Clinical trial results:
A Phase IIb, Randomized, Double-blind Study in Subjects with Rheumatoid Arthritis Evaluating the Safety and Efficacy of Evobrutinib Compared with Placebo in Subjects with an Inadequate Response to Methotrexate

Summary

EudraCT number	2017-000384-32
Trial protocol	BG CZ
Global end of trial date	23 September 2019

Results information

Result version number	v1 (current)
This version publication date	20 September 2020
First version publication date	20 September 2020

Trial information

Trial identification

Sponsor protocol code	MS200527-0060

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03233230
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +41 6151725200, service@merckgroup.com
Scientific contact	Communication Centre, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	23 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the efficacy and dose response of 12 weeks of treatment with M2951 compared with placebo in rheumatoid arthritis (RA) subjects with inadequate response to methotrexate (MTX-IR) on stable methotrexate (MTX) therapy by assessment of the signs and symptoms of RA, as measured by ACR20 response assessed using hsCRP at Week 12.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2017
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: 44
Country: Number of subjects enrolled	Bulgaria: 35
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	Colombia: 36
Country: Number of subjects enrolled	Czech Republic: 17
Country: Number of subjects enrolled	Mexico: 27
Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Russian Federation: 28
Country: Number of subjects enrolled	Serbia: 26
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Ukraine: 84
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	390
EEA total number of subjects	101

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)	327
From 65 to 84 years	63
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 933 subjects with rheumatoid arthritis were screened. Out of which, 390 subjects were randomized in ratio of 1:1:1:1 to 1 of the 4 treatment groups: Placebo; M2951 25 milligrams (mg) once daily (QD), M2951 75 mg QD and M2951 50 mg twice daily (BID).

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	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to M2951 orally for 12 weeks.

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

Dosage and administration details:

Placebo matched to M2951 was administered orally.

Arm title	M2951 25 mg QD

Arm description:

Subjects received 25 milligrams (mg) of M2951 orally once daily (QD) for 12 weeks.

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

Dosage and administration details:

25 mg of M2951 was administered orally once daily for 12 weeks.

Arm title	M2951 75 mg QD

Arm description:

Subjects received 75 mg of M2951 orally QD for 12 weeks.

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

Dosage and administration details:
75 mg of M2951 was administered orally once daily for 12 weeks.

Arm title	M2951 50 mg BID

Arm description:
Subjects received 50 mg of M2951 orally twice daily (BID) for 12 weeks.

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

Dosage and administration details:
50 mg of M2951 was administered orally twice daily for 12 weeks.

Number of subjects in period 1	Placebo	M2951 25 mg QD	M2951 75 mg QD
Started	97	98	96
Completed	82	83	84
Not completed	15	15	12
Consent withdrawn by subject	2	2	-
Adverse event, non-fatal	6	3	6
Unspecified	5	5	5
Lost to follow-up	-	3	-
Protocol deviation	1	2	1
Lack of efficacy	1	-	-

Number of subjects in period 1	M2951 50 mg BID
Started	99
Completed	91
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	3
Unspecified	3
Lost to follow-up	-
Protocol deviation	1
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to M2951 orally for 12 weeks.	
Reporting group title	M2951 25 mg QD
Reporting group description:	
Subjects received 25 milligrams (mg) of M2951 orally once daily (QD) for 12 weeks.	
Reporting group title	M2951 75 mg QD
Reporting group description:	
Subjects received 75 mg of M2951 orally QD for 12 weeks.	
Reporting group title	M2951 50 mg BID
Reporting group description:	
Subjects received 50 mg of M2951 orally twice daily (BID) for 12 weeks.	

Reporting group values	Placebo	M2951 25 mg QD	M2951 75 mg QD
Number of subjects	97	98	96
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	52.9	50.9	53.3
standard deviation	± 12.24	± 13.15	± 11.33
Sex: Female, Male Units: subjects			
Female	77	82	76
Male	20	16	20
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	0
White	92	94	91
More than one race	0	0	0
Unknown or Not Reported	3	1	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	32	33	35
Not Hispanic or Latino	65	65	61
Unknown or Not Reported	0	0	0

Reporting group values	M2951 50 mg BID	Total	
Number of subjects	99	390	

Age categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	53.7		
standard deviation	± 12.13	-	
Sex: Female, Male Units: subjects			
Female	77	312	
Male	22	78	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	3	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	3	
White	97	374	
More than one race	0	0	
Unknown or Not Reported	2	10	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	38	138	
Not Hispanic or Latino	61	252	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to M2951 orally for 12 weeks.	
Reporting group title	M2951 25 mg QD
Reporting group description:	
Subjects received 25 milligrams (mg) of M2951 orally once daily (QD) for 12 weeks.	
Reporting group title	M2951 75 mg QD
Reporting group description:	
Subjects received 75 mg of M2951 orally QD for 12 weeks.	
Reporting group title	M2951 50 mg BID
Reporting group description:	
Subjects received 50 mg of M2951 orally twice daily (BID) for 12 weeks.	

Primary: Percentage of Subjects Who Achieved American College of Rheumatology 20 Percent (%) Response Criteria (ACR20) Assessed Using High-Sensitivity C-reactive Protein (hsCRP) at Week 12

End point title	Percentage of Subjects Who Achieved American College of Rheumatology 20 Percent (%) Response Criteria (ACR20) Assessed Using High-Sensitivity C-reactive Protein (hsCRP) at Week 12
End point description:	
ACR20 response: a subject has at least 20% improvement in both tender joint counts (based on a total of 68 joints) and swollen joint counts (based on a total of 66 joints) together with 20% improvement in at least 3 of the following: 1) subject's assessment of pain; 2) subject's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) subject's assessment of physical function measured by Health Assessment Questionnaire-Disability Index (HAQ-DI); and 5) acute phase reactant as measured by high-sensitivity C-reactive protein (hsCRP). Percentage of subjects with ACR20 response using hsCRP = Number of subjects with ACR20 response using hsCRP divided by total modified intent-to-treat (mITT) subjects * 100. mITT analysis set included all randomized subjects who received at least one dose of Investigational Medicinal Product (IMP) (M2951 or placebo).	
End point type	Primary
End point timeframe:	
Week 12	

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	49.5	59.2	51.0	59.6

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1746
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.61

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8283
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.87

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1298
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.74

Secondary: Percentage of Subjects with Low Disease Activity Score (DAS28 Less Than [<] 3.2) Based on 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point title	Percentage of Subjects with Low Disease Activity Score (DAS28 Less Than [<] 3.2) Based on 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point description:

DAS based on a 28 joint count hsCRP consisted of composite numerical score of following variables: tender joint count (TJC28), swollen joint count (SJC28), hsCRP (mg/mL), and subject's global assessment of disease activity. DAS28-hsCRP was calculated using following formula: DAS28-hsCRP equals to (=) 0.56*square root (sqrt) (TJC28) plus (+) 0.28*sqrt (SJC28) + 0.36*natural log(hsCRP+1) + 0.014* subject's global assessment of disease activity + 0.96. Scores ranged 0-9.4, where lower scores indicated less disease activity. Percentage of subjects with low DAS28 < 3.2 based on DAS28-hsCRP at Week 12 were reported. mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	7.2	20.4	24.0	20.2

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.23

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0013
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.27

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.23

Secondary: Percentage of Subjects with Remission Disease Activity Score (DAS28 Less Than [<] 2.6) Based on a 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point title	Percentage of Subjects with Remission Disease Activity Score (DAS28 Less Than [<] 2.6) Based on a 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point description:

DAS based on a 28 joint count hsCRP consisted of composite numerical score of following variables: tender joint count (TJC28), swollen joint count (SJC28), hsCRP (mg/mL), and subject's global assessment of disease activity. DAS28-hsCRP was calculated using following formula: DAS28-hsCRP equals to (=) 0.56*square root (sqrt) (TJC28) plus (+) 0.28*sqrt (SJC28) + 0.36*natural log(hsCRP+1) + 0.014* subject's global assessment of disease activity + 0.96. Scores ranged 0-9.4, where lower scores indicated less disease activity. A DAS28 score less than (<) 2.6 indicated clinical remission. Percentage of subjects with low DAS28 < 2.6 based on DAS28- hsCRP at Week 12 were reported. mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	1.0	10.2	10.4	10.1

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0056
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.17

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.17

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID

Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0053
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.17

Secondary: Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50)

End point title	Percentage of Subjects Achieving American College of Rheumatology 50% Response Criteria (ACR50)

End point description:

ACR50 response: a subject has at least 50% improvement in both tender joint counts (based on a total of 68 joints) and swollen joint counts (based on a total of 66 joints) together with 50% improvement in at least 3 of the following: 1) subject's assessment of pain; 2) subjects's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) subjects's assessment of physical function measured by HAQ-DI; and 5) acute phase reactant as measured by hsCRP. Percentage of subjects with ACR50 response = Number of subjects with ACR50 response divided by total mITT subjects * 100. mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	19.6	28.6	27.1	26.3

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1419
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.21

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2202
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.19

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2328
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.19

Secondary: Percentage of Subjects Achieving American College of Rheumatology

70% Response Criteria (ACR70) Assessed Using High-Sensitivity C-reactive Protein (hsCRP)

End point title	Percentage of Subjects Achieving American College of Rheumatology 70% Response Criteria (ACR70) Assessed Using High-Sensitivity C-reactive Protein (hsCRP)

End point description:

ACR70 response: a subject has at least 70% improvement ACR70 response in both tender joint counts (based on a total of 68 joints) and swollen joint counts (based on a total of 66 joints) together with 70% improvement in at least 3 of the following: 1) subject's assessment of pain; 2) subject's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) subject's assessment of physical function measured by HAQ-DI; and 5) acute phase reactant as measured by hsCRP. Percentage of subjects with ACR70 response = Number of subjects with ACR70 response divided by total mITT subjects * 100. mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	5.2	11.2	10.4	10.1

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1232
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.15

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1725
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.14

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1795
Method	Cochran-Mantel-Haenszel
Parameter estimate	Response rate difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.13

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in subject, which does not necessarily have causal relationship with treatment. A serious AE was defined as an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged insubject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs: events between first dose of study drug that were absent before treatment/that worsened relative to pre-treatment state up to 16 weeks. TEAEs included both Serious TEAEs and non-serious TEAEs. Number of subjects with TEAEs and serious TEAEs were reported. The safety analysis set (SAF) included all subjects who received at least 1 dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

up to Week 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: subjects				
TEAEs	44	48	48	50
Serious TEAEs	2	2	2	1

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) by Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) by Severity According to National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v4.03)

End point description:

Severity of TEAEs were graded using NCI-CTCAE v4.03 toxicity grades, as follows: Grade 1= Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. Number of subjects with TEAEs by severity were reported. The SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

up to Week 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: subjects				
Grade 1	33	42	37	40
Grade 2	19	14	23	17
Grade 3	2	5	1	1
Grade 4	0	1	0	0
Grade 5	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Change from Baseline in Vital Signs

End point title	Number of Subjects with Clinically Significant Change from Baseline in Vital Signs

End point description:

Vital signs included body temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, weight and height. Clinical significance was determined by the investigator. The number of subjects with clinically significant changes from baseline in vital signs were reported. The SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

up to Week 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Change from Baseline in Laboratory Parameters

End point title	Number of Subjects with Clinically Significant Change from Baseline in Laboratory Parameters

End point description:

Laboratory investigation included hematology, biochemistry, urinalysis and coagulation. Clinical significance was determined by the investigator. The number of subjects with clinically significant changes from baseline in laboratory parameters were reported. The SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

up to Week16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Clinically Significant Change from Baseline in 12-Lead Electrocardiogram (ECG) Findings

End point title	Number of Subjects with Clinically Significant Change from Baseline in 12-Lead Electrocardiogram (ECG) Findings

End point description:

12-lead ECG recordings included rhythm, heart rate (as measured by RR interval), PR interval, QRS duration, and QT interval. The corrected QT interval (QTcF) was calculated using Fridericia's formula. 12-lead ECG recordings were obtained after the subjects have rested for at least 10 minutes in semisupine position. Clinical significance was determined by the investigator. The number of subjects with clinically significant changes from baseline in 12-lead ECG findings were reported. The SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

up to Week 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Serum Immunoglobulin (Ig) Levels (IgG, IgA, IgM) at Week 2, 4, 8, 12 and 16

End point title	Change from Baseline in Serum Immunoglobulin (Ig) Levels (IgG, IgA, IgM) at Week 2, 4, 8, 12 and 16

End point description:

Change in the serum levels of IgG, IgA, IgM from baseline were assessed. SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint and "n" signifies those subjects who were evaluable for the specified category at given time points.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 8, 12 and 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	96	95	99
Units: gram per liter (g/L)				
arithmetic mean (standard deviation)				

IgG: Week 2 (n = 95, 96, 95, 99)	-0.02 (± 1.083)	-0.07 (± 1.042)	-0.21 (± 0.968)	-0.09 (± 1.062)
IgG: Week 4 (n = 94, 94, 93, 96)	-0.05 (± 1.465)	-0.15 (± 1.576)	-0.34 (± 1.254)	-0.17 (± 1.168)
IgG: Week 8 (n = 90, 94, 87, 95)	0.12 (± 1.513)	-0.28 (± 2.052)	-0.37 (± 1.565)	-0.35 (± 2.037)
IgG: Week 12 (n = 83, 89, 81, 88)	0.47 (± 1.617)	-0.17 (± 2.080)	-0.33 (± 1.493)	-0.23 (± 1.781)
IgG: Week 16 (n = 60, 60, 63, 67)	0.08 (± 1.829)	-0.14 (± 2.349)	-0.14 (± 1.808)	0.06 (± 1.960)
IgA: Week 2 (n = 95, 96, 95, 99)	-0.01 (± 0.253)	-0.15 (± 1.187)	0.00 (± 0.242)	0.03 (± 0.369)
IgA: Week 4 (n = 94, 94, 93, 96)	-0.05 (± 0.326)	-0.01 (± 0.359)	-0.05 (± 0.333)	0.02 (± 0.396)
IgA: Week 8 (n = 90, 94, 87, 95)	-0.02 (± 0.346)	-0.16 (± 1.322)	-0.06 (± 0.373)	0.07 (± 0.567)
IgA: Week 12 (n = 83, 89, 81, 88)	0.02 (± 0.373)	0.01 (± 0.444)	-0.08 (± 0.388)	0.05 (± 0.545)
IgA: Week 16 (n = 60, 60, 63, 67)	0.01 (± 0.466)	0.07 (± 0.465)	-0.11 (± 0.380)	0.05 (± 0.478)
IgM: Week 2 (n = 95, 96, 95, 99)	-0.04 (± 0.198)	-0.04 (± 0.183)	-0.03 (± 0.281)	-0.01 (± 0.323)
IgM: Week 4 (n = 94, 94, 93, 96)	-0.04 (± 0.199)	-0.11 (± 0.224)	-0.11 (± 0.217)	-0.05 (± 0.385)
IgM: Week 8 (n = 90, 94, 87, 95)	-0.03 (± 0.310)	-0.20 (± 0.243)	-0.23 (± 0.327)	-0.10 (± 0.485)
IgM: Week 12 (n = 83, 89, 81, 88)	-0.01 (± 0.265)	-0.20 (± 0.309)	-0.25 (± 0.296)	-0.17 (± 0.406)
IgM: Week 16 (n = 60, 60, 63, 67)	-0.16 (± 0.776)	-0.12 (± 0.436)	-0.22 (± 0.246)	-0.12 (± 0.487)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in B Cell Count at Week 2, 4, 8, 12 and 16

End point title	Change from Baseline in B Cell Count at Week 2, 4, 8, 12 and 16

End point description:

Flow cytometry analysis of lymphocyte populations using four-color fluorescence-activated cell sorting was performed for the analysis of B cell counts. The SAF included all subjects who received at least 1 dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" specifies those subjects who were evaluable for this endpoint and "n" signified those subjects who were evaluable for the specified category at given time point.

End point type	Secondary

End point timeframe:

Baseline, Week 2, 4, 8, 12 and 16

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	90	90	92	97
Units: cells per microliter (cells/microliter)				
arithmetic mean (standard deviation)				
Week 2: (n = 87, 90, 92, 97)	-13 (± 111.0)	264 (± 1832.7)	161 (± 648.3)	74 (± 144.8)
Week 4: (n = 90, 90, 91, 93)	-20 (± 115.7)	71 (± 130.1)	66 (± 145.3)	93 (± 137.6)
Week 8: (n = 81, 90, 82, 91)	-21 (± 87.5)	35 (± 103.1)	56 (± 188.1)	59 (± 145.4)
Week 12: (n = 82, 85, 77, 83)	-22 (± 136.4)	41 (± 111.8)	51 (± 156.2)	54 (± 145.0)
Week 16: (n = 56, 58, 60, 64)	-20 (± 121.9)	-3 (± 108.5)	-40 (± 133.5)	-19 (± 235.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Remission Assessed by American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) Boolean at Week 12

End point title	Percentage of Subjects Remission Assessed by American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) Boolean at Week 12

End point description:

ACR-EULAR Boolean remission was when a subject satisfied all of the following: tender joint count, swollen joint count (both based on a 28-joint assessment), C-reactive Protein (in milligrams per deciliter [mg/dL]), and subject's global assessment (visual analog scale [VAS]: 0 centimeter (cm) [very well] to 10 cm [worst], higher scores indicated worse health condition) and all scores were less than or equal to (<=) 1. Percentage of subjects with ACR-EULAR Boolean Remission were reported. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	0.0	0.0	1.0	3.0

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.04

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.06

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.09

Secondary: Percentage of Subjects with Clinical Disease Activity Index (CDAI) Score Less Than or Equal to [=<] 2.8 at Week 12

End point title	Percentage of Subjects with Clinical Disease Activity Index (CDAI) Score Less Than or Equal to [=<] 2.8 at Week 12

End point description:

CDAI: a composite index (without acute-phase reactant) for assessing disease activity. The CDAI was calculated based on following formula: CDAI = 28 joint count for swelling (SJC28) + 28 joint count for tenderness (TJC28) + GH + PhGA where, GH = general health component of the Disease Activity Score

[DAS] (i.e., Subject's Global Assessment of Disease Activity, assessed using a scale of 0 to 10 centimeter (cm) Visual Analogue Scale (VAS) where 0 = very well and 10 = very poor activity and PhGA = Physician's Global Assessment of Disease Activity assessed using a scale of 0 to 10 cm VAS, where 0 = very well and 10 = very poor activity. The total CDAI score ranges from 0 to 76, where 0 (none) to 76 (extreme disease activity). CDAI score =< 2.8 indicated clinical remission. Percentage of subjects with CDAI score =< 2.8 were reported. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	1.0	4.1	6.3	3.0

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.09

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.12

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.08

Secondary: Percentage of Subjects with Simplified Disease Activity Index (SDAI) Score Less Than or Equal to [=<] 3.3 at Week 12

End point title	Percentage of Subjects with Simplified Disease Activity Index (SDAI) Score Less Than or Equal to [=<] 3.3 at Week 12

End point description:

SDAI was calculated based on following formula: SDAI = 28 joint count for swelling (SJC28) + 28 joint count for tenderness (TJC28)+ GH+PGA+ hsCRP where, GH = general health component of the Disease Activity Score [DAS] (i.e., Subject's Global Assessment of Disease Activity, assessed using a scale of 0 to 10 centimeter (cm) Visual Analogue Scale (VAS) where 0 = very well and 10 = very poor activity and PhGA = Physician's Global Assessment of Disease Activity assessed using a scale of 0 to 10 cm VAS, where 0 = very well and 10 = very poor activity. The total SDAI score ranges from 0 to 86, where 0 (none) to 86 (extreme disease activity). SDAI score =< 3.3 indicated clinical remission. Percentage of subjects with SDAI score =< 3.3 at Week 12 were reported. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	0.0	3.1	4.2	3.0

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.09

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.1

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.09

Secondary: Percentage of Subjects with Good or Moderate European League Against Rheumatism (EULAR) Responses at Week 12

End point title	Percentage of Subjects with Good or Moderate European League Against Rheumatism (EULAR) Responses at Week 12

End point description:

EULAR Responder index based on 28 joint counts categorizes clinical response based on improvement since baseline in DAS28-CRP. DAS28-CRP scores range from 0-9.4, where lower scores indicated less disease activity. High disease activity: DAS28-CRP >5.1, low disease activity: DAS28-CRP <3.2, and

remission: DAS28-CRP <2.6. EULAR DAS28-CRP responder index: good (absolute: <3.2 or >1.2 improvement from baseline), moderate (absolute: 3.2-5.1 or 0.6-1.2 improvement from baseline), or no response (absolute: >5.1 or <0.6 improvement from baseline). Percentage of subjects with DAS28-CRP based EULAR response =(number of subjects with specific response)/(number of subjects analyzed in the group) * 100. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo).

End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	97	98	96	99
Units: percentage of subjects				
number (not applicable)	54.6	65.3	66.7	71.7

Statistical analyses

Statistical analysis title	Placebo vs M2951 25 mg QD
Comparison groups	Placebo v M2951 25 mg QD
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.03
upper limit	0.24

Statistical analysis title	Placebo vs M2951 75 mg QD
Comparison groups	Placebo v M2951 75 mg QD
Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.02
upper limit	0.25

Statistical analysis title	Placebo vs M2951 50 mg BID
Comparison groups	Placebo v M2951 50 mg BID
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Response rate difference
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	0.31

Secondary: American College of Rheumatology (ACR) Hybrid Scores Computed Using High-Sensitivity C-reactive Protein (hsCRP)

End point title	American College of Rheumatology (ACR) Hybrid Scores Computed Using High-Sensitivity C-reactive Protein (hsCRP)

End point description:

Hybrid ACR combines the ACR 20/50/70 response with the mean percent change in all 7 ACR core components, thus providing a percent improvement from baseline on a continuous scale. For each subject, the mean percent improvement from baseline across the 7 ACR core set measures (TJC, SJC, Subject's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity, disability index of the Health Assessment Questionnaire [HAQ], and C-reactive protein [CRP]) was calculated (a positive change indicates improvement, and the maximum worst change is limited to -100%) and the ACR20, ACR50, and ACR70 response was determined. The hybrid ACR was determined from a reference table taking into account both ACR response and mean percent improvement in the core set measures. Scores can range from -100% (maximal worsening) to 100% (maximal improvement). mITT analysis set was used. "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: percent change				
arithmetic mean (standard deviation)	26.51 (± 25.779)	34.66 (± 29.033)	33.09 (± 27.724)	36.99 (± 26.241)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Disease Activity Score (DAS) Based on a 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point title	Change from Baseline in Disease Activity Score (DAS) Based on a 28 Joint Count-High-Sensitivity C-reactive Protein (DAS28-hsCRP) at Week 12

End point description:

DAS28 was a composite score used for measuring disease activity in subjects with rheumatoid arthritis. The calculation was based on the tender joint count (out of 28 joints), swollen joint count (out of 28 joints), hs-CRP (milligrams per liter [mg/L]) and Subject's Global Assessment of Disease Activity. Total DAS28-hsCRP score ranged from 0 (none) to 9.4 (extreme disease activity). DAS28-hsCRP < 3.2 implied low disease activity and >= 3.2 to <= 5.1 implied moderate disease activity, > 5.1 implied high disease activity. DAS28-hsCRP = 0.56*sqrt(TJC28) + 0.28*sqrt(SJC28) + 0.36 * ln(hsCRP in mg/L +1) + 0.014 * Subject's Global Assessment of Disease Activity + 0.96; ln = natural logarithm, sqrt = square root. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: units on a scale				
arithmetic mean (standard deviation)	-1.21 (± 1.048)	-1.45 (± 1.230)	-1.62 (± 1.257)	-1.75 (± 1.229)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 12

End point title	Change from Baseline in Clinical Disease Activity Index (CDAI) at Week 12

End point description:

The CDAI was a composite index (without acute-phase reactant) for assessing disease activity. The CDAI was calculated based on following formula: CDAI = 28 joint count for swelling (SJC28) + 28 joint count for tenderness (TJC28) + GH + PhGA where, GH = general health component of the DAS (i.e., Subject's Global Assessment of Disease Activity, assessed using a scale of 0 to 10 centimeter (cm) Visual Analogue Scale (VAS) where 0 = very well and 10 = very poor activity and PhGA = Physician's Global Assessment of Disease Activity assessed using a scale of 0 to 10 cm VAS, where 0 = very well and 10 = very poor activity. The total CDAI score ranges from 0 to 76, where 0 (none) to 76 (extreme disease activity). CDAI score =< 2.8 indicated clinical remission. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: units on a scale				
arithmetic mean (standard deviation)	-16.9 (± 13.09)	-18.0 (± 13.00)	-18.9 (± 14.33)	-20.3 (± 13.90)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Simplified Disease Activity Index (SDAI) at Week 12

End point title	Change from Baseline in Simplified Disease Activity Index (SDAI) at Week 12

End point description:

SDAI was numerical sum of 5 outcome parameters: 28 joint count for swelling (SJC28) + 28 joint count for tenderness (TJC28)+ GH+PGA+ hsCRP where, GH = general health component of the DAS (i.e., Subject's Global Assessment of Disease Activity, assessed using a scale of 0 to 10 centimeter (cm) Visual Analogue Scale (VAS) where 0 = very well and 10 = very poor activity and PhGA = Physician's Global Assessment of Disease Activity assessed using a scale of 0 to 10 cm VAS, where 0 = very well and 10 = very poor activity. The total SDAI score ranges from 0 to 86, where 0 (none) to 86 (extreme disease activity). SDAI score =< 3.3 indicated clinical remission. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: units on a scale				
arithmetic mean (standard deviation)	-17.000 (± 13.5175)	-18.647 (± 13.5957)	-19.404 (± 14.1591)	-21.053 (± 14.3720)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 12

End point title	Change from Baseline in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 12

End point description:

Sixty-eight joints were assessed and classified as tender/not tender and Sixty –six joints were classified as swollen/not swollen by pressure and joint manipulation on physical examination. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: joints				
arithmetic mean (standard deviation)				
TJC: Week 12	-11 (± 12.0)	-11 (± 10.6)	-13 (± 13.2)	-12 (± 10.8)
SJC: Week 12	-7 (± 7.5)	-8 (± 6.1)	-8 (± 7.7)	-8 (± 6.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject's Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Change from Baseline in Subject's Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The subject's overall assessment of disease activity was recorded using the 100 millimeter (mm) horizontal visual analog scale (VAS). The scale ranged from 0-100 mm, where 0 indicated no disease activity (symptom free and no arthritis symptoms) and 100 represented maximum disease activity (maximum arthritis disease activity). The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: millimeter (mm)				
arithmetic mean (standard deviation)	-20 (± 29.6)	-19 (± 27.9)	-17 (± 29.6)	-25 (± 25.7)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Subject's Assessment of Pain Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Change from Baseline in Subject's Assessment of Pain Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The subjects were asked to assess their level of pain by marking a vertical tick on a 100 mm horizontal VAS scale. The scale ranged from 0-100 mm, where 0 indicated no pain and 100 indicated worst possible pain. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	95	98
Units: millimeter				
arithmetic mean (standard deviation)	-21 (± 24.7)	-24 (± 26.9)	-22 (± 24.7)	-25 (± 26.6)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

HAQ-DI score was an evaluation of the functional status for a subject. The 20-question instrument assess the degree of difficulty a subject had in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area were scored from 0, indicated no difficulty, to 3, indicated inability to perform a task in that area. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range: 0-3 where 0 = least difficulty and 3 = extreme difficulty. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	95	98
Units: units on a scale				
arithmetic mean (standard deviation)	-0.38 (± 0.567)	-0.58 (± 0.662)	-0.40 (± 0.658)	-0.52 (± 0.616)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Physician's Global Assessment of Disease Activity Scale Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Change from Baseline in Physician's Global Assessment of Disease Activity Scale Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The Physician's Global Assessment of Disease Activity was recorded using the 100 mm horizontal VAS. Physician rated subject's arthritis disease activity on a scale ranged from 0-100 mm, where 0 indicated no disease activity (no arthritis) and 100 represented maximum disease activity (maximum arthritis). The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: millimeter				
arithmetic mean (standard deviation)	-29 (± 21.2)	-33 (± 26.5)	-34 (± 26.1)	-37 (± 25.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Week 12

End point title	Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Week 12

End point description:

hsCRP was the American College of Rheumatology (ACR) Core Set measure of acute phase reactant. It was measured at the central laboratory to help assess the effect of M2951 on the subject's rheumatoid arthritis. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	99
Units: milligram per liter (mg/L)				
arithmetic mean (standard deviation)	-1.11 (± 25.925)	-6.42 (± 23.280)	-5.45 (± 28.807)	-7.69 (± 23.007)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 12

End point title	Percent Change from Baseline in Tender Joint Count (TJC) and Swollen Joint Count (SJC) at Week 12

End point description:

Sixty-eight joints were assessed and classified as tender/not tender and Sixty –six joints were classified as swollen/not swollen by pressure and joint manipulation on physical examination. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: percent change				
arithmetic mean (standard deviation)				
TJC	-39 (± 45.6)	-46 (± 44.2)	-51 (± 42.8)	-49 (± 37.5)
SJC	-46 (± 52.7)	-53 (± 42.6)	-56 (± 40.3)	-58 (± 43.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Subject's Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Percent Change from Baseline in Subject's Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The subject's overall assessment of disease activity was recorded using the 100 millimeter (mm) horizontal visual analog scale (VAS). The scale ranged from 0-100 mm, where 0 indicated no disease activity (symptom free and no arthritis symptoms) and 100 represented maximum disease activity (maximum arthritis disease activity). The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	96	96	98
Units: percent change				
arithmetic mean (standard deviation)	-13 (± 111.0)	-21 (± 69.3)	-13 (± 65.7)	-33 (± 35.9)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Subject's Assessment of Pain Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Percent Change from Baseline in Subject's Assessment of Pain Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The subjects were asked to assess their level of pain by marking a vertical tick on a 100 mm horizontal VAS scale. The scale ranged from 0-100 mm, where 0 indicated no pain and 100 indicated worst possible pain. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	95	99
Units: percent change				
arithmetic mean (standard deviation)	-23 (± 65.0)	-32 (± 38.4)	-29 (± 40.5)	-32 (± 48.4)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

HAQ-DI score was an evaluation of the functional status for a subject. The 20-question instrument assess the degree of difficulty a subject had in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living). Responses in each functional area were scored from 0, indicated no difficulty, to 3, indicated inability to perform a task in that area. Overall score was computed as the sum of domain scores and divided by the number of domains answered. Total possible score range: 0-3 where 0 = least difficulty and 3 = extreme difficulty. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	97	95	98
Units: percent change				
arithmetic mean (standard deviation)	-20.09 (± 40.084)	-31.85 (± 37.124)	-21.27 (± 44.571)	-27.12 (± 42.624)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in Physician's Global Assessment of Disease Activity Scale Based on Visual Analog Scale (VAS) Score at Week 12

End point title	Percent Change from Baseline in Physician's Global Assessment of Disease Activity Scale Based on Visual Analog Scale (VAS) Score at Week 12

End point description:

The Physician's Global Assessment of Disease Activity was recorded using the 100 mm horizontal VAS. Physician rated subject's arthritis disease activity on a scale ranged from 0-100 mm, where 0 indicated no disease activity (no arthritis) and 100 represented maximum disease activity (maximum arthritis). The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	98
Units: percent change				
arithmetic mean (standard deviation)	-42 (± 31.4)	-44 (± 51.9)	-47 (± 34.9)	-52 (± 33.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Week 12

End point title	Percent Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Week 12

End point description:

hsCRP was the American College of Rheumatology (ACR) Core Set measure of acute phase reactant. It was measured at the central laboratory to help assess the effect of M2951 on the subject's rheumatoid arthritis. The mITT analysis set included all randomized subjects who received at least one dose of IMP (M2951 or placebo). Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	96	97	96	99
Units: percent change				
arithmetic mean (standard deviation)	95.01 (± 380.161)	10.93 (± 167.257)	182.57 (± 1775.154)	-13.91 (± 105.688)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Synovitis Score According to the Outcomes Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (OMERACT RAMRIS) at Week 12

End point title	Change from Baseline in Synovitis Score According to the Outcomes Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (OMERACT RAMRIS) at Week 12

End point description:

A total of 8 joints in the hand and wrist were evaluated for RAMRIS synovitis. Individual joint scores were assessed on a scale of 0 (no synovitis) to 3 (67 to 100 percent volume enhancement). The final synovitis score was the sum of the individual joint scores. The total score from 8 joints ranges from 0 to 24, with 0 implying normal (no synovitis) and 24 implying 67 to 100 percent volume enhancement. The Magnetic Resonance Imaging (MRI) analysis set included all randomized subjects who have at least at least 1 pre-dose and 1 post-dose MRI assessment. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	49	47	51
Units: units on a scale				
arithmetic mean (standard deviation)	0 (± 1.9)	-1 (± 2.5)	-1 (± 3.4)	-1 (± 2.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bone Marrow Edema (Osteitis) Score According to the Outcomes Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (OMERACT RAMRIS) at Week 12

End point title	Change from Baseline in Bone Marrow Edema (Osteitis) Score According to the Outcomes Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring System (OMERACT RAMRIS) at Week 12

End point description:

A total of 25 locations in the hand and wrist were evaluated for RAMRIS bone edema or osteitis. Individual location scores range from 0 (no edema) to 3 (67 to 100 percent involvement of original articular bone) based on the proportion of estimated originally non-eroded bone involved. The final bone

edema or osteitis score is the sum of the individual location scores. The total score from the 25 locations ranges from 0 to 75, with 0 implying no bone edema or osteitis and 75 implying 67 to 100 percent involvement of original articular bone. The Magnetic Resonance Imaging (MRI) analysis set included all randomized subjects who have at least at least 1 pre-dose and 1 post-dose MRI assessment. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	44	49	47	51
Units: units on a scale				
arithmetic mean (standard deviation)	-1 (± 5.8)	0 (± 4.6)	0 (± 5.4)	0 (± 4.0)

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in Physical Function Using Health Assessment Questionnaire-Disability Index (HAQ-DI) at Week 12

End point description:

The HAQ-DI questionnaire assessed the subject's self-perception on the degree of difficulty [0 (without any difficulty), 1 (with some difficulty), 2 (with much difficulty), and 3 (unable to do)] when dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and performing other daily activities. Scores for each functional area were averaged to calculate HAQ-DI scores, which ranged from 0 (no disability) to 3 (worst disability). A decrease in HAQ-DI score indicated an improvement in the subject's condition. Quality of Life (QoL) Analysis Set: all randomized subjects who have received at least 1 dose of IMP (M2951 or placebo) and had at least 1 Baseline and 1 post baseline QoL assessment. "Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	93	86	92
Units: units on a scale				
arithmetic mean (standard deviation)	-0.41 (± 0.543)	-0.61 (± 0.637)	-0.45 (± 0.657)	-0.53 (± 0.631)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Short-Form (SF-36) Health Survey Physical Component Score and Mental Component Score at Week 12

End point title	Change from Baseline in the Short-Form (SF-36) Health Survey Physical Component Score and Mental Component Score at Week 12

End point description:

SF-36: a standardized survey evaluating 8 aspects of functional health and well-being. These 8 subscales were summarized as relating to either physical health/mental health. Physical component summary (PCS) was based primarily on physical functioning, role-physical, bodily pain and general health scales and mental component summary (MCS) encompasses vitality, social functioning, role-emotional, and mental health scales. Score from mental health, role emotional, social functioning, and vitality domains were averaged to calculate MCS. Total score range for MCS was 0-100 (100 = highest level of mental functioning). Score from physical function, role physical, bodily pain, and general health domains were averaged to calculate PCS. Total score range for PCS was 0-100 (100 = highest level of physical functioning). QoL analysis set was used. Here, "Number of Subjects Analyzed" = subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	93	86	92
Units: units on a scale				
arithmetic mean (standard deviation)				
PCS	5.9 (± 7.10)	7.1 (± 8.50)	6.4 (± 8.50)	7.1 (± 8.28)
MCS	4.9 (± 11.46)	5.7 (± 8.41)	5.0 (± 11.72)	4.7 (± 8.95)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score at Week 12

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue Score at Week 12

End point description:

The FACIT-Fatigue score was calculated according to a 13-item questionnaire that assess self-reported fatigue and its impact upon daily activities and function. It uses a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). The sum of all responses resulted in the FACIT-Fatigue score for a total possible score of 0 (worse possible score) to 52 (best score). A higher score reflected an improvement in the subject's health status. Quality of Life (QoL) Analysis Set: all randomized subjects who have received at least 1 dose of IMP (M2951 or placebo) and had at least 1 Baseline and 1 post baseline QoL assessment. "Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:
Baseline, Week 12

End point values	Placebo	M2951 25 mg QD	M2951 75 mg QD	M2951 50 mg BID
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	93	86	92
Units: units on a scale				
arithmetic mean (standard deviation)	9 (± 11.4)	10 (± 9.4)	9 (± 9.0)	8 (± 10.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to Week 16	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: Subjects received placebo matched to M2951 orally for 12 weeks.	
Reporting group title	M2951 25 mg QD
Reporting group description: Subjects received 25 milligrams (mg) of M2951 orally once daily (QD) for 12 weeks.	
Reporting group title	M2951 75 mg QD
Reporting group description: Subjects received 75 mg of M2951 orally QD for 12 weeks.	
Reporting group title	M2951 50 mg BID
Reporting group description: Subjects received 50 mg of M2951 orally twice daily (BID) for 12 weeks.	

Serious adverse events	Placebo	M2951 25 mg QD	M2951 75 mg QD
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 97 (2.06%)	2 / 98 (2.04%)	2 / 96 (2.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Tibia fracture			
subjects affected / exposed	0 / 97 (0.00%)	0 / 98 (0.00%)	1 / 96 (1.04%)
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			
Lymphoedema			
subjects affected / exposed	1 / 97 (1.03%)	1 / 98 (1.02%)	0 / 96 (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
Thrombophlebitis superficial			

subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	0 / 96 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 97 (0.00%)	1 / 98 (1.02%)	0 / 96 (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
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 97 (0.00%)	0 / 98 (0.00%)	0 / 96 (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			
subjects affected / exposed	1 / 97 (1.03%)	0 / 98 (0.00%)	0 / 96 (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
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 97 (0.00%)	0 / 98 (0.00%)	1 / 96 (1.04%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 98 (1.02%)	0 / 96 (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

Serious adverse events	M2951 50 mg BID		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 99 (1.01%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			

Tibia fracture			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 99 (1.01%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Osteomyelitis			
subjects affected / exposed	0 / 99 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinusitis			

subjects affected / exposed	0 / 99 (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	Placebo	M2951 25 mg QD	M2951 75 mg QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 97 (11.34%)	13 / 98 (13.27%)	8 / 96 (8.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 97 (5.15%)	6 / 98 (6.12%)	5 / 96 (5.21%)
occurrences (all)	5	6	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 97 (6.19%)	2 / 98 (2.04%)	3 / 96 (3.13%)
occurrences (all)	6	2	3
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 97 (0.00%)	5 / 98 (5.10%)	0 / 96 (0.00%)
occurrences (all)	0	5	0

Non-serious adverse events	M2951 50 mg BID		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 99 (17.17%)		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 99 (8.08%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 99 (7.07%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	2 / 99 (2.02%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 December 2017	• added fasting requirements • reduced the treatment Period from 24 weeks to 12 weeks • removed rescue therapy • increased safety monitoring by adding visits at Week 6 and Week 10 during the Treatment Period, and reduced the length of the Open Label Extension (OLE) Period from 24 months to 12 months
12 July 2018	After receiving feedback from multiple regulatory agencies, the study Sponsor decided not to initiate the Open Label Extension Period outside the US.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported