



## Clinical trial results:

### A Randomized, Double-blind, Placebo-and Active-controlled, Multicenter, Phase 3 Study to Assess the Efficacy and Safety of Filgotinib Administered for 52 Weeks Alone and in Combination with Methotrexate (MTX) to Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are Naïve to MTX Therapy

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2016-000570-37             |
| Trial protocol           | SK BE GB HU DE CZ ES PL BG |
| Global end of trial date | 08 May 2019                |

#### Results information

|                                |             |
|--------------------------------|-------------|
| Result version number          | v1          |
| This version publication date  | 24 May 2020 |
| First version publication date | 24 May 2020 |

#### Trial information

##### Trial identification

|                       |                |
|-----------------------|----------------|
| Sponsor protocol code | GS-US-417-0303 |
|-----------------------|----------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02886728 |
| 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                       | 08 May 2019     |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 05 October 2018 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 08 May 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 evaluate the effects of filgotinib in combination with methotrexate (MTX) versus MTX alone 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 24.

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: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 08 August 2016 |
| 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: 109        |
| Country: Number of subjects enrolled | Slovakia: 8        |
| Country: Number of subjects enrolled | Spain: 34          |
| Country: Number of subjects enrolled | United Kingdom: 8  |
| Country: Number of subjects enrolled | Belgium: 19        |
| Country: Number of subjects enrolled | Bulgaria: 54       |
| Country: Number of subjects enrolled | Czech Republic: 20 |
| Country: Number of subjects enrolled | Germany: 30        |
| Country: Number of subjects enrolled | Hungary: 18        |
| Country: Number of subjects enrolled | Ireland: 2         |
| Country: Number of subjects enrolled | United States: 319 |
| Country: Number of subjects enrolled | Canada: 21         |
| Country: Number of subjects enrolled | South Africa: 19   |
| Country: Number of subjects enrolled | Australia: 18      |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | New Zealand: 16        |
| Country: Number of subjects enrolled | Italy: 3               |
| Country: Number of subjects enrolled | Israel: 2              |
| Country: Number of subjects enrolled | India: 116             |
| Country: Number of subjects enrolled | Ukraine: 69            |
| Country: Number of subjects enrolled | Russian Federation: 31 |
| Country: Number of subjects enrolled | Serbia: 16             |
| Country: Number of subjects enrolled | Romania: 10            |
| Country: Number of subjects enrolled | Mexico: 116            |
| Country: Number of subjects enrolled | Argentina: 40          |
| Country: Number of subjects enrolled | Chile: 14              |
| Country: Number of subjects enrolled | Taiwan: 23             |
| Country: Number of subjects enrolled | Thailand: 13           |
| Country: Number of subjects enrolled | Malaysia: 6            |
| Country: Number of subjects enrolled | Hong Kong: 3           |
| Country: Number of subjects enrolled | Japan: 71              |
| Country: Number of subjects enrolled | Korea, Republic of: 24 |
| Worldwide total number of subjects   | 1252                   |
| EEA total number of subjects         | 315                    |

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)                      | 997 |
| From 65 to 84 years                       | 253 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

Participants were enrolled at study sites in Asia, Africa, Australia, Europe, North America, South America, and New Zealand. The first participant was screened on 08 August 2016. The last study visit occurred on 08 May 2019.

### Pre-assignment

Screening details:

1855 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                     |
| <b>Arm title</b>             | Filgotinib 200 mg + MTX |

Arm description:

Participants were administered filgotinib 200 mg orally, once daily + placebo to match (PTM) filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Filgotinib         |
| Investigational medicinal product code |                    |
| Other name                             | GS-6034, GLPG0634  |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

200 mg administered once daily

|  |   |
|--|---|
| Investigational medicinal product name | Placebo to match (PTM ) Filgotinib 100 mg |
| 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 | MTX      |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Up to 20 mg administered once weekly

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Filgotinib 100 mg + MTX |
|------------------|-------------------------|

Arm description:

Participants were administered filgotinib 100 mg orally, once daily + PTM filgotinib 200 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|   |                               |
|---|-------------------------------|
| Investigational medicinal product name  | Filgotinib                    |
| Investigational medicinal product code  |                               |
| Other name  | GS-6034, GLPG0634             |
| Pharmaceutical forms  | Film-coated tablet            |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>100 mg administered once daily  |                               |
| Investigational medicinal product name  | PTM Filgotinib 200 mg         |
| Investigational medicinal product code  |                               |
| Other name  |                               |
| Pharmaceutical forms  | Film-coated tablet            |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>PTM filgotinib 200 mg administered once daily   |                               |
| Investigational medicinal product name  | MTX                           |
| Investigational medicinal product code  |                               |
| Other name  |                               |
| Pharmaceutical forms  | Capsule                       |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>Up to 20 mg administered once weekly  |                               |
| <b>Arm title</b>  | Filgotinib 200 mg Monotherapy |
| Arm description:<br>Participants were administered filgotinib 200 mg orally, once daily + PTM filgotinib 100 mg orally, once daily + PTM MTX orally, once weekly for up to 54 weeks.            |                               |
| Arm type  | Experimental                  |
| Investigational medicinal product name  | Filgotinib                    |
| Investigational medicinal product code  |                               |
| Other name  | GS-6034, GLPG0634             |
| Pharmaceutical forms  | Film-coated tablet            |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>200 mg administered once daily  |                               |
| Investigational medicinal product name  | PTM Filgotinib 100 mg         |
| Investigational medicinal product code  |                               |
| Other name  |                               |
| Pharmaceutical forms  | Film-coated tablet            |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>PTM filgotinib 100 mg administered once daily   |                               |
| Investigational medicinal product name  | PTM MTX                       |
| Investigational medicinal product code  |                               |
| Other name  |                               |
| Pharmaceutical forms  | Capsule                       |
| Routes of administration  | Oral use                      |
| Dosage and administration details:<br>PTM MTX capsules administered once weekly   |                               |
| <b>Arm title</b>  | MTX Monotherapy               |
| Arm description:<br>Participants were administered PTM filgotinib 200 mg orally, once daily+ PTM filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 56 weeks. |                               |
| Arm type  | Experimental                  |

|   |                       |
|---|-----------------------|
| Investigational medicinal product name        | PTM Filgotinib 200 mg |
| 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 |                       |
| Investigational medicinal product name        | PTM Filgotinib 100 mg |
| 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        | MTX                   |
| Investigational medicinal product code        |                       |
| Other name                                    |                       |
| Pharmaceutical forms                          | Capsule               |
| Routes of administration                      | Oral use              |
| Dosage and administration details:            |                       |
| Up to 20 mg administered once weekly          |                       |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy |
|---|-------------------------|-------------------------|-------------------------------|
| Started   | 416                     | 207                     | 210                           |
| Completed   | 345                     | 175                     | 174                           |
| Not completed                                       | 71                      | 32                      | 36                            |
| Withdrew Consent                                    | 31                      | 13                      | 11                            |
| Adverse Event                                       | 13                      | 5                       | 5                             |
| Non-Compliance with Study Drug                      | 1                       | -                       | 1                             |
| Death   | 3                       | 1                       | -                             |
| Pregnancy   | -                       | -                       | 1                             |
| Protocol Violation                                  | -                       | -                       | -                             |
| Lost to follow-up                                   | 12                      | 6                       | 13                            |
| Investigator`s Discretion                           | 11                      | 7                       | 5                             |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | MTX Monotherapy |
|---|-----------------|
| Started   | 416             |
| Completed   | 331             |
| Not completed                                       | 85              |
| Withdrew Consent                                    | 47              |
| Adverse Event                                       | 11              |
| Non-Compliance with Study Drug                      | -               |

|                           |    |
|---------------------------|----|
| Death                     | -  |
| Pregnancy                 | -  |
| Protocol Violation        | 4  |
| Lost to follow-up         | 12 |
| Investigator`s Discretion | 11 |

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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: Three participants who were randomised but did not receive the study drug are not included in the subject disposition table.

## Baseline characteristics

### Reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Filgotinib 200 mg + MTX       |
| Reporting group description:  |                               |
| Participants were administered filgotinib 200 mg orally, once daily + placebo to match (PTM) filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks. |                               |
| Reporting group title   | Filgotinib 100 mg + MTX       |
| Reporting group description:  |                               |
| Participants were administered filgotinib 100 mg orally, once daily + PTM filgotinib 200 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks.                    |                               |
| Reporting group title   | Filgotinib 200 mg Monotherapy |
| Reporting group description:  |                               |
| Participants were administered filgotinib 200 mg orally, once daily + PTM filgotinib 100 mg orally, once daily + PTM MTX orally, once weekly for up to 54 weeks.                            |                               |
| Reporting group title   | MTX Monotherapy               |
| Reporting group description:  |                               |
| Participants were administered PTM filgotinib 200 mg orally, once daily+ PTM filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 56 weeks.                 |                               |

| Reporting group values | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy |
|------------------------|-------------------------|-------------------------|-------------------------------|
| Number of subjects     | 416                     | 207                     | 210                           |
| Age categorical        |                         |                         |                               |
| Units: Subjects        |                         |                         |                               |

|  |        |        |        |
|--|--------|--------|--------|
| Age continuous                             |        |        |        |
| Units: years                               |        |        |        |
| arithmetic mean                            | 53     | 54     | 52     |
| standard deviation                         | ± 13.8 | ± 12.6 | ± 13.9 |
| Gender categorical                         |        |        |        |
| Units: Subjects                            |        |        |        |
| Female                                     | 325    | 158    | 166    |
| Male                                       | 91     | 49     | 44     |
| Race                                       |        |        |        |
| Units: Subjects                            |        |        |        |
| American Indian or Alaska Native           | 26     | 12     | 18     |
| Asian: Japanese                            | 23     | 11     | 12     |
| Asian: Chinese/Taiwanese/Hong Kong Chinese | 7      | 4      | 6      |
| Asian: Vietnamese                          | 1      | 0      | 0      |
| Asian: Korean                              | 6      | 8      | 2      |
| Asian: Other                               | 53     | 28     | 27     |
| Black or African American                  | 15     | 8      | 8      |
| Native Hawaiian or Pacific Islander        | 1      | 0      | 1      |
| White                                      | 278    | 132    | 135    |
| Other                                      | 6      | 4      | 0      |
| Not Permitted                              | 0      | 0      | 1      |
| Ethnicity                                  |        |        |        |
| Units: Subjects                            |        |        |        |
| Hispanic or Latino                         | 93     | 40     | 45     |



|                        |     |     |     |
|------------------------|-----|-----|-----|
| Not Hispanic or Latino | 322 | 167 | 165 |
| Not Permitted          | 1   | 0   | 0   |

|  |          |          |          |
|--|----------|----------|----------|
| Health Assessment Questionnaire-Disability Index (HAQ-DI) Score  |          |          |          |
| Full Analysis Set included participants who were randomised and received at least 1 dose of study drug. It is scored on a scale of 0-3, 0 indicating no disability and 3 indicating complete disability. For additional description, please see outcome measure 2 (N=414,207,210,416).                 |          |          |          |
| Units: score on a scale  |          |          |          |
| arithmetic mean  | 1.52     | 1.56     | 1.56     |
| standard deviation   | ± 0.622  | ± 0.654  | ± 0.655  |
| Modified Total Sharp Score [mTSS]  |          |          |          |
| Participants in the Full Analysis Set with available data were analyzed. It is scored on a scale of 0-448, 0 indicating no erosion, normal joint spaces and 3 indicating maximum erosion, complete loss of joint spaces. For additional description, please see outcome measure 4 (N=410,204,204,408). |          |          |          |
| Units: score on a scale  |          |          |          |
| arithmetic mean  | 11.35    | 13.31    | 16.53    |
| standard deviation   | ± 19.922 | ± 26.980 | ± 32.372 |

| Reporting group values | MTX Monotherapy | Total |  |
|------------------------|-----------------|-------|--|
| Number of subjects     | 416             | 1249  |  |
| Age categorical        |                 |       |  |
| Units: Subjects        |                 |       |  |

|  |        |     |  |
|--|--------|-----|--|
| Age continuous                             |        |     |  |
| Units: years                               |        |     |  |
| arithmetic mean                            | 53     |     |  |
| standard deviation                         | ± 13.7 | -   |  |
| Gender categorical                         |        |     |  |
| Units: Subjects                            |        |     |  |
| Female                                     | 312    | 961 |  |
| Male                                       | 104    | 288 |  |
| Race                                       |        |     |  |
| Units: Subjects                            |        |     |  |
| American Indian or Alaska Native           | 33     | 89  |  |
| Asian: Japanese                            | 25     | 71  |  |
| Asian: Chinese/Taiwanese/Hong Kong Chinese | 10     | 27  |  |
| Asian: Vietnamese                          | 0      | 1   |  |
| Asian: Korean                              | 8      | 24  |  |
| Asian: Other                               | 42     | 150 |  |
| Black or African American                  | 14     | 45  |  |
| Native Hawaiian or Pacific Islander        | 3      | 5   |  |
| White                                      | 278    | 823 |  |
| Other                                      | 3      | 13  |  |
| Not Permitted                              | 0      | 1   |  |
| Ethnicity                                  |        |     |  |
| Units: Subjects                            |        |     |  |
| Hispanic or Latino                         | 84     | 262 |  |
| Not Hispanic or Latino                     | 332    | 986 |  |
| Not Permitted                              | 0      | 1   |  |

|  |          |   |  |
|--|----------|---|--|
| Health Assessment Questionnaire-Disability Index (HAQ-DI) Score  |          |   |  |
| Full Analysis Set included participants who were randomised and received at least 1 dose of study drug. It is scored on a scale of 0-3, 0 indicating no disability and 3 indicating complete disability. For additional description, please see outcome measure 2 (N=414,207,210,416).                 |          |   |  |
| Units: score on a scale  |          |   |  |
| arithmetic mean  | 1.60     |   |  |
| standard deviation   | ± 0.625  | - |  |
| Modified Total Sharp Score [mTSS]  |          |   |  |
| Participants in the Full Analysis Set with available data were analyzed. It is scored on a scale of 0-448, 0 indicating no erosion, normal joint spaces and 3 indicating maximum erosion, complete loss of joint spaces. For additional description, please see outcome measure 4 (N=410,204,204,408). |          |   |  |
| Units: score on a scale  |          |   |  |
| arithmetic mean  | 13.72    |   |  |
| standard deviation   | ± 29.168 | - |  |

## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Filgotinib 200 mg + MTX       |
| Reporting group description:<br>Participants were administered filgotinib 200 mg orally, once daily + placebo to match (PTM) filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks. |                               |
| Reporting group title   | Filgotinib 100 mg + MTX       |
| Reporting group description:<br>Participants were administered filgotinib 100 mg orally, once daily + PTM filgotinib 200 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks.                    |                               |
| Reporting group title   | Filgotinib 200 mg Monotherapy |
| Reporting group description:<br>Participants were administered filgotinib 200 mg orally, once daily + PTM filgotinib 100 mg orally, once daily + PTM MTX orally, once weekly for up to 54 weeks.                            |                               |
| Reporting group title   | MTX Monotherapy               |
| Reporting group description:<br>Participants were administered PTM filgotinib 200 mg orally, once daily+ PTM filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 56 weeks.                 |                               |

### Primary: Percentage of Participants who Achieved an American College of Rheumatology (ACR) 20% Improvement (ACR20) Response at Week 24

|  |   |
|--|---|
| End point title  | Percentage of Participants who Achieved an American College of Rheumatology (ACR) 20% Improvement (ACR20) Response at Week 24 |
| End point description:<br>ACR20 response is achieved when the participant has: $\geq 20\%$ improvement (reduction) from baseline in tender joint count based on 68 joints (TJC68), swollen joint count based on 66 joints (SJC66) and in at least 3 of the following 5 items: physician's global assessment of disease activity (PGA) and subject's global assessment of disease activity (SGA) assessed using visual analog scale (VAS) on a scale of 0-100(0 and 100 indicate no disease activity and maximum disease activity)participant`s pain assessment using VAS on a scale of 0-100(0 and 100 indicate no pain and unbearable pain) health assessment questionnaire-disability index (HAQ-DI) score contains 20 questions,8 components: dressing/grooming,arising,eating, walking,hygiene,reach,grip and activities and scored on a scale of 0-3(0 and 3 indicate without difficulty and unable to do)high-sensitivity C-reactive protein (hsCRP).The Full Analysis Set included participants who were randomised and received at least 1 dose of study drug. |   |
| End point type   | Primary   |
| End point timeframe:<br>Week 24  |   |

| End point values                 | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy | MTX Monotherapy     |
|----------------------------------|-------------------------|-------------------------|-------------------------------|---------------------|
| Subject group type               | Reporting group         | Reporting group         | Reporting group               | Reporting group     |
| Number of subjects analysed      | 416                     | 207                     | 210                           | 416                 |
| Units: percentage of responders  |                         |                         |                               |                     |
| number (confidence interval 95%) | 81.0 (77.1 to 84.9)     | 80.2 (74.5 to 85.9)     | 78.1 (72.3 to 83.9)           | 71.4 (66.9 to 75.9) |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 200 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 832  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.001 <sup>[1]</sup>                     |
| Method                                  | Regression, Logistic                       |
| Parameter estimate                      | Difference in Response Rates               |
| Point estimate                          | 9.6  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 3.6  |
| upper limit                             | 15.6                                       |

Notes:

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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 100 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 100 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 623  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | = 0.017 <sup>[2]</sup>                     |
| Method                                  | Regression, Logistic                       |
| Parameter estimate                      | Difference in Response Rates               |
| Point estimate                          | 8.8  |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 1.5  |
| upper limit                             | 16.1                                       |

Notes:

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

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Filgotinib 200 mg Monotherapy vs MTX Monotherapy |
| Comparison groups                 | Filgotinib 200 mg Monotherapy v MTX Monotherapy  |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 626                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.058 <sup>[3]</sup>       |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Difference in Response Rates |
| Point estimate                          | 6.7                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -0.7                         |
| upper limit                             | 14.1                         |

Notes:

[3] - 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 24

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in the Health Assessment Questionnaire-Disability Index (HAQ-DI) Score at Week 24 |
|-----------------|--|

End point description:

The HAQ-DI score is defined as the average of the scores of eight functional categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities), usually administered by the participant. Responses in each functional category are collected as 0 (without any difficulty) to 3 (unable to do a task in that area), with or without aids or devices. The eight category scores are averaged into an overall HAQ-DI score on a scale from 0 (no disability) to 3 (completely disabled) when 6 or more categories are non-missing, total possible score is 3. If more than 2 categories are missing, the HAQ-DI score is set to missing. Negative change from baseline indicates improvement (less disability). Mixed-effects model for repeated measures (MMRM) was used for analyses. Participants in the Full Analysis Set with available data were analyzed.

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

End point timeframe:

Baseline; Week 24

| End point values                     | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy | MTX Monotherapy |
|--------------------------------------|-------------------------|-------------------------|-------------------------------|-----------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group               | Reporting group |
| Number of subjects analysed          | 372                     | 190                     | 185                           | 370             |
| Units: score on a scale              |                         |                         |                               |                 |
| arithmetic mean (standard deviation) | -0.94 (± 0.722)         | -0.90 (± 0.675)         | -0.89 (± 0.631)               | -0.79 (± 0.634) |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Filgotinib 200 mg + MTX vs MTX Monotherapy |
| Comparison groups          | Filgotinib 200 mg + MTX v MTX Monotherapy  |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 742                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[4]</sup>    |
| P-value                                 | < 0.001 <sup>[5]</sup>        |
| Method                                  | MMRM                          |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | -0.19                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.27                         |
| upper limit                             | -0.11                         |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.041                         |

Notes:

[4] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[5] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 100 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 100 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 560  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[6]</sup>                 |
| P-value                                 | = 0.009 <sup>[7]</sup>                     |
| Method                                  | MMRM                                       |
| Parameter estimate                      | Least Squares Mean Difference              |
| Point estimate                          | -0.13                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.23                                      |
| upper limit                             | -0.03                                      |
| Variability estimate                    | Standard error of the mean                 |
| Dispersion value                        | 0.049                                      |

