



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
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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
Arm title	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

Arm title	Filgotinib 100 mg + MTX
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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
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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: 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: 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: Up to 20 mg administered once weekly	
Arm title	Filgotinib 200 mg Monotherapy
Arm 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.	
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	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	PTM MTX
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: PTM MTX capsules administered once weekly	
Arm title	MTX Monotherapy
Arm 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.	
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	

Number of subjects in period 1^[1]	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

Number of subjects in period 1^[1]	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

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: 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.	

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: 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: 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

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 ^[1]
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.

Statistical analysis title	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 ^[2]
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.

Statistical analysis title	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 ^[3]
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
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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
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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 ^[4]
P-value	< 0.001 ^[5]
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.

Statistical analysis title	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 ^[6]
P-value	= 0.009 ^[7]
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.

Statistical analysis title	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 ^[8]
P-value	= 0.032 ^[9]
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
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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 ^[10]
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.

Statistical analysis title	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 ^[11]
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.

Statistical analysis title	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 ^[12]
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
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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

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	711
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.068 ^[14]
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.

Statistical analysis title	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 ^[15]
P-value	= 0.14 ^[16]
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.

Statistical analysis title	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 ^[17]
P-value	= 0.006 ^[18]
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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Filgotinib 200 mg + MTX
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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
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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
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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
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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 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
Nervous system disorders			
Cerebral amyloid angiopathy 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
Cerebral artery occlusion 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
Cervical radiculopathy 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
Facial paralysis 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
Haemorrhagic stroke 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
Intracranial 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
Ischaemic stroke 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
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		
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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 subjects affected / exposed	0 / 416 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Accidental overdose			
subjects affected / exposed	0 / 416 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incisional hernia, obstructive			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 416 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 416 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 416 (0.24%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to 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 %

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

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

subjects affected / exposed occurrences (all)	25 / 416 (6.01%) 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">• Added urine biomarker samples as an exploratory endpoint• Updated study procedures to collect body weight at all study visits• Updated study procedures to include Treatment Satisfaction Questionnaire for Medication (TSQM) collection every 3 months• Updated the Prior and Concomitant Medications section to clarify documentation of prior medications and restriction window on injectable corticosteroids• Added an assessment of quantitative immunoglobulin (Ig) at Day 1, Week 24, and Week 52/ET• Updated to remove peripheral blood mononuclear cell substudy• Clarified eligibility criteria as needed• Updated the definition of postmenopausal females• 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• Clarified that radiographs performed after Day 1 could be done \pm 7 days of the scheduled visit• Terminology for the open label extension study was changed to long-term extension (LTE) study• Updated the disease specific questionnaires and activity scales to accurately reflect the relevant literature

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported