Clinical trial results:
A Randomised, Phase 2, Double-blind, Placebo-controlled Study to Assess the Safety and Efficacy of Filgotinib, GS-9876 and GS-4059 in Adult Subjects with Active Sjogren's Syndrome

Summary

EudraCT number	2016-003558-34
Trial protocol	GB ES PL
Global end of trial date	02 October 2019

Results information

Result version number	v1
This version publication date	04 January 2020
First version publication date	04 January 2020

Trial information

Trial identification

Sponsor protocol code	GS-US-445-4189

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03100942
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Gilead Sciences
Sponsor organisation address	333 Lakeside Drive, Foster City, CA, United States, 94404
Public contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.com
Scientific contact	Gilead Clinical Study Information Center, Gilead Sciences, GileadClinicalTrials@gilead.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	10 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 January 2019
Global end of trial reached?	Yes
Global end of trial date	02 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of filgotinib, lanraplenib, and tirabrutinib in adults with active Sjogren's Syndrome (SjS).

Protection of trial subjects:

The protocol and consent forms were submitted for each investigator to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent forms (if applicable) after initial IEC/IRB approval were submitted on behalf of the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements.
This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 106
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	152
EEA total number of subjects	46

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	130
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at study sites in the United States and Europe. The first participant was screened on 01 May 2017. The last study visit occurred on 02 Oct 2019.

Pre-assignment

Screening details:

347 participants were screened. Data submitted represent interim analysis performed on data collected by the participants through Week 24. Complete data will be submitted in October 2020.

Period 1

Period 1 title	Overall Study (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:

Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

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

Dosage and administration details:

1 x 200 mg tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Lanraplenib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Tirabrutinib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

Arm title	Lanraplenib

Arm description:

Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks

Arm type	Experimental

Investigational medicinal product name	Lanraplenib
Investigational medicinal product code	
Other name	GS-9876
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 30 mg tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Filgotinib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Tirabrutinib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

Arm title	Tirabrutinib

Arm description:

Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks

Arm type	Experimental
Investigational medicinal product name	Tirabrutinib
Investigational medicinal product code	
Other name	GS-4059
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 40 mg tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Filgotinib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1x tablet administered orally once daily for 48 weeks

Investigational medicinal product name	Lanraplenib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 48 weeks

Arm title	Placebo

Arm description:

Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48:

• filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
• lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
• tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

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

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:
• lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
• tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

Investigational medicinal product name	Lanraplenib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:
• filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
• tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)

Investigational medicinal product name	Tirabrutinib placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x tablet administered orally once daily for 24 weeks. At Week 24 visit, 1 x tablet administered orally once daily through Week 48 in either of the following experimental arms:
• filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)
• lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet)

Investigational medicinal product name	Filgotinib
Investigational medicinal product code	
Other name	GS-6034
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 200 mg tablet administered once daily from Week 24 through Week 48

Investigational medicinal product name	Lanraplenib
Investigational medicinal product code	
Other name	GS-9876
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1x 30 mg tablet administered orally once daily from Week 24 through Week 48

Investigational medicinal product name	Tirabrutinib
Investigational medicinal product code	
Other name	GS-4059
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 x 40 mg tablet administered orally once daily from Week 24 through Week 48

Number of subjects in period 1[1]	Filgotinib	Lanraplenib	Tirabrutinib
Started	38	37	39
Completed up to Week 24	35	30	37
Completed	9	11	13
Not completed	29	26	26
Withdrew Consent	4	4	2
Adverse Event	1	6	1
Investigator's Discretion	1	1	-
Still on the Study	22	15	23
Protocol Violation	1	-	-

Number of subjects in period 1[1]	Placebo
Started	36
Completed up to Week 24	32
Completed	14
Not completed	22
Withdrew Consent	4
Adverse Event	-
Investigator's Discretion	-
Still on the Study	17
Protocol Violation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 2 participants (Lanraplenib arm: N = 1; Placebo arm: N= 1) were randomised but did not receive a single dose of study drug and therefore are not included in the subject disposition or any further analysis.

Comment regarding the number in the placebo arm for 'Completed up to week 24': 32 participants in the placebo group were rerandomized at Week 24.

Baseline characteristics

Reporting groups	
Reporting group title	Filgotinib
Reporting group description:	
Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Lanraplenib
Reporting group description:	
Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Tirabrutinib
Reporting group description:	
Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48: • filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)	

Reporting group values	Filgotinib	Lanraplenib	Tirabrutinib
Number of subjects	38	37	39
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.2	56.2	55.8
standard deviation	± 10.54	± 9.72	± 10.06
Gender categorical Units: Subjects			
Female	38	36	37
Male	0	1	2
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Black	5	5	4
White	32	31	34
Other	0	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	4	6	1
Not Hispanic or Latino	34	31	38
Not Permitted	0	0	0

European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI)			
Overall score (ranged from 0 (best) to 123 (worst activity)) was calculated as sum of all individual weighted domain scores . For additional details on this index, please see Endpoints section.			
Units: Score on a scale			
arithmetic mean	10.2	10.5	10.4
standard deviation	± 6.23	± 4.89	± 5.36
EULAR Sjogren's syndrome patient reported index (ESSPRI)			
The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 =no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10.			
Units: Score on a scale			
arithmetic mean	6.3	6.6	5.9
standard deviation	± 2.31	± 1.90	± 2.39

Reporting group values	Placebo	Total	
Number of subjects	36	150	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	53.2		
standard deviation	± 10.28	-	
Gender categorical			
Units: Subjects			
Female	35	146	
Male	1	4	
Race			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	0	2	
Black	5	19	
White	30	127	
Other	0	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	6	17	
Not Hispanic or Latino	29	132	
Not Permitted	1	1	
European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI)			
Overall score (ranged from 0 (best) to 123 (worst activity)) was calculated as sum of all individual weighted domain scores . For additional details on this index, please see Endpoints section.			
Units: Score on a scale			
arithmetic mean	9.3		
standard deviation	± 3.96	-	
EULAR Sjogren's syndrome patient reported index (ESSPRI)			
The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3			

domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 =no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10.			
Units: Score on a scale			
arithmetic mean	5.9		
standard deviation	± 2.24	-	

End points

End points reporting groups

Reporting group title	Filgotinib
Reporting group description:	
Filgotinib (1 x 200 mg) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Lanraplenib
Reporting group description:	
Lanraplenib (1 x 30 mg) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Tirabrutinib
Reporting group description:	
Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48: • filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)	

Primary: Percentage of Participants Fulfilling Protocol-Specified Response Criteria at Week 12, as Compared to Baseline

End point title	Percentage of Participants Fulfilling Protocol-Specified Response Criteria at Week 12, as Compared to Baseline
End point description:	
Response was defined as: Improvement ≥ 20% in ≥ 3 of 5 participant-reported Sjogren's syndrome (SjS) related visual analogue score (VAS) measures (participant's assessment of global disease, pain, oral dryness, ocular dryness and fatigue), with no increase defined as > 30 mm from baseline (Day 1) in any of the above 5 VAS measures, AND either ≥ 20% improvement in high sensitivity C-reactive protein (hsCRP) (if hsCRP ≥ 1.5 x ULN on Day 1) or no increase in hsCRP to ≥ 1.5 x ULN (if hsCRP < 1.5 x ULN on Day 1). Missing data were imputed using multiple imputations with logistic regression. The Full Analysis Set included all randomised participants who received at least one dose of study drug.	
End point type	Primary
End point timeframe:	
Week 12	

End point values	Filgotinib	Lanraplenib	Tirabrutinib	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	39	36
Units: Percentage of participants				
number (confidence interval 95%)	43.0 (27.1 to 59.0)	42.3 (25.9 to 58.7)	34.7 (19.6 to 49.9)	26.4 (11.5 to 41.3)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Filgotinib v Placebo
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2082
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Statistical Analysis 2
Comparison groups	Lanraplenib v Placebo
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1373
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Statistical Analysis 3
Comparison groups	Tirabrutinib v Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3732
Method	Cochran-Mantel-Haenszel

Secondary: Change From Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) at Week 12

End point title	Change From Baseline in European League Against Rheumatism (EULAR) Sjogren's Syndrome Disease Activity Index (ESSDAI) at Week 12

End point description:

The ESSDAI is a physician-administered tool designed to measure disease activity. It consists of 12 organ-specific 'domains' contributing to disease activity associated with the patient's Sjogren's Syndrome only (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, biological). Each domain is assessed for activity level (i.e., no, low, moderate, high) and assigned a numerical score based on pre-determined weighting of each individual domain. Overall score (ranges from 0 (best) to 123 (worst activity)) is calculated as sum of all individual weighted domain scores. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Filgotinib	Lanraplenib	Tirabrutinib	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	39	36
Units: Score on a scale				
least squares mean (standard error)	-4.7 (± 0.73)	-2.6 (± 0.76)	-3.2 (± 0.73)	-3.8 (± 0.76)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) at Week 12

End point title	Change From Baseline in EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI) at Week 12

End point description:

The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 = no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 12

End point values	Filgotinib	Lanraplenib	Tirabrutinib	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	39	36
Units: Score on a scale				
least squares mean (standard error)	-1.4 (± 0.33)	-1.0 (± 0.34)	-1.3 (± 0.33)	-1.0 (± 0.35)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSDAI at Week 24

End point title	Change From Baseline in ESSDAI at Week 24

End point description:

The ESSDAI is a physician-administered tool designed to measure disease activity. It consists of 12 organ-specific 'domains' contributing to disease activity associated with the patient's Sjogren's Syndrome only (constitutional, lymphadenopathy, articular, muscular, cutaneous, glandular, pulmonary, renal, peripheral nervous system, central nervous system, hematological, biological). Each domain is assessed for activity level (i.e., no, low, moderate, high) and assigned a numerical score based on pre-determined weighting of each individual domain. An overall score is then calculated as the sum of all individual weighted domain scores. Overall score (ranges from 0 (best) to 123 (worst activity)) is calculated as sum of all individual weighted domain scores. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Filgotinib	Lanraplenib	Tirabrutinib	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	39	36
Units: Score on a scale				
least squares mean (standard error)	-5.4 (± 0.75)	-4.3 (± 0.81)	-4.0 (± 0.75)	-4.2 (± 0.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in ESSPRI at Week 24

End point title	Change From Baseline in ESSPRI at Week 24

End point description:

The ESSPRI is a patient-reported questionnaire to assess subjective patient symptoms and includes 3 domains (dryness, pain, and fatigue). Each domain scored on scale of 0-10 (0 = no symptom at all and 10 = worst symptom imaginable), and an overall score is calculated as the mean of the three individual domains where all domains carry the same weight. Minimum score can be 0 and maximum score can be 10. Participants in the Full Analysis Set were analyzed.

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Filgotinib	Lanraplenib	Tirabrutinib	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	38	37	39	36
Units: Score on a scale				
least squares mean (standard error)	-0.8 (± 0.31)	-1.1 (± 0.35)	-1.2 (± 0.31)	-0.8 (± 0.33)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
First dose date up to Week 24	
Adverse event reporting additional description:	
The Safety Analysis Set included participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	Filgotinib
Reporting group description:	
Filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Lanraplenib
Reporting group description:	
Lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Tirabrutinib
Reporting group description:	
Tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet) orally once daily for 48 weeks	
Reporting group title	Placebo
Reporting group description:	
Participants received filgotinib placebo + lanraplenib placebo + tirabrutinib placebo tablets orally once daily for 24 weeks. At Week 24 Visit, participants were rerandomised 1:1:1, in a blinded fashion and received either of the three experimental study drugs orally once daily through Week 48: • filgotinib (1 x 200 mg tablet) + lanraplenib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • lanraplenib (1 x 30 mg tablet) + filgotinib placebo (1 x tablet) + tirabrutinib placebo (1 x tablet) • tirabrutinib (1 x 40 mg tablet) + filgotinib placebo (1 x tablet) + lanraplenib placebo (1 x tablet)	

Serious adverse events	Filgotinib	Lanraplenib	Tirabrutinib
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	3 / 37 (8.11%)	1 / 39 (2.56%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 39 (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
Gastrointestinal disorders			

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 39 (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
Pancreatitis acute			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 39 (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
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 39 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	0 / 39 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	0 / 39 (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
Infections and infestations			
Diverticulitis			

subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	0 / 39 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 36 (5.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Filgotinib	Lanraplenib	Tirabrutinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 38 (60.53%)	16 / 37 (43.24%)	22 / 39 (56.41%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 38 (2.63%)	4 / 37 (10.81%)	1 / 39 (2.56%)
occurrences (all)	1	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 38 (2.63%)	4 / 37 (10.81%)	1 / 39 (2.56%)
occurrences (all)	1	5	1
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	2

Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 39 (2.56%)
occurrences (all)	2	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	1 / 39 (2.56%)
occurrences (all)	0	2	1
Headache			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	3
Sciatica			
subjects affected / exposed	3 / 38 (7.89%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 38 (5.26%)	2 / 37 (5.41%)	0 / 39 (0.00%)
occurrences (all)	2	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	2 / 39 (5.13%)
occurrences (all)	0	2	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	3 / 37 (8.11%)	0 / 39 (0.00%)
occurrences (all)	1	3	0
Nausea			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	1 / 39 (2.56%)
occurrences (all)	3	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	2 / 39 (5.13%)
occurrences (all)	0	0	2
Oropharyngeal pain			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	2 / 38 (5.26%)	2 / 37 (5.41%)	3 / 39 (7.69%)
occurrences (all)	2	2	3
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	2 / 39 (5.13%)
occurrences (all)	2	0	2
Pruritus generalised			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	0 / 39 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	2 / 39 (5.13%)
occurrences (all)	0	1	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	4 / 39 (10.26%)
occurrences (all)	1	2	4
Muscle spasms			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	1 / 39 (2.56%)
occurrences (all)	2	0	1
Pain in extremity			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 38 (15.79%)	2 / 37 (5.41%)	4 / 39 (10.26%)
occurrences (all)	7	2	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 38 (10.53%)	2 / 37 (5.41%)	4 / 39 (10.26%)
occurrences (all)	4	2	5
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	0 / 37 (0.00%)	1 / 39 (2.56%)
occurrences (all)	0	0	1
Bronchitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	1 / 39 (2.56%)
occurrences (all)	1	1	1

Gastroenteritis viral			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	3 / 39 (7.69%)
occurrences (all)	2	1	3
Sinusitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	1 / 39 (2.56%)
occurrences (all)	0	2	1
Pharyngitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0
Oral herpes			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	0 / 39 (0.00%)
occurrences (all)	2	1	0
Pneumonia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	0 / 39 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 36 (58.33%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 4		
Headache subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Sciatica subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Nausea subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 36 (8.33%) 3		
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2		
Alopecia			

subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Pruritus generalised			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 36 (2.78%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	4 / 36 (11.11%)		
occurrences (all)	5		
Urinary tract infection			
subjects affected / exposed	6 / 36 (16.67%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Gastroenteritis viral			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Sinusitis			

subjects affected / exposed	3 / 36 (8.33%)		
occurrences (all)	3		
Pharyngitis			
subjects affected / exposed	2 / 36 (5.56%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 36 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 July 2018	- Protocol Amendment included: 1) Addition of biomarker sample collection at Day 1 and Week 18 visits. 2) Addition of a primary and secondary analysis to be conducted after all subjects either complete Week 24 visit or prematurely discontinue from the study. 3) Assembly of an internal unblinded team independent of the blinded study team to closely monitor study progress and drug safety. - "Pharmacogenomic" was changed to "Genomic" for consistency with the Patient Information Sheet/Informed Consent Form.

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.

An unplanned review of unblinded clinical trial data was performed in this study that was not prospectively specified in the protocol. There was no impact on the overall integrity or conclusions of the study.

Notes: