Clinical trial results:
A 52-week, phase 3, multicentre, randomised, double blind, efficacy and safety study comparing GSK3196165 with placebo and with tofacitinib, in combination with methotrexate in participants with moderately to severely active rheumatoid arthritis who have an inadequate response to methotrexate

Summary

EudraCT number	2019-000797-39
Trial protocol	GB LV ES PL LT CZ HU IT
Global end of trial date	16 August 2022

Results information

Result version number	v1
This version publication date	27 August 2023
First version publication date	27 August 2023

Trial information

Trial identification

Sponsor protocol code	201790

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03980483
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 GreatWest Road, Brentford, Middlesex, United Kingdom, TW8 9GS
Public contact	GSK Response Center, GlaxoSmithKline, +1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, +1 8664357343, GSKClinicalSupportHD@gsk.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	04 October 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of GSK3196165 at doses of 90 mg and 150 mg weekly versus placebo for the treatment of participants with moderately to severely active RA who are on a stable background of MTX and who have had an inadequate response to MTX.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 May 2019
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	Argentina: 163
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	China: 13
Country: Number of subjects enrolled	Czechia: 48
Country: Number of subjects enrolled	Hungary: 35
Country: Number of subjects enrolled	India: 103
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Lithuania: 40
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Mexico: 49
Country: Number of subjects enrolled	Poland: 451
Country: Number of subjects enrolled	Russian Federation: 100
Country: Number of subjects enrolled	Serbia: 20
Country: Number of subjects enrolled	South Africa: 116
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Ukraine: 247
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 123
Worldwide total number of subjects	1537
EEA total number of subjects	591

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)	1267
From 65 to 84 years	269
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants were randomized in a ratio of 6:6:3:1:1:1 to 3 experimental and 3 Placebo arms. At Week 12, participants randomized to one of the three placebo arms switched to experimental arms, receiving the active intervention for 40 weeks. Participants randomized to experimental arms from study day 1, received the active intervention for 52 weeks.

Pre-assignment

Screening details:

Analysis of this study were reported for GSK3196165 90mg, GSK3196165 150mg, Tofacitinib 5 mg and all placebo arms are pooled to a single group to serve as reference for comparison of active treatment arms versus Placebo for primary efficacy endpoint analysis at Week 12.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK3196165 90mg + MTX

Arm description:

Participants received GSK3196165 90 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with methotrexate (MTX).

Arm type	Experimental
Investigational medicinal product name	GSK3196165
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 90mg of GSK3196165 once every week.

Arm title	GSK3196165 150mg + MTX

Arm description:

Participants received GSK3196165 150 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with MTX.

Arm type	Experimental
Investigational medicinal product name	GSK3196165
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150mg of GSK3196165 once every week.

Arm title	Tofacitinib 5mg + MTX

Arm description:

Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.

Arm type	Active comparator

Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 5mg of Tofacitinib once every alternate week.

Arm title	Placebo + MTX and GSK3196165 90mg + MTX

Arm description:

Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 90 mg, SC injection, once weekly in combination with MTX until Week 52.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo once every week until Week 12

Investigational medicinal product name	GSK3196165
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 90mg of GSK3196165 once every week from week 12 to week 52.

Arm title	Placebo + MTX and GSK3196165 150mg + MTX

Arm description:

Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 150 mg, SC injection, once weekly in combination with MTX until Week 52.

Arm type	Placebo
Investigational medicinal product name	GSK3196165
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 150mg of GSK3196165 once every week from week 12 to week 52.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo once every week until Week 12.

Arm title	Placebo + MTX and Tofacitinib 5mg + MTX

Arm description:

Participants received Placebo tablet weekly in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo tablet to Tofacitinib 5mg, capsule, orally, BID in combination with MTX plus placebo injection to maintain the blind for 52 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received placebo once every week until Week 12.

Investigational medicinal product name	Tofacitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 5mg of Tofacitinib once every alternate week from week 12 to week 52.

Number of subjects in period 1	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX
Started	513	510	258
Completed	431	436	221
Not completed	82	74	37
Physician decision	14	10	7
Consent withdrawn by subject	38	21	15
Adverse event, non-fatal	13	29	11
UNKNOWN	-	1	-
PROTOCOL-SPECIFIED WITHDRAWAL CRITERION MET	4	-	1
INVESTIGATOR SITE CLOSED	-	1	-
Lost to follow-up	2	4	2
Lack of efficacy	7	6	-
Protocol deviation	4	2	1

Number of subjects in period 1	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX
Started	85	86	85
Completed	69	73	75
Not completed	16	13	10
Physician decision	4	4	2
Consent withdrawn by subject	5	3	4
Adverse event, non-fatal	2	2	2
UNKNOWN	-	-	-
PROTOCOL-SPECIFIED WITHDRAWAL CRITERION MET	-	1	1
INVESTIGATOR SITE CLOSED	-	-	-
Lost to follow-up	1	2	-

Lack of efficacy	3	1	1
Protocol deviation	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	GSK3196165 90mg + MTX
Reporting group description:	
Participants received GSK3196165 90 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with methotrexate (MTX).	
Reporting group title	GSK3196165 150mg + MTX
Reporting group description:	
Participants received GSK3196165 150 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with MTX.	
Reporting group title	Tofacitinib 5mg + MTX
Reporting group description:	
Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.	
Reporting group title	Placebo + MTX and GSK3196165 90mg + MTX
Reporting group description:	
Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 90 mg, SC injection, once weekly in combination with MTX until Week 52.	
Reporting group title	Placebo + MTX and GSK3196165 150mg + MTX
Reporting group description:	
Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 150 mg, SC injection, once weekly in combination with MTX until Week 52.	
Reporting group title	Placebo + MTX and Tofacitinib 5mg + MTX
Reporting group description:	
Participants received Placebo tablet weekly in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo tablet to Tofacitinib 5mg, capsule, orally, BID in combination with MTX plus placebo injection to maintain the blind for 52 weeks.	

Reporting group values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX
Number of subjects	513	510	258
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	417	426	205
>=65 years	96	84	53
Age Continuous Units: YEARS			
arithmetic mean	53.7	54.2	54.3
standard deviation	± 12.14	± 10.77	± 11.66
Sex: Female, Male Units: Participants			
Female	401	399	209
Male	112	111	49
Race/Ethnicity, Customized Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE	11	11	9
ASIAN	48	39	29
BLACK OR AFRICAN AMERICAN	11	11	12

MISSING	1	0	0
MULTIPLE	10	15	7
WHITE	432	434	201

Reporting group values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX
Number of subjects	85	86	85
Age categorical Units: Subjects			
<=18 years	0	0	0
Between 18 and 65 years	72	71	76
>=65 years	13	15	9
Age Continuous Units: YEARS			
arithmetic mean	51.3	52.7	53.2
standard deviation	± 13.12	± 12.41	± 10.24
Sex: Female, Male Units: Participants			
Female	62	72	68
Male	23	14	17
Race/Ethnicity, Customized Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE	2	3	2
ASIAN	5	7	4
BLACK OR AFRICAN AMERICAN	3	2	2
MISSING	1	1	1
MULTIPLE	2	2	1
WHITE	72	71	75

Reporting group values	Total		
Number of subjects	1537		
Age categorical Units: Subjects			
<=18 years	0		
Between 18 and 65 years	1267		
>=65 years	270		
Age Continuous Units: YEARS			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	1211		
Male	326		
Race/Ethnicity, Customized Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE	38		
ASIAN	132		
BLACK OR AFRICAN AMERICAN	41		
MISSING	4		

MULTIPLE	37		
WHITE	1285		

Subject analysis sets

Subject analysis set title	Pooled Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants received Placebo weekly SC injection in combination with MTX until Week 12. The placebo arms are pooled into a single placebo arm.

Subject analysis set title	Tofacitinib 5mg + MTX
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.

Subject analysis set title	Pooled Placebo
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants received Placebo weekly SC injection in combination with MTX until Week 12. The placebo arms are pooled into a single placebo arm.

Reporting group values	Pooled Placebo	Tofacitinib 5mg + MTX	Pooled Placebo
Number of subjects	256	273	241
Age categorical Units: Subjects			
<=18 years Between 18 and 65 years >=65 years			
Age Continuous Units: YEARS arithmetic mean standard deviation	 42.7 ±	 ±	 ±
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
AMERICAN INDIAN OR ALASKA NATIVE ASIAN BLACK OR AFRICAN AMERICAN MISSING MULTIPLE WHITE			

End points

End points reporting groups

Reporting group title	GSK3196165 90mg + MTX
Reporting group description:	
Participants received GSK3196165 90 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with methotrexate (MTX).	
Reporting group title	GSK3196165 150mg + MTX
Reporting group description:	
Participants received GSK3196165 150 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with MTX.	
Reporting group title	Tofacitinib 5mg + MTX
Reporting group description:	
Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.	
Reporting group title	Placebo + MTX and GSK3196165 90mg + MTX
Reporting group description:	
Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 90 mg, SC injection, once weekly in combination with MTX until Week 52.	
Reporting group title	Placebo + MTX and GSK3196165 150mg + MTX
Reporting group description:	
Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 150 mg, SC injection, once weekly in combination with MTX until Week 52.	
Reporting group title	Placebo + MTX and Tofacitinib 5mg + MTX
Reporting group description:	
Participants received Placebo tablet weekly in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo tablet to Tofacitinib 5mg, capsule, orally, BID in combination with MTX plus placebo injection to maintain the blind for 52 weeks.	
Subject analysis set title	Pooled Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received Placebo weekly SC injection in combination with MTX until Week 12. The placebo arms are pooled into a single placebo arm.	
Subject analysis set title	Tofacitinib 5mg + MTX
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.	
Subject analysis set title	Pooled Placebo
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants received Placebo weekly SC injection in combination with MTX until Week 12. The placebo arms are pooled into a single placebo arm.	

Primary: Percentage of participants achieving 20 percentage (%) improvement in American College of Rheumatology Criteria (ACR20) at Week 12 superiority comparison with placebo

End point title	Percentage of participants achieving 20 percentage (%) improvement in American College of Rheumatology Criteria (ACR20) at Week 12 superiority comparison with placebo[1]
End point description:	
ACR20 is calculated as 20% improvement from Baseline in Tender Joint Count 68 (TJC68), Swollen Joint Count 66 (SJC66) and 20% improvement in 3 of the following 5 measures:Patient's Global Assessment of Arthritis Disease Activity (PtGA), Physician Global Assessment of Arthritis Disease Activity (PhGA)	

(visual analogue scale [VAS] with values from 0=best to 100=worst), Patient Assessment of Arthritis Pain (VAS with values from 0=no pain and 100=most severe pain), Health Assessment Questionnaire-Disability Index (HAQ-DI) (ranges from 0=least difficulty to 3=extreme difficulty) and an acute-phase reactant [high sensitivity C-reactive Protein milligram per liter (mg/L) (hsCRP)]. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as reference for the comparison of active treatment arms. The analysis was performed on Intent-to-Treat (ITT) set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Primary

End point timeframe:

Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	54.7	50.9	63.6	42.7

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is defined as there is no difference between the 150mg dose of GSK3196165 and placebo in the proportion of participants achieving ACR20 response at Week 12, versus the alternative hypothesis that the 150mg dose of GSK3196165 differs from placebo in the proportion of participants achieving ACR20 response at Week 12.