Notes:

[6] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[7] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 200 mg Monotherapy vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg Monotherapy v MTX Monotherapy  |
| Number of subjects included in analysis | 555  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority <sup>[8]</sup>                       |
| P-value                                 | = 0.032 <sup>[9]</sup>                           |
| Method                                  | MMRM   |
| Parameter estimate                      | Least Squares Mean Difference                    |
| Point estimate                          | -0.11  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.2                       |
| upper limit          | -0.01                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.05                       |

Notes:

[8] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[9] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

### Secondary: Percentage of Participants who Achieved Disease Activity Score for 28 Joint Count Using C-Reactive Protein [DAS28 (CRP)] < 2.6 at Week 24

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants who Achieved Disease Activity Score for 28 Joint Count Using C-Reactive Protein [DAS28 (CRP)] < 2.6 at Week 24 |
|-----------------|---|

End point description:

The DAS28 score is a measure of the participant's disease activity calculated using the tender joint counts (28 joints), swollen joint counts (28 joints), Patient's Global Assessment of Disease Activity (visual analog scale: 0 = no disease activity to 100 = maximum disease activity), and CRP for a total possible score of 1 to 9.4. Higher values indicate higher disease activity. Participants in the Full Analysis Set were analyzed.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Week 24              |           |

| End point values                 | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy | MTX Monotherapy     |
|----------------------------------|-------------------------|-------------------------|-------------------------------|---------------------|
| Subject group type               | Reporting group         | Reporting group         | Reporting group               | Reporting group     |
| Number of subjects analysed      | 416                     | 207                     | 210                           | 416                 |
| Units: percentage of responders  |                         |                         |                               |                     |
| number (confidence interval 95%) | 54.1 (49.2 to 59.0)     | 42.5 (35.5 to 49.5)     | 42.4 (35.5 to 49.3)           | 29.1 (24.6 to 33.6) |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Filgotinib 200 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 832  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.001 <sup>[10]</sup>                    |
| Method                                  | Regression, Logistic                       |
| Parameter estimate                      | Difference in Response Rates               |
| Point estimate                          | 25   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 18.3    |
| upper limit         | 31.7    |

Notes:

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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 100 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 100 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 623  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority                                |
| P-value                                 | < 0.001 <sup>[11]</sup>                    |
| Method                                  | Regression, Logistic                       |
| Parameter estimate                      | Difference in Response Rates               |
| Point estimate                          | 13.4                                       |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | 5  |
| upper limit                             | 21.8                                       |

Notes:

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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 200 mg Monotherapy vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg Monotherapy v MTX Monotherapy  |
| Number of subjects included in analysis | 626  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority                                      |
| P-value                                 | < 0.001 <sup>[12]</sup>                          |
| Method                                  | Regression, Logistic                             |
| Parameter estimate                      | Difference in Response Rates                     |
| Point estimate                          | 13.3   |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | 5  |
| upper limit                             | 21.6   |

Notes:

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

## **Secondary: Change from Baseline in Modified Total Sharp Score (mTSS) at Week 24**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Modified Total Sharp Score (mTSS) at Week 24 |
|-----------------|--|

End point description:

Participant`s radiographs of bilateral hands, wrists and feet are taken and evaluated through central review using the mTSS method. The mTSS (range [0, 448]) is defined as the erosion score (range [0, 280]) plus the joint space narrowing (JSN) score (range [0, 168]). An erosion score of 0 to 5 is given to each joint in the hands and wrists, and a score of 0 to 10 is given to each joint in the feet where 0 indicates no erosion while 5 or 10 indicates extensive loss of bone (maximum erosion). JSN is scored



from 0 to 4, with 0 indicating no/normal JSN and 4 indicating complete loss of joint space. The maximal TSS is 448. Positive change in value indicates improvement (less erosion of bone, normal joint spaces). MMRM was used for analyses. Participants in the Full Analysis Set with available data were analyzed.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline; Week 24    |           |

| End point values                     | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy | MTX Monotherapy     |
|--------------------------------------|-------------------------|-------------------------|-------------------------------|---------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group               | Reporting group     |
| Number of subjects analysed          | 355                     | 184                     | 173                           | 356                 |
| Units: score on a scale              |                         |                         |                               |                     |
| arithmetic mean (standard deviation) | 0.21 ( $\pm$ 1.684)     | 0.22 ( $\pm$ 1.526)     | -0.04 ( $\pm$ 1.710)          | 0.51 ( $\pm$ 2.887) |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 200 mg + MTX vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg + MTX v MTX Monotherapy  |
| Number of subjects included in analysis | 711  |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | superiority <sup>[13]</sup>                |
| P-value                                 | = 0.068 <sup>[14]</sup>                    |
| Method                                  | MMRM                                       |
| Parameter estimate                      | Least Squares Mean Difference              |
| Point estimate                          | -0.29                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -0.61                                      |
| upper limit                             | 0.02                                       |
| Variability estimate                    | Standard error of the mean                 |
| Dispersion value                        | 0.161                                      |

Notes:

[13] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[14] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Filgotinib 100 mg + MTX vs MTX Monotherapy |
| Comparison groups                 | Filgotinib 100 mg + MTX v MTX Monotherapy  |

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 540                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority <sup>[15]</sup>   |
| P-value                                 | = 0.14 <sup>[16]</sup>        |
| Method                                  | MMRM                          |
| Parameter estimate                      | Least Squares Mean Difference |
| Point estimate                          | -0.29                         |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | -0.67                         |
| upper limit                             | 0.1                           |
| Variability estimate                    | Standard error of the mean    |
| Dispersion value                        | 0.195                         |

Notes:

[15] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[16] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | Filgotinib 200 mg Monotherapy vs MTX Monotherapy |
| Comparison groups                       | Filgotinib 200 mg Monotherapy v MTX Monotherapy  |
| Number of subjects included in analysis | 529  |
| Analysis specification                  | Pre-specified                                    |
| Analysis type                           | superiority <sup>[17]</sup>                      |
| P-value                                 | = 0.006 <sup>[18]</sup>                          |
| Method                                  | MMRM   |
| Parameter estimate                      | Least Squares Mean Difference                    |
| Point estimate                          | -0.55  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -0.94  |
| upper limit                             | -0.16  |
| Variability estimate                    | Standard error of the mean                       |
| Dispersion value                        | 0.199  |

Notes:

[17] - LS-Mean, 95% CI, and P-value were provided from MMRM. Missing change scores were not imputed using the MMRM approach assuming an unstructured variance-covariance matrix for the repeated measures.

[18] - MMRM model included treatment, visit, treatment by visit, stratification factors, and baseline value as fixed effects, and subjects being the random effect.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First dose date up to last dose date (Maximum: 56 weeks) plus 30 days

Adverse event reporting additional description:

The 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 | 22.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants were administered filgotinib 200 mg orally, once daily + placebo to match (PTM) filgotinib 100 mg orally, once daily + methotrexate (MTX) up to 20 mg orally, once weekly for up to 54 weeks.

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

Reporting group description:

Participants were administered filgotinib 100 mg orally, once daily + PTM filgotinib 200 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 54 weeks.

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

Reporting group description:

Participants were administered filgotinib 200 mg orally, once daily + PTM filgotinib 100 mg orally, once daily + PTM MTX orally, once weekly for up to 54 weeks.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | MTX Monotherapy |
|-----------------------|-----------------|

Reporting group description:

Participants were administered PTM filgotinib 200 mg orally, once daily+ PTM filgotinib 100 mg orally, once daily + MTX up to 20 mg orally, once weekly for up to 56 weeks.

| Serious adverse events  | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy |
|---|-------------------------|-------------------------|-------------------------------|
| Total subjects affected by serious adverse events                   |                         |                         |                               |
| subjects affected / exposed   | 26 / 416 (6.25%)        | 13 / 207 (6.28%)        | 17 / 210 (8.10%)              |
| number of deaths (all causes)                                       | 3                       | 1                       | 0                             |
| number of deaths resulting from adverse events                      |                         |                         |                               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                         |                               |
| Breast cancer   |                         |                         |                               |
| subjects affected / exposed   | 1 / 416 (0.24%)         | 0 / 207 (0.00%)         | 0 / 210 (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                         |
| Giant cell tumour of tendon sheath                                  |                         |                         |                               |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Ovarian adenoma                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Small cell lung cancer                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Vascular disorders                              |                 |                 |                 |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Rheumatoid vasculitis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Varicose vein                                   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyrexia  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| 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 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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      |                 |                 |                 |
| Pulmonary embolism                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Acute respiratory failure                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Bronchiectasis                                       |                 |                 |                 |
| subjects affected / exposed                          | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Emphysema  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Interstitial lung disease                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| Lung consolidation                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleurisy  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Investigations                                  |                 |                 |                 |
| White blood cell count decreased                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Accidental overdose                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Incisional hernia, obstructive                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Atrial septal defect                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Lupus myocarditis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Supraventricular tachycardia<br>subjects affected / exposed | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                                    |                 |                 |                 |
| Cerebral amyloid angiopathy<br>subjects affected / exposed  | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral artery occlusion<br>subjects affected / exposed    | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical radiculopathy<br>subjects affected / exposed       | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial paralysis<br>subjects affected / exposed             | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke<br>subjects affected / exposed          | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Intracranial aneurysm<br>subjects affected / exposed        | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 0           |
| Ischaemic stroke<br>subjects affected / exposed             | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to<br>treatment / all          | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all               | 0 / 0           | 0 / 0           | 0 / 0           |
| Subarachnoid haemorrhage                                    |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vertebral artery aneurysm                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Bone marrow failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukocytosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Pancytopenia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Thrombocytosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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                      |                 |                 |                 |
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 416 (0.48%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Proctitis                                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Appendiceal mucocoele                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Diverticular perforation                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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 fistula                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Megacolon                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Prurigo   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Endocrine disorders                             |                 |                 |                 |
| Hyperthyroidism                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 2 / 207 (0.97%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal osteoarthritis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 2 / 207 (0.97%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc disorder                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Pathological fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Spinal stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Infections and infestations                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 4 / 416 (0.96%) | 1 / 207 (0.48%) | 0 / 210 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abdominal hernia infection                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Arthritis infective                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Lymphangitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumocystis jirovecii pneumonia                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Pneumonia bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Pneumonia cryptococcal                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Pulmonary sepsis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Pyelonephritis                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Pyonephrosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 1 / 207 (0.48%) | 0 / 210 (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           |
| Skin infection                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Tracheobronchitis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 1 / 210 (0.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Hypertriglyceridaemia                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 416 (0.00%) | 0 / 207 (0.00%) | 0 / 210 (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           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 416 (0.24%) | 0 / 207 (0.00%) | 0 / 210 (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

MTX Monotherapy

|   |                  |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 28 / 416 (6.73%) |  |  |
| number of deaths (all causes)                                       | 0                |  |  |
| number of deaths resulting from adverse events                      |                  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Breast cancer   |                  |  |  |
| subjects affected / exposed   | 1 / 416 (0.24%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Giant cell tumour of tendon sheath                                  |                  |  |  |
| subjects affected / exposed   | 0 / 416 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Ovarian adenoma   |                  |  |  |
| subjects affected / exposed   | 0 / 416 (0.00%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 0            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Prostate cancer   |                  |  |  |
| subjects affected / exposed   | 1 / 416 (0.24%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Small cell lung cancer  |                  |  |  |
| subjects affected / exposed   | 1 / 416 (0.24%)  |  |  |
| occurrences causally related to treatment / all                     | 1 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Squamous cell carcinoma   |                  |  |  |
| subjects affected / exposed   | 1 / 416 (0.24%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders  |                  |  |  |
| Deep vein thrombosis  |                  |  |  |
| subjects affected / exposed   | 1 / 416 (0.24%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Hypertension   |                 |  |  |
| subjects affected / exposed                          | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Rheumatoid vasculitis                                |                 |  |  |
| subjects affected / exposed                          | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Varicose vein  |                 |  |  |
| subjects affected / exposed                          | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Systemic inflammatory response syndrome              |                 |  |  |
| subjects affected / exposed                          | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders      |                 |  |  |
| Pulmonary embolism                                   |                 |  |  |
| subjects affected / exposed                          | 2 / 416 (0.48%) |  |  |
| occurrences causally related to treatment / all      | 1 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Acute respiratory failure                            |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchiectasis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Emphysema                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Interstitial lung disease                       |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung consolidation                              |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pleurisy  |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| White blood cell count decreased<br>subjects affected / exposed | 0 / 416 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Injury, poisoning and procedural<br>complications               |                 |  |  |
| Femur fracture  |                 |  |  |
| subjects affected / exposed                                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Accidental overdose   |                 |  |  |
| subjects affected / exposed                                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Incisional hernia, obstructive                                  |                 |  |  |
| subjects affected / exposed                                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Subdural haematoma  |                 |  |  |
| subjects affected / exposed                                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Congenital, familial and genetic<br>disorders                   |                 |  |  |
| Atrial septal defect  |                 |  |  |
| subjects affected / exposed                                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Cardiac disorders   |                 |  |  |
| Atrial fibrillation   |                 |  |  |
| subjects affected / exposed                                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to<br>treatment / all              | 1 / 2           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Acute myocardial infarction                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lupus myocarditis                               |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial infarction                           |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Supraventricular tachycardia                    |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Cerebral amyloid angiopathy                     |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebral artery occlusion                       |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cervical radiculopathy                          |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Facial paralysis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhagic stroke                             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intracranial aneurysm                           |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Subarachnoid haemorrhage                        |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vertebral artery aneurysm                       |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Bone marrow failure                             |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Leukocytosis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancytopenia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombocytosis                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain upper                            |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastritis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Proctitis                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Appendiceal mucocoele                           |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticular perforation                        |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal fistula                        |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal haemorrhage                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Megacolon                                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Small intestinal obstruction                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Upper gastrointestinal haemorrhage              |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Prurigo   |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endocrine disorders                             |                 |  |  |
| Hyperthyroidism                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Osteoarthritis                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal osteoarthritis                           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Arthralgia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc disorder                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intervertebral disc protrusion                  |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pathological fracture                           |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal stenosis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis                                      |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Abdominal hernia infection                      |                 |  |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Appendicitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Arthritis infective                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Herpes zoster                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lymphangitis                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumocystis jirovecii pneumonia                |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia bacterial                             |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia cryptococcal                          |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary sepsis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyelonephritis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pyonephrosis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tracheobronchitis                               |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypertriglyceridaemia                           |                 |  |  |
| subjects affected / exposed                     | 1 / 416 (0.24%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypoglycaemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 416 (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 %

| <b>Non-serious adverse events</b>                     | Filgotinib 200 mg + MTX | Filgotinib 100 mg + MTX | Filgotinib 200 mg Monotherapy |
|---|-------------------------|-------------------------|-------------------------------|
| Total subjects affected by non-serious adverse events |                         |                         |                               |
| subjects affected / exposed                           | 179 / 416 (43.03%)      | 88 / 207 (42.51%)       | 78 / 210 (37.14%)             |
| Investigations  |                         |                         |                               |
| Alanine aminotransferase increased                    |                         |                         |                               |
| subjects affected / exposed                           | 23 / 416 (5.53%)        | 6 / 207 (2.90%)         | 3 / 210 (1.43%)               |
| occurrences (all)                                     | 26                      | 8                       | 3                             |
| Vascular disorders                                    |                         |                         |                               |
| Hypertension  |                         |                         |                               |
| subjects affected / exposed                           | 21 / 416 (5.05%)        | 10 / 207 (4.83%)        | 15 / 210 (7.14%)              |
| occurrences (all)                                     | 25                      | 10                      | 15                            |
| Nervous system disorders                              |                         |                         |                               |
| Headache  |                         |                         |                               |
| subjects affected / exposed                           | 23 / 416 (5.53%)        | 8 / 207 (3.86%)         | 8 / 210 (3.81%)               |
| occurrences (all)                                     | 24                      | 10                      | 8                             |
| Gastrointestinal disorders                            |                         |                         |                               |

|  |                         |                         |                        |
|--|-------------------------|-------------------------|------------------------|
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 51 / 416 (12.26%)<br>58 | 35 / 207 (16.91%)<br>43 | 15 / 210 (7.14%)<br>15 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 17 / 416 (4.09%)<br>18  | 12 / 207 (5.80%)<br>15  | 6 / 210 (2.86%)<br>8   |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)               | 17 / 416 (4.09%)<br>17  | 15 / 207 (7.25%)<br>16  | 4 / 210 (1.90%)<br>4   |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 42 / 416 (10.10%)<br>48 | 9 / 207 (4.35%)<br>11   | 14 / 210 (6.67%)<br>15 |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 21 / 416 (5.05%)<br>27  | 17 / 207 (8.21%)<br>20  | 17 / 210 (8.10%)<br>22 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 19 / 416 (4.57%)<br>23  | 13 / 207 (6.28%)<br>14  | 11 / 210 (5.24%)<br>11 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)   | 12 / 416 (2.88%)<br>15  | 11 / 207 (5.31%)<br>11  | 4 / 210 (1.90%)<br>4   |

|  |                        |  |  |
|--|------------------------|--|--|
| <b>Non-serious adverse events</b>  | MTX Monotherapy        |  |  |
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                     | 164 / 416 (39.42%)     |  |  |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 11 / 416 (2.64%)<br>12 |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                   | 14 / 416 (3.37%)<br>14 |  |  |
| Nervous system disorders<br>Headache   |                        |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 25 / 416 (6.01%)<br>30 |  |  |
| Gastrointestinal disorders                       |                        |  |  |
| Nausea   |                        |  |  |
| subjects affected / exposed                      | 50 / 416 (12.02%)      |  |  |
| occurrences (all)                                | 62                     |  |  |
| Diarrhoea  |                        |  |  |
| subjects affected / exposed                      | 21 / 416 (5.05%)       |  |  |
| occurrences (all)                                | 23                     |  |  |
| Skin and subcutaneous tissue disorders           |                        |  |  |
| Alopecia   |                        |  |  |
| subjects affected / exposed                      | 20 / 416 (4.81%)       |  |  |
| occurrences (all)                                | 20                     |  |  |
| Infections and infestations                      |                        |  |  |
| Upper respiratory tract infection                |                        |  |  |
| subjects affected / exposed                      | 34 / 416 (8.17%)       |  |  |
| occurrences (all)                                | 40                     |  |  |
| Nasopharyngitis                                  |                        |  |  |
| subjects affected / exposed                      | 25 / 416 (6.01%)       |  |  |
| occurrences (all)                                | 31                     |  |  |
| Urinary tract infection                          |                        |  |  |
| subjects affected / exposed                      | 11 / 416 (2.64%)       |  |  |
| occurrences (all)                                | 12                     |  |  |
| Bronchitis                                       |                        |  |  |
| subjects affected / exposed                      | 15 / 416 (3.61%)       |  |  |
| occurrences (all)                                | 16                     |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment  |
|--------------|--|
| 05 July 2016 | <ul style="list-style-type: none"><li>• Added urine biomarker samples as an exploratory endpoint</li><li>• Updated study procedures to collect body weight at all study visits</li><li>• Updated study procedures to include Treatment Satisfaction Questionnaire for Medication (TSQM) collection every 3 months</li><li>• Updated the Prior and Concomitant Medications section to clarify documentation of prior medications and restriction window on injectable corticosteroids</li><li>• Added an assessment of quantitative immunoglobulin (Ig) at Day 1, Week 24, and Week 52/ET</li><li>• Updated to remove peripheral blood mononuclear cell substudy</li><li>• Clarified eligibility criteria as needed</li><li>• Updated the definition of postmenopausal females</li><li>• Clarified that the magnetic resonance imaging (MRI) substudy would be performed post randomization within 7 days of first dose, at Week 12, and at Week 24</li><li>• Clarified that radiographs performed after Day 1 could be done <math>\pm</math> 7 days of the scheduled visit</li><li>• Terminology for the open label extension study was changed to long-term extension (LTE) study</li><li>• Updated the disease specific questionnaires and activity scales to accurately reflect the relevant literature</li></ul> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported