Clinical trial results:
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

Summary

EudraCT number	2018-003933-14
Trial protocol	LV EE BG BE CZ ES
Global end of trial date	

Results information

Result version number	v2
This version publication date	09 September 2023
First version publication date	11 June 2023
Version creation reason	• Correction of full data set Update to provide unblinded safety data

Trial information

Trial identification

Sponsor protocol code	GLPG0634-CL-227

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03926195
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Galapagos NV
Sponsor organisation address	Generaal De Wittelaan L11 A3, Mechelen, Belgium, 2800
Public contact	Galapagos Medical Information, Galapagos NV, medicalinfo@glpg.com
Scientific contact	Galapagos Medical Information, Galapagos NV, medicalinfo@glpg.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	29 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

This clinical study was conducted in accordance with the ethical principles that have their origin in the "Declaration of Helsinki" and its amendments in force at the time of the clinical study (2013-version). It was also carried out in conformity with the protocol, the International Council for Harmonisation for Good Clinical Practice (ICH-GCP) Guideline E6 (R2), and local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 13
Country: Number of subjects enrolled	Czechia: 23
Country: Number of subjects enrolled	Estonia: 6
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Georgia: 4
Country: Number of subjects enrolled	Ukraine: 23
Worldwide total number of subjects	109
EEA total number of subjects	82

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	109
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Bulgaria, Czech Republic, Estonia, Georgia, Latvia, Poland, Spain, and Ukraine. The first participant was screened on 28 May 2019. A total of 308 participants were screened of which 109 participants were randomized into the study.

Pre-assignment

Screening details:

There are 3 distinct parts to the study: 1) Double-Blind Treatment Phase (DB Phase; Day 1 through Week 13 study visit); 2) Extension Phase (EXT Phase; after Week 13 study visit & up to Week 156); & 3) Monitoring Phase (up to 52 weeks). The study is ongoing. Results based on data cut-off date 30 September 2021 (up to Week 26 analysis) are reported.

Period 1

Period 1 title	DB Treatment Phase (Through Week 13)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Filgonitib

Arm description:

Participants received filgotinib 200 milligrams (mg) tablet, orally, once daily up to Week 13 in the double-blind (DB) phase. At Week 13, participants who were arthritis responders, were unblinded and received open-label (OL) treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the extension (EXT) phase and participants who were arthritis nonresponders discontinued blinded study drug and started standard of care (SOC) treatment in the EXT phase. Participants on DB treatment or OL filgotinib who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) discontinued the study drug and started SOC for up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Filgonitib
Investigational medicinal product code	GS-6034
Other name	Jyseleca®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200-mg tablet administered orally once daily

Arm title	Placebo

Arm description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156). Participants who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) continued on SOC treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to match filgotinib tablet administered orally once daily.

Number of subjects in period 1	Filgonitib	Placebo
Started	54	55
Completed	54	53
Not completed	0	2
Withdrawal by Subject	-	2

Period 2

Period 2 title	EXT Phase (Through Week 26)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Filgonitib

Arm description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants who were arthritis responders, were unblinded and received OL treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the EXT phase and participants who were arthritis nonresponders discontinued blinded study drug and started SOC treatment in the EXT phase. Participants on DB treatment or OL filgotinib who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) discontinued the study drug and started SOC for up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Filgonitib
Investigational medicinal product code	GS-6034
Other name	Jyseleca®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200-mg tablet administered orally once daily

Arm title	Placebo

Arm description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156). Participants who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) continued on SOC treatment.

Arm type	Placebo

Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

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.

Number of subjects in period 2[1]	Filgonitib	Placebo
Started	46	49
Completed	0	0
Not completed	46	49
Adverse Event	5	-
Pre- Specified Decrease In Sperm Parameters	12	11
Withdrawal by Subject	-	2
Ongoing in the study	29	36

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 26 arthritis responder participants and 23 arthritis nonresponder participants entered the EXT phase and received SOC treatment. 39 arthritis responder participants entered the EXT phase and received OL treatment filgotinib. 7 arthritis nonresponder participants entered the EXT phase and received SOC treatment.

Baseline characteristics

Reporting groups	
Reporting group title	Filgonitib
Reporting group description:	
Participants received filgotinib 200 milligrams (mg) tablet, orally, once daily up to Week 13 in the double-blind (DB) phase. At Week 13, participants who were arthritis responders, were unblinded and received open-label (OL) treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the extension (EXT) phase and participants who were arthritis nonresponders discontinued blinded study drug and started standard of care (SOC) treatment in the EXT phase. Participants on DB treatment or OL filgotinib who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) discontinued the study drug and started SOC for up to 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156). Participants who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) continued on SOC treatment.	

Reporting group values	Filgonitib	Placebo	Total
Number of subjects	54	55	109
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	40	39	
standard deviation	± 8.5	± 7.8	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	54	55	109
Ethnicity (NIH/ OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	53	55	108
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	54	55	109
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Sperm Concentration Units: million sperms/ milliliter (mL)			
arithmetic mean	71.2	66.9	

standard deviation	± 41.00	± 38.72	-
Total Sperm Count			
Units: million sperms/ejaculate			
arithmetic mean	208.4	225.2	
standard deviation	± 136.94	± 137.39	-
Sperm Total Motility			
Units: percentage of motile sperm			
arithmetic mean	55.9	58.2	
standard deviation	± 8.99	± 8.48	-
Ejaculate Volume			
Units: mL			
arithmetic mean	3.1	3.5	
standard deviation	± 1.26	± 1.29	-
Percent Normal Sperm Morphology			
Units: percentage of normal sperm			
arithmetic mean	43	43	
standard deviation	± 6.2	± 6.0	-

End points

End points reporting groups

Reporting group title	Filgonitib

Reporting group description:

Participants received filgotinib 200 milligrams (mg) tablet, orally, once daily up to Week 13 in the double-blind (DB) phase. At Week 13, participants who were arthritis responders, were unblinded and received open-label (OL) treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the extension (EXT) phase and participants who were arthritis nonresponders discontinued blinded study drug and started standard of care (SOC) treatment in the EXT phase. Participants on DB treatment or OL filgotinib who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) discontinued the study drug and started SOC for up to 52 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156). Participants who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) continued on SOC treatment.

Reporting group title	Filgonitib

Reporting group description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants who were arthritis responders, were unblinded and received OL treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the EXT phase and participants who were arthritis nonresponders discontinued blinded study drug and started SOC treatment in the EXT phase. Participants on DB treatment or OL filgotinib who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) discontinued the study drug and started SOC for up to 52 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156). Participants who entered the monitoring phase (if their sperm parameters met ≥50% decrease threshold in pre-specified semen parameters) continued on SOC treatment.

Subject analysis set title	Filgotinib/OL Filgotinib (Responder)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants who were arthritis responders, were unblinded and received OL treatment filgotinib 200 mg, tablet, orally, once daily up to approximately 143 weeks (until Week 156) in the EXT phase.

Subject analysis set title	Placebo/SOC (Responder)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants who were arthritis responders, were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156).

Subject analysis set title	Filgotinib/SOC (Nonresponder)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase. At Week 13, participants who were arthritis nonresponders discontinued blinded study drug and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156).

Subject analysis set title	Placebo/SOC (Nonresponder)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB

phase. At Week 13, participants who were arthritis nonresponders, were unblinded and started SOC treatment in the EXT phase for up to approximately 143 weeks (until Week 156).

Primary: Percentage of Participants With a ≥ 50% Decrease From Baseline in Sperm Concentration at Week 13

End point title	Percentage of Participants With a ≥ 50% Decrease From Baseline in Sperm Concentration at Week 13

End point description:

Baseline for sperm/semen parameters was the mean of 2 evaluable semen samples at screening. The normal range for sperm concentration is ≥15 million sperms/ mL.
Percentage change = ([mean at Week 13 − baseline] / baseline) × 100; value at Week 13 was the mean of 2 evaluable samples collected at Week 13. The Semen Analysis Set included all randomized and treated (≥ 1 dose of double-blind study drug) participants who had 2 semen samples that were eligible for mean calculation at baseline and at the Week 13 analysis visit with the date of the first chronologic semen sample used for purposes of assigning analysis visit windows.

End point type	Primary

End point timeframe:

Baseline to Week 13

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: percentage of participants				
number (not applicable)	13.0	7.5		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgonitib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Difference in Percentage
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	19.2

Notes:

[1] - Difference in percentage and 95% confidence interval (CI) was based on a stratified Mantel-Haenszel test.

Secondary: Percentage of Participants With a ≥ 50% Decrease From Baseline in Sperm Concentration at Week 26

End point title	Percentage of Participants With a ≥ 50% Decrease From Baseline in Sperm Concentration at Week 26

End point description:

Arthritis responder: For rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS),

and nonradiographic axial spondyloarthritis (nrAxSpA), a participant with an improvement in the Physician's Global Assessment of Disease Activity (PhGADA) of at least 20% compared with baseline (Day 1) at the specified assessment time. Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint. PhGADA: Physician measured the participant's disease severity on a visual analogue scale (VAS) ranged from 0 (no disease)-100 (worst disease) millimeters (mm). The normal range for sperm concentration is ≥15 million sperms/ mL.
The Week 26 Semen Analysis Set included all participants treated (≥ 1 dose of open-label filgotinib or SOC in the extension phase) who had 2 evaluable samples at baseline and at Week 26.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	25	7	23
Units: percentage of participants				
number (not applicable)	10.3	8.0	14.3	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sperm Total Motility at Week 13

End point title	Change From Baseline in Sperm Total Motility at Week 13

End point description:

The normal range for sperm total motility is ≥40%. Participants in the Semen Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	52		
Units: percentage of motile sperms				
median (confidence interval 95%)	-2.3 (-8.1 to 1.4)	-1.7 (-5.8 to 0.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgonitib v Placebo
Number of subjects included in analysis	106
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Median difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	3.5

Notes:

[2] - Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.

Secondary: Change From Baseline in Sperm Total Motility at Week 26

End point title	Change From Baseline in Sperm Total Motility at Week 26

End point description:

Arthritis responder: For RA, PsA, AS, and nrAxSpA, a participant with an improvement in the PhGADA of at least 20% compared with baseline (Day 1) at the specified assessment time.
Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint.
PhGADA: Physician measured the participant's disease severity on a VAS ranged from 0 (no disease)-100 (worst disease) mm.
The normal range for sperm total motility is ≥40%.
Participants in the Week 26 Semen Analysis Set with available data were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	25	7	23
Units: percentage of motile sperms				
median (confidence interval 95%)	-2.4 (-9.3 to 1.0)	0.9 (-5.2 to 6.3)	-1.4 (-13.3 to 13.0)	-2.8 (-8.5 to 2.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Total Sperm Count at Week 13

End point title	Change From Baseline in Total Sperm Count at Week 13

End point description:

The normal range for total sperm count is ≥ 39 million sperms/ejaculate. Participants in the Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: million sperms/ejaculate				
median (confidence interval 95%)	-2.1 (-41.7 to 31.0)	-9.6 (-36.2 to 18.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgonitib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Median difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.1
upper limit	36.8

Notes:

[3] - Difference in medians and 95% CI for change from baseline at Week 13 was based on quantile regression.

Secondary: Change From Baseline in Total Sperm Count at Week 26

End point title	Change From Baseline in Total Sperm Count at Week 26

End point description:

Arthritis responder: For RA, PsA, AS, and nrAxSpA, a participant with an improvement in the PhGADA of at least 20% compared with baseline (Day 1) at the specified assessment time.
Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint.
PhGADA: Physician measured the participant's disease severity on a VAS ranged from 0 (no disease)-100 (worst disease) mm.
The normal range for total sperm count is ≥ 39 million sperms/ejaculate.
Participants in the Week 26 Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	25	7	23
Units: million sperms/ejaculate				
median (confidence interval 95%)	-0.2 (-39.5 to 44.5)	16.8 (-49.3 to 60.6)	32.2 (-60.8 to 121.3)	-29.9 (-79.8 to 36.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Sperm Concentration at Week 13

End point title	Change From Baseline in Sperm Concentration at Week 13
End point description: The normal range for sperm concentration is ≥15 million sperms/mL. Participants in the Semen Analysis Set were analyzed.	
End point type	Secondary
End point timeframe: Baseline, Week 13	

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: million sperms/mL				
median (confidence interval 95%)	3.7 (-7.2 to 13.1)	-0.4 (-6.1 to 7.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v Filgonitib
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Mean difference (final values)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	19.9

Notes:

[4] - Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.

Secondary: Change From Baseline in Sperm Concentration at Week 26

End point title	Change From Baseline in Sperm Concentration at Week 26

End point description:

Arthritis responder: For RA, PsA, AS, and nrAxSpA, a participant with an improvement in the PhGADA of at least 20% compared with baseline (Day 1) at the specified assessment time.
Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint.
PhGADA: Physician measured the participant's disease severity on a VAS ranged from 0 (no disease)-100 (worst disease) mm.
The normal range for sperm concentration is ≥15 million sperms/mL.
Participants in the Week 26 Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	25	7	23
Units: million sperms/mL				
median (confidence interval 95%)	1.7 (-8.9 to 21.2)	9.6 (-3.7 to 29.0)	10.3 (-43.5 to 36.3)	-5.8 (-12.9 to 4.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Ejaculate Volume at Week 13

End point title	Change From Baseline in Ejaculate Volume at Week 13

End point description:

The normal range for ejaculate volume is ≥1.5 mL. Participants in the Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: mL				
median (confidence interval 95%)	-0.3 (-0.6 to 0.1)	-0.2 (-0.4 to 0.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgonitib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Median difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	0.1

Notes:

[5] - Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.

Secondary: Change From Baseline in Ejaculate Volume at Week 26

End point title	Change From Baseline in Ejaculate Volume at Week 26

End point description:

Arthritis responder: For RA, PsA, AS, and nrAxSpA, a participant with an improvement in the PhGADA of at least 20% compared with baseline (Day 1) at the specified assessment time.
Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint.
PhGADA: Physician measured the participant's disease severity on a VAS ranged from 0 (no disease)-100 (worst disease) mm.
The normal range for ejaculate volume is ≥1.5 mL.
Participants in the Week 26 Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	25	7	23
Units: mL				
median (confidence interval 95%)	-0.2 (-0.7 to 0.4)	-0.6 (-0.7 to -0.2)	0.2 (-1.0 to 1.1)	-0.3 (-0.6 to 0.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Percent Normal Sperm Morphology at Week 13

End point title	Change From Baseline in Percent Normal Sperm Morphology at Week 13

End point description:

The normal range for percent normal sperm morphology is ≥30% normal sperms. Participants in the Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgonitib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: percentage of normal sperms				
median (confidence interval 95%)	1 (-1 to 2)	1 (-1 to 3)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgonitib v Placebo
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Median difference (final values)
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1

Notes:

[6] - Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.

Secondary: Change From Baseline in Percent Normal Sperm Morphology at Week 26

End point title	Change From Baseline in Percent Normal Sperm Morphology at Week 26

End point description:

Arthritis responder: For RA, PsA, AS, and nrAxSpA, a participant with an improvement in the PhGADA of at least 20% compared with baseline (Day 1) at the specified assessment time.
Arthritis nonresponder: For RA, PsA, AS, or nrAxSpA, a participant who did not fulfill the definition of arthritis responder at the specified assessment timepoint.
PhGADA: Physician measured the participant's disease severity on a VAS ranged from 0 (no disease)-100 (worst disease) mm.
The normal range for percent normal sperm morphology is ≥30% normal sperms.
Participants in the Week 26 Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	Filgotinib/OL Filgotinib (Responder)	Placebo/SOC (Responder)	Filgotinib/SOC (Nonresponder)	Placebo/SOC (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39	25	7	23
Units: percentage of normal sperms				
median (confidence interval 95%)	1 (-2 to 5)	3 (-2 to 8)	3 (-15 to 6)	4 (1 to 8)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after last dose or up to approximately 143 weeks (until Week 156) in the EXT phase, whichever occurred first

Adverse event reporting additional description:

The Safety Analysis Set included all randomized participants who took ≥ 1 dose of double-blind study drug. The Extension Phase Safety Analysis Set included all participants who took ≥ 1 dose of open-label filgotinib or standard of care in the extension phase of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Double-Blind Phase: Filgotinib 200 mg

Reporting group description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase.

Reporting group title	Double-Blind Phase: Placebo

Reporting group description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase.

Reporting group title	Extension Phase: Placebo - SOC

Reporting group description:

At Week 13, participants were unblinded and started SOC treatment in the EXT phase, for up to approximately 143 weeks (until Week 156).

Reporting group title	Extension Phase: Filgotinib 200 mg - SOC

Reporting group description:

At Week 13, participants who were arthritis nonresponders discontinued blinded study drug and started SOC treatment in the EXT phase, for up to approximately 143 weeks (until Week 156).

Reporting group title	Extension Phase: Filgotinib 200 mg - OL Filgotinib 200 mg

Reporting group description:

At Week 13, participants who were arthritis responders, were unblinded and received OL treatment filgotinib 200 mg, tablet, orally, once daily in the EXT phase, for up to approximately 143 weeks (until Week 156).

Serious adverse events	Double-Blind Phase: Filgotinib 200 mg	Double-Blind Phase: Placebo	Extension Phase: Placebo - SOC
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 54 (3.70%)	1 / 55 (1.82%)	1 / 49 (2.04%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meniscus injury			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 49 (2.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Radiculopathy			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tenosynovitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Extension Phase: Filgotinib 200 mg - SOC	Extension Phase: Filgotinib 200 mg - OL Filgotinib 200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	3 / 39 (7.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Radiculopathy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Intervertebral disc disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tenosynovitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Double-Blind Phase: Filgotinib 200 mg	Double-Blind Phase: Placebo	Extension Phase: Placebo - SOC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 54 (18.52%)	10 / 55 (18.18%)	12 / 49 (24.49%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 54 (3.70%)	2 / 55 (3.64%)	0 / 49 (0.00%)
occurrences (all)	2	2	0
Nervous system disorders			

Headache			
subjects affected / exposed	2 / 54 (3.70%)	1 / 55 (1.82%)	1 / 49 (2.04%)
occurrences (all)	2	1	1
Sciatica			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	1 / 49 (2.04%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Drug hypersensitivity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Splenic artery aneurysm			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Renal aneurysm			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	3 / 49 (6.12%)
occurrences (all)	0	0	3
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	6 / 49 (12.24%)
occurrences (all)	0	0	6
Latent tuberculosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	4 / 54 (7.41%)	4 / 55 (7.27%)	1 / 49 (2.04%)
occurrences (all)	4	4	1
Pharyngitis			
subjects affected / exposed	2 / 54 (3.70%)	2 / 55 (3.64%)	1 / 49 (2.04%)
occurrences (all)	2	2	1
Pyospermia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 55 (1.82%)	1 / 49 (2.04%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 55 (0.00%)	0 / 49 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Extension Phase: Filgotinib 200 mg - SOC	Extension Phase: Filgotinib 200 mg - OL Filgotinib 200 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	15 / 39 (38.46%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Alanine aminotransferase increased			

subjects affected / exposed	1 / 7 (14.29%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	4	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 7 (14.29%)	1 / 39 (2.56%)	
occurrences (all)	1	1	
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Splenic artery aneurysm			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatic steatosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Dermatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal aneurysm			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 39 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 7 (14.29%)	3 / 39 (7.69%)	
occurrences (all)	1	3	
Latent tuberculosis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 39 (7.69%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 39 (5.13%)	
occurrences (all)	2	2	
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	2 / 39 (5.13%)	
occurrences (all)	0	2	
Pyospermia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 39 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 May 2020	This amendment was initiated to address comments related to new safety information suggesting an increased risk of thromboembolic events in participants 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37137672

http://www.ncbi.nlm.nih.gov/pubmed/35614292