Comparison groups	GSK3196165 150mg + MTX v Pooled Placebo
Number of subjects included in analysis	766
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0362
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.39
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	1.02
upper limit	1.89

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is defined as there is no difference between the 90mg dose of GSK3196165 and placebo in the proportion of participants achieving ACR20 response at Week 12, versus the alternative hypothesis that the 90mg dose of GSK3196165 differs from placebo in the proportion of participants achieving ACR20 response at Week 12.

Comparison groups	GSK3196165 90mg + MTX v Pooled Placebo
Number of subjects included in analysis	769
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0023
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.62
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	1.19
upper limit	2.21

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The null hypothesis is defined as there is no difference between the 90mg dose of GSK3196165 and 05mg dose of Tofacitinib in the proportion of participants achieving ACR20 response at Week 12, versus the alternative hypothesis that the 90mg dose of GSK3196165 differs from 05mg dose of Tofacitinib in the proportion of participants achieving ACR20 response at Week 12.

Comparison groups	GSK3196165 90mg + MTX v Tofacitinib 5mg + MTX
Number of subjects included in analysis	771
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.023
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.5
upper limit	0.95

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

The null hypothesis is defined as there is no difference between the 150mg dose of GSK3196165 and 05mg dose of Tofacitinib in the proportion of participants achieving ACR20 response at Week 12, versus the alternative hypothesis that the 150mg dose of GSK3196165 differs from 05mg dose of Tofacitinib in the proportion of participants achieving ACR20 response at Week 12.

Comparison groups	GSK3196165 150mg + MTX v Tofacitinib 5mg + MTX
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0013
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.59

Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	0.43
upper limit	0.82

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The null hypothesis is defined as there is no difference between the 05mg dose of Tofacitinib and placebo in the proportion of participants achieving ACR20 response at Week 12, versus the alternative hypothesis that the 05mg dose of Tofacitinib differs from placebo in the proportion of participants achieving ACR20 response at Week 12.

Comparison groups	Tofacitinib 5mg + MTX v Pooled Placebo
Number of subjects included in analysis	514
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	Other: 0.95 %
sides	2-sided
lower limit	1.62
upper limit	3.37

Secondary: Percentage of participants achieving Clinical disease activity index (CDAI) total score less than or equal to (<=)10 [CDAI Low disease activity (LDA)] at Week 12

End point title	Percentage of participants achieving Clinical disease activity index (CDAI) total score less than or equal to (<=)10 [CDAI Low disease activity (LDA)] at Week 12[2]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	20.9	19.8	32.5	13.9

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12

End point title	Change from Baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) at Week 12[3]

End point description:

Health Assessment Questionnaire-Disability Index (HAQ-DI) is 20-question instrument that assesses degree of difficulty in accomplishing tasks in eight functional areas:dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Overall HAQ-DI score is sum of domain scores divided by number of domains answered. The score ranges from 0 to 3 where 0=least difficulty and 3=extreme difficulty. Higher overall score indicates greater disability. A negative change from baseline indicates an improvement. Baseline was defined as latest pre-dose assessment with a non-missing value, including from unscheduled visits. Change from Baseline was calculated by subtracting post dose value from Baseline. For the purpose of all analyses up to week 12, placebo arms were pooled into single placebo arm to primarily serve as reference for comparison of active treatment arms. The analysis was performed on ITT set using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	-0.46 (± 0.025)	-0.38 (± 0.024)	-0.5 (± 0.034)	-0.27 (± 0.034)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving 50%/70% improvement in American College of Rheumatology Criteria (ACR50/70) at Week 12

End point title	Percentage of participants achieving 50%/70% improvement in American College of Rheumatology Criteria (ACR50/70) at Week 12[4]

End point description:

ACR50/70 is calculated as 50%/70% improvement from Baseline in Tender Joint Count 68 (TJC68) and Swollen Joint Count 66 (SJC66) and 50%/70% improvement in 3 of the following 5 measures:Patient's Global Assessment of Arthritis Disease Activity (PtGA), Physician Global Assessment of Arthritis Disease Activity (PhGA) [VAS with values from 0=best to 100=worst), Patient Assessment of Arthritis Pain (VAS with values from 0=no pain and 100=most severe pain), Health Assessment Questionnaire-Disability Index (HAQ-DI) (ranges from 0 = least difficulty to 3 = extreme difficulty) and an acute-phase reactant (high sensitivity C-reactive Protein mg/L (hsCRP)]. For the purpose of all analyses up to week 12, placebo arms were pooled into single placebo arm to primarily serve as reference for comparison of active treatment arms. The analysis was performed on the ITT set using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)				
ACR50, Week 12	23.3	20.0	34.1	12.2
ACR70, Week 12	8.5	6.1	13.9	3.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving 20% improvement in ACR20 at Week 24 (Non-Inferiority versus tofacitinib)

End point title	Percentage of participants achieving 20% improvement in ACR20 at Week 24 (Non-Inferiority versus tofacitinib)[5]

End point description:

ACR20 is calculated as a 20% improvement from Baseline in Tender Joint Count 68 (TJC68) and Swollen Joint Count 66 (SJC66) and a 20% improvement in 3 of the following 5 measures: Patient's Global Assessment of Arthritis Disease Activity (PtGA) [visual analogue scale (VAS) with values from 0=best to 100=worst], Physician Global Assessment of Arthritis Disease Activity (PhGA) (VAS with values from 0=best to 100=worst), Patient Assessment of Arthritis Pain (VAS with values from 0=no pain and 100=most severe pain), Health Assessment Questionnaire-Disability Index (HAQ-DI) (ranges from 0 to 3 where 0 = least difficulty and 3 = extreme difficulty) and an acute-phase reactant [high sensitivity C-reactive Protein milligram per liter (mg/L) (hsCRP)]. The analysis was performed on the ITT set using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)	63.9	61.3	74.4	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	GSK3196165 150mg + MTX v Tofacitinib 5mg + MTX
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-13
Confidence interval	
level	Other: 0.98 %
sides	2-sided
lower limit	-21.2
upper limit	-4.8

Statistical analysis title	Statistical Analysis 1
Comparison groups	GSK3196165 90mg + MTX v Tofacitinib 5mg + MTX
Number of subjects included in analysis	771
Analysis specification	Pre-specified
Analysis type	
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	-10.4
Confidence interval	
level	Other: 0.98 %
sides	2-sided
lower limit	-18.6
upper limit	-2.3

Secondary: Percentage of participants achieving 50%/70% improvement in American College of Rheumatology Criteria (ACR50/70) at Week 24 and ACR 20/50/70 at and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving 50%/70% improvement in American College of Rheumatology Criteria (ACR50/70) at Week 24 and ACR 20/50/70 at and Week 52 for treatment arms who started study intervention from Day 1[6]

End point description:

ACR20/50/70 is calculated as a 20%/50%/70% improvement from Baseline in Tender Joint Count 68 (TJC68) and Swollen Joint Count 66 (SJC66) and a 20%/50%/70% improvement in 3 of the following 5 measures: Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale (VAS) with values from 0=best to 100=worst), Physician Global Assessment of Arthritis Disease Activity (PhGA) [VAS with values from 0=best to 100=worst], Patient Assessment of Arthritis Pain (VAS with values from 0=no pain and 100=most severe pain), Health Assessment Questionnaire-Disability Index (HAQ- DI) (ranges from 0 to 3 where 0 = least difficulty and 3 = extreme difficulty) and an acute-phase reactant [high sensitivity C-reactive Protein mg/L (hsCRP)]. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
ACR20, Week 52	63.9	61.1	75.8	
ACR50, Week 24	31.4	29.1	46.7	
ACR50, Week 52	35.0	34.2	48.4	
ACR70, Week 24	12.5	10.1	25.1	
ACR70, Week 52	16.7	14.4	26.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving ACR20/50/70 at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving ACR20/50/70 at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[7]

End point description:

ACR20/50/70 is calculated as a 20%/50%/70% improvement from Baseline in Tender Joint Count 68 (TJC68) and Swollen Joint Count 66 (SJC66) and a 20%/50%/70% improvement in 3 of the following 5 measures: Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale (VAS) with values from 0=best to 100=worst), Physician Global Assessment of Arthritis Disease Activity (PhGA) [VAS with values from 0=best to 100=worst], Patient Assessment of Arthritis Pain (VAS with values from 0=no pain and 100=most severe pain), Health Assessment Questionnaire-Disability Index (HAQ- DI) (ranges from 0 to 3 where 0 = least difficulty and 3 = extreme difficulty) and an acute-phase reactant [high sensitivity C-reactive Protein mg/L (hsCRP)]. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
ACR20, Week 24	56.7	71.2	69.9	
ACR20, Week 52	70.5	67.8	84.6	
ACR50, Week 24	37.0	35.0	40.7	
ACR50, Week 52	28.6	42.5	50.7	
ACR70, Week 24	7.9	15.0	19.6	
ACR70, Week 52	10.3	20.2	25.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving CDAI total score <=10 (CDAI LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving CDAI total score <=10 (CDAI LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[8]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	29.9	29.8	45.9	
Week 52	35.5	37.1	51.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving CDAI total score <=10 (CDAI LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving CDAI total score <=10 (CDAI LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[9]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	32.9	37.4	45.8	
Week 52	38.5	44	52.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 12

End point title	Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 12[10]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. CDAI remission is achieved when CDAI total score <=2.8. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	3.8	2.4	5.8	1.0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[11]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. CDAI remission is achieved when CDAI total score <=2.8. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	6.1	5.2	12.1	
Week 52	9.4	4.4	15.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving CDAI total score <=2.8 (CDAI Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[12]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of the sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (visual analogue scale with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale before computing the CDAI total score. CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. CDAI remission is achieved when CDAI total score <=2.8. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				

Week 24	4.4	8.4	6.4	
Week 52	4.6	9.6	11.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28 Erythrocyte Sedimentation Rate (ESR) <=3.2 (DAS28-ESR LDA) at Week 12

End point title	Percentage of participants achieving DAS28 Erythrocyte Sedimentation Rate (ESR) <=3.2 (DAS28-ESR LDA) at Week 12[13]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in millimeter [mm]/hour[hr]), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-ESR<=3.2. A negative change from baseline in DAS28-ESR indicates an improvement. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	13.6	12.2	19.7	8.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-CRP <=3.2 (DAS28-CRP LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving DAS28-CRP <=3.2 (DAS28-CRP LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[14]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28),

Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-CRP greater than or equal to (<=)3.2. A negative change from baseline in DAS28-CRP indicates an improvement. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	26.8	29.0	47.4	
Week 52	32.8	31.3	49.8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving Disease Activity Score using 28 joint count and C-Reactive Protein (DAS28-CRP) <=3.2 (DAS28-CRP LDA) at Week 12

End point title	Percentage of participants achieving Disease Activity Score using 28 joint count and C-Reactive Protein (DAS28-CRP) <=3.2 (DAS28-CRP LDA) at Week 12[15]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-CRP greater than or equal to (<=)3.2. A negative change from baseline in DAS28-CRP indicates an improvement. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	20.2	19.4	33.5	11.3

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-ESR <=3.2 (DAS28-ESR LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving DAS28-ESR <=3.2 (DAS28-ESR LDA) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[16]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in millimeter [mm]/hour[hr]), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-ESR<=3.2. A negative change from baseline in DAS28-ESR indicates an improvement. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	17.2	18.3	28.3	
Week 52	23.3	18.7	34.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-CRP <=3.2 (DAS28-CRP LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving DAS28-CRP <=3.2 (DAS28-CRP LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[17]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-CRP greater than or equal to (<=)3.2. A negative change from baseline in DAS28-CRP indicates an improvement. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	26.3	31.0	44.9	
Week 52	34.2	34.9	50.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-ESR <=3.2 (DAS28-ESR LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving DAS28-ESR <=3.2 (DAS28-ESR LDA) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[18]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in millimeter [mm]/hour[hr]), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Low disease activity (LDA) is achieved when DAS28-ESR<=3.2. A negative change from baseline in DAS28-ESR indicates an improvement. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	20.7	22.7	30.4	
Week 52	22.9	21.8	30.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 12

End point title	Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 12[19]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in mm/hr), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-ESR <2.6. A negative change from baseline in DAS28-ESR indicates an improvement. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	6.0	5.3	11.5	5.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[20]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-CRP less than (<)2.6. A negative change from baseline in DAS28-CRP indicates an improvement. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	14.5	14.1	26.3	
Week 52	19.3	15.3	34.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 12

End point title	Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 12[21]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-CRP less than (<)2.6. A negative change from baseline in DAS28-CRP indicates an improvement. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. Analysis was performed using multiple imputation method to handle missing data. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	10.3	8.4	17.1	5.2

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[22]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in mm/hr), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-ESR <2.6. A negative change from baseline in DAS28-ESR indicates an improvement. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	8.6	7.8	13.7	
Week 52	14.1	8.8	18.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving DAS28-CRP <2.6 (DAS28-CRP Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[23]

End point description:

The DAS28-CRP is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), C-reactive protein (CRP) (in mg/L), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-CRP scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-CRP less than (<)2.6. A negative change from baseline in DAS28-CRP indicates an improvement. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	14.7	20.2	28.2	
Week 52	18.2	18.7	31.2	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving a good/moderate (European League Against Rheumatism) EULAR response at Week 12

End point title	Percentage of participants achieving a good/moderate (European League Against Rheumatism) EULAR response at

	Week 12[24]

End point description:

DAS28-CRP and DAS28-ESR scores were categorized using EULAR response criteria. Response was defined based on combination of current DAS28 score and improvement in current score relative to Baseline. The definition of no response, moderate response and good response was as; DAS28 <=3.2 and DAS28 decrease from Baseline (>1.2:good response, >0.6 to <=1.2:moderate response, <=0.6:no response); DAS28 >3.2 to <=5.1 and DAS28 decrease from Baseline (>1.2:moderate response, >0.6 to <=1.2:moderate response, <=0.6:no response) and DAS28 >5.1 and DAS28 decrease from Baseline (>1.2:moderate response, >0.6 to <=1.2:no response, <=0.6:no response). If the post-Baseline DAS28-CRP score was missing, then the corresponding EULAR category was set to missing. For purpose of all analyses up to week 12, placebo arms were pooled into single arm to primarily serve as reference for comparison of active treatment arms. Analysis was performed on ITT set using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	73.1	69.3	83.0	54.5

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving DAS28 ESR <2.6 (DAS28-ESR Remission) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[25]

End point description:

The DAS28-ESR is a measure of RA disease activity calculated using Tender Joint Count 28 (TJC28), Swollen Joint Count 28 (SJC28), Erythrocyte sedimentation rate (ESR) (in mm/hr), Patient's Global Assessment of Arthritis Disease Activity (PtGA) (visual analogue scale with values from 0=best to 100=worst). DAS28-ESR scores range from 1.0 to 9.4, where lower scores indicate less disease activity. Remission is achieved when DAS28-ESR <2.6. A negative change from baseline in DAS28-ESR indicates an improvement. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	10.8	14.8	12	
Week 52	11.0	11.8	15.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving a good/moderate EULAR response at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving a good/moderate EULAR response at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[26]

End point description:

DAS28-CRP and DAS28-ESR scores were categorized using EULAR response criteria. Response was defined based on combination of current DAS28 score and improvement in current score relative to Baseline. The definition of no response, moderate response and good response was as; DAS28 <=3.2 and DAS28 decrease from Baseline (>1.2:good response, >0.6 to <=1.2:moderate response, <=0.6:no response); DAS28 >3.2 to <=5.1 and DAS28 decrease from Baseline (>1.2:moderate response, >0.6 to <=1.2:moderate response, <=0.6:no response) and DAS28 >5.1 and DAS28 decrease from Baseline (>1.2:moderate response, >0.6 to <=1.2:no response, <=0.6:no response). If the post-Baseline DAS28-CRP score was missing, then the corresponding EULAR category was set to missing. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
Week 24	76.3	82.4	88.9	
Week 52	87.1	79.1	92.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving ACR/EULAR remission at Week 12

End point title	Number of participants achieving ACR/EULAR remission at Week 12[27]

End point description:

Boolean-based ACR/EULAR remission is achieved if all of the following requirements are met at the same timepoint: Tender Joint Count 68 (TJC68) <= 1, Swollen Joint Count 66 (SJC66) <= 1, high sensitivity C-reactive Protein (hsCRP) <= 1mg/dl and patient's global assessment of disease activity (PtGA) <= 10. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set that inlcudes all randomized participants who received at least one dose of study treatment. This population was based on the treatment the participant was randomized to. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	475	477	228	
Units: Participants	11	9	11	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving a good/moderate EULAR response at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving a good/moderate EULAR response at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[28]

End point description:

DAS28-CRP and DAS28-ESR scores were categorized using EULAR response criteria. Response was defined based on combination of current DAS28 score and improvement in current score relative to Baseline. The definition of no response, moderate response and good response was as; DAS28 <=3.2 and DAS28 decrease from Baseline (>1.2:good response, >0.6 to <=1.2:moderate response, <=0.6:no response); DAS28 >3.2 to <=5.1 and DAS28 decrease from Baseline (>1.2:moderate response, >0.6 to <=1.2:moderate response, <=0.6:no response) and DAS28 >5.1 and DAS28 decrease from Baseline

(>1.2:moderate response, >0.6 to <=1.2:no response, <=0.6:no response). If the post-Baseline DAS28-CRP score was missing, then the corresponding EULAR category was set to missing. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[28] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
Week 24	78.4	74.9	89.8	
Week 52	79.1	78.6	89.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving no radiographic progression (Van der Heijde modified total sharp scores (mTSS <= 0.5) at Week 12

End point title	Percentage of participants achieving no radiographic progression (Van der Heijde modified total sharp scores (mTSS <= 0.5) at Week 12[29]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score ranges from 0 to 448 for mTSS with higher values representing higher disease activity. No radiographic progression is defined as a change from Baseline in van der Heijde mTSS score of <=0.5. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Percentage of participants				
number (not applicable)	83.8	82.6	88.9	76.7

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving ACR/EULAR remission at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Number of participants achieving ACR/EULAR remission at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[30]

End point description:

Boolean-based ACR/EULAR remission is achieved if all of the following requirements are met at the same timepoint: Tender Joint Count 68 (TJC68) <= 1, Swollen Joint Count 66 (SJC66) <= 1, high sensitivity C-reactive Protein (hsCRP) <= 1mg/dl and patient's global assessment of disease activity (PtGA) <= 10. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	453	467	227	
Units: Participants				
Week 24	16	13	14	
Week 52	24	13	18	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants achieving ACR/EULAR remission at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Number of participants achieving ACR/EULAR remission at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[31]

End point description:

Boolean-based ACR/EULAR remission is achieved if all of the following requirements are met at the same

timepoint: Tender Joint Count 68 (TJC68) <= 1, Swollen Joint Count 66 (SJC66) <= 1, high sensitivity C-reactive Protein (hsCRP) <= 1mg/dl and patient's global assessment of disease activity (PtGA) <= 10. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[31] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	76	80	78	
Units: Participants				
Week 24	2	4	3	
Week 52	3	3	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving no radiographic progression (mTSS <= 0.5) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Percentage of participants achieving no radiographic progression (mTSS <= 0.5) at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[32]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score ranges from 0 to 448 for mTSS with higher values representing higher disease activity. No radiographic progression is defined as a change from Baseline in van der Heijde mTSS score of <=0.5. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Percentage of participants				
number (not applicable)				
mTSS <= 0.5, Week 24	79.5	79.6	84.6	
mTSS <= 0.5, Week 52	71.8	72.8	79.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants achieving no radiographic progression (mTSS <= 0.5) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Percentage of participants achieving no radiographic progression (mTSS <= 0.5) at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[33]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score ranges from 0 to 448 for mTSS with higher values representing higher disease activity. No radiographic progression is defined as a change from Baseline in van der Heijde mTSS score of <=0.5. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Week 24 and Week 52

Notes:

[33] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Percentage of participants				
number (not applicable)				
mTSS <= 0.5, Week 24	78.6	74.6	77.7	
mTSS <= 0.5, Week 52	76.0	68.3	69.5	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CDAI total score at Week 12

End point title	Change from Baseline in CDAI total score at Week 12[34]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (VAS with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale . CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. Baseline was defined as latest pre-dose assessment with a non-missing value, including from unscheduled visits. Change from Baseline was calculated by subtracting post dose value from Baseline. For purpose of all analyses up to week 12, placebo arms were pooled into single arm to primarily serve as reference for comparison of active treatment arms. The analysis was performed on the ITT set using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[34] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	-17.85 (± 0.574)	-17.15 (± 0.563)	-21.39 (± 0.801)	-13.01 (± 0.798)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CDAI total score at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in CDAI total score at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[35]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (VAS with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale . CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. Baseline was defined as latest pre-dose assessment with a non-missing value, including from unscheduled visits. Change from Baseline was calculated by subtracting post dose value from Baseline. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	-20.63 (± 0.561)	-19.88 (± 0.551)	-24.5 (± 0.781)	
Week 52	-21.79 (± 0.558)	-21.81 (± 0.549)	-25.55 (± 0.77)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CDAI total score at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in CDAI total score at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[36]

End point description:

Clinical Disease Activity Index (CDAI) total score is a composite score consisting of sum of Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), Patient's Global Assessment of Arthritis Disease Activity (PtGA) and Physician Global Assessment of Arthritis Disease Activity (PhGA) (VAS with values from 0=best to 100=worst). PtGA and PhGA are transformed to a 0-10 scale . CDAI total score ranges from 0 to 76 with higher values representing higher disease activity. Low disease activity (LDA) is achieved when CDAI total score <=10. Baseline was defined as latest pre-dose assessment with a non-missing value, including from unscheduled visits. Change from Baseline was calculated by subtracting post dose value from Baseline. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				

Week 24	-21.41 (± 1.359)	-22.93 (± 1.31)	-24.5 (± 1.307)	
Week 52	-23.49 (± 1.365)	-22.91 (± 1.291)	-25.83 (± 1.28)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-CRP/DAS28-ESR at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in DAS28-CRP/DAS28-ESR at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[37]

End point description:

DAS28-CRP and DAS28-ESR are measure of RA disease activity calculated using Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), high sensitivity C-reactive Protein (hsCRP in mg/L)/Erythrocyte sedimentation rate (ESR) [ESR in millimeter/hour (mm/hr)] and patient's global assessment of disease activity (PtGA) transformed to a 0-10 scale. Total score range from 0-9.4, with higher scores indicating more disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[37] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
DAS28-CRP, Week 24	-1.74 (± 0.056)	-1.67 (± 0.055)	-2.31 (± 0.078)	
DAS28-CRP, Week 52	-1.85 (± 0.06)	-1.82 (± 0.059)	-2.39 (± 0.083)	
DAS28-ESR, Week 24	-1.79 (± 0.059)	-1.74 (± 0.057)	-2.3 (± 0.082)	
DAS28-ESR, Week 52	-1.92 (± 0.063)	-1.84 (± 0.062)	-2.36 (± 0.087)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-CRP/DAS28-ESR at Week 12

End point title	Change from Baseline in DAS28-CRP/DAS28-ESR at Week

End point description:

DAS28-CRP and DAS28-ESR are measure of RA disease activity calculated using Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), high sensitivity C-reactive Protein (hsCRP in mg/L)/Erythrocyte sedimentation rate (ESR) [ESR in millimeter/hour (mm/hr)] and patient's global assessment of disease activity (PtGA) transformed to a 0-10 scale. Total score range from 0-9.4, with higher scores indicating more disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)				
DAS28-CRP	-1.49 (± 0.054)	-1.44 (± 0.053)	-1.96 (± 0.076)	-1.01 (± 0.075)
DAS28-ESR	-1.53 (± 0.057)	-1.48 (± 0.056)	-1.97 (± 0.079)	-1.07 (± 0.079)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-CRP/DAS28-ESR at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in DAS28-CRP/DAS28-ESR at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[39]

End point description:

DAS28-CRP and DAS28-ESR are measure of RA disease activity calculated using Swollen Joint Count 28 (SJC28), Tender Joint Count 28 (TJC28), high sensitivity C-reactive Protein (hsCRP in mg/L)/Erythrocyte sedimentation rate (ESR) [ESR in millimeter/hour (mm/hr)] and patient's global assessment of disease activity (PtGA) transformed to a 0-10 scale. Total score range from 0-9.4, with higher scores indicating more disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[39] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
DAS28-CRP, Week 24	-1.77 (± 0.136)	-1.95 (± 0.131)	-2.29 (± 0.131)	
DAS28-CRP, Week 52	-1.92 (± 0.146)	-1.96 (± 0.139)	-2.37 (± 0.137)	
DAS28-ESR, Week 24	-1.84 (± 0.143)	-2.05 (± 0.137)	-2.23 (± 0.137)	
DAS28-ESR, Week 52	-2.06 (± 0.151)	-2.06 (± 0.145)	-2.43 (± 0.145)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Van der Heijde mTSS at Week 12

End point title	Change from Baseline in Van der Heijde mTSS at Week 12[40]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score range from 0 to 448 for mTSS with higher values representing higher disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	0.15 (± 0.075)	0.19 (± 0.073)	0.13 (± 0.104)	0.55 (± 0.103)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Van der Heijde mTSS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in Van der Heijde mTSS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[41]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score range from 0 to 448 for mTSS with higher values representing higher disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	0.71 (± 0.215)	0.77 (± 0.208)	0.67 (± 0.208)	
Week 52	0.9 (± 0.309)	1.24 (± 0.306)	1.06 (± 0.297)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Van der Heijde mTSS at Week 24 and Week 52

for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in Van der Heijde mTSS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[42]

End point description:

Van der Heijde mTSS is utilized for scoring radiographs of hands and feet in rheumatoid arthritis. This method includes 16 areas of erosions, and 15 areas for joint space narrowing (JSN) in each hand, and 6 areas for erosions and 6 areas JSN in each foot. The total mTSS score is the sum of erosion (maximum of 280) and JSN (maximum of 168) scores. The score range from 0 to 448 for mTSS with higher values representing higher disease activity. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	0.25 (± 0.08)	0.38 (± 0.078)	0.2 (± 0.112)	
Week 52	0.61 (± 0.117)	0.63 (± 0.114)	0.35 (± 0.158)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HAQ-DI at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in HAQ-DI at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[43]

End point description:

HAQ-DI is a 20-question instrument that assesses the degree of difficulty of a participant in accomplishing tasks in eight functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Overall HAQ-DI score was computed as sum of the domain scores divided by the number of domains answered. The total possible score ranges from 0 to 3 where 0 = least difficulty and 3 = extreme difficulty. Higher overall score indicates greater disability. A negative change from baseline indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[43] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	-0.53 (± 0.065)	-0.46 (± 0.062)	-0.58 (± 0.062)	
Week 52	-0.47 (± 0.069)	-0.45 (± 0.066)	-0.67 (± 0.065)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in HAQ-DI at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in HAQ-DI at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[44]

End point description:

HAQ-DI is a 20-question instrument that assesses the degree of difficulty of a participant in accomplishing tasks in eight functional areas: dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. Overall HAQ-DI score was computed as sum of the domain scores divided by the number of domains answered. The total possible score ranges from 0 to 3 where 0 = least difficulty and 3 = extreme difficulty. Higher overall score indicates greater disability. A negative change from baseline indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				

Week 24	-0.51 (± 0.027)	-0.41 (± 0.026)	-0.56 (± 0.037)	
Week 52	-0.54 (± 0.028)	-0.46 (± 0.028)	-0.58 (± 0.039)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Arthritis pain VAS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in Arthritis pain VAS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[45]

End point description:

For the Arthritis Pain VAS, participants assess the severity of their current arthritis pain using a continuous visual analogue scale (VAS) with anchors at "0" (no pain) and "100" (most severe pain). A negative change from baseline indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who switched from placebo to study intervention at Week 12. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[45] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	-26.91 (± 2.666)	-28.02 (± 2.564)	-29.13 (± 2.566)	
Week 52	-24.08 (± 2.902)	-29.22 (± 2.765)	-34.8 (± 2.742)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Short form (SF)-36 physical component scores (PCS) at Week 12

End point title	Change from Baseline in Short form (SF)-36 physical component scores (PCS) at Week 12[46]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning (PF), bodily pain (BP), role limitations due to physical/emotional issues, general health (GH), mental health, social functioning, vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. PCS combines 4 domains (PF, role-physical, BP, GH) for overall physical health. PCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall physical health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose NMV, including unscheduled visits. CB=subtracting PD value from BV. For analysis up to week 12, placebo arms were pooled into single arm to serve as reference for active treatment arm comparison. ITT set was analyzed using multiple imputation to manage missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	5.38 (± 0.305)	4.96 (± 0.297)	6.93 (± 0.427)	3.19 (± 0.423)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Arthritis pain VAS at Week 12

End point title	Change from Baseline in Arthritis pain VAS at Week 12[47]

End point description:

For the Arthritis Pain VAS, participants assess the severity of their current arthritis pain using a continuous visual analogue scale (VAS) with anchors at "0" (no pain) and "100" (most severe pain). A negative change from baseline indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	-22 (± 1.056)	-19.56 (± 1.033)	-27.26 (± 1.473)	-14.58 (± 1.466)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 domain scores at Week 12

End point title	Change from Baseline in SF-36 domain scores at Week 12[48]

End point description:

SF-36 survey assessed health-related quality of life, covering physical functioning, bodily pain, role limitations due to physical/emotional issues, general health, mental health, social functioning, and vitality. MCS consists of four domains (MH, vitality, SF, role-emotional), and PCS consists of four domains (PF, role-physical, BP, GH).Individual question items were totaled within items under various sections, and these domain scores were then scaled from 0 to 100, with higher scores indicating better health. Positive changes from the baseline indicated improvements. Scoring of SF-36 utilized Quality Metric software. Baseline=latest pre-dose assessment with NMV, including those from unscheduled visits. CB=subtracting PD visit value from BV. For analysis up to week 12, placebo arms were pooled into single arm to serve as reference for active treatment arm comparison. ITT set was analyzed only those participants with data available at the specified time points.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	474	483	235	
Units: Scores on a scale				
arithmetic mean (standard error)				
Bodily Pain	15.21 (± 21.448)	14.65 (± 21.208)	20.83 (± 22.432)	
General Health	8.23 (± 15.662)	7.32 (± 15.462)	11.11 (± 16.447)	
Mental Health	7.03 (± 18.222)	6.4 (± 18.993)	10.19 (± 18.659)	
Physical Function	13.2 (± 21.092)	12.9 (± 21.564)	17.81 (± 19.957)	
Role Emotional	7.47 (± 25.231)	7.35 (± 25.162)	9.25 (± 25.836)	
Role Physical	12.51 (± 21.751)	12.56 (± 23.345)	16.28 (± 22.117)	
Social Function	9.2 (± 23.558)	8.72 (± 26.227)	14.15 (± 25.092)	

Vitality	11.05 (± 20.216)	9.82 (± 19.662)	14.63 (± 20.185)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 mental component scores (MCS) at Week 12

End point title	Change from Baseline in SF-36 mental component scores (MCS) at Week 12[49]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning, bodily pain, role limitations due to physical/emotional issues, general health, mental health (MH), social functioning (SF), vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. MCS combines 4 domains (MH,vitality,SF,role-emotional) for overall mental health. MCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall mental health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose NMV, including unscheduled visits. CB=subtracting PD value from BV. For analysis up to week 12, placebo arms were pooled into single arm to serve as reference for active treatment arm comparison. ITT set was analyzed using multiple imputation to manage missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[49] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	2.88 (± 0.41)	2.54 (± 0.399)	4.04 (± 0.574)	2.46 (± 0.569)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 PCS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in SF-36 PCS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[50]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning (PF), bodily pain (BP), role limitations due to physical/emotional issues, general health (GH), mental health, social

functioning, vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. PCS combines 4 domains (PF, role-physical, BP, GH) for overall physical health. PCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall physical health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose visit value from Baseline value. Participants who received study intervention from Day 1 to Week 52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	6.26 (± 0.319)	5.82 (± 0.313)	8.07 (± 0.448)	
Week 52	6.5 (± 0.364)	6.04 (± 0.358)	8.23 (± 0.507)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 MCS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in SF-36 MCS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[51]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning, bodily pain, role limitations due to physical/emotional issues, general health, mental health (MH), social functioning (SF), vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. MCS combines 4 domains (MH,vitality,SF,role-emotional) for overall mental health. MCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall mental health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose visit value from Baseline value. Participants who received study intervention from Day 1 to Week 52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	3.69 (± 0.401)	3.87 (± 0.393)	2.92 (± 0.563)	
Week 52	3.13 (± 0.443)	2.75 (± 0.437)	3.53 (± 0.616)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 domain scores at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in SF-36 domain scores at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[52]

End point description:

SF-36 survey assessed health-related quality of life, covering physical functioning, bodily pain, role limitations due to physical/emotional issues, general health, mental health, social functioning, and vitality. MCS consists of four domains (MH,vitality,SF,role-emotional), and PCS consists of four domains (PF,role-physical,BP,GH).Individual question items were totaled within items under various sections, and these domain scores were then scaled from 0 to 100, with higher scores indicating better health. Positive changes from the baseline indicated improvements. Scoring of SF-36 utilized Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose value from Baseline value. Analysis was performed on all randomized participants who received study intervention from Day01 to Week52. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	459	469	227	
Units: Scores on a scale				
arithmetic mean (standard error)				
Bodily Pain, Week 24	18.8 (± 21.717)	18.06 (± 21.303)	23.07 (± 22.7)	
Bodily Pain, Week 52	18.93 (± 23.084)	18.39 (± 22.667)	24.87 (± 23.427)	
General Health, Week 24	9.7 (± 15.747)	9.01 (± 15.577)	11.46 (± 16.416)	
General Health, Week 52	10.2 (± 16.795)	8.81 (± 17.426)	12.4 (± 19.371)	
Mental Health, Week 24	9.14 (± 17.511)	8.88 (± 19.515)	9.89 (± 18.461)	

Mental Health, Week 52	8.65 (± 18.468)	7.43 (± 20.048)	10.44 (± 21.685)	
Physical Function, Week 24	16.35 (± 22.51)	16.2 (± 23.122)	20.9 (± 21.808)	
Physical Function, Week 52	16.18 (± 24.737)	17.22 (± 23.464)	21.77 (± 25.534)	
Role Emotional, Week 24	10.75 (± 25.123)	10.54 (± 25.451)	7.86 (± 25.124)	
Role Emotional, Week 52	10.08 (± 26.113)	9.24 (± 26.689)	9.3 (± 26.279)	
Role Physical, Week 24	15.35 (± 22.432)	14.87 (± 23.361)	18.81 (± 22.588)	
Role Physical, Week 52	16.5 (± 23.981)	14.74 (± 24.325)	19.16 (± 24.391)	
Social Function, Week 24	11.6 (± 23.543)	12.95 (± 26.72)	13.49 (± 24.164)	
Social Function, Week 52	11.66 (± 25.523)	10.51 (± 26.367)	15.29 (± 24.872)	
Vitality, Week 24	13.37 (± 19.908)	13.02 (± 20.115)	15.5 (± 19.854)	
Vitality, Week 52	13.37 (± 20.358)	12.23 (± 20.712)	15.73 (± 21.767)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 MCS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in SF-36 MCS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[53]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning (PF), bodily pain (BP), role limitations due to physical/emotional issues, general health (GH), mental health, social functioning, vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. MCS combines 4 domains (MH,vitality,SF,role-emotional) for overall mental health. MCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall mental health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose visit value from Baseline value. Participants who received study intervention from Week12 to Week52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[53] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	3.76 (± 0.973)	4.43 (± 0.938)	4.2 (± 0.942)	
Week 52	3.06 (± 1.081)	3.77 (± 1.032)	5.47 (± 1.027)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 PCS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in SF-36 PCS at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[54]

End point description:

SF-36 survey evaluates health-related quality of life, covering physical functioning (PF), bodily pain (BP), role limitations due to physical/emotional issues, general health (GH), mental health, social functioning, vitality. Each domain's score was average of individual question scores, range from 0-100 with higher scores representing better health. PCS combines 4 domains (PF, role-physical, BP, GH) for overall physical health. PCS employs T-score scale with a mean of 50 and standard deviation of 10; higher scores indicate better health. Positive change from baseline indicated improvement in overall physical health. SF-36 was scored using Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose visit value from Baseline value. Participants who received study intervention from Week12 to Week52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	6.31 (± 0.773)	7.07 (± 0.746)	8.21 (± 0.747)	
Week 52	5.68 (± 0.89)	6.27 (± 0.852)	8.81 (± 0.848)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SF-36 domain scores at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in SF-36 domain scores at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[55]

End point description:

SF-36 survey assessed health-related quality of life, covering physical functioning, bodily pain, role limitation due to physical/emotional issues, general health, mental health, social functioning, and vitality. MCS consists of four domains (MH,vitality,SF,role-emotional), and PCS consists of four domains (PF,role-physical,BP,GH).Individual question items were totaled within items under various sections, and these domain scores were then scaled from 0 to 100, with higher scores indicating better health. Positive changes from the baseline indicated improvements. Scoring of SF-36 utilized Quality Metric software. Baseline was defined as most recent pre-dose non-missing value, including unscheduled visits. Change from baseline was calculated by subtracting post dose value from Baseline value. Analysis was performed on all randomized participants who received study intervention from Week12 to Week52. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[55] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	81	80	
Units: Scores on a scale				
arithmetic mean (standard error)				
Bodily Pain, Week 24	20.13 (± 23.373)	23.28 (± 20.682)	22.23 (± 20.389)	
Bodily Pain, Week 52	21.00 (± 24.696)	24.96 (± 22.495)	26.68 (± 22.838)	
General Health, Week 24	9.6 (± 18.212)	12.02 (± 15.209)	9.44 (± 13.61)	
General Health, Week 52	9.46 (± 16.95)	9.00 (± 15.591)	9.38 (± 15.469)	
Mental Health, Week 24	8.67 (± 18.405)	9.81 (± 16.21)	6.94 (± 16.41)	
Mental Health, Week 52	9.55 (± 22.271)	9.87 (± 18.214)	9.14 (± 17.576)	
Physical Function, Week 24	18.2 (± 20.725)	21.42 (± 24.94)	20.69 (± 22.385)	
Physical Function, Week 52	15.6 (± 25.13)	18.87 (± 26.655)	22.89 (± 20.22)	
Role Emotional, Week 24	12.89 (± 27.478)	14.71 (± 24.73)	10.83 (± 26.131)	
Role Emotional, Week 52	10.07 (± 28.705)	13.11 (± 29.612)	13.92 (± 28.231)	
Role Physical, Week 24	17.83 (± 24.739)	17.36 (± 24.065)	17.58 (± 19.053)	

Role Physical, Week 52	18.38 (± 25.35)	17.08 (± 26.443)	21.05 (± 19.144)	
Social Function, Week 24	16.83 (± 21.503)	16.36 (± 22.504)	15.47 (± 23.804)	
Social Function, Week 52	16.6 (± 25.505)	14.00 (± 25.165)	20.56 (± 25.389)	
Vitality, Week 24	15.92 (± 19.176)	18.36 (± 19.196)	15.31 (± 17.731)	
Vitality, Week 52	16.14 (± 19.769)	16.42 (± 17.671)	16.12 (± 19.345)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Arthritis pain VAS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in Arthritis pain VAS at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[56]

End point description:

For the Arthritis Pain VAS, participants assess the severity of their current arthritis pain using a continuous visual analogue scale (VAS) with anchors at "0" (no pain) and "100" (most severe pain). A negative change from baseline indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on all randomized participants who received study intervention from Day 01 to Week 52. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	-25.43 (± 1.096)	-22.56 (± 1.069)	-31.02 (± 1.53)	
Week 52	-28.36 (± 1.188)	-25.22 (± 1.175)	-33.34 (± 1.646)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACIT-Fatigue at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in FACIT-Fatigue at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[57]

End point description:

The Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue is a validated patient-reported measure of 13 statements regarding the feeling of fatigue. The total score ranges from 0 to 52 with higher values representing a lower fatigue and a better quality of life. A positive change from baseline in FACIT-fatigue indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Participants who received study intervention from Day 1 to Week 52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[57] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	513	510	258	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	8.52 (± 0.418)	7.59 (± 0.406)	8.56 (± 0.585)	
Week 52	7.71 (± 0.453)	6.76 (± 0.446)	8.55 (± 0.632)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional assessment of chronic illness therapy (FACIT)-Fatigue at Week 12

End point title	Change from Baseline in Functional assessment of chronic illness therapy (FACIT)-Fatigue at Week 12[58]

End point description:

The Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue is a validated patient-reported measure of 13 statements regarding the feeling of fatigue. The total score ranges from 0 to 52 with higher values representing a lower fatigue and a better quality of life. A positive change from baseline in FACIT-fatigue indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the ITT set. Analysis was performed using multiple imputation method to handle missing data.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[58] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	513	510	258	256
Units: Scores on a scale				
least squares mean (standard error)	7.07 (± 0.41)	6.3 (± 0.399)	8.28 (± 0.577)	4.72 (± 0.57)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in FACIT-Fatigue at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in FACIT-Fatigue at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[59]

End point description:

The Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue is a validated patient-reported measure of 13 statements regarding the feeling of fatigue. The total score ranges from 0 to 52 with higher values representing a lower fatigue and a better quality of life. A positive change from baseline in FACIT-fatigue indicates an improvement. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Participants who received study intervention from Week 12 to Week 52 were analyzed. Missing data was handled by multiple imputation method.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[59] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85	86	85	
Units: Scores on a scale				
least squares mean (standard error)				
Week 24	7.57 (± 1.002)	7.91 (± 0.965)	9.44 (± 0.969)	
Week 52	7.08 (± 1.102)	7.2 (± 1.051)	11.05 (± 1.043)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI)

End point title	Number of participants with adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESI)[60]

End point description:

AE is defined as any untoward medical occurrence in a clinical study participant, temporally associated with use of a study intervention, whether or not considered related to study intervention. SAEs are defined as any untoward medical occurrence that, at any dose: results in death, cause life threatening events which requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability or incapacity and birth defect or congenital anomaly. Protocol defined AESIs were included. Fifteen participants in Pooled placebo received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm. The analysis was performed on Safety Set that includes all randomized participants who received at least one dose of study treatment. Pooled Placebo collected data from Day 01 to Week 12. Placebo switched arms collected data from Week 12 to 59. Experimental arms collected data from Day 01 to Week 59.

