# Clinical trial results:
# A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 24 Weeks in Combination with Conventional Synthetic Disease-Modifying Anti-Rheumatic Drug(s) (csDMARDs) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Have an Inadequate Response to Biologic DMARD(s) Treatment

## Summary

| | |
|---|---|
| EudraCT number | 2016-000569-21 |
| Trial protocol | BE GB DE FR HU ES PL NL |
| Global end of trial date | 26 June 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 04 July 2019 |
| First version publication date | 04 July 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | GS-US-417-0302 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02873936 |
| 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 | Final |
| Date of interim/final analysis | 26 June 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 June 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the effects of filgotinib versus placebo for the treatment of signs and symptoms of rheumatoid arthritis (RA) as measured by the proportion of participants achieving an American College of Rheumatology 20% improvement response (ACR20) at Week 12.

Protection of trial subjects:

The protocol and consent/assent forms were submitted by 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/assent forms (if applicable) after initial IEC/IRB approval were submitted by 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:

All participants continued to receive a stable dose of a permitted protocol-specified conventional synthetic disease-modifying antirheumatic drug (csDMARD(s)) (methotrexate, hydroxychloroquine, sulfasalazine, or leflunomide).

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 July 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 6 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Poland: 19 |
| Country: Number of subjects enrolled | Spain: 16 |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Hungary: 16 |
| Country: Number of subjects enrolled | United States: 255 |
| Country: Number of subjects enrolled | Japan: 40 |

| | |
|---|---|
| Country: Number of subjects enrolled | Mexico: 30 |
| Country: Number of subjects enrolled | Argentina: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Worldwide total number of subjects | 449 |
| EEA total number of subjects | 98 |

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) | 336 |
| From 65 to 84 years | 113 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in Argentina, Australia, Europe, Israel, Japan, Mexico, South Korea, and the United States. The first participant was screened on 27 July 2016. The last study visit occurred on 26 June 2018.

### Pre-assignment

Screening details:

688 participants were screened.

### 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 200 mg |

Arm description:

Filgotinib 200 mg tablet + placebo to match (PTM) filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Filgotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

200 mg tablet administered once daily

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PTM filgotinib 100 mg administered once daily

| | |
|---|---|
| **Arm title** | Filgotinib 100 mg |

Arm description:

Filgotinib 100 mg tablet + PTM filgotinib 200 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Filgotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg tablet administered once daily

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PTM filgotinib 200 mg administered once daily

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

PTM filgotinib 200 mg tablet + PTM filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PTM filgotinib 100 mg administered once daily

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

PTM filgotinib 200 mg administered once daily

| **Number of subjects in period 1[1]** | Filgotinib 200 mg | Filgotinib 100 mg | Placebo |
|---|---|---|---|
| Started | 147 | 153 | 148 |
| Completed | 135 | 130 | 116 |
| Not completed | 12 | 23 | 32 |
| Withdrew Consent | 4 | 11 | 20 |
| Adverse Event | 3 | 5 | 3 |
| Non-Compliance with Study Drug | 1 | - | 1 |
| Investigator's Discretion | 3 | 5 | 4 |
| Protocol Violation | - | 1 | 3 |
| Lost to follow-up | 1 | 1 | 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: 1 participant who was randomized but not treated is not included in the subject disposition table.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Filgotinib 200 mg |
| Reporting group description: | |
| Filgotinib 200 mg tablet + placebo to match (PTM) filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |
| Reporting group title | Filgotinib 100 mg |
| Reporting group description: | |
| Filgotinib 100 mg tablet + PTM filgotinib 200 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |
| Reporting group title | Placebo |
| Reporting group description: | |
| PTM filgotinib 200 mg tablet + PTM filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |

| Reporting group values | Filgotinib 200 mg | Filgotinib 100 mg | Placebo |
|---|---|---|---|
| Number of subjects | 147 | 153 | 148 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 56 | 55 | 56 |
| standard deviation | ± 12.5 | ± 12.0 | ± 12.1 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 120 | 119 | 121 |
| Male | 27 | 34 | 27 |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 7 | 9 | 10 |
| Asian | 15 | 20 | 15 |
| Black or African American | 14 | 12 | 21 |
| White | 110 | 109 | 97 |
| Other | 1 | 3 | 2 |
| Not Permitted | 0 | 0 | 3 |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 26 | 40 | 41 |
| Not Hispanic or Latino | 120 | 112 | 107 |
| Not Permitted | 1 | 1 | 0 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 448 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br> | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 360 | | |
| Male | 88 | | |
| Race<br>Units: Subjects | | | |
| American Indian or Alaska Native | 26 | | |
| Asian | 50 | | |
| Black or African American | 47 | | |
| White | 316 | | |
| Other | 6 | | |
| Not Permitted | 3 | | |
| Ethnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 107 | | |
| Not Hispanic or Latino | 339 | | |
| Not Permitted | 2 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Filgotinib 200 mg |
| Reporting group description: | |
| Filgotinib 200 mg tablet + placebo to match (PTM) filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |
| Reporting group title | Filgotinib 100 mg |
| Reporting group description: | |
| Filgotinib 100 mg tablet + PTM filgotinib 200 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |
| Reporting group title | Placebo |
| Reporting group description: | |
| PTM filgotinib 200 mg tablet + PTM filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks | |

### Primary: Percentage of Participants who Achieve an American College of Rheumatology (ACR) 20% Improvement (ACR20) Response at Week 12 using the Full Analysis Set

| | |
|---|---|
| End point title | Percentage of Participants who Achieve an American College of Rheumatology (ACR) 20% Improvement (ACR20) Response at Week 12 using the Full Analysis Set |
| End point description: | |
| ACR20 response was defined as having ≥ 20% improvement from baseline in tender joint count based on 68 joints (TJC68), ≥ 20% improvement from baseline in swollen joint count based on 66 joints (SJC66), and ≥ 20% improvement in at least 3 of the following 5 criteria: Physician's Global Assessment of Disease Activity (PGA), Subject's Global Assessment of Disease Activity (SGA), participant's pain assessment, Health Assessment Questionnaire - Disability Index (HAQ-DI) score, and high-sensitivity C-reactive protein (hsCRP). Full Analysis Set included all randomized participants who received at least 1 dose of study drug. Participants with missing outcomes were set as non-responders. For statistical analyses, the hierarchical testing procedure was performed to control the overall type I error rate for the primary and key secondary endpoints. | |
| End point type | Primary |
| End point timeframe: | |
| Week 12 | |

| End point values | Filgotinib 200 mg | Filgotinib 100 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 147 | 153 | 148 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 66.0 (58.0 to 74.0) | 57.5 (49.4 to 65.7) | 31.1 (23.3 to 38.9) | |

## Statistical analyses

| **Statistical analysis title** | ACR20 - Filgotinib 200 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 200 mg v Placebo |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [1] |
| Method | Regression, Logistic |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 34.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 23.5 |
| upper limit | 46.3 |

Notes:

[1] - P-value was calculated from the logistic regression with treatment groups and stratification factors in the model.

| **Statistical analysis title** | ACR20 - Filgotinib 100 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 100 mg v Placebo |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [2] |
| Method | Regression, Logistic |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 26.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 15 |
| upper limit | 37.9 |

Notes:

[2] - P-value was calculated from the logistic regression with treatment groups and stratification factors in the model.

## Secondary: Percentage of Participants who Achieve Disease Activity Score 28 C-Reactive Protein (DAS28(CRP)) ≤ 3.2 at Week 12 using the Full Analysis Set

| End point title | Percentage of Participants who Achieve Disease Activity Score 28 C-Reactive Protein (DAS28(CRP)) ≤ 3.2 at Week 12 using the Full Analysis Set |
|---|---|

End point description:

DAS28(CRP) is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), SGA, and hsCRP for a total possible score of 1 to 9.4. Higher values indicate more severe disease activity. Participants in the Full Analysis Set were analyzed. Participants with missing outcomes were set as non-responders. For statistical analyses, the hierarchical testing procedure was performed to control the overall type I error rate for the primary and key secondary endpoints.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 12

| End point values | Filgotinib 200 mg | Filgotinib 100 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 147 | 153 | 148 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 40.8 (32.5 to 49.1) | 37.3 (29.3 to 45.2) | 15.5 (9.4 to 21.7) | |

**Statistical analyses**

| Statistical analysis title | DAS28(CRP) Response - Filgotinib 200 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 200 mg v Placebo |
| Number of subjects included in analysis | 295 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [3] |
| Method | Regression, Logistic |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 25.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.7 |
| upper limit | 35.8 |

Notes:

[3] - P-value was calculated from the logistic regression with treatment groups and stratification factors in the model.

| Statistical analysis title | DAS28(CRP) Response - Filgotinib 100 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 100 mg v Placebo |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [4] |
| Method | Regression, Logistic |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 21.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 11.4 |
| upper limit | 32 |

Notes:

[4] - P-value was calculated from the logistic regression with treatment groups and stratification factors in the model.

**Secondary: Change from Baseline in the Health Assessment Questionnaire -**

## Disability Index (HAQ-DI) Score at Week 12

| End point title | Change from Baseline in the Health Assessment Questionnaire - Disability Index (HAQ-DI) Score at Week 12 |
|---|---|

End point description:

HAQ-DI is a self-reported tool used to assess the ability to perform tasks in 8 functional categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Responses in each functional category were collected as 0 (without any difficulty) to 3 (unable to do a task in that area). The HAQ-DI score was calculated as the average of the scores of the 8 functional areas and ranges from 0 (no disability) to 3 (completely disabled), when 6 or more categories are non-missing. Participants in the Full Analysis Set with available data were analyzed. For statistical analyses, the hierarchical testing procedure was performed to control the overall type I error rate for the primary and key secondary endpoints.

| End point type | Secondary |
|---|---|

End point timeframe:

Week 12

| **End point values** | Filgotinib 200 mg | Filgotinib 100 mg | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 137 | 140 | 129 | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | -0.55 (± 0.590) | -0.48 (± 0.602) | -0.23 (± 0.547) | |

### Statistical analyses

| **Statistical analysis title** | HAQ-DI Score - Filgotinib 200 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 200 mg v Placebo |
| Number of subjects included in analysis | 266 |
| Analysis specification | Pre-specified |
| Analysis type | other[5] |
| P-value | < 0.001 [6] |
| Method | Mixed models analysis |
| Parameter estimate | LSM of Treatment Difference |
| Point estimate | -0.32 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.45 |
| upper limit | -0.19 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.066 |

Notes:

[5] - The mixed-effects model for repeated measures (MMRM) included treatment, visit (as categorical), treatment by visit, stratification factors, and baseline value as fixed effects, and participants being the random effect.

[6] - Least square mean (LSM), 95% CI, and P-value were calculated using the MMRM. Missing change

scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

| **Statistical analysis title** | HAQ-DI Score - Filgotinib 100 mg vs Placebo |
|---|---|
| Comparison groups | Filgotinib 100 mg v Placebo |
| Number of subjects included in analysis | 269 |
| Analysis specification | Pre-specified |
| Analysis type | other[7] |
| P-value | < 0.001 [8] |
| Method | Mixed models analysis |
| Parameter estimate | LSM of Treatment Difference |
| Point estimate | -0.27 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.4 |
| upper limit | -0.14 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.065 |

Notes:

[7] - The MMRM included treatment, visit (as categorical), treatment by visit, stratification factors, and baseline value as fixed effects, and participants being the random effect.
[8] - LSM, 95% CI, and P-value were calculated using the MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events: Enrollment up to Week 24 plus 30 days; All-Cause Mortality: Enrollment up to Posttreatment Week 4

Adverse event reporting additional description:

Safety Analysis Set included all participants who received at least 1 dose of study drug.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Filgotinib 200 mg |

Reporting group description:

Filgotinib 200 mg tablet + PTM filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| | |
|---|---|
| Reporting group title | Filgotinib 100 mg |

Reporting group description:

Filgotinib 100 mg tablet + PTM filgotinib 200 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

PTM filgotinib 200 mg tablet + PTM filgotinib 100 mg tablet once daily + a stable dose of permitted csDMARDs for up to 24 weeks

| Serious adverse events | Filgotinib 200 mg | Filgotinib 100 mg | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 147 (4.08%) | 8 / 153 (5.23%) | 5 / 148 (3.38%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Laceration | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Lumbar vertebral fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Nausea | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Uterine haemorrhage | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 | | | |
| Depression | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Osteitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 2 / 148 (1.35%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess oral | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |
| Gallbladder empyema | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Vulval abscess | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 1 / 153 (0.65%) | 0 / 148 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 147 (0.00%) | 0 / 153 (0.00%) | 1 / 148 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 1 / 147 (0.68%) | 0 / 153 (0.00%) | 0 / 148 (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 |

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

| **Non-serious adverse events** | Filgotinib 200 mg | Filgotinib 100 mg | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 147 (26.53%) | 35 / 153 (22.88%) | 31 / 148 (20.95%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 9 / 153 (5.88%) | 2 / 148 (1.35%) |
| occurrences (all) | 8 | 11 | 2 |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 7 / 147 (4.76%) | 8 / 153 (5.23%) | 5 / 148 (3.38%) |
| occurrences (all) | 9 | 8 | 5 |
| Musculoskeletal and connective tissue disorders | | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 2 / 147 (1.36%) | 2 / 153 (1.31%) | 8 / 148 (5.41%) |
| occurrences (all) | 2 | 2 | 11 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 15 / 147 (10.20%) | 9 / 153 (5.88%) | 7 / 148 (4.73%) |
| occurrences (all) | 15 | 11 | 7 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 9 / 153 (5.88%) | 6 / 148 (4.05%) |
| occurrences (all) | 9 | 9 | 6 |
| Bronchitis | | | |
| subjects affected / exposed | 8 / 147 (5.44%) | 3 / 153 (1.96%) | 8 / 148 (5.41%) |
| occurrences (all) | 9 | 5 | 8 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 05 July 2016 | • Updated to reflect the removal of radiologic assessments (including removal of modified Total Sharp Score [mTSS] objectives as a measure of joint structural damage derived from x-rays)<br>• Added urine biomarker samples as an exploratory endpoint<br>• Updated study procedures to collect body weight at all study visits<br>• Updated study procedures to include Treatment Satisfaction Questionnaire for Medication (TSQM) collection at several study visits<br>• Added a carotid artery ultrasound substudy<br>• Added an assessment of quantitative immunoglobulin (Ig) at Day 1 and Week 24 (Early Termination)<br>• Added assessments of hemoglobin A1c (HbA1c), leptin, low-density lipoprotein (LDL) particle, homocysteine, and Apo A1/B for subjects participating in the carotid artery ultrasound substudy<br>• Removed peripheral blood mononuclear cell biomarker sampling<br>• Clarified criteria for interruption of study drugs<br>• Updated the definition of postmenopausal females |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported