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

Summary

EudraCT number	2017-000402-38
Trial protocol	GB DE AT PT NL SE BE ES RO
Global end of trial date	24 October 2023

Results information

Result version number	v3 (current)
This version publication date	25 September 2024
First version publication date	20 July 2023
Version creation reason	• New data added to full data set Final study report

Trial information

Trial identification

Sponsor protocol code	GS-US-418-4279

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03201445
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	Final
Date of interim/final analysis	29 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 October 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main aim of this study was to evaluate the testicular safety of filgotinib in adult males with moderately to severely active inflammatory bowel disease (IBD).

Protection of trial subjects:

This study is being conducted under a US investigational new drug (IND) application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the EU Clinical Trials Directive 2001/20/EC as well as other local legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2017
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	Poland: 9
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	India: 75
Country: Number of subjects enrolled	United States: 20
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	New Zealand: 1
Worldwide total number of subjects	139
EEA total number of subjects	17

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)	139
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in Australia, Austria, Germany, India, New Zealand, Poland, Romania, Russian Federation, Ukraine, United Kingdom, and United States. The first participant was screened on 11 July 2017. A total of 323 participants were screened of which 139 participants were randomized into the study.

Pre-assignment

Screening details:

Study had 5 parts: Part A: Double-Blind Phase (DB Phase; Day 1 up to Week 13); Part B: DB Phase (Week 13 up to Week 26); Open-label (OL) Phase (after Week 13 study visit for up to 13 weeks); Monitoring Phase (MP; up to 52 weeks); and Long-term Extension (LTE) Phase (after Week 26 or end of OL Phase for up to 195 weeks).

Period 1

Period 1 title	Overall (overall period)
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	Filgotinib

Arm description:

Participants received filgotinib 200 mg tablet, orally once daily (OD) up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 & prior to Week 26 (in Part B), & whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, & received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders & who had not experienced disease worsening, & whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug & switched to standard of care (SOC) regimen selected by investigator & entered the MP for up to 52 weeks.

Arm type	Experimental
Investigational medicinal product name	Filgotinib
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

Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

Locally approved treatment, accepted by medical experts as a proper treatment for IBD conditions, prescribed according to best clinical practice, with no known testicular toxicity.

Arm title	Placebo

Arm description:

Participants received placebo (matched to filgotinib) tablet, orally OD up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, and received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders and who had not experienced disease worsening, and whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug and switched to SOC regimen selected by investigator and entered the MP for up to 52 weeks.

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.

Investigational medicinal product name	Filgotinib
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

Investigational medicinal product name	Standard of Care
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Not assigned
Routes of administration	Not mentioned

Dosage and administration details:

Locally approved treatment, accepted by medical experts as a proper treatment for IBD conditions, prescribed according to best clinical practice, with no known testicular toxicity.

Number of subjects in period 1	Filgotinib	Placebo
Started	69	70
Completed	25	28
Not completed	44	42
Physician decision	3	4
Consent withdrawn by subject	9	10
Adverse event, non-fatal	13	14
Progressive Disease	1	-
Study Terminated by Sponsor	17	12
Lost to follow-up	1	1
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Filgotinib
Reporting group description:	
Participants received filgotinib 200 mg tablet, orally once daily (OD) up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 & prior to Week 26 (in Part B), & whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, & received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders & who had not experienced disease worsening, & whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug & switched to standard of care (SOC) regimen selected by investigator & entered the MP for up to 52 weeks.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo (matched to filgotinib) tablet, orally OD up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, and received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders and who had not experienced disease worsening, and whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug and switched to SOC regimen selected by investigator and entered the MP for up to 52 weeks.	

Reporting group values	Filgotinib	Placebo	Total
Number of subjects	69	70	139
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	36	34	
standard deviation	± 8.5	± 8.4	-
Gender categorical Units: Subjects			
Female	0	0	0
Male	69	70	139
Ethnicity			
Not Permitted = local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
Not Hispanic or Latino	68	68	136
Hispanic or Latino	1	1	2
Not Permitted	0	1	1
Race			
Not Permitted = local regulators did not allow collection of race or ethnicity information.			
Units: Subjects			
American Indian or Alaska Native	2	0	2
Asian	37	38	75
Black or African American	1	0	1

White	29	31	60
Not Permitted	0	1	1

Sperm Concentration			
Units: million sperm cells/milliliter (mL)			
arithmetic mean	63.4	61.8	
standard deviation	± 34.34	± 34.96	-
Total Sperm Count			
Units: million sperm cells/ejaculate			
arithmetic mean	190.6	171.1	
standard deviation	± 107.08	± 100.74	-
Sperm Total Motility			
Units: percentage of motile sperm			
arithmetic mean	59.6	58.6	
standard deviation	± 11.33	± 10.94	-
Ejaculate Volume			
Units: mL			
arithmetic mean	3.2	3.0	
standard deviation	± 1.20	± 1.48	-
Percent Normal Sperm Morphology			
Units: percentage of normal sperm			
arithmetic mean	41	41	
standard deviation	± 6.4	± 5.5	-

End points

End points reporting groups

Reporting group title	Filgotinib

Reporting group description:

Participants received filgotinib 200 mg tablet, orally once daily (OD) up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 & prior to Week 26 (in Part B), & whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, & received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders & who had not experienced disease worsening, & whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug & switched to standard of care (SOC) regimen selected by investigator & entered the MP for up to 52 weeks.

Reporting group title	Placebo

Reporting group description:

Participants received placebo (matched to filgotinib) tablet, orally OD up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, and received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders and who had not experienced disease worsening, and whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug and switched to SOC regimen selected by investigator and entered the MP for up to 52 weeks.

Subject analysis set title	Filgotinib/DB Filgotinib (Responder)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase (Part A). At Week 13, participants who were IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B).

Subject analysis set title	Filgotinib/OL Filgotinib (Nonresponder)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received filgotinib 200 mg tablet, orally, once daily up to Week 13 in the DB phase (Part A). Participants who were IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet a prespecified decrease threshold, entered the OL Phase and received OL filgotinib 200 mg, tablet, orally, once daily for up to Week 13 during the OL phase.

Subject analysis set title	Placebo/DB Placebo (Responder)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase (Part A). At Week 13, participants who were IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B).

Subject analysis set title	Placebo/OL Filgotinib (Nonresponder)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received placebo (matched to filgotinib) tablet, orally, once daily up to Week 13 in the DB phase (Part A). Participants who were IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet a prespecified decrease threshold, entered the OL Phase and received OL filgotinib 200 mg, tablet, orally, once daily for up to Week 13 during the OL phase.

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 sperm cells/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	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: percentage of participants				
number (not applicable)	1.5	9.0		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in Percentage
Point estimate	-7.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.3
upper limit	0.7

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:

IBD responder: For ulcerative colitis (UC), a participant who had a reduction of ≥ 2 in partial Mayo Clinic Score (pMCS) compared with baseline at specified time. For Crohn's disease (CD), a participant who had a reduction of ≥ 100 points in total Crohn's Disease Activity Index (CDAI) score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤250 was considered an IBD responder if a CDAI score of <150 was attained at specified time.
IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time.
pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease).
CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity.
The normal range for sperm concentration is ≥15 million sperm cells/mL.

End point type	Secondary

End point timeframe:

Baseline to Week 26

End point values	Filgotinib/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	38	17
Units: percentage of participants				
number (not applicable)	5.0	0	7.9	11.8

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 were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: percentage of motile sperms				
median (confidence interval 95%)	-0.3 (-1.6 to 1.7)	0.4 (-1.3 to 1.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.	
Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.8

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:	
IBD responder: For UC, a participant who had a reduction of ≥ 2 in pMCS compared with baseline at specified time. For CD, a participant who had a reduction of ≥ 100 points in total CDAI score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤ 250 was considered an IBD responder if a CDAI score of <150 was attained at specified time. IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time. pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease). CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity. 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/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	36	17
Units: percentage of motile sperms				
median (confidence interval 95%)	-2.3 (-4.7 to -0.3)	-1.5 (-5.8 to 2.6)	0.0 (-3.4 to 2.4)	0.8 (-7.3 to 5.8)

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 sperm cells/ejaculate. Participants in the Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: million sperm cells/ejaculate				
median (confidence interval 95%)	-11.6 (-19.8 to 9.7)	-9.5 (-23.8 to 0.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	5.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.4
upper limit	24.7

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:

IBD responder: For UC, a participant who had a reduction of ≥ 2 in pMCS compared with baseline at specified time. For CD, a participant who had a reduction of ≥ 100 points in total CDAI score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤ 250 was considered an IBD responder if a CDAI score of <150 was attained at specified time.
IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time.
pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease).
CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity.
The normal range for total sperm count is ≥ 39 million sperm cells/ejaculate.
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/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	38	17
Units: million sperm cells/ejaculate				
median (confidence interval 95%)	2.0 (-19.6 to 17.2)	-4.6 (-42.3 to 18.3)	-4.1 (-39.8 to 15.9)	12.7 (-61.4 to 40.8)

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 sperm cells/mL. Participants in the Semen Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline, Week 13

End point values	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: million sperm cells/mL				
median (confidence interval 95%)	1.0 (-2.2 to 3.9)	0.7 (-2.7 to 1.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Difference in Medians and 95% CI for change from baseline at Week 13 was based on quantile regression.	
Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	4.9

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:	
IBD responder: For UC, a participant who had a reduction of ≥ 2 in pMCS compared with baseline at specified time. For CD, a participant who had a reduction of ≥ 100 points in total CDAI score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤ 250 was considered an IBD responder if a CDAI score of <150 was attained at specified time. IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time. pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease). CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity. The normal range for sperm concentration is ≥15 million sperm cells/mL. 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/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	38	17
Units: million sperm cells/mL				
median (confidence interval 95%)	1.2 (-3.2 to 10.8)	-0.6 (-8.5 to 23.0)	0.8 (-2.4 to 5.3)	-3.7 (-11.1 to 15.7)

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	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: mL				
median (confidence interval 95%)	-0.2 (-0.3 to 0.1)	-0.1 (-0.3 to 0.0)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Filgotinib v Placebo

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.3

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:

IBD responder: For UC, a participant who had a reduction of ≥ 2 in pMCS compared with baseline at specified time. For CD, a participant who had a reduction of ≥ 100 points in total CDAI score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤ 250 was considered an IBD responder if a CDAI score of <150 was attained at specified time.
IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time.
pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease).
CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity.
The normal range for ejaculate volume is ≥1.5 mL.
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/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	38	17
Units: mL				
median (confidence interval 95%)	0.0 (-0.5 to 0.2)	-0.3 (-0.8 to 0.2)	-0.2 (-0.5 to 0.1)	-0.1 (-0.7 to 0.4)

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	Filgotinib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	67		
Units: percentage of normal sperms				
median (confidence interval 95%)	2 (-1 to 4)	1 (-1 to 2)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Median difference (final values)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	4

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:

IBD responder: For UC, a participant who had a reduction of ≥ 2 in pMCS compared with baseline at specified time. For CD, a participant who had a reduction of ≥ 100 points in total CDAI score compared with baseline at specified time. A participant with a baseline total CDAI score of ≥ 220 to ≤ 250 was considered an IBD responder if a CDAI score of <150 was attained at specified time.
IBD nonresponder: For UC or CD, a participant who did not fulfil the definition of IBD responder at specified time.
pMCS score: Sum of 3 subscores (rectal bleeding, stool frequency, and physician's global assessment) excluding endoscopic subscore; ranging from 0 (none) to 9 (severe disease).
CDAI score: A weighted sum of 8 disease activity variables with scores ranging from 0 to over 600, where higher score = higher disease activity.
The normal range for percent normal sperm morphology is ≥30% normal sperms.
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/DB Filgotinib (Responder)	Filgotinib/OL Filgotinib (Nonresponder)	Placebo/DB Placebo (Responder)	Placebo/OL Filgotinib (Nonresponder)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	21	38	17
Units: percentage of normal sperms				
median (confidence interval 95%)	3 (1 to 5)	1 (-2 to 3)	2 (-4 to 5)	2 (-2 to 3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to Week 226

Adverse event reporting additional description:

All on-treatment safety data during the study were reported under the treatment received at the onset of the event (As-treated set).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo (matched to filgotinib) tablet, orally OD up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, and received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders and who had not experienced disease worsening, and whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug and switched to SOC regimen selected by investigator and entered the MP for up to 52 weeks.

Reporting group title	Filgotinib

Reporting group description:

Participants received filgotinib 200 mg tablet, orally OD up to Week 13 in DB phase (Part A). At Week 13, IBD responders, without meeting pre-specified sperm decrease thresholds, continued DB phase treatment up to Week 26 (Part B). IBD non-responders at Week 13 (end of Part A) or had disease worsening after Week 13 and prior to Week 26 (in Part B), and whose sperm parameters did not meet prespecified decrease threshold, entered the OL Phase, and received OL filgotinib 200 mg, tablet orally OD for up to Week 13 during the OL phase. At Week 26/OL Week 13, IBD responders and who had not experienced disease worsening, and whose sperm parameters did not meet prespecified decrease threshold, continued receiving the same study drug they were responding to, as part of LTE for up to 195 weeks. Participants who met prespecified sperm decrease threshold(s) discontinued study drug and switched to SOC regimen selected by investigator and entered the MP for up to 52 weeks.

Serious adverse events	Placebo	Filgotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 70 (2.86%)	3 / 92 (3.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Colitis ulcerative			
subjects affected / exposed	1 / 70 (1.43%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			

subjects affected / exposed	0 / 70 (0.00%)	1 / 92 (1.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 70 (1.43%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 92 (1.09%)	
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	Placebo	Filgotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 70 (34.29%)	47 / 92 (51.09%)	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 70 (0.00%)	7 / 92 (7.61%)	
occurrences (all)	0	8	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 70 (5.71%)	5 / 92 (5.43%)	
occurrences (all)	4	6	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 70 (7.14%)	3 / 92 (3.26%)	
occurrences (all)	5	4	
Colitis ulcerative			
subjects affected / exposed	3 / 70 (4.29%)	14 / 92 (15.22%)	
occurrences (all)	3	18	
Gastritis			

subjects affected / exposed	1 / 70 (1.43%)	7 / 92 (7.61%)	
occurrences (all)	1	7	
Infections and infestations			
Furuncle			
subjects affected / exposed	4 / 70 (5.71%)	1 / 92 (1.09%)	
occurrences (all)	4	1	
Latent tuberculosis			
subjects affected / exposed	5 / 70 (7.14%)	5 / 92 (5.43%)	
occurrences (all)	5	5	
Nasopharyngitis			
subjects affected / exposed	3 / 70 (4.29%)	17 / 92 (18.48%)	
occurrences (all)	4	18	
COVID-19			
subjects affected / exposed	3 / 70 (4.29%)	9 / 92 (9.78%)	
occurrences (all)	3	9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2017	It included following changes: - Increased the target enrollment number from 200 to 250 to account for potential dropouts; - Clarified IBD nonresponders as those with a decrease in pMCS of < 2 points or an increase in pMCS; - After the Week 13 visit, IBD nonresponders discontinued study drug and commenced OL filgotinib 200 mg once daily; and at Week 26, if they did not have a ≥ 50% decrease in sperm concentration from baseline, had the option to continue receiving OL filgotinib as part of the LTE; - Any participants who demonstrated a ≥ 50% decrease in sperm concentration from baseline entered the MP regardless of when it occurred; - Clarified that participants would be allowed on conventional immunomodulators as defined by the inclusion criteria; - LTE defined as Week 26 to Week 221; - Updated the 30-day follow-up visit and the posttreatment visit to a safety follow-up visit; - Added a required safety follow-up visit 30 days after last dose of study drug at the end of the LTE and after an ET visit; - Clarified the inclusion criteria for tumor necrosis factor alpha (TNFα) antagonists; - Clarified for participants at screening who were taking allowed therapies for UC that they had to remain on stable doses for the noted times; - Excluded ustekinumab 12 weeks prior to screening; - Updated the inclusion criteria to require that semen volume be ≥ 1.5 mL, total sperm per ejaculate to be ≥ 39 M, and that participants be up to date on colorectal cancer surveillance as per local guidelines prior to screening; - Updated participants meeting the disease worsening criteria to be offered the option to commence OL filgotinib; - End of study defined as when the last participant completed the Week 225 visit or the last participant completed their last visit, whichever was sooner; - Updated study visit windows to ± 5 days for the primary study and ± 10 days during the LTE.
22 August 2018	It included following changes: - Revised study title from UC to IBD to encompass CD; - Increased the number of study centers from approximately 150 centers to approximately 175 centers worldwide; - Broadened the age range from 25 to 55 years of age (inclusive) to 21 to 65 years of age (inclusive); - Included ≥ 50% decrease in sperm total motility and/or sperm morphology as decision criteria for participants to enter the MP; - Removed Week 28 and Week 32 visits from LTE; - Amended the definition of evaluable participants; - Added the option of pooling the results of this study with a separate study being conducted in participants with rheumatic diseases (Study GLPG0634-CL-227 [2018-003933-14]) with the same objective, and having the total planned number of participants in both studies combined of up to approximately 250 participants.
18 January 2019	It included following changes: - Updated ejaculation-free period from ≥ 48 hours and < 5 days to ≥ 48 hours and ≤ 7 days, per the recommendation of the updated Food and Drug Administration (FDA) guidance for industry on testicular toxicity studies; - Clarified OL Week 13 study visit and visit schedule of LTE; - Amended lower threshold of baseline sperm concentration for inclusion (≥ 10 million sperm cells/mL changed to ≥ 15 million sperm cells/mL) in line with FDA recommendation, and amended corresponding sperm concentration randomization strata (lower range of stratum changed from 10 to 20 million sperm cells/mL to 15 to 25 million sperm cells/mL); - Added the option for an unblinded interim analyses when 200 participants (eg, pooled data from Studies GS-US-418-4279 and GLPG0634-CL-227) and/or when some defined subset(s) of participants had completed their Week 13 assessments.
17 March 2020	It included following changes: - Included discontinuation criteria for thromboembolic events; - Included a criterion to trigger an ad-hoc data monitoring committee (DMC) meeting; - Clarified that the CDAI score calculation excluded days that involved an endoscopy procedure or preparation for that procedure; - Added section on blinding procedures.
27 June 2022	The primary reason for this amendment was to change sponsorship from Gilead Sciences, Inc. to Galapagos NV.

09 September 2022	It included following changes: - Text was revised to specify the decommissioning of the DMC and transfer the role of the DMC to the Sponsor Safety Management Team (SSMT). All planned DMC reviews were completed, and no additional reviews were expected. At this advanced stage of the study, treatment assignments were 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 included regular reviews of safety summary updates and provided similar options for escalated issue review as described in the DMC charter by following the SSMT standard procedures; - Text about blinding was revised to allow publication of the treatment assignments of subjects who completed the study before IA2; - 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 the current Investigator's Brochure; - Text was added to specify the decommissioning of the Internal Independent Safety Review Team as of this amendment. The internal independent SSMT covered the objectives of the DMC and the Internal Independent Safety Review Team.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated based on the sponsor's decision for reasons other than safety.

Notes: