Clinical trial results:
A Phase 3B/4 Randomized Double Blind Placebo Controlled Study of Methotrexate (MTX) Withdrawal in Subjects With Rheumatoid Arthritis (RA) Treated With Tofacitinib 11mg Modified Release (MR) Formulation

Summary

EudraCT number	2016-001825-15
Trial protocol	SK BG BE DE GB PL ES CZ HU IT
Global end of trial date	17 December 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	A3921192

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 18007181021, ClinicalTrials.gov_Inquiries@pfizer.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	30 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2018
Global end of trial reached?	Yes
Global end of trial date	17 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of tofacitinib MR 11mg monotherapy to tofacitinib MR 11mg with continued MTX, as measured by the change in the Disease Activity Score utilizing 4 components including erythrocyte sedimentation rate (DAS28-4 [ESR]) from randomization (at Week 24) to the end of the double-blind MTX withdrawal phase (at Week 48).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Mexico: 25
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 49
Country: Number of subjects enrolled	Czech Republic: 60
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 30
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 17
Country: Number of subjects enrolled	Philippines: 12
Country: Number of subjects enrolled	Poland: 130
Country: Number of subjects enrolled	Russian Federation: 37
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 276
Worldwide total number of subjects	694
EEA total number of subjects	318

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)	508
From 65 to 84 years	184
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 136 sites in the 16 countries from 01 September 2016 to 17 December 2018.

Pre-assignment

Screening details:

A total of 873 subjects were screened in the open label phase. 694 subjects were treated.

Period 1

Period 1 title	Open Label Phase (24 Weeks)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Open Label: Tofacitinib 11 mg + Methotrexate

Arm description:

Subjects with moderate to severe rheumatoid arthritis (RA) and who were insufficiently responding to their stable dose of methotrexate treatment previous to enrollment in this study, received Tofacitinib modified release (MR) 11 milligram (mg) tablet once daily (QD) with methotrexate (as background therapy) at their previous stable dose for 24 weeks in open label phase (OL).

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tofacitinib MR 11 mg tablet QD for 24 weeks in open label phase.

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

Dosage and administration details:

Subjects received methotrexate at their previous stable dose for 24 weeks in open label phase.

Number of subjects in period 1	Open Label: Tofacitinib 11 mg + Methotrexate
Started	694
Completed	623
Not completed	71
Consent withdrawn by subject	6
Adverse event, non-fatal	39
Insufficient Clinical Response	7

Medication error,no linked adverse event	2
Unspecified	4
Lost to follow-up	8
Protocol deviation	5

Period 2

Period 2 title	Double Blind Phase (24 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	No
Arm title	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo

Arm description:

Subjects with low disease activity (LDA) at the end of open label phase were randomized to receive Tofacitinib MR 11 mg tablet once daily with matching placebo to blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tofacitinib MR 11 mg tablet QD for 24 weeks in double blind phase.

Investigational medicinal product name	Methotrexate Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received methotrexate matching placebo at their previous stable dose for 24 weeks in double blind phase.

Arm title	Double Blind: Tofacitinib 11 mg + Methotrexate

Arm description:

Subjects with LDA at the end of open label phase received Tofacitinib MR 11 mg tablet once daily with blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.

Arm type	Experimental
Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Tofacitinib MR 11 mg tablet QD for 24 weeks in double blind phase.

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

Dosage and administration details:

Subjects received methotrexate at their previous stable dose for 24 weeks in double blind phase.

Number of subjects in period 2	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate
Started	267	266
Treated	264	266
Completed	238	247
Not completed	29	19
Adverse event, serious fatal	-	2
Consent withdrawn by subject	5	2
Screen Failure	1	-
Adverse event, non-fatal	6	6
Insufficient Clinical Response	6	1
Randomized but not Treated	3	-
Unspecified	2	5
Lost to follow-up	1	1
Protocol deviation	5	2

Baseline characteristics

Reporting groups	
Reporting group title	Open Label: Tofacitinib 11 mg + Methotrexate

Reporting group description:

Subjects with moderate to severe rheumatoid arthritis (RA) and who were insufficiently responding to their stable dose of methotrexate treatment previous to enrollment in this study, received Tofacitinib modified release (MR) 11 milligram (mg) tablet once daily (QD) with methotrexate (as background therapy) at their previous stable dose for 24 weeks in open label phase (OL).

Reporting group values	Open Label: Tofacitinib 11 mg + Methotrexate	Total	
Number of subjects	694	694	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	508	508	
From 65-84 years	184	184	
85 years and over	2	2	
Age Continuous Units: Years			
arithmetic mean	56.77		
standard deviation	± 11.83	-	
Sex: Female, Male Units: Subjects			
Female	532	532	
Male	162	162	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	37	37	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	33	33	
White	594	594	
More than one race	0	0	
Other	30	30	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	59	59	
Not Hispanic or Latino	635	635	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Open Label: Tofacitinib 11 mg + Methotrexate
Reporting group description:	
Subjects with moderate to severe rheumatoid arthritis (RA) and who were insufficiently responding to their stable dose of methotrexate treatment previous to enrollment in this study, received Tofacitinib modified release (MR) 11 milligram (mg) tablet once daily (QD) with methotrexate (as background therapy) at their previous stable dose for 24 weeks in open label phase (OL).	
Reporting group title	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo
Reporting group description:	
Subjects with low disease activity (LDA) at the end of open label phase were randomized to receive Tofacitinib MR 11 mg tablet once daily with matching placebo to blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.	
Reporting group title	Double Blind: Tofacitinib 11 mg + Methotrexate
Reporting group description:	
Subjects with LDA at the end of open label phase received Tofacitinib MR 11 mg tablet once daily with blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.	

Primary: Double Blind Phase: Change From Randomization in Disease Activity Score in 28 Joints Using 4 Variables (DAS28-4) (Erythrocyte Sedimentation Rate [ESR]) at Week 48

End point title	Double Blind Phase: Change From Randomization in Disease Activity Score in 28 Joints Using 4 Variables (DAS28-4) (Erythrocyte Sedimentation Rate [ESR]) at Week 48
End point description:	
DAS28 is a measure of disease activity in subjects with RA. DAS28-4 (ESR) was calculated from swollen joint count(SJC) and tender/painful joint count (TJC) using 28 joints count, ESR (millimeters per hour [mm/hr]) & subject global assessment of arthritis (PtGA) on a 100 millimeter (mm) visual analog scale (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition). Total DAS28-4 (ESR) score range: 0(none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (ESR) less than or equal to (<=) 3.2 implied low disease activity and greater than (>) 3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity & DAS28-4 (ESR) less than (<) 2.6 implied remission. DAS28-4 (ESR) =0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm; ln =natural logarithm, sqrt =square root of. FAS-DB. Overall number of subjects analyzed=subjects evaluable for this endpoint.	
End point type	Primary
End point timeframe:	
Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 48	

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	235	237		
Units: units on a scale				
least squares mean (standard error)	0.33 (± 0.07)	0.03 (± 0.07)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Linear mixed-effect model of repeated measures (MMRM) was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline DAS28-4 (ESR) value as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0005 [2]
Method	MMRM
Parameter estimate	Least Square (LS) Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.48
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[1] - Non-inferiority of Tofacitinib monotherapy to Tofacitinib with continued MTX treatment was concluded if the upper bound of 95% 2-sided CI for difference between the 2 arms (Tofacitinib monotherapy arm - Tofacitinib with MTX arm) was lower than 0.6.

[2] - The reported p-value (one-sided) is for the non-inferiority test at the margin of 0.6

Secondary: Double Blind Phase: Change From Randomization in DAS28-4 ESR at Week 36

End point title	Double Blind Phase: Change From Randomization in DAS28-4 ESR at Week 36

End point description:

DAS28 is a measure of disease activity in subjects with RA. DAS28-4 (ESR) was calculated from SJC and TJC using 28 joints count, ESR (mm/hr) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition).Total DAS28-4 (ESR) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (ESR) <=3.2 implied low disease activity and >3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity, and DAS28-4 (ESR) <2.6 implied remission. DAS28-4(ESR) =0.56*sqrt(TJC28) +0.28*sqrt(SJC28) +0.70*In(ESR in mm/hour)+ 0.014*PtGA in mm. Double-blind period full analysis set(FAS-DB) included all subjects who received at least 1 dose of investigational drug during the OL phase,were randomized & received at least 1 dose of the randomized investigational drug regimen during DB phase.Overall number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	253	253		
Units: units on a scale				
least squares mean (standard error)	0.40 (± 0.07)	0.18 (± 0.07)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD and baseline DAS28-4 (ESR) value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Double Blind Phase: Change From Randomization in DAS28-4 (C-reactive protein [CRP]) at Weeks 36 and 48

End point title	Double Blind Phase: Change From Randomization in DAS28-4 (C-reactive protein [CRP]) at Weeks 36 and 48
End point description:	
DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (CRP) was calculated from SJC and TJC using 28 joints count, CRP (milligrams per liter [mg/L]) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition). Total DAS28-4 (CRP) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (CRP) <= 3.2 implied low disease activity and > 3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity, and DAS28-4 (CRP) < 2.6 implied remission. DAS28-4 (CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP in mg/L +1) + 0.014*PtGA in mm+ 0.96. FAS-DB was analyzed. Here, 'n' = Subjects evaluable for this endpoint at specified time points.	
End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =250 , 254)	0.38 (± 0.06)	0.13 (± 0.06)		
Change at Week 48 (n =231 , 235)	0.29 (± 0.06)	0.01 (± 0.06)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit, treatment -by-visit interaction, prior use of a bDMARD and baseline DAS28-4 (CRP) value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.09

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment -by-visit interaction, prior use of a bDMARD and baseline DAS28-4 (CRP) value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	0.45
Variability estimate	Standard error of the mean
Dispersion value	0.09

Secondary: Double Blind Phase: Change From Randomization in Clinical Disease Activity Index (CDAI) at Weeks 36 and 48

End point title	Double Blind Phase: Change From Randomization in Clinical Disease Activity Index (CDAI) at Weeks 36 and 48

End point description:

CDAI was calculated from tender and swollen joints using 28 joint count, PtGA and physician global assessment of arthritis (PhyGA). PtGA and PhyGA both were assessed on 0-10 centimeter (cm) VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity). CDAI total score ranged from 0 to 76, where higher scores indicated higher disease activity. CDAI score of <=10 indicated low disease activity and a score of <= 2.8 indicated remission. CDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm). FAS-DB was analyzed. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =254, 259)	3.58 (± 0.49)	1.84 (± 0.48)		
Change at Week 48 (n =238, 244)	2.97 (± 0.48)	0.84 (± 0.47)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD and baseline CDAI value as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.07
Variability estimate	Standard error of the mean
Dispersion value	0.68

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD and baseline CDAI value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	3.43
Variability estimate	Standard error of the mean
Dispersion value	0.66

Secondary: Double Blind Phase: Change From Randomization in Simplified Disease Activity Index (SDAI) at Weeks 36 and 48

End point title	Double Blind Phase: Change From Randomization in Simplified Disease Activity Index (SDAI) at Weeks 36 and 48
End point description:	
SDAI was calculated from tender and swollen joints using 28 joint count, PtGA, PhyGA and CRP (in mg/dL). PtGA and PhyGA both were assessed on 0-10 cm VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity. SDAI total score ranged from 0 to 86, where higher scores indicated higher disease activity). SDAI score of <=11 indicates low disease activity and a score of <=3.3 indicates remission. SDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm) + (CRP in mg/dL). FAS-DB was analyzed. Here, 'n' = Subjects evaluable for this endpoint at specified time points.	
End point type	Secondary
End point timeframe:	
Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Weeks 36 and 48	

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =249, 254)	3.83 (± 0.52)	1.88 (± 0.51)		
Change at Week 48 (n =231, 235)	3.16 (± 0.50)	0.94 (± 0.49)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD and baseline SDAI value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	3.37
Variability estimate	Standard error of the mean
Dispersion value	0.72

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD and baseline SDAI value as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	3.59
Variability estimate	Standard error of the mean
Dispersion value	0.69

Secondary: Double Blind Phase: Percentage of Subjects With Low Disease Activity (LDA) Assessed by DAS28-4 (ESR) Less Than or Equal to (<=) 3.2 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With Low Disease Activity (LDA) Assessed by DAS28-4 (ESR) Less Than or Equal to (<=) 3.2 at Weeks 36 and 48

End point description:

DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (ESR) was calculated from SJC and TJC using 28 joints count, ESR (mm/hr) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicated worse health condition). Total DAS28-4 (ESR) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (ESR) <=3.2 implied low disease activity and >3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity, and DAS28-4 (ESR) <2.6 implied remission. DAS28-4 (ESR) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm. Non-responder imputation (NRI) method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	42.42	48.12		
Week 48	45.08	49.62		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-5.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.15
upper limit	2.76

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-4.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.04
upper limit	3.94

Secondary: Double Blind Phase: Percentage of Subjects With LDA Assessed by DAS28-4 (CRP) <=3.2 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With LDA Assessed by DAS28-4 (CRP) <=3.2 at Weeks 36 and 48

End point description:

DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (CRP) was calculated from SJC and TJC using 28 joints count, CRP (mg/dL) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition). Total DAS28-4 (CRP) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (CRP) <=3.2 implied low disease activity and >3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity, and DAS28-4 (CRP) <2.6 implied remission. DAS28-4 (CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP in mg/L +1) + 0.014*PtGA in mm+ 0.96. NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DWH 3ODFHER	'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DWH		
6XEMHFW JUROXS W\SH	5HSRUWLQJ JUROXS	5HSRUWLQJ JUROXS	JUROXS	
1XPEHU RI VXEMHFWV DQDO\VHG				
8QLWV SHUFHQWDJH RI VXEMHFWV				
QXPEHU QRW DSSOLFDEOH				
:HHN :HHN				

Statistical analyses

Statistical analysis title	7RIDFLWLQLE 07; 3ODFHER 9V 7RIDFLWLQLE 07;
6WDWLVWLFDO DQDO\VLV GHVFULSWLRQ :HHN	
&RPSDULVRQ JUROXSV	'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DW 'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DW
1XPEHU RI VXEMHFWV LQFOXGHG LQ DQDO\VLV	
$QDO\VLV VSHFLILFDWLRQ	3UH VSHFLILHG
$QDO\VLV W\SH	VXSHULRULW\
3DUDPHWHU HVWLPDWH	'LIIHUHQFH LQ SHUFHQWDJH RI VXEMHFWV
3RLQW HVWLPDWH	
&RQILGHQFH LQWHUYDO	
OHYHO	
VLGHV	VLGHG
ORZHU OLPLW	
XSSHU OLPLW	

Statistical analysis title	7RIDFLWLQLE 07; 3ODFHER 9V 7RIDFLWLQLE 07;
6WDWLVWLFDO DQDO\VLV GHVFULSWLRQ :HHN /LQHDU 0050 ZDV XVHG WKDW LQFOXGHG WKH IL[HG HIIHFWV RI WUHDW LQWHUDFWLRQ SULRU XVH RI D ELRORJLFDO '0$5' DQG EDVHOLQH '$6 &53	
&RPSDULVRQ JUROXSV	'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DW 'RXEOH %OLQG 7RIDFLWLQLE PJ 0HWKRWUH[DW
1XPEHU RI VXEMHFWV LQFOXGHG LQ DQDO\VLV	
$QDO\VLV VSHFLILFDWLRQ	3UH VSHFLILHG
$QDO\VLV W\SH	VXSHULRULW\
3DUDPHWHU HVWLPDWH	'LIIHUHQFH LQ SHUFHQWDJH RI VXEMHFWV
3RLQW HVWLPDWH	

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.28
upper limit	-0.76

Secondary: Double Blind Phase: Percentage of Subjects With LDA Assessed by CDAI <=10 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With LDA Assessed by CDAI <=10 at Weeks 36 and 48

End point description:

CDAI was calculated from tender and swollen joints using 28 joint count, PtGA and PhyGA. PtGA and PhyGA both were assessed on 0-10 cm VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity). CDAI total score ranged from 0 to 76, where higher scores indicated higher disease activity. CDAI score of <=10 indicated low disease activity and a score of <= 2.8 indicated remission. Percentage of subjects with CDAI <=10 were reported. CDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm). NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	66.29	73.68		
Week 48	65.15	77.07		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 36

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-7.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.17
upper limit	0.38

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-11.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.56
upper limit	-4.26

Secondary: Double Blind Phase: Percentage of Subjects With LDA Assessed by SDAI <=11 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With LDA Assessed by SDAI <=11 at Weeks 36 and 48

End point description:

SDAI was calculated from tender and swollen joints using 28 joint count, PtGA, PhyGA and CRP (in mg/dL). PtGA and PhyGA both were assessed on 0-10 cm VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity). SDAI total score ranged from 0 to 86, where higher scores indicated higher disease activity. SDAI score of <=11 indicates low disease activity and a score of <=3.3 indicates remission. SDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm) + (CRP in mg/dL). NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	66.29	73.31		
Week 48	66.29	76.32		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-7.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.81
upper limit	0.77

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-10.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.68
upper limit	-2.37

Secondary: Double Blind Phase: Percentage of Subjects With Remission Assessed by American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) Boolean at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With Remission Assessed by American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) Boolean at Weeks 36 and 48

End point description:

ACR-EULAR Boolean remission was when a subject satisfied all of the following: tender joint count, swollen joint count (both based on a 28-joint assessment), CRP (in mg/dL), and PtGA (VAS: 0 cm [very well] to 10 cm [worst], higher scores indicated worse health condition) and all scores were <=1. NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	15.53	24.06		
Week 48	22.35	23.68		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 36

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-8.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.27
upper limit	-1.78

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	5.83

Secondary: Double Blind Phase: Percentage of Subjects With Remission Assessed by DAS28-4 (ESR) Less Than [<] 2.6 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With Remission Assessed by DAS28-4 (ESR) Less Than [<] 2.6 at Weeks 36 and 48

End point description:

DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (ESR) was calculated from SJC and TJC using 28 joints count, ESR (mm/hr) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition). Total DAS28-4 (ESR) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (ESR) <= 3.2 implied low disease activity & >3.2 to <=5.1 implied moderate disease activity,>5.1 implied high disease activity, & DAS28-4 (ESR) <2.6 implied remission. DAS28-4 (ESR)=0.56*sqrt(TJC28)+0.28*sqrt(SJC28) + 0.70*In(ESR in mm/ hour) + 0.014*PtGA in mm. Percentage of subjects with DAS remission (DAS28-4-ESR<2.6) were reported in this endpoint. NRI method was used to impute missing data. FAS-DB was analyzed.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	20.45	28.57		
Week 48	23.86	30.08		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-8.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.4
upper limit	-0.82

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-6.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.74
upper limit	1.32

Secondary: Double Blind Phase: Percentage of Subjects With Remission Assessed by DAS28-4 (CRP) <2.6 at Weeks 48 and 36

End point title	Double Blind Phase: Percentage of Subjects With Remission Assessed by DAS28-4 (CRP) <2.6 at Weeks 48 and 36

End point description:

DAS28 is a measure of disease activity in subjects with rheumatoid arthritis. DAS28-4 (CRP) was calculated from SJC and TJC using 28 joints count, CRP (mg/L) and PtGA on a 100 mm VAS (VAS: scores ranging from 0 mm [very well] to 100 mm [worst], higher scores indicate worse health condition). Total DAS28-4 (CRP) score range: 0 (none) to 9.4 (extreme disease activity), higher score indicated more disease activity. DAS28-4 (CRP) <=3.2 implied low disease activity and >3.2 to <=5.1 implied moderate disease activity, >5.1 implied high disease activity, and DAS28-4 (CRP) <2.6 implied remission. DAS28-4 (CRP) = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36*ln(CRP in mg/L +1) + 0.014*PtGA in mm+ 0.96. Percentage of subjects with DAS remission (DAS28-4-CRP<2.6) were reported in this endpoint. NRI method was used to impute missing data. FAS-DB was analyzed.

End point type	Secondary

End point timeframe:
Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	50.00	55.64		
Week 48	50.38	54.51		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-5.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.12
upper limit	2.84

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-4.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.62
upper limit	4.36

Secondary: Double Blind Phase: Percentage of Subjects With Remission Assessed by CDAI <=2.8 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With Remission Assessed by CDAI <=2.8 at Weeks 36 and 48

End point description:

CDAI was calculated from tender and swollen joints using 28 joint count, PtGA and PhyGA. PtGA and PhyGA both were assessed on 0-10 cm VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity). CDAI total score ranged from 0 to 76, where higher scores indicated higher disease activity. CDAI score of <=10 indicated low disease activity and a score of <= 2.8 indicated remission. CDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm). NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	23.48	32.33		
Week 48	28.41	30.83		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 36

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-8.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.44
upper limit	-1.24

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.18
upper limit	5.35

Secondary: Double Blind Phase: Percentage of Subjects With Remission Assessed by SDAI <=3.3 at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects With Remission Assessed by SDAI <=3.3 at Weeks 36 and 48

End point description:

SDAI was calculated from tender and swollen joints using 28 joint count, PtGA, PhyGA and CRP (in mg/dL). PtGA and PhyGA both were assessed on 0-10 cm VAS scale (VAS: scores ranging from 0 cm [very well] to 10 cm [worst]), where higher scores indicated greater affliction due to disease activity. SDAI total score ranged from 0 to 86, where higher scores indicated higher disease activity. SDAI score of <=11 indicates low disease activity and a score of <=3.3 indicates remission. SDAI = (28TJC) + (28SJC) + (PhyGA in cm) + (PtGA in cm) + (CRP in mg/dL). NRI method was used to impute missing data. FAS-DB included all subjects who received at least 1 dose of investigational drug during the OL phase, were randomized and received at least 1 dose of the randomized investigational drug regimen during DB phase.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	22.73	31.58		
Week 48	28.79	31.95		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-8.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.38
upper limit	-1.31

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-3.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.99
upper limit	4.65

Secondary: Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 20 Percent (%) (ACR20) Response at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 20 Percent (%) (ACR20) Response at Weeks 36 and 48

End point description:

Subjects with 20% improvement in tender and swollen joint counts and 20% improvement in at least 3 of the 5 measures: PtGA, PhyGA, subject's assessment of arthritis pain, HAQ-DI and CRP. PtGA: subject assessed health on VAS, 0 mm (very well) to 100 mm (worst health condition), higher scores = worse condition. PhyGA: physician judged subjects' pain on VAS, 0 (no pain) to 100 mm (extreme pain), higher scores = more pain. Subject's assessment of arthritis pain: subject assessed pain on VAS, 0 mm (no pain) to 100 mm (most severe pain), higher score = more pain. HAQ-DI: functional disability evaluation, score: 0 (no difficulty) to 3 (extreme difficulty), higher score implied more disability. The improvement was relative to baseline (Day 1). NRI method was used to impute missing data. FAS-DB was analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Weeks 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	73.86	80.83		
Week 48	73.11	79.70		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 36

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-6.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.06
upper limit	0.14

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-6.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	0.61

Secondary: Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 50% (ACR50) Response at Week 36 and 48

End point title	Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 50% (ACR50) Response at Week 36 and 48
End point description: Subjects with 50% improvement in tender and swollen joint counts and 50% improvement in at least 3 of the 5 measures: PtGA, PhyGA, subject's assessment of arthritis pain, HAQ-DI and CRP. PtGA: subject assessed health on VAS, 0 mm (very well) to 100 mm (worst health condition), higher scores = worse condition. PhyGA: physician judged subjects' pain on VAS, 0 (no pain) to 100 mm (extreme pain), higher scores = more pain. Subject's assessment of arthritis pain: subject assessed pain on VAS, 0 mm (no pain) to 100 mm (most severe pain), higher score = more pain. HAQ-DI: functional disability evaluation, score: 0 (no difficulty) to 3 (extreme difficulty), higher score implied more disability. The improvement was relative to baseline (Day 1). NRI method was used to impute missing data. FAS-DB was analyzed.	
End point type	Secondary
End point timeframe: Baseline (Day 1), Week 36 and 48	

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-12.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.01
upper limit	-4.48

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-11.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.22
upper limit	-3.75

Secondary: Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 70% (ACR70) Response at Week 36 and 48

End point title	Double Blind Phase: Percentage of Subjects Achieving an American College of Rheumatology 70% (ACR70) Response at Week 36 and 48

End point description:

Subjects with 70% improvement in tender and swollen joint counts and 70% improvement in at least 3 of the 5 measures: PtGA, PhyGA, subject's assessment of arthritis pain, health assessment

questionnaire-disability index (HAQ-DI) and CRP. PtGA: subject assessed health on VAS, 0 mm (very well) to 100 mm (worst health condition), higher scores = worse condition. PhyGA: physician judged subjects' pain on VAS, 0 (no pain) to 100 mm (extreme pain), higher scores = more pain. Subject's assessment of arthritis pain: subject assessed pain on VAS, 0 mm (no pain) to 100 mm (most severe pain), higher score=more pain. HAQ-DI: functional disability evaluation, score: 0 (no difficulty) to 3 (extreme difficulty), higher score implied more disability. The improvement was relative to baseline (Day 1). NRI method was used to impute missing data. FAS-DB was analyzed.

End point type	Secondary
End point timeframe: Baseline (Day 1), Week 36 and 48	

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	35.61	40.98		
Week 48	37.88	42.86		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 36	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-5.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.63
upper limit	2.89

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description: Week 48	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-4.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.32
upper limit	3.36

Secondary: Double Blind Phase: Change From Randomization in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 36 and 48

End point description:

HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing/grooming; arising; eating; walking; reach; grip; hygiene; and other activities.. There were total of 30 items distributed in these 8 domains. Each item was scored on a 4-point scale from 0 to 3: 0= no difficulty; 1= some difficulty; 2= much difficulty; 3= unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0 (least difficulty) and 3 (extreme difficulty), where higher scores indicate more difficulty while performing daily living activities. FAS-DB was analyzed. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =252, 259)	0.10 (± 0.03)	0.01 (± 0.03)		
Change at Week 48 (n =238, 246)	0.01 (± 0.03)	0.00 (± 0.03)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological DMARD and baseline HAQ-DI.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.16
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological DMARD and baseline HAQ-DI.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.04

Secondary: Double Blind Phase: Change From Randomization in the Short Form 36 (SF-36) Health Survey 8 Domain Scores at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in the Short Form 36 (SF-36) Health Survey 8 Domain Scores at Week 36 and 48

End point description:

SF-36 is a subject reported standardized survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: physical functioning, role physical, bodily pain, social functioning, mental health, role emotional, vitality, and general health perception. The score range for each of the 8 health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health condition. Scores of 8 health aspects were summarized to derive the 2 component scores (physical component scores [PCS], mental component scores [MCS]) ranging from 0 (worst) to 100 (best), where higher PCS/MCS indicated good health condition. FAS-DB was analyzed. Here, ‘n’ = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36:Physical Functioning(n=252, 259)	-1.32 (± 0.50)	-0.88 (± 0.49)		
Change at Week 36:Role Physical Score(n=252, 259)	-1.69 (± 0.48)	-0.02 (± 0.47)		
Change at Week 36: Social Functioning(n=252, 259)	-0.98 (± 0.50)	-0.84 (± 0.49)		
Change at Week 36: Bodily Pain Score (n=252, 259)	-2.03 (± 0.53)	-0.58 (± 0.52)		
Change at Week 36: Mental Health Score(n=251,259)	-1.22 (± 0.51)	-0.32 (± 0.50)		
Change at Week 36: Role Emotional Score(n=252,259)	-1.80 (± 0.56)	-0.69 (± 0.55)		
Change at Week 36: Vitality Score (n =251, 259)	-1.30 (± 0.50)	-0.15 (± 0.50)		
Change at Week 36: GH Perception Score (n=252,259)	-0.98 (± 0.44)	-0.87 (± 0.43)		
Change at Week 48:Physical Functioning(n=238,246)	-0.46 (± 0.49)	-0.97 (± 0.48)		
Change at Week 48: Role Physical Score(n=238,246)	-0.88 (± 0.51)	-0.15 (± 0.50)		
Change at Week 48: Social Functioning (n=238,246)	-1.06 (± 0.53)	-0.55 (± 0.52)		
Change at Week 48: Bodily Pain Score (n=238,246)	-1.46 (± 0.54)	-0.71 (± 0.54)		
Change at Week 48: Mental Health Score(n=238,246)	-0.34 (± 0.54)	0.12 (± 0.54)		
Change at Week 48:Role Emotional Score(n=238,246)	-0.83 (± 0.54)	-0.36 (± 0.54)		
Change at Week 48: Vitality Score (n =238, 246)	-0.77 (± 0.52)	-0.25 (± 0.52)		
Change at Week 48: GH Perception Score(n=238,246)	-0.43 (± 0.45)	-1.05 (± 0.44)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 36: Physical Functioning- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 physical component score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v

	Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.79
upper limit	0.92
Variability estimate	Standard error of the mean
Dispersion value	0.69

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Physical Functioning- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 physical component score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	1.85
Variability estimate	Standard error of the mean
Dispersion value	0.68

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Role Physical Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 role physical score score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.97
upper limit	-0.37
Variability estimate	Standard error of the mean
Dispersion value	0.66

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Role Physical Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 role physical score score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	0.66
Variability estimate	Standard error of the mean
Dispersion value	0.66

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Social functioning- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 Social functioning score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.21
Variability estimate	Standard error of the mean
Dispersion value	0.69

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Social functioning- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 social functioning score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	0.93
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Bodily Pain Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 bodily pain score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.74

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Bodily Pain Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 bodily pain score as a covariate.	

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.23
upper limit	0.73
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Mental Health Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 mental health score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.29
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.71

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Mental Health Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 mental health score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Role Emotional Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 role emotional score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.64
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.78

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Role Emotional Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 role emotional score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.95
upper limit	1.01
Variability estimate	Standard error of the mean
Dispersion value	0.75

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Vitality Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 vitality score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.52
upper limit	0.22
Variability estimate	Standard error of the mean
Dispersion value	0.7

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Vitality Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 vitality score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.94
upper limit	0.91
Variability estimate	Standard error of the mean
Dispersion value	0.73

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: General Health Perception Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 general health perception score as a covariate.	

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.08
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 48: General Health Perception Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 general health perception score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.83
Variability estimate	Standard error of the mean
Dispersion value	0.62

Secondary: Double Blind Phase: Change From Randomization in the SF-36 Health Survey Component Scores at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in the SF-36 Health Survey Component Scores at Week 36 and 48

End point description:

SF-36 is a subject reported standardized survey designed to assess generic health related quality of life. It consisted of 36 items evaluating 8 aspects of functional health and well-being: physical functioning, role physical, bodily pain, social functioning, mental health, role emotional, vitality, and general health perception. The score range for each of the 8 health aspects was from 0 (poor health) to 100 (better health), higher scores indicating good health condition. Scores of 8 health aspects were summarized aggregated to derive the two 2 component scores PCS and MCS ranging from 0 (worst) to 100 (best), where higher PCS/MCS indicated good health condition. FAS-DB was analyzed. Here, ‘n’ = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:
Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36: PCS (n =251, 259)	-1.42 (± 0.44)	-0.60 (± 0.43)		
Change at Week 36:MCS (n =251, 259)	-1.25 (± 0.48)	-0.43 (± 0.47)		
Change at Week 48: PCS (n =238, 246)	-0.83 (± 0.44)	-0.92 (± 0.43)		
Change at Week 48: MCS (n =238, 246)	-0.65 (± 0.51)	0.03 (± 0.50)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Physical Component Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 physical component score- as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.01
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Physical Component Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 physical component score- as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	1.29
Variability estimate	Standard error of the mean
Dispersion value	0.61

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Mental Component Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 mental component score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.13
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.67

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Mental Component Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a biological disease-modifying anti-rheumatic drug (DMARD), and baseline SF-36 mental component score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	0.7
Variability estimate	Standard error of the mean
Dispersion value	0.7

Secondary: Double Blind Phase: Change From Randomization in the Work Productivity and Activity Impairment (WPAI) Scores at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in the Work Productivity and Activity Impairment (WPAI) Scores at Week 36 and 48

End point description:

WPAI is 6-question subject rated questionnaire to determine the impact of rheumatoid arthritis and yields 4 types of outcomes: absenteeism (work time missed), presenteeism (impairment while working), work productivity loss (overall work impairment), and daily activity (DA) impairment (activity impairment) for a period of 7 days prior to a visit. These 4 outcomes are expressed as an impairment percentage (range from 0 to 100), with higher numbers indicating greater impairment and less productivity. FAS-DB was analyzed. Here, 'n' = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage impairment				
least squares mean (standard error)				
Change at Week 36: Absenteeism (n =90, 104)	-1.39 (± 1.79)	-3.00 (± 1.69)		
Change at Week 36: DA impairment (n =252, 256)	4.00 (± 1.35)	0.81 (± 1.34)		
Change at Week 36: Presenteeism (n =96, 104)	3.68 (± 2.20)	0.67 (± 2.07)		
Change at Week 36:Work productivity loss(n=90,101)	3.03 (± 2.57)	0.19 (± 2.41)		
Change at Week 48: Absenteeism (n =89, 101)	-2.21 (± 1.70)	-1.69 (± 1.61)		
Change at Week 48: DA impairment (n =238, 243)	2.86 (± 1.47)	1.25 (± 1.46)		
Change at Week 48: Presenteeism (n =93, 101)	2.82 (± 2.78)	3.72 (± 2.61)		
Change at Week 48:Work productivity loss(n=89,98)	2.98 (± 3.09)	5.45 (± 2.91)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Absenteeism Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI absenteeism score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.14
upper limit	6.37
Variability estimate	Standard error of the mean
Dispersion value	2.41

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Absenteeism Score- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI absenteeism score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.01
upper limit	3.99
Variability estimate	Standard error of the mean
Dispersion value	2.28

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Daily activity impairment- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI daily activity impairment score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	6.89
Variability estimate	Standard error of the mean
Dispersion value	1.88

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Daily activity impairment- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI daily activity impairment score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.41
upper limit	5.61
Variability estimate	Standard error of the mean
Dispersion value	2.04

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Presenteeism- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI presenteeism score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	3.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.84
upper limit	8.87
Variability estimate	Standard error of the mean
Dispersion value	2.97

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 48: Presenteeism- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI presenteeism score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.34
upper limit	6.54
Variability estimate	Standard error of the mean
Dispersion value	3.77

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 36: Work productivity loss- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI work productivity loss score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	2.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	9.65
Variability estimate	Standard error of the mean
Dispersion value	3.45

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Work productivity loss- Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline WPAI work productivity loss score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-2.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.72
upper limit	5.8
Variability estimate	Standard error of the mean
Dispersion value	4.19

Secondary: Double Blind Phase: Change From Randomization in the European Quality of Life - 5 Dimensions Questionnaire (EQ-5D) Scores at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in the European Quality of Life - 5 Dimensions Questionnaire (EQ-5D) Scores at Week 36 and 48
End point description:	
EQ-5D was a subject completed instrument designed to assess impact on quality of life in terms of a single utility score in 5 domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. 3 possible answers for mobility: 1=no problem in walking, 2=moderate problems in walking, 3= confined to bed; self-care: 1=no problem, 2=moderate problems, 3= unable to wash/dress; usual activities: 1=no problem, 2=moderate problems, 3= unable to do usual activities; pain and discomfort: 1=no pain or discomfort, 2=moderate pain or discomfort, 3= extreme pain or discomfort; anxiety and depression: 1=not anxious or depressed, 2=moderately anxious or depressed, 3= extremely anxious or depressed. The 5-dimensional systems are converted into a single index utility score between 0 and 1, where higher score indicated a better health state. FAS-DB population was analyzed. Here, ‘n’ = Subjects evaluable for this endpoint at specified time points.	
End point type	Secondary
End point timeframe:	
Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48	

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =251, 258)	-0.05 (± 0.01)	-0.01 (± 0.01)		
Change at Week 48 (n =237, 245)	-0.02 (± 0.01)	0.00 (± 0.01)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline EQ-5D score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX
Statistical analysis description:	
Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline EQ-5D score as a covariate.	
Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.02

Secondary: Double Blind Phase: Change From Randomization in the Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Scale Scores at Week 36 and 48

End point title	Double Blind Phase: Change From Randomization in the Functional Assessment of Chronic Illness Therapy (FACIT)- Fatigue Scale Scores at Week 36 and 48

End point description:

The FACIT-Fatigue scale was a subject completed questionnaire consisted of 13 items that assessed fatigue. Each item was scored on a scale of 0 (maximum fatigue) to 4 (no fatigue), higher scores indicate less fatigue. Total FACIT-fatigue score was obtained by addition of scores from 13 items, giving a possible overall range from 0 (maximum fatigue) to 52 (no fatigue). Higher FACIT-fatigue scores indicated lower level of fatigue, better subject status. FAS-DB population was analyzed. Here, ‘n’ = Subjects evaluable for this endpoint at specified time points.

End point type	Secondary

End point timeframe:

Randomization (last non-missing measurement on or prior to the first dosing date in DB phase at Week 24), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: units on a scale				
least squares mean (standard error)				
Change at Week 36 (n =252, 258)	-0.99 (± 0.43)	-0.80 (± 0.43)		
Change at Week 48 (n =237, 245)	-0.34 (± 0.46)	-0.52 (± 0.45)		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 36: Linear MMRM was used that included the fixed effects of treatment, visit,

treatment-by-visit interaction, prior use of a bDMARD, and baseline FACIT - fatigue scale score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	-0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.37
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.6

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Change at Week 48: Linear MMRM was used that included the fixed effects of treatment, visit, treatment-by-visit interaction, prior use of a bDMARD, and baseline FACIT - fatigue scale score as a covariate.

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	LS Mean Difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	1.44
Variability estimate	Standard error of the mean
Dispersion value	0.64

Secondary: Double Blind Phase: Percentage of Subjects Achieving an Improvement of at Least 0.22 Units in HAQ-DI at Weeks 36 and 48

End point title	Double Blind Phase: Percentage of Subjects Achieving an Improvement of at Least 0.22 Units in HAQ-DI at Weeks 36 and 48

End point description:

HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing/grooming; arising; eating; walking; reach; grip; hygiene; and other activities.. There were total of 30 items distributed in these 8 domains. Each item was scored on a 4-point scale from 0 to 3: 0= no difficulty; 1= some difficulty; 2= much difficulty; 3= unable to do. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0 (least difficulty) and 3 (extreme difficulty), where higher scores indicate more difficulty while performing daily living activities. Percentage of subjects with an improvement of at least 0.22 units in HAQ scores from baseline (Day 1) to Week 36 and 48 were

reported in this endpoint. NRI method was used to impute missing data. FAS-DB population was analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 36 and 48

End point values	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	266		
Units: percentage of subjects				
number (not applicable)				
Week 36	67.05	77.07		
Week 48	68.56	75.19		

Statistical analyses

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 36

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate
Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-10.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.61
upper limit	-2.42
Variability estimate	Standard error of the mean
Dispersion value	3.87

Statistical analysis title	Tofacitinib + MTX Placebo Vs Tofacitinib + MTX

Statistical analysis description:

Week 48

Comparison groups	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo v Double Blind: Tofacitinib 11 mg + Methotrexate

Number of subjects included in analysis	530
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in percentage of subjects
Point estimate	-6.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.26
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	3.89

Other pre-specified: Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious AEs

End point title	Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious AEs

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent were events between first dose of study drug and up to Week 52 (up to 28 days after last dose) that were absent before treatment or that worsened relative to pretreatment state. AEs included both serious and non-serious AEs. Overall study safety analysis set included all subjects who received at least one dose of study drug during the study.

End point type	Other pre-specified

End point timeframe:

For OL Phase: Baseline up to Week 24; For DB Phase: Week 24 up to Week 52 (up to 28 days after last dose)

End point values	Open Label: Tofacitinib 11 mg + Methotrexate	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	694	264	266	
Units: subjects				
AEs|	362	107	109	
SAEs|	20	10	5	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of Subjects With Abnormal Laboratory Parameters

End point title	Number of Subjects With Abnormal Laboratory Parameters

End point description:	
Hemoglobin (Hb),Hematocrit,Erythrocytes:<0.8*LLN; Ery. mean corpuscular volume <0.9*LLN, >1.1*ULN;Platelets:<0.5*LLN,>1.75*ULN;WBCs:<0.6*LLN,>1.5*ULN; Lymphocytes/WBCs, Neutrophils/WBCs:<0.8*LLN,>1.2x ULN;Basophils/WBCs, Eosinophils/WBCs,Monocytes, Monocytes/WBCs: >1.2*ULN;Prothrombin Time, Prothrombin Intl. Normalized Ratio:>1.1*ULN; ESR:>1.5*ULN; Bilirubin,Direct Bilirubin,Indirect Bilirubin: >1.5*ULN; Aspartate Aminotransferase,Alanine Aminotransferase,Gamma Glutamyl Transferase,Alkaline Phosphatase:>3.0*ULN; Protein,Albumin: <0.8*LLN, >1.2*ULN; Blood Urea Nitrogen, Creatinine,Triglycerides: >1.3*ULN;HDL Cholesterol:<0.8*LLN;Sodium <0.95*LLN, >1.05*ULN;Potassium,Chloride, Calcium, Bicarbonate: <0.9*LLN, >1.1*ULN; Glucose: <0.6*LLN, >1.5*ULN;Creatine Kinase: >2.0*ULN; Cholesterol:>1.3*ULN;Specific Gravity:<1.003;pH:<4.5;urine glucose,Ketones,urine protein,urine Hb,WBCs Esterase:>=1.Overall safety analysis set.Overall number	
End point type	Other pre-specified
End point timeframe:	
For OL Phase: Baseline up to Week 24; For DB Phase: Week 24 up to Week 48	

End point values	Open Label: Tofacitinib 11 mg + Methotrexate	Double Blind: Tofacitinib 11 mg + Methotrexate Placebo	Double Blind: Tofacitinib 11 mg + Methotrexate	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	688	263	263	
Units: subjects	682	263	263	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Day 1) up to Week 52

Adverse event reporting additional description:

Same event may appear as AE and SAE, what is presented are distinct events. Event may be categorized as serious in 1 subject and as non-serious in another subject or 1 subject may have experienced both serious and non-serious event during study. AEs were evaluated for subjects with at least 1 dose of the study drug during the study.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Open Label: Tofacitinib 11 mg + Methotrexate

Reporting group description:

Subjects with moderate to severe rheumatoid arthritis (RA) and who were insufficiently responding to their stable dose of methotrexate treatment previous to enrollment in this study, received Tofacitinib modified release (MR) 11 milligram (mg) tablet once daily (QD) with methotrexate at their previous stable dose for 24 weeks in open label phase (OL).

Reporting group title	Double Blind: Tofacitinib 11mg + Methotrexate

Reporting group description:

Subjects with LDA at the end of open label phase received Tofacitinib MR 11 mg tablet once daily with blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.

Reporting group title	Double Blind: Tofacitinib + Methotrexate Placebo

Reporting group description:

Subjects with low disease activity (LDA) at the end of open label phase were randomized to receive Tofacitinib MR 11 mg tablet once daily with matching placebo to blinded methotrexate at their previously stabilized dose for 24 weeks in double blind phase.

Serious adverse events	Open Label: Tofacitinib 11 mg + Methotrexate	Double Blind: Tofacitinib 11mg + Methotrexate	Double Blind: Tofacitinib + Methotrexate Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 694 (2.88%)	5 / 266 (1.88%)	10 / 264 (3.79%)
number of deaths (all causes)	0	2	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glioblastoma			

subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Prostate cancer			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Thyroid cancer metastatic			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Reproductive system and breast disorders			
Cervical dysplasia			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 694 (0.00%)	2 / 266 (0.75%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis chronic			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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

Interstitial lung disease			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Hip fracture			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Patella fracture			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Tibia fracture			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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			
Angina unstable			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Atrial fibrillation			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Nervous system disorders			
Nerve root compression			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Umbilical hernia			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Pancreatitis acute			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Peritoneal disorder			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 694 (0.00%)	1 / 266 (0.38%)	0 / 264 (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			
Encephalitis viral			
subjects affected / exposed	0 / 694 (0.00%)	1 / 266 (0.38%)	0 / 264 (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
Infective exacerbation of chronic obstructive airways disease			

subjects affected / exposed	0 / 694 (0.00%)	1 / 266 (0.38%)	0 / 264 (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
Osteomyelitis			
subjects affected / exposed	0 / 694 (0.00%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 694 (0.43%)	0 / 266 (0.00%)	1 / 264 (0.38%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Respiratory tract infection			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 694 (0.14%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Open Label: Tofacitinib 11 mg + Methotrexate	Double Blind: Tofacitinib 11mg + Methotrexate	Double Blind: Tofacitinib + Methotrexate Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 694 (22.77%)	31 / 266 (11.65%)	24 / 264 (9.09%)
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	16 / 694 (2.31%)	10 / 266 (3.76%)	5 / 264 (1.89%)
occurrences (all)	20	11	6
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 694 (0.00%)	6 / 266 (2.26%)	5 / 264 (1.89%)
occurrences (all)	0	6	5
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 694 (2.45%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	18	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 694 (2.45%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	19	0	0
Dizziness			
subjects affected / exposed	15 / 694 (2.16%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	15	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 694 (2.31%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	17	0	0
Nausea			
subjects affected / exposed	20 / 694 (2.88%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	23	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 694 (0.00%)	2 / 266 (0.75%)	7 / 264 (2.65%)
occurrences (all)	0	2	7
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 694 (0.00%)	7 / 266 (2.63%)	3 / 264 (1.14%)
occurrences (all)	0	8	3
Nasopharyngitis			
subjects affected / exposed	35 / 694 (5.04%)	7 / 266 (2.63%)	5 / 264 (1.89%)
occurrences (all)	40	7	6
Upper respiratory tract infection			

subjects affected / exposed	33 / 694 (4.76%)	6 / 266 (2.26%)	4 / 264 (1.52%)
occurrences (all)	41	6	4
Urinary tract infection			
subjects affected / exposed	19 / 694 (2.74%)	0 / 266 (0.00%)	0 / 264 (0.00%)
occurrences (all)	20	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported