 100 indicating "unbearable pain".

Instructions:

Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your arthritis over the last week.



0 100

No pain Unbearable pain

Note: the VAS scale must be 100 mm long.

Patient pain assessment will be used to calculate the DAPSA score: DAPSA = TJC68 + SJC66 + PtGADA (cm) + PPain (cm) + CRP (mg/dL).

– Source: ASAS Handbook (Sieper, et al., 2009; Schoels, et al., 2010)

Appendix 7.Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please tick the box which represents your answer.
All questions refer to the last week.

1. FATIGUE

How would you describe the overall level of fatigue/tiredness you have experienced?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

2. SPINAL PAIN

How would you describe the overall level of AS neck, back or hip pain you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

3. PERIPHERAL ARTHRITIS

How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

4. ENTHESITIS

How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

5. INTENSITY OF MORNING STIFFNESS

How would you describe the overall level of morning stiffness you have had from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

None Very severe

6. DURATION OF MORNING STIFFNESS

How long does your morning stiffness last from the time you wake up?

0	1	2	3	4	5	6	7	8	9	10

0 h 1 h 2 or more h

– Source: ASAS Handbook (Sieper, et al., 2009)

Note: The BASDAI is part of the ASAS Core Set. The total score is calculated as follows:

$$BASDAI = \frac{\left[Q1 + Q2 + Q3 + Q4 + \frac{(Q5 + Q6)}{2}\right]}{5}$$

Appendix 8.Disease Specific Classification Criteria

The 2010 American College of Rheumatology –European League Against Rheumatism Collaborative Initiative Classification Criteria for Rheumatoid Arthritis

Target population (Who should be tested?): Patients who have at least 1 joint with definite clinical synovitis (swelling)[a] with the synovitis not better explained by another disease[b]	
Classification criteria for RA (score-based algorithm: add score of categories A - D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)[c]	
A. Joint involvement[d]	
1 large joint[e]	0
2-10 large joints	1
1-3 small joints (with or without involvement of large joints)[f]	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)[g]	5
B. Serology (at least 1 test result is needed for classification)[h]	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)[i]	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms[j]	
<6 weeks	0
≥6 weeks 1	≥6 weeks 1

a The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

b Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

c Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

d Joint involvement refers to any *swollen* or *tender* joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are *excluded from assessment*. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

e "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

f "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

g In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular).

h Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF.

ACPA = anti-citrullinated protein antibody.

i Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

j Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (eg, pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

CASPAR Classification Criteria for Psoriatic Arthritis

The classification of PsA based on the CASPAR criteria requires the presence of established inflammatory arthritis (joints, spine, or enthuses) with at least 3 points from the following 5 features:

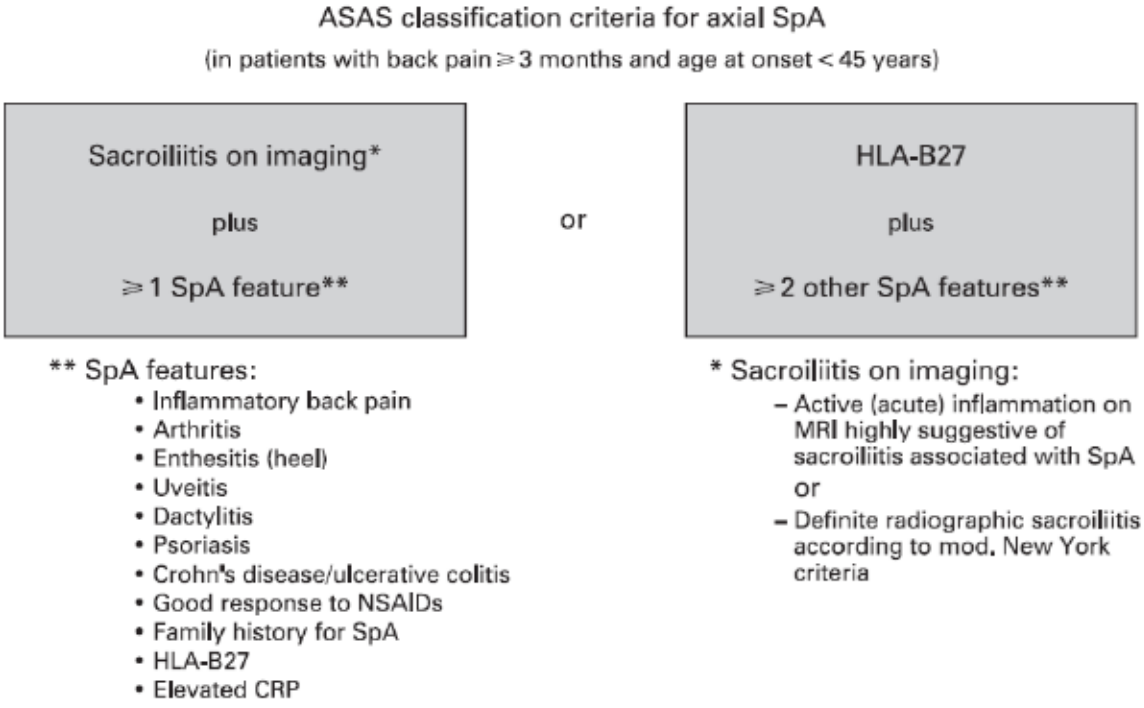
- Current psoriasis, OR

  A history of psoriasis, OR

  A family history of psoriasis
- Current or prior history of dactylitis
- Radiographic evidence of juxta-articular new-bone formation
- Absence of serum rheumatoid factor
- Nail dystrophy

Current psoriasis is assigned 2 points, while all other clinical features are assigned 1 point

ASAS Classification Criteria for Axial SpA



The classification of AS based on the modified New York criteria requires one of the following clinical criteria AND one of the radiological criteria.

Clinical Criteria

Low back pain ≥3 months, improved by exercise and not relieved by rest

Limitation of lumbar spine in sagittal and frontal planes

Limitation of chest expansion (relative to normal values corrected for age and sex)

Radiological criteria

Bilateral grade 2-4 sacroiliitis OR

Unilateral grade 3-4 sacroiliitis

Appendix 9.CTCAE Grading Scale for Severity of Adverse Events

Please refer to the 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 10. 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, men must agree to use condoms during the study and for 90 days after the last dose of study drug. Female sexual partners of childbearing potential, defined below, should also consider use of highly effective contraception as outlined below.

1) Definitions

a) Definition of Childbearing Potential (for Female Sexual Partners of Male Subjects)

For the purposes of this study, a female-born partner is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

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

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

b) Definition of Male Fertility

For the purposes of this study, a male-born subject is considered fertile after the initiation of puberty unless permanently sterilized by bilateral orchidectomy or has medical documentation of permanent male infertility.

2) Contraception for Female Sexual Partners of Male Subjects

1. Study Drug Effects on Pregnancy and Hormonal Contraception

Filgotinib is contraindicated in pregnancy as there is a possibility of human teratogenicity/fetotoxicity in early pregnancy based on non-clinical data. Data from a drug-drug interaction study of filgotinib and hormonal contraceptives (GS-US-417-3916) have demonstrated co-administration with filgotinib did not alter the pharmacokinetics of representative hormonal contraceptives (levonorgestrel/ethinyl estradiol). For male subjects, male condom should be used; for their female partners of childbearing potential an accepted contraceptive method should also be considered. Details are outlined below.

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

2. Contraception for Female Sexual Partners of Childbearing Potential

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

Contraceptive Methods include:

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

OR

Consistent and correct use of 1 of the following methods of birth control listed below.

Intrauterine device (IUD) with a failure rate of <1% per year

Tubal sterilization

Essure micro-insert system (provided confirmation of success 3 months after procedure)

Hormonal methods (each method *must* be used with a condom in the male partner)

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

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

3) Contraception for Male Subjects

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

4) Unacceptable Birth Control Methods

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

5) Procedures to be Followed in the Event of Pregnancy in a Female Sexual Partner

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

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

Appendix 11. Clinical Laboratory Assessment Table

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

Appendix 12. Procedures and Specifications

Complete Physical Examination

A complete PE should include source documentation of general appearance, and the following body systems: Head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; and neurological.

Vital Signs

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

Blood pressure should be measured using the following standardized process:

Subject should be resting for ≥ 5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level;

Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery;

Measure and record the blood pressure to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device.

Creatinine Clearance

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

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

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

12-Lead ECG

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

The investigator (or qualified designee) should review the ECG traces (including heart rate, PR-interval, QRS-interval, QT-interval) recorded in real time for clinically significant abnormalities.

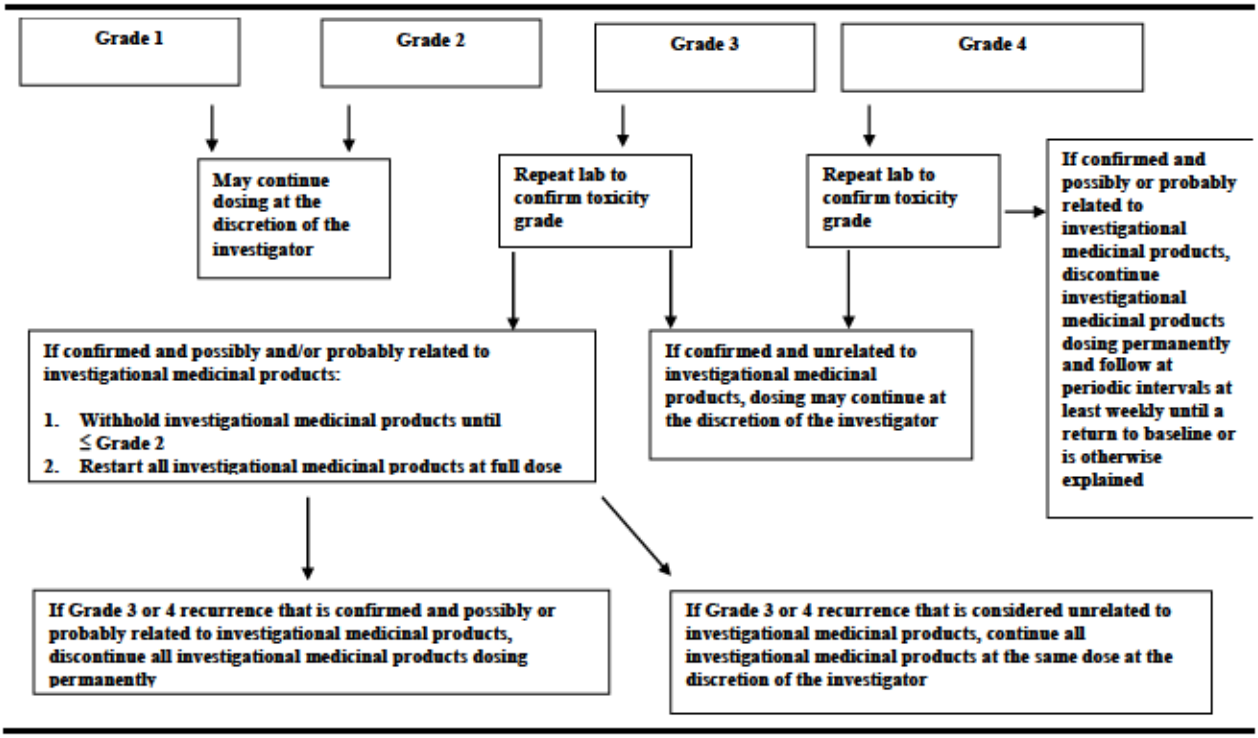
Appendix 13. Prednisone Conversion Table

The following table will be used for converting non-prednisone medications to prednisone equivalent:

*Example: Patient is taking 8 mg of Methylprednisolone orally daily. To get the equivalent dose of prednisone: 8 mg Methylprednisolone = (5*8)/ 4 = 10 mg prednisone.*

Corticosteroids Name	Equivalent Dose (mg) to 5 mg Prednisone
Betamethasone	0.75
Betamethasone Dipropionate	0.75
Betamethasone Sodium Phosphate	0.75
Cortisone	20
Dexamethasone	0.75
Dexamethasone Palmitate	0.75
Dexamethasone Phosphate	0.75
Dexamethasone Sodium Phosphate	0.75
Hydrocortisone	20
Meprednisone	4
Methylprednisolone	4
Methylprednisolone Acetate	4
Methylprednisolone Sodium Succinate	4
Prednisone	5
Prednisolone	5
Prednisolone Farnesylate	5
Prednisolone Sodium Succinate	5
Triamcinolone	4

Appendix 14. Management of Clinical and Laboratory Adverse Events



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