End point type	Secondary

End point timeframe:

Up to Week 59

Notes:

[60] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	513	510	80	82
Units: Participants				
AE	367	383	49	52
SAE	33	39	8	9
AESI	65	58	9	9

End point values	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	68	273	241	
Units: Participants				
AE	44	207	95	

SAE	5	23	8	
AESI	3	22	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in white blood cell (WBC) count at Week 12

End point title	Change from Baseline in white blood cell (WBC) count at Week 12[61]

End point description:

Blood samples were collected for the assessment of hematology parameter white blood cell count. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[61] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	456	455	230	213
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)	-0.55 (± 2.267)	-0.63 (± 2.065)	-1.03 (± 2.16)	-0.3 (± 2.005)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WBC count at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in WBC count at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[62]

End point description:

Blood samples were collected for the assessment of hematology parameter white blood cell count. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Fifteen participants in Pooled placebo

group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	443	465	246	
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)				
Week 24	-0.59 (± 2.279)	-0.5 (± 2.123)	-0.94 (± 2.31)	
Week 52	-0.54 (± 2.386)	-0.52 (± 2.051)	-1.21 (± 2.407)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in WBC count at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in WBC count at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[63]

End point description:

Blood samples were collected for the assessment of hematology parameter white blood cell count. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[63] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)				
Week 24	-0.06 (± 1.94)	-0.31 (± 1.642)	-0.61 (± 2.052)	
Week 52	-0.21 (± 2.129)	-0.03 (± 2.459)	-0.96 (± 2.013)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 12

End point title	Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 12[64]

End point description:

Blood samples were collected for the assessment of hematology parameters including platelet count, neutrophils, lymphocytes. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[64] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	453	454	229	211
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)				
Lymphocytes	0.006 (± 0.5341)	0.016 (± 0.5552)	0.084 (± 0.5789)	-0.009 (± 0.5367)
Neutrophils	-0.565 (± 2.2309)	-0.66 (± 2.0562)	-1.076 (± 2.162)	-0.268 (± 2.025)
Platelets	-18.6 (± 58.93)	-16.3 (± 59.51)	-26.7 (± 63.56)	-1.0 (± 58.79)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[65]

End point description:

Blood samples were collected for the assessment of hematology parameters including platelet count, neutrophils, lymphocytes. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[65] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	442	464	246	
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)				
Lymphocytes, Week 24	0.031 (± 0.583)	-0.003 (± 0.5395)	0.017 (± 0.62)	
Lymphocytes, Week 52	0.015 (± 0.5485)	-0.034 (± 0.5771)	-0.102 (± 0.5877)	
Neutrophils, Week 24	-0.629 (± 2.2736)	-0.515 (± 1.9997)	-0.899 (± 2.2436)	
Neutrophils, Week 52	-0.583 (± 2.3708)	-0.493 (± 1.9958)	-1.049 (± 2.3054)	
Platelets, Week 24	-13.7 (± 65.69)	-15.4 (± 67.72)	-27.1 (± 70.17)	
Platelets, Week 52	-18.7 (± 66.07)	-18.5 (± 64.59)	-30.2 (± 56.67)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in hematology parameter of platelet count, neutrophils, lymphocytes at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[66]

End point description:

Blood samples were collected for the assessment of hematology parameters including platelet count, neutrophils, lymphocytes. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[66] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: Giga cells per liter (10^9/L)				
arithmetic mean (standard deviation)				
Lymphocytes, Week 24	-0.055 (± 0.5751)	0.038 (± 0.5294)	0.085 (± 0.5052)	
Lymphocytes, Week 52	-0.091 (± 0.6046)	0.09 (± 0.5744)	-0.079 (± 0.4538)	
Neutrophils, Week 24	-0.053 (± 1.8784)	-0.405 (± 1.5633)	-0.685 (± 1.9031)	
Neutrophils, Week 52	-0.118 (± 2.0773)	-0.289 (± 2.3914)	-0.847 (± 1.8472)	
Platelets, Week 24	-11.3 (± 59.64)	-17.4 (± 63.81)	-9.3 (± 43.83)	
Platelets, Week 52	-19 (± 65.35)	-11.7 (± 86.52)	-19.6 (± 51.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of hemoglobin at Week 12

End point title	Change from Baseline in hematology parameter of hemoglobin at Week 12[67]

End point description:

Blood samples were collected for the assessment of change from baseline in hematology parameters hemoglobin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[67] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	457	459	231	214
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)	-0.0 (± 8.14)	0.5 (± 8.5)	0.0 (± 8.56)	-1.7 (± 7.83)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of hemoglobin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in hematology parameter of hemoglobin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[68]

End point description:

Blood samples were collected for the assessment of change from baseline in hematology parameters hemoglobin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	444	466	246	
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 24	0.5 (± 8.96)	1.3 (± 9.22)	1.1 (± 9.23)	
Week 52	0.4 (± 9.5)	0.7 (± 9.24)	-0.2 (± 9.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter of hemoglobin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in hematology parameter of hemoglobin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[69]

End point description:

Blood samples were collected for the assessment of change from baseline in hematology parameters hemoglobin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[69] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 24	0.7 (± 8.72)	2 (± 9.02)	1.8 (± 6.71)	
Week 52	1.4 (± 9.85)	1.1 (± 10.57)	0.8 (± 8.81)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of aspartate

aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), Gamma-Glutamyl transpeptidase (GGT) at Week 12

End point title	Change from Baseline in clinical chemistry parameter of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), Gamma-Glutamyl transpeptidase (GGT) at Week 12[70]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameters including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP) and gamma-glutamyl transferase (GGT) levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[70] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	468	475	242	220
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
Alkaline Phosphatase	-1.5 (± 17.97)	-1.2 (± 15.64)	-3.7 (± 16.07)	-0.7 (± 15.29)
ALT	0.5 (± 15.69)	2 (± 19.66)	2.2 (± 15.07)	-1.1 (± 11.76)
AST	1.2 (± 9.71)	2.4 (± 13.09)	3.1 (± 14.09)	-0.4 (± 7.38)
Gamma Glutamyl Transferase	-2.1 (± 17.67)	-2.3 (± 16.05)	1.2 (± 23.21)	-0.5 (± 16.31)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of AST, ALT, AP, GGT at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in clinical chemistry parameter of AST, ALT, AP, GGT at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[71]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameters including AST, ALT, AP and GGT levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[71] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	448	467	246	
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
Alkaline Phosphatase, Week 24	0.5 (± 17.77)	1.8 (± 19.16)	-3.0 (± 17.41)	
Alkaline Phosphatase, Week 52	2.8 (± 19.52)	1.5 (± 17.35)	-1.0 (± 18.12)	
ALT, Week 24	1.5 (± 22.98)	2.5 (± 17.22)	4.5 (± 40.51)	
ALT, Week 52	0.4 (± 12.31)	-0.2 (± 13.95)	1.9 (± 15.72)	
AST, Week 24	1.3 (± 11.36)	2.4 (± 11.25)	8.6 (± 94.12)	
AST, Week 52	1 (± 8.97)	1 (± 8.22)	3.1 (± 14.21)	
Gamma Glutamyl Transferase, Week 24	-1.7 (± 18.05)	-1.2 (± 17.71)	0.2 (± 19.7)	
Gamma Glutamyl Transferase, Week 52	-0.3 (± 22.26)	-0.4 (± 22.03)	1.6 (± 20.52)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of AST, ALT, AP, GGT at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in clinical chemistry parameter of AST, ALT, AP, GGT at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[72]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameters including AST, ALT, AP and GGT levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[72] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: International units per liter (IU/L)				
arithmetic mean (standard deviation)				
Alkaline Phosphatase, Week 24	0.9 (± 13.07)	-0.3 (± 18.04)	0.7 (± 14.91)	
Alkaline Phosphatase, Week 52	5.5 (± 24.05)	-1.9 (± 16.07)	-1 (± 14.6)	
ALT, Week 24	0.3 (± 10.76)	3.6 (± 18.43)	3.3 (± 13.9)	
ALT, Week 52	2.6 (± 15.59)	2.6 (± 11.55)	2.7 (± 15.03)	
AST, Week 24	1.5 (± 11.4)	2.9 (± 13.53)	3.2 (± 10.53)	
AST, Week 52	1.8 (± 6.89)	2 (± 9.08)	3.6 (± 9.88)	
Gamma Glutamyl Transferase, Week 24	0.8 (± 13.65)	0.9 (± 16.68)	-0.5 (± 32.46)	
Gamma Glutamyl Transferase, Week 52	8.1 (± 55.51)	1 (± 14.4)	-2.2 (± 35.14)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of total bilirubin at Week 12

End point title	Change from Baseline in clinical chemistry parameter of total bilirubin at Week 12[73]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter total bilirubin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[73] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	468	475	242	220
Units: Micromoles per liter (umol/L)				
arithmetic mean (standard deviation)	0.3 (± 2.63)	0.4 (± 2.52)	0.5 (± 2.96)	-0.2 (± 3.13)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of total bilirubin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in clinical chemistry parameter of total bilirubin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[74]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter total bilirubin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: Micromoles per liter (umol/L)				
arithmetic mean (standard deviation)				
Week 24	0.2 (± 2.65)	0.6 (± 2.8)	0.1 (± 2.62)	
Week 52	0.3 (± 3.16)	0.6 (± 2.75)	0.6 (± 2.64)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of total bilirubin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in clinical chemistry parameter of total bilirubin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[75]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter total bilirubin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[75] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	448	467	246	
Units: Micromoles per liter (umol/L)				
arithmetic mean (standard deviation)				
Week 24	0.5 (± 2.93)	0.6 (± 2.79)	0.6 (± 2.95)	
Week 52	0.5 (± 2.73)	0.4 (± 2.81)	0.5 (± 3.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of albumin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in clinical chemistry parameter of albumin at Week 24 and Week 52 for placebo switched arms who started study intervention from Week 12[76]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter albumin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Week 12), Week 24 and Week 52

Notes:

[76] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	78	78	63	
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 24	0.3 (± 2.57)	1.1 (± 2.54)	1.8 (± 2.47)	
Week 52	0.3 (± 2.94)	0.8 (± 2.77)	1.2 (± 2.24)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of albumin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in clinical chemistry parameter of albumin at Week 24 and Week 52 for treatment arms who started study intervention from Day 1[77]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter albumin level. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Week 24 and Week 52

Notes:

[77] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	448	466	246	
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)				
Week 24	0.2 (± 2.85)	0.3 (± 2.69)	1.3 (± 3.17)	
Week 52	-0.2 (± 3.08)	0.3 (± 3.03)	0.6 (± 2.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in clinical chemistry parameter of albumin at Week 12

End point title	Change from Baseline in clinical chemistry parameter of albumin at Week 12[78]

End point description:

Blood samples were collected for the assessment of clinical chemistry parameter albumin level. Baseline

was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[78] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	468	475	242	220
Units: Grams per liter (g/L)				
arithmetic mean (standard deviation)	-0.2 (± 2.7)	0.2 (± 2.53)	0.8 (± 3.05)	-0.7 (± 2.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of total cholesterol at Week 12

End point title	Change from Baseline in lipid profile parameter of total cholesterol at Week 12[79]

End point description:

Blood samples were collected for the assessment of lipid profile of total cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 12 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 4 and not at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[79] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	0[80]	0[81]	0[82]	0[83]
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[80] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[81] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[82] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[83] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of total cholesterol at Week 24 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of total cholesterol at Week 24 for treatment arms who started study intervention from Day 1[84]

End point description:

Blood samples were collected for the assessment of lipid profile of total cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[84] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[85]	0[86]	0[87]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[85] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[86] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[87] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein-cholesterol at Week 12

End point title	Change from Baseline in lipid profile parameter of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein-cholesterol at Week 12[88]

End point description:

Blood samples were collected for the assessment of fasting lipid profile including LDL cholesterol, HDL cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 12 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 4 and not at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[88] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	0[89]	0[90]	0[91]	0[92]
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[89] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[90] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[91] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[92] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of total cholesterol at Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of total cholesterol at Week 52 for treatment arms who started study intervention from Day 1[93]

End point description:

Blood samples were collected for the assessment of lipid profile of total cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[93] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	405	223	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.084 (± 0.846)	0.074 (± 0.9528)	0.535 (± 0.9012)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of total cholesterol at Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of total cholesterol at Week 52 for placebo switched arms who started study intervention from Week 12[94]

End point description:

Blood samples were collected for the assessment of lipid profile of total cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[94] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	69	56	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.334 (± 0.7608)	0.045 (± 0.7931)	0.486 (± 0.8974)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of total cholesterol at Week 24 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of total cholesterol at Week 24 for placebo switched arms who started study intervention from Week 12[95]

End point description:

Blood samples were collected for the assessment of lipid profile of total cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[95] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[96]	0[97]	0[98]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[96] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[97] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[98] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 24 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 24 for treatment arms who started study intervention from Day 1[99]

End point description:

Blood samples were collected for the assessment of fasting lipid profile including LDL cholesterol, HDL cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[99] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[100]	0[101]	0[102]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[100] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[101] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[102] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 52 for treatment arms who started study intervention from Day 1[103]

End point description:

Blood samples were collected for the assessment of fasting lipid profile including LDL cholesterol, HDL cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[103] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	405	223	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
HDL Cholesterol, Direct	-0.046 (± 0.3024)	0.011 (± 0.2887)	0.117 (± 0.2986)	
LDL Cholesterol	0.089 (± 0.7062)	0.053 (± 0.736)	0.369 (± 0.758)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 24 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 24 for placebo switched arms who started study intervention from Week 12[104]

End point description:

Blood samples were collected for the assessment of fasting lipid profile including LDL cholesterol, HDL cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[104] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[105]	0[106]	0[107]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[105] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[106] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[107] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of triglycerides at Week 24 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of triglycerides at Week 24 for treatment arms who started study intervention

	from Day 1[108]

End point description:

Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[108] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	0[109]	0[110]	0[111]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[109] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[110] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[111] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of LDL cholesterol, high-density lipoprotein-cholesterol at Week 52 for placebo switched arms who started study intervention from Week 12[112]

End point description:

Blood samples were collected for the assessment of fasting lipid profile including LDL cholesterol, HDL cholesterol levels. Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[112] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	69	56	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
HDL Cholesterol, Direct	0.083 (± 0.302)	0.033 (± 0.209)	0.092 (± 0.2701)	
LDL Cholesterol	0.221 (± 0.6669)	-0.003 (± 0.697)	0.304 (± 0.8315)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of triglycerides at Week 12

End point title	Change from Baseline in lipid profile parameter of triglycerides at Week 12[113]

End point description:

Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. For the purpose of all analyses up to week 12, the placebo arms were pooled into a single placebo arm to primarily serve as a reference for the comparison of active treatment arms. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 12 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 4 and not at Week 12.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 12

Notes:

[113] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	0[114]	0[115]	0[116]	0[117]
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	()

Notes:

[114] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[115] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[116] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[117] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of triglycerides at Week 24 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of triglycerides at Week 24 for placebo switched arms who started study intervention from Week 12[118]

End point description:

Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. Blood samples were collected at indicated time points as per schedule of assessment in the protocol. The Objectives and Endpoints section incorrectly states that Change from baseline in key laboratory parameters at Week 24 was a secondary objective, however for the lipid panel, there is no corresponding time point in the schedule of assessment. Consequently, the only objective that can be assessed for the lipid panel is Week 16 and not at Week 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 24

Notes:

[118] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[119]	0[120]	0[121]	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[119] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[120] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

[121] - Data was not collected as there is no corresponding time point in schedule of activity of Protocol.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of triglycerides at Week 52 for treatment arms who started study intervention from Day 1

End point title	Change from Baseline in lipid profile parameter of triglycerides at Week 52 for treatment arms who started study intervention from Day 1[122]

End point description:

Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set participants. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[122] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	394	405	223	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.081 (± 0.5531)	0.051 (± 0.7413)	0.119 (± 0.7325)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in lipid profile parameter of triglycerides at Week 52 for placebo switched arms who started study intervention from Week 12

End point title	Change from Baseline in lipid profile parameter of triglycerides at Week 52 for placebo switched arms who started study intervention from Week 12[123]

End point description:

Baseline was defined as the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. Change from Baseline was calculated by subtracting the post dose visit value from the Baseline value. The analysis was performed on the Safety Set. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 52

Notes:

[123] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	69	56	
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	0.066 (± 0.5071)	0.03 (± 0.6306)	0.241 (± 0.5357)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with National Cancer Institute-Common terminology criteria for adverse events (NCI-CTCAE) >=Grade 3 hematological/clinical chemistry abnormalities

End point title	Number of participants with National Cancer Institute-Common terminology criteria for adverse events (NCI-CTCAE) >=Grade 3 hematological/clinical chemistry abnormalities[124]

End point description:

Number of participants with NCI-CTCAE >=Grade 3 hematological/clinical chemistry abnormalities were summarized. Hematological and Clinical chemistry parameters were summarized according to the NCI-CTCAE, version 5.0: Grade 1: mild; Grade 2: moderate; Grade 3: severe; Grade 4: life-threatening or disabling. Higher grade indicates more severity. Data is presented for only those parameters for which participants had worst case >=Grade 3 shifts from Baseline. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. The analysis was performed on the Safety Set that includes all randomized participants who received at least one dose of study treatment. Pooled Placebo collected data till Week 12. Placebo switched arms collected data from Week 12 to 59. Experimental arm collected data from Day 01 to Week 59.

End point type	Secondary

End point timeframe:

Up to Week 59

Notes:

[124] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	513	510	80	82
Units: Participants				
Aspartate aminotransferase increased,Total,Grade 3	0	5	0	0
Aspartate aminotransferase increased,Total,Grade 4	0	0	0	0
Hypertriglyceridemia, Total, Grade 3	2	1	1	2
Hypertriglyceridemia, Total, Grade 4	1	1	0	0
Neutrophil count decreased, Grade 3, Grade 4	0	0	0	0
Neutrophil count decreased, Grade 4, Grade 3	0	0	1	0
Alanine aminotransferase increased, Total, Grade 3	5	6	0	0
Alanine aminotransferase increased, Total, Grade 4	0	1	0	0
Blood bilirubin increased, Total, Grade 3	0	1	0	0
Cholesterol - high, Total, Grade 3	0	1	0	0
Creatinine increased, Total, Grade 3	0	1	1	0
Chronic Kidney Disease, Total Grade 3	2	2	2	0
Chronic Kidney Disease, Total Grade 4	0	1	0	0
Anemia, Total, Grade 3	2	4	1	2
White blood cell decreased, Total , Grade 3	1	1	1	0
Lymphocyte count decreased, Total, Grade 3	6	9	0	0
Lymphocyte count decreased, Total, Grade 4	0	1	0	1

Neutrophil count decreased, Total, Grade 3	4	0	2	0
Neutrophil count decreased, Total, Grade 4	2	3	0	0
Platelet count decreased, Total Grade 3	1	0	0	0
Platelet count decreased, Total, Grade 4	0	0	0	0

End point values	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX	Pooled Placebo	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	68	273	241	
Units: Participants				
Aspartate aminotransferase increased,Total,Grade 3	0	1	0	
Aspartate aminotransferase increased,Total,Grade 4	0	1	0	
Hypertriglyceridemia, Total, Grade 3	0	2	1	
Hypertriglyceridemia, Total, Grade 4	0	0	0	
Neutrophil count decreased, Grade 3, Grade 4	1	0	0	
Neutrophil count decreased, Grade 4, Grade 3	0	0	0	
Alanine aminotransferase increased, Total, Grade 3	0	1	0	
Alanine aminotransferase increased, Total, Grade 4	0	0	0	
Blood bilirubin increased, Total, Grade 3	0	0	0	
Cholesterol - high, Total, Grade 3	0	0	0	
Creatinine increased, Total, Grade 3	0	0	0	
Chronic Kidney Disease, Total Grade 3	0	1	0	
Chronic Kidney Disease, Total Grade 4	0	0	0	
Anemia, Total, Grade 3	0	1	0	
White blood cell decreased, Total , Grade 3	0	0	0	
Lymphocyte count decreased, Total, Grade 3	1	5	1	
Lymphocyte count decreased, Total, Grade 4	0	0	0	
Neutrophil count decreased, Total, Grade 3	0	0	2	
Neutrophil count decreased, Total, Grade 4	2	1	1	
Platelet count decreased, Total Grade 3	1	0	0	
Platelet count decreased, Total, Grade 4	0	1	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of Granulocyte-macrophage colony stimulating factor (GM-CSF) autoantibody

End point title	Concentrations of Granulocyte-macrophage colony stimulating factor (GM-CSF) autoantibody[125]

End point description:

Concentrations of GM-CSF autoantibodies were determined. The analysis was performed on the Safety Set. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis. Only those participants with data available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

At baseline

Notes:

[125] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	491	486	82	85
Units: Microgram per liter (ug/L)				
arithmetic mean (standard deviation)	832.827 (± 12355.2805)	218.456 (± 632.5733)	231.376 (± 446.1713)	357.087 (± 629.3471)

End point values	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	70	264		
Units: Microgram per liter (ug/L)				
arithmetic mean (standard deviation)	240.109 (± 624.4536)	203.31 (± 444.708)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-GSK3196165 antibodies

End point title	Number of participants with anti-GSK3196165 antibodies[126]

End point description:

Serum samples were collected for determination of anti-GSK3196165 antibodies (ADA) using a validated electrochemiluminescence (ECL) immunoassay. The assay involved screening, confirmation and titration steps. If serum samples tested positive in the screening assay, they were considered 'potentially positive' and were further analyzed for specificity using the confirmation assay. Samples that confirmed positive in confirmation assay were reported as 'positive'. Confirmed positive ADA samples were further characterized in the titration assay to quasi-quantitate the amount of ADA in sample. Additionally, confirmed positive ADA samples were also tested in a validated neutralizing antibody assay to determine the potential neutralizing activity of ADA. The analysis was performed on the Safety set. Fifteen participants in Pooled placebo group who received active treatment of Tofacitinib from Week 4 instead of Week 12 as planned. They were pooled with the Tofacitinib arm in safety analysis.

End point type	Secondary

End point timeframe:

Up to Week 59

Notes:

[126] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The endpoints are different for the different parts of the study.

End point values	GSK3196165 90mg + MTX	GSK3196165 150mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 150mg + MTX
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	513	510	85	86
Units: Participants	7	7	0	1

End point values	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	70	273		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Pooled Placebo arm collected during the timeframe Week 0 to Week 12. Placebo switched to active treatment arms collected during the timeframe Week 12 to Week 59. Experimental arms collected during from Week 0 to Week 59.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	GSK3196165 150mg + MTX

Reporting group description:

Participants received GSK3196165 150 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with MTX.

Reporting group title	GSK3196165 90mg + MTX

Reporting group description:

Participants received GSK3196165 90 mg subcutaneous (SC) injection once weekly for 52 weeks in combination with methotrexate (MTX).

Reporting group title	Placebo + MTX and GSK3196165 90mg + MTX

Reporting group description:

Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 90 mg, SC injection, once weekly in combination with MTX until Week 52.

Reporting group title	Placebo + MTX and GSK3196165 150mg + MTX

Reporting group description:

Participants received Placebo weekly SC injection in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo to GSK3196165 150 mg, SC injection, once weekly in combination with MTX until Week 52.

Reporting group title	Placebo + MTX and Tofacitinib 5mg + MTX

Reporting group description:

Participants received Placebo tablet weekly in combination with MTX for 12 weeks. At Week 12, participants were switched from placebo tablet to Tofacitinib 5mg, capsule, orally, BID in combination with MTX plus placebo injection to maintain the blind for 52 weeks.

Reporting group title	Tofacitinib 5mg + MTX

Reporting group description:

Participants received Tofacitinib 5mg capsule, orally, twice daily (BID) in combination with MTX plus placebo injection weekly to maintain the blind for 52 weeks.

Reporting group title	Pooled Placebo

Reporting group description:

Participants received Placebo weekly SC injection in combination with MTX until Week 12. The placebo arms are pooled into a single placebo arm.

Serious adverse events	GSK3196165 150mg + MTX	GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 510 (7.65%)	33 / 513 (6.43%)	8 / 80 (10.00%)
number of deaths (all causes)	7	2	0
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Endometrial adenocarcinoma			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Hepatic cancer			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian adenoma			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Pancoast's tumour			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian fibroma			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Circulatory collapse			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypertension			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Death			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	2 / 510 (0.39%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Reproductive system and breast disorders			
Intermenstrual bleeding			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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			
Chronic obstructive pulmonary disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Conversion disorder			
alternative dictionary used: v25.0			

25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Femur fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Ankle fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Cervical vertebral fracture			
alternative dictionary used: v25.0			

25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Forearm fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Multiple injuries			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Post procedural complication			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Radius fracture			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Tendon rupture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	2 / 513 (0.39%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Coronary artery disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Myocardial infarction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Nervous system disorders			
Cerebral infarction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Cerebrovascular accident			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Haemorrhagic stroke			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Neuropathy peripheral			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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

Hypertensive encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Vertebrobasilar insufficiency			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Vascular encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Syncope			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Blood and lymphatic system disorders			
Neutropenia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Anaemia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	2 / 510 (0.39%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Ear and labyrinth disorders			
Meniere's disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Vertigo			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic ischaemic neuropathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intussusception			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Gastritis erosive			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Gastric ulcer perforation			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatorenal failure			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatic cirrhosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Drug-induced liver injury			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Chronic hepatitis			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Neurogenic bladder			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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 failure			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Tubulointerstitial nephritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Cushing's syndrome			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Goitre			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Costochondritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture nonunion			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Osteoarthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	2 / 513 (0.39%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	5 / 510 (0.98%)	2 / 513 (0.39%)	2 / 80 (2.50%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	1 / 80 (1.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	2 / 510 (0.39%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acinetobacter sepsis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Cellulitis staphylococcal			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
COVID-19 pneumonia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	10 / 510 (1.96%)	7 / 513 (1.36%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
COVID-19			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bursitis infective			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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

Arthritis bacterial alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Diverticulitis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Chronic tonsillitis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Diverticulitis intestinal perforated alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Gastroenteritis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Hepatitis E alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Joint abscess alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Pneumonia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	3 / 510 (0.59%)	2 / 513 (0.39%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Postoperative wound infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Post procedural cellulitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Sepsis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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
Wound infection pseudomonas			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (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
Urinary tract infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 510 (0.20%)	0 / 513 (0.00%)	0 / 80 (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

Sinusitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	2 / 510 (0.39%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	1 / 513 (0.19%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemic hyperosmolar nonketotic syndrome			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 82 (10.98%)	5 / 68 (7.35%)	23 / 273 (8.42%)
number of deaths (all causes)	1	0	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Breast cancer alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial adenocarcinoma alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	1 / 68 (1.47%)	0 / 273 (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
Lung adenocarcinoma alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	2 / 273 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (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
Ovarian adenoma alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancoast's tumour alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian fibroma			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Intermenstrual bleeding			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (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
Haemothorax			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Conversion disorder			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			

Device malfunction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			

alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	1 / 68 (1.47%)	0 / 273 (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
Lower limb fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	1 / 68 (1.47%)	0 / 273 (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
Nervous system disorders			
Cerebral infarction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (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
Headache			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vertebrobasilar insufficiency			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular encephalopathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	1 / 68 (1.47%)	0 / 273 (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
Anaemia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	1 / 68 (1.47%)	0 / 273 (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
Eye disorders			
Optic ischaemic neuropathy			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intussusception			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatorenal failure			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic hepatitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurogenic bladder			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Cushing's syndrome			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 9
Musculoskeletal and connective tissue disorders			
Arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture nonunion			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	2 / 273 (0.73%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial cyst			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (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
Osteochondrosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acinetobacter sepsis			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis staphylococcal			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	2 / 273 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	4 / 273 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	2 / 273 (0.73%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bursitis infective			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Diverticulitis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic tonsillitis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal perforated alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint abscess alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia alternative dictionary used: v25.0 25.0			

subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural cellulitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection pseudomonas			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 82 (1.22%)	0 / 68 (0.00%)	0 / 273 (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

Septic shock			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection staphylococcal			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	0 / 273 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemic hyperosmolar nonketotic syndrome			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	1 / 273 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Pooled Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 241 (3.32%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Breast cancer			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			

alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal squamous cell carcinoma				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cancer				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian adenoma				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancoast's tumour				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian fibroma				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Circulatory collapse			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Intermenstrual bleeding			
alternative dictionary used: v25.0 25.0			

subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemothorax			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Conversion disorder			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	1 / 241 (0.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device malfunction			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Alanine aminotransferase increased			

alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femoral neck fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ankle fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Forearm fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple injuries				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Tibia fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral infarction				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolic encephalopathy				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertensive encephalopathy				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar insufficiency				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular encephalopathy				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Syncope				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Neutropenia				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Meniere's disease				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertigo				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Optic ischaemic neuropathy				

alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Intussusception				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis erosive				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer perforation				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatorenal failure				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic cirrhosis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug-induced liver injury				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic hepatitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neurogenic bladder				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal failure				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tubulointerstitial nephritis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Cushing's syndrome				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Goitre				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthritis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Costochondritis				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot deformity				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal chest pain				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc disorder				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture nonunion				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Synovial cyst				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Rheumatoid arthritis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteochondrosis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abscess limb				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acinetobacter sepsis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis staphylococcal				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bursitis infective				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic tonsillitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis intestinal perforated				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Gastroenteritis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatitis E				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Joint abscess				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural cellulitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	1 / 241 (0.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection pseudomonas				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection staphylococcal				
alternative dictionary used: v25.0 25.0				
subjects affected / exposed	0 / 241 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemic hyperosmolar nonketotic syndrome				
alternative dictionary used: v25.0 25.0				

subjects affected / exposed	0 / 241 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	GSK3196165 150mg + MTX	GSK3196165 90mg + MTX	Placebo + MTX and GSK3196165 90mg + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	137 / 510 (26.86%)	127 / 513 (24.76%)	22 / 80 (27.50%)
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	31 / 510 (6.08%)	23 / 513 (4.48%)	0 / 80 (0.00%)
occurrences (all)	36	29	0
Blood and lymphatic system disorders			
Lymphopenia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	35 / 510 (6.86%)	30 / 513 (5.85%)	2 / 80 (2.50%)
occurrences (all)	50	54	2
Anaemia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	4 / 80 (5.00%)
occurrences (all)	0	0	5
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	2 / 80 (2.50%)
occurrences (all)	0	0	2
Infections and infestations			
COVID-19			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	48 / 510 (9.41%)	43 / 513 (8.38%)	6 / 80 (7.50%)
occurrences (all)	48	44	6
Urinary tract infection			
alternative dictionary used: v25.0			

25.0			
subjects affected / exposed	22 / 510 (4.31%)	23 / 513 (4.48%)	4 / 80 (5.00%)
occurrences (all)	26	26	5
Upper respiratory tract infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	20 / 510 (3.92%)	22 / 513 (4.29%)	3 / 80 (3.75%)
occurrences (all)	23	23	4
Latent tuberculosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	5 / 80 (6.25%)
occurrences (all)	0	0	5
Nasopharyngitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 510 (0.00%)	0 / 513 (0.00%)	0 / 80 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo + MTX and GSK3196165 150mg + MTX	Placebo + MTX and Tofacitinib 5mg + MTX	Tofacitinib 5mg + MTX
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 82 (35.37%)	17 / 68 (25.00%)	83 / 273 (30.40%)
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	0 / 68 (0.00%)	12 / 273 (4.40%)
occurrences (all)	0	0	15
Blood and lymphatic system disorders			
Lymphopenia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	2 / 82 (2.44%)	4 / 68 (5.88%)	16 / 273 (5.86%)
occurrences (all)	3	4	20
Anaemia			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	4 / 82 (4.88%)	1 / 68 (1.47%)	0 / 273 (0.00%)
occurrences (all)	5	1	0
Musculoskeletal and connective tissue disorders			

Rheumatoid arthritis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	8 / 82 (9.76%)	1 / 68 (1.47%)	0 / 273 (0.00%)
occurrences (all)	8	1	0
Infections and infestations			
COVID-19			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	9 / 82 (10.98%)	2 / 68 (2.94%)	29 / 273 (10.62%)
occurrences (all)	9	3	29
Urinary tract infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 82 (0.00%)	2 / 68 (2.94%)	19 / 273 (6.96%)
occurrences (all)	0	2	23
Upper respiratory tract infection			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	4 / 82 (4.88%)	5 / 68 (7.35%)	18 / 273 (6.59%)
occurrences (all)	5	6	22
Latent tuberculosis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	3 / 82 (3.66%)	1 / 68 (1.47%)	0 / 273 (0.00%)
occurrences (all)	3	1	0
Nasopharyngitis			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	2 / 82 (2.44%)	4 / 68 (5.88%)	0 / 273 (0.00%)
occurrences (all)	2	4	0

Non-serious adverse events	Pooled Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 241 (0.00%)		
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: v25.0 25.0			
subjects affected / exposed	0 / 241 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			

Lymphopenia alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Anaemia alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Musculoskeletal and connective tissue disorders Rheumatoid arthritis alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Infections and infestations COVID-19 alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Urinary tract infection alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Upper respiratory tract infection alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Latent tuberculosis alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		
Nasopharyngitis alternative dictionary used: v25.0 25.0 subjects affected / exposed occurrences (all)	0 / 241 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2019	Correction of contraceptive requirements for Women of Child Bearing Potential (WOCBP) and additional clarifications.
21 January 2020	To detail revised risks, entry and stopping criteria following the update to comparator drug (tofacitinib) label. To introduce new medical device safety reporting wording, required in advance of roll out of pre-filled syringes to this study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported