Clinical trial results:
Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects with Rheumatoid Arthritis on Stable Methotrexate Therapy

Summary

EudraCT number	2016-000064-42
Trial protocol	SK HU CZ BG
Global end of trial date	14 November 2017

Results information

Result version number	v1 (current)
This version publication date	16 May 2018
First version publication date	16 May 2018

Trial information

Trial identification

Sponsor protocol code	MS200527-0081

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02784106
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Centre Merck KGaA, Merck KGaA, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Centre Merck KGaA, Merck KGaA, +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	14 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to assess the efficacy of M2951 in participants with rheumatoid arthritis (RA) currently treated with stable dose of methotrexate (MTX).

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	31 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Ukraine: 15
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	65
EEA total number of subjects	38

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)	57

From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a 12-week double-blind period and a 26-week open-label extension period. Primary and secondary outcome measures were planned to be analyzed for double-blind treatment period only.

Period 1

Period 1 title	Double-Blind Treatment Period (12 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo: Double-Blind Treatment Period

Arm description:

Participants received placebo matched to M2951 twice daily up to Day 84 during the double-blind treatment period.

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

Dosage and administration details:

Participants received placebo matched to M2951 twice daily up to Day 84 during the double-blind treatment period.

Arm title	M2951: Double-Blind Treatment Period

Arm description:

Participants received 50 milligrams (mg) M2951 orally twice daily up to Day 84 during the double-blind treatment period.

Arm type	Experimental
Investigational medicinal product name	M2951
Investigational medicinal product code	
Other name	Evobrutinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 2 capsules of 25 milligrams(mg) of M2951 orally twice daily up to Day 84 during the double-blind treatment period.

Number of subjects in period 1	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period
Started	32	33
Completed	24	27
Not completed	8	6
Consent withdrawn by subject	2	1
Adverse event, non-fatal	3	5
Not specified	2	-
Lack of efficacy	1	-

Period 2

Period 2 title	Open-Label Extension Period (26 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/M2951: Open-Label Extension Period

Arm description:

Participants who received placebo matched to M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.

Arm type	Experimental
Investigational medicinal product name	M2951
Investigational medicinal product code	
Other name	Evobrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who received placebo in double-blind treatment period received 50 mg M2951 in the open-label extension period.

Arm title	M2951/M2951: Open-Label Extension Period

Arm description:

Participants who received M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.

Arm type	Experimental
Investigational medicinal product name	M2951
Investigational medicinal product code	
Other name	Evobrutinib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants who received M2951 in double-blind treatment period received 50 mg M2951 in the open-label extension period.

Number of subjects in period 2[1]	Placebo/M2951: Open-Label Extension Period	M2951/M2951: Open-Label Extension Period
Started	18	21
Completed	15	19
Not completed	3	2
Adverse event, non-fatal	2	1
Lack of efficacy	1	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All participants who completed the double-blind treatment period didn't enter the open-lable extension period as this was optional.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo: Double-Blind Treatment Period
Reporting group description:	
Participants received placebo matched to M2951 twice daily up to Day 84 during the double-blind treatment period.	
Reporting group title	M2951: Double-Blind Treatment Period
Reporting group description:	
Participants received 50 milligrams (mg) M2951 orally twice daily up to Day 84 during the double-blind treatment period.	

Reporting group values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period	Total
Number of subjects	32	33	65
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	53.1	53.8	
standard deviation	± 12.19	± 10.73	-
Sex: Female, Male Units: Subjects			
Female	25	24	49
Male	7	9	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	1	1	2
White	31	31	62
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	2
Not Hispanic or Latino	31	32	63
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Placebo: Double-Blind Treatment Period
Reporting group description:	
Participants received placebo matched to M2951 twice daily up to Day 84 during the double-blind treatment period.	
Reporting group title	M2951: Double-Blind Treatment Period
Reporting group description:	
Participants received 50 milligrams (mg) M2951 orally twice daily up to Day 84 during the double-blind treatment period.	
Reporting group title	Placebo/M2951: Open-Label Extension Period
Reporting group description:	
Participants who received placebo matched to M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.	
Reporting group title	M2951/M2951: Open-Label Extension Period
Reporting group description:	
Participants who received M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.	

Primary: Proportion of Participants who Achieved American College of Rheumatology-20 (ACR20) Response

End point title	Proportion of Participants who Achieved American College of Rheumatology-20 (ACR20) Response
End point description:	
ACR 20 response: greater than or equal to (>=) 20 percent (%) 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) participant's assessment of pain; 2) participant's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) participant'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). The Modified Intent-to-Treat (mITT) Analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Proportion of ACR20 responders = Number of participants with ACR20 response divided by total participants.	
End point type	Primary
End point timeframe:	
Day 84	

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: proportion of participants				
number (not applicable)	0.42	0.52		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Responders
Point estimate	0.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.07
upper limit	0.25

Secondary: Mean Change From Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Day 28

End point title	Mean Change From Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Day 28

End point description:

Mean change in the hsCRP concentration from baseline at Day 28 was reported. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose.

End point type	Secondary

End point timeframe:

Baseline, Day 28

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: milligram/milliliter (mg/mL)				
arithmetic mean (standard error)	-0.80 (± 2.00)	-2.72 (± 1.93)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Mean Changes
Point estimate	-1.93
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.54
upper limit	1.69

Secondary: Proportion of Participants Achieving American College of Rheumatology-50 (ACR50) Response

End point title	Proportion of Participants Achieving American College of Rheumatology-50 (ACR50) Response

End point description:

ACR 50 response: >=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) participant's assessment of pain; 2) participant's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) participant's assessment of physical function measured by HAQ-DI; and 5) acute phase reactant as measured by hsCRP. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Proportion of ACR50 responders = Number of participants with ACR50 response divided by total participants.

End point type	Secondary

End point timeframe:

Day 28, Day 56 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: proportion of participants				
number (not applicable)				
Day 28	0.10	0.06		
Day 56	0.23	0.18		
Day 84	0.23	0.21		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Day 28

Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Responders
Point estimate	-0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.13
upper limit	0.06

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Day 56	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Responders
Point estimate	-0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.18
upper limit	0.09

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Day 84	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Responders
Point estimate	-0.01
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.15
upper limit	0.12

Secondary: Proportion of Participants Achieving American College of Rheumatology-

70 (ACR70) Response

End point title	Proportion of Participants Achieving American College of Rheumatology-70 (ACR70) Response

End point description:

ACR 70 response: >=70% 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 >=70% improvement in at least 3 of the following: 1) participant's assessment of pain; 2) participant's global assessment of disease activity; 3) physician's global assessment of disease activity; 4) participant's assessment of physical function measured by HAQ-DI; and 5) acute phase reactant as measured by hsCRP. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Proportion of ACR70 responders = Number of participants with ACR70 response divided by total participants.

End point type	Secondary

End point timeframe:

Day 28, Day 56 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: proportion of participants				
number (not applicable)				
Day 28	0.00	0.06		
Day 56	0.03	0.06		
Day 84	0.13	0.09		

Statistical analyses

Statistical analysis title	Statistical Analysis

Statistical analysis description:

Day 28

Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Proportion of Responders
Point estimate	0.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.01
upper limit	0.14

Statistical analysis title	Statistical Analysis

Statistical analysis description:	
Day 56	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Proportion of Responders
Point estimate	0.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.05
upper limit	0.11

Statistical analysis title	Statistical Analysis
Statistical analysis description:	
Day 84	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Responders
Point estimate	-0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.15
upper limit	0.07

Secondary: Mean Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Day 84

End point title	Mean Change from Baseline in High-Sensitivity C-Reactive Protein (hsCRP) at Day 84
End point description:	
Mean change in the hsCRP concentration from baseline at Day 84 was reported. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose.	
End point type	Secondary
End point timeframe:	
Baseline, Day 84	

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: mg/mL				
arithmetic mean (standard error)	-2.14 (± 2.20)	-3.54 (± 2.13)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Mean Changes
Point estimate	-1.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.37
upper limit	2.58

Secondary: Mean Change from Baseline in Disease Activity Score Based on a 28 Joint Count High-Sensitivity C-Reactive Protein (DAS28-hsCRP) at Day 28 and 84

End point title	Mean Change from Baseline in Disease Activity Score Based on a 28 Joint Count High-Sensitivity C-Reactive Protein (DAS28-hsCRP) at Day 28 and 84

End point description:

Disease Activity Score (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 participant'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)+ 0.014* participant's global assessment of disease activity + 0.36*natural log(hsCRP+1) +0.96. Scores ranged 1.0-9.4, where lower scores indicated less disease activity. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: units on a scale				
arithmetic mean (standard error)				
Change at Day 28	-0.79 (± 0.14)	-0.87 (± 0.13)		
Change at Day 84	-1.35 (± 0.20)	-1.28 (± 0.19)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Statistical analysis description: Day 28	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Mean Changes
Point estimate	-0.08
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.33
upper limit	0.16

Statistical analysis title	Statistical Analysis
Statistical analysis description: Day 84	
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Mean Changes
Point estimate	0.07
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.29
upper limit	0.43

Secondary: Proportion of Participants With Disease Activity Score- High Sensitivity C-Reactive Protein (DAS28-hsCRP) Value Less Than (<) 3.2

End point title	Proportion of Participants With Disease Activity Score- High Sensitivity C-Reactive Protein (DAS28-hsCRP) Value Less Than (<) 3.2

End point description:

DAS28-hsCRP consisted of composite score of following variables: TJC28, SJC28, hsCRP (mg/mL), and participant's global assessment of disease activity. DAS28-hsCRP was calculated using following formula: DAS28-hsCRP =0.56* sqrt(TJC28) + 0.28*sqrt(SJC28)+ 0.014* participant's global assessment of disease activity + 0.36*natural log(hsCRP+1) +0.96. Scores ranged 1.0-9.4, where lower scores indicated less disease activity. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Proportion of participants with DAS28-hsCRP value <3.2 were reported.

End point type	Secondary

End point timeframe:

Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: proportion of participants				
number (not applicable)	0.13	0.21		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Participants
Point estimate	0.08
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.04
upper limit	0.21

Secondary: Proportion of Participants With Disease Activity Score- High Sensitivity C-Reactive Protein (DAS28-hsCRP) Value Less Than (<) 2.6

End point title	Proportion of Participants With Disease Activity Score- High Sensitivity C-Reactive Protein (DAS28-hsCRP) Value Less Than (<) 2.6

End point description:

DAS28 consisted of composite score of following variables: TJC28, SJC28, hsCRP (mg/mL), and participant's global assessment of disease activity. DAS28-hsCRP was calculated using following formula: DAS28-hsCRP =0.56* sqrt (TJC28) + 0.28*sqrt(SJC28)+ 0.014* participant's global assessment of disease activity + 0.36*natural log(hsCRP+1) +0.96. Scores ranged 1.0-9.4, where lower scores indicated less disease activity. mITT analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Proportion of participants with DAS28-hsCRP value <2.6 were reported.

End point type	Secondary

End point timeframe:

Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: proportion of participants				
number (not applicable)	0.10	0.06		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Placebo: Double-Blind Treatment Period v M2951: Double-Blind Treatment Period
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportion of Participants
Point estimate	-0.04
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.13
upper limit	0.06

Secondary: Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Day 28 and 84

End point title	Change From Baseline in Erythrocyte Sedimentation Rate (ESR) at Day 28 and 84

End point description:

Erythrocyte sedimentation rate (ESR) is a type of blood test that measures how quickly erythrocytes (red blood cells) settle at the bottom of a test tube that contains a blood sample. Higher values indicate inflammation in the body. mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: millimeter/hour (mm/hour)				
arithmetic mean (standard deviation)				
Change at Day 28 (n=29,32)	-3 (± 36.9)	-7 (± 22.1)		
Change at Day 84 (n=25,35)	-3 (± 21.0)	-9 (± 21.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Anti-cyclic Citrullinated Peptide (anti-CCP) Antibody Levels at Day 28 and 84

End point title	Change From Baseline in Anti-cyclic Citrullinated Peptide (anti-CCP) Antibody Levels at Day 28 and 84

End point description:

Anti-cyclic citrullinated peptide (anti-CCP) is an antibody present in most rheumatoid arthritis participants. mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: units/milliliter				
arithmetic mean (standard deviation)				
Change at Day 28 (n=29,32)	168 (± 991.1)	-138 (± 720.9)		
Change at Day 84 (n=25,25)	301 (± 1282.6)	-396 (± 736.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Rheumatoid Factor (RF) at Day 28 and 84

End point title	Change From Baseline in Rheumatoid Factor (RF) at Day 28 and 84

End point description:

Rheumatoid Factor is an anti-body present in the blood. mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 28 and Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: kiloUnit/Liter (kU/L)				
arithmetic mean (standard deviation)				
Change at Day 28 (n=29,32)	-30 (± 124.2)	-7 (± 59.7)		
Change at Day 84 (n=25,25)	-34 (± 132.1)	-26 (± 79.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Day 84

End point title	Change From Baseline in Global Assessment of Disease Activity Based on Visual Analog Scale (VAS) Score at Day 84

End point description:

The participant'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). mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "Number of Subjects Analysed" signified those participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: millimeter				
arithmetic mean (standard deviation)	-21 (± 23.5)	-24 (± 24.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-assessment of Pain Based on Visual Analog Scale (VAS) Score at Day 84

End point title	Change From Baseline in Self-assessment of Pain Based on Visual Analog Scale (VAS) Score at Day 84

End point description:

The participants 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. mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "Number of Subjects Analysed" signified those participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: millimeter				
arithmetic mean (standard deviation)	-19 (± 21.8)	-22 (± 22.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Self-assessment of Disability Using Health Assessment Questionnaire - Disability Index (HAQ-DI) Score at Day 84

End point title	Change From Baseline in Self-assessment of Disability Using Health Assessment Questionnaire - Disability Index (HAQ-DI) Score at Day 84

End point description:

The HAQ-DI questionnaire assessed the participant'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 participant's condition. mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "Number of Subjects Analysed" signified those participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.3 (± 0.44)	-0.3 (± 0.41)		

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 Day 84

End point title	Change From Baseline in Physician's Global Assessment of Disease Activity Scale Based on Visual Analog Scale (VAS) Score at Day 84

End point description:

The Physician’s Global Assessment of Disease Activity was recorded using the 100 mm horizontal VAS. Physician rated participant’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). mITT analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 available ACR20 evaluation at a time point post-dose. Here "Number of Subjects Analysed" signified those participants who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Day 84

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	26		
Units: millimeter				
arithmetic mean (standard deviation)	-33 (± 20.3)	-30 (± 22.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs)

End point description:

An Adverse event (AE) was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug or worsening of pre-existing medical condition, whether or not related to study drug. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent are events between first dose of study drug that were absent before treatment or that worsened relative to pre-treatment state. TEAEs included both Serious TEAEs and non-serious TEAEs. The Safety Analysis Set included all participants who received at least 1 dose of M2951 or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 16 Weeks

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants				
TEAEs	16	22		
SAEs	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs) by Severity

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs) by Severity

End point description:

Grade 3 and 4 TEAES as per National Cancer Institute Common Terminology Criteria for Adverse Experience version 4.03 (NCI-CTCAE v 4.03) were presented. Grade 3 refers to severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization

indicated; disabling; limiting self-care and Activity of daily living (ADL).Grade 4 refers to Life-threatening consequences; where urgent intervention indicated. The Safety Analysis Set included all participants who received at least 1 dose of M2951 or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 16 Weeks

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants				
NCI-CTCAE Severity grade >=3	2	3		
NCI-CTCAE Severity grade >=4	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Grade 3 or Higher Clinically Significant Abnormality for Hematology, Biochemistry, Urinalysis or Coagulation

End point title	Number of Participants With Grade 3 or Higher Clinically Significant Abnormality for Hematology, Biochemistry, Urinalysis or Coagulation

End point description:

Clinically significant abnormalities for hematology, biochemistry or coagulation were graded with National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 toxicity grades, where Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4 = life threatening and Grade 5 = death. Participants with grade 3 or higher were reported. The Safety Analysis Set included all participants who received at least 1 dose of M2951 or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 16 Weeks

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants				
Hematology	2	0		
Biochemistry	4	2		
Coagulation	0	0		
Urinalysis	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant Vital Signs Abnormalities

End point title	Number of Participants With Clinically Significant Vital Signs Abnormalities

End point description:

Vital sign assessment included blood pressure, pulse rate, respiratory rate and temperature. Clinical significance was determined by the investigator. The Safety Analysis Set included all participants who received at least 1 dose of M2951 or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 16 Weeks

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Clinically Significant 12-lead Electrocardiogram (ECG) Findings

End point title	Number of Participants With Clinically Significant 12-lead Electrocardiogram (ECG) Findings

End point description:

The 12-lead ECG recordings were obtained after 10 minutes of rest in a semi-supine position. The ECG parameters obtained directly from the computerized 12-lead ECG recordings included rhythm, ventricular rate, PR interval, QRS duration, and QT interval. Clinical significance was determined by the investigator. The Safety Analysis Set included all participants who received at least 1 dose of M2951 or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 16 Weeks

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of M2951

End point title	Plasma Concentration of M2951[1]

End point description:

The Pharmacokinetic (PK) Analysis Set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point. "9999" represents statistical analysis was not applicable as mean concentration of the drug is zero.

End point type	Secondary

End point timeframe:

Pre-dose at Day 1; 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Day 1: Pre-Dose (n=33)	0.00 (± 99999)			
Day 1: 0.25 hours post-dose (n=33)	10.3 (± 23.37)			
Day 1: 0.5 hours post-dose (n=33)	80.5 (± 136.9)			
Day 1: 1 hour post-dose (n=33)	160 (± 219.7)			
Day 1: 2 hours post-dose (n=33)	125 (± 111.9)			
Day 1: 4 hours post-dose (n=33)	47.3 (± 41.62)			
Day 1: 6 hours post-dose (n=33)	23.7 (± 20.92)			
Day 29: 0.25 hours post-dose (n=28)	22.0 (± 71.57)			
Day 29: 0.5 hours post-dose (n=28)	88.4 (± 114.1)			
Day 29: 1 hour post-dose (n=28)	120 (± 107.2)			
Day 29: 2 hours post-dose (n=27)	82.3 (± 53.82)			
Day 29: 4 hours post-dose (n=28)	62.1 (± 82.39)			
Day 29: 6 hour post-dose (n=27)	37.2 (± 43.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve From Time Zero to 6 Hours (AUC 0-6h) of M2951

End point title	Area Under the Concentration-Time Curve From Time Zero to 6 Hours (AUC 0-6h) of M2951[2]

End point description:

PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: hours*nanogram/milliliter				
arithmetic mean (standard deviation)				
Day 1 (n=33)	431 (± 390.9)			
Day 29 (n=26)	414 (± 268.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of M2951

End point title	Maximum Observed Plasma Concentration (Cmax) of M2951[3]

End point description:

PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1 (n=33) Day 29 (n=27)	206 (± 214.7) 171 (± 130.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration Observed Immediately Before Dosing on Day 29 (Cpre) of M2951

End point title	Plasma Concentration Observed Immediately Before Dosing on Day 29 (Cpre) of M2951[4]

End point description:

PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose on Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: ng/mL				
arithmetic mean (standard deviation)	5.47 (± 4.735)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (Tmax) of M2951

End point title	Time to Reach Maximum Plasma Concentration (Tmax) of M2951[5]

End point description:

PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "n" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: hour				
median (full range (min-max))				
Day 1 (n=33) Day 29 (n=27)	1.00 (0.50 to 4.00) 1.00 (0.50 to 6.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio for Area under the Concentration-Time Curve from Time Zero to 6 Hours (Racc [AUC0-6h]) of M2951

End point title	Accumulation Ratio for Area under the Concentration-Time Curve from Time Zero to 6 Hours (Racc [AUC0-6h]) of M2951[6]

End point description:

Accumulation ratio for AUC was calculated as AUC 0-6h, Day 29 divided by AUC 0-6h, Day 1. PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: ratio				
arithmetic mean (standard deviation)	1.38 (± 1.134)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio for Observed Maximum Plasma Concentration (Racc [Cmax]) of M2951

End point title	Accumulation Ratio for Observed Maximum Plasma Concentration (Racc [Cmax]) of M2951[7]

End point description:

Accumulation ratio for Cmax , was calculated as Cmax, Day 29 divided by Cmax, Day1. PK analysis set included all participants who receive at least 1 dose of M2951 and have at least 1 quantifiable M2951 plasma concentration at a scheduled PK time point post-dose. Here "Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 0.25, 0.5, 1.0, 2.0, 4.0, 6.0 hours post-dose at Day 1 and Day 29

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 end point was planned to be analyzed only for the double-blind treatment period arm.

End point values	M2951: Double-Blind Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: ratio				
arithmetic mean (standard deviation)	1.52 (± 1.929)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Immunoglobulin Levels at Day 85

End point title	Absolute Immunoglobulin Levels at Day 85

End point description:

Following immunoglobulin levels were measured: Immunoglobulin A , Immunoglobulin G, Immunoglobulin G Subclass 1, Immunoglobulin G Subclass 2, Immunoglobulin G Subclass 3, Immunoglobulin G Subclass 4, Immunoglobulin M. The Pharmacodynamic (PD) Analysis Set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 measured PD endpoint, not including Bruton's tyrosine kinase(BTK) occupancy, at a scheduled PD time point post-

dose. Here "Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Day 85

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: gram/Liter				
arithmetic mean (standard deviation)				
Immunoglobulin A	2.09 (± 0.968)	2.77 (± 1.323)		
Immunoglobulin G	10.61 (± 3.897)	9.88 (± 2.498)		
Immunoglobulin G Subclass 1	6.20 (± 2.338)	5.41 (± 1.574)		
Immunoglobulin G Subclass 2	3.59 (± 1.644)	3.74 (± 1.205)		
Immunoglobulin G Subclass 3	1.05 (± 0.551)	0.93 (± 0.510)		
Immunoglobulin G Subclass 4	0.394 (± 0.2474)	0.684 (± 0.6286)		
Immunoglobulin M	1.16 (± 0.365)	1.16 (± 0.642)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Immunoglobulin Levels at Day 85

End point title	Absolute Change From Baseline in Immunoglobulin Levels at Day 85

End point description:

Following immunoglobulin levels were measured: Immunoglobulin A , Immunoglobulin G, Immunoglobulin G Subclass 1, Immunoglobulin G Subclass 2, Immunoglobulin G Subclass 3, Immunoglobulin G Subclass 4, Immunoglobulin M. PD analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 measured PD endpoint, not including Bruton's tyrosine kinase(BTK) occupancy, at a scheduled PD time point post-dose. Here "Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Baseline, Day 85

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	12		
Units: gram/Liter				
arithmetic mean (standard deviation)				
Immunoglobulin A	-0.07 (± 0.263)	-0.04 (± 0.133)		
Immunoglobulin G	0.02 (± 1.281)	-0.30 (± 0.517)		
Immunoglobulin G Subclass 1	0.11 (± 0.857)	-0.15 (± 0.410)		
Immunoglobulin G Subclass 2	-0.13 (± 0.477)	-0.17 (± 0.404)		
Immunoglobulin G Subclass 3	0.07 (± 0.214)	-0.04 (± 0.209)		
Immunoglobulin G Subclass 4	-0.028 (± 0.1073)	-0.046 (± 0.2576)		
Immunoglobulin M	-0.04 (± 0.177)	-0.25 (± 0.255)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute B-Cell Levels at Day 85

End point title	Absolute B-Cell Levels at Day 85

End point description:

PD analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 measured PD endpoint, not including Bruton’s tyrosine kinase (BTK) occupancy, at a scheduled PD time point post-dose. Here “Number of Subjects Analyzed" signified those participants who were evaluable for this endpoint at the specified time point.

End point type	Secondary

End point timeframe:

Day 85

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: cells per micro-liter				
arithmetic mean (standard deviation)	243 (± 265.0)	204 (± 154.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in B-cell Levels at Day 85

End point title	Absolute Change From Baseline in B-cell Levels at Day 85

End point description:

PD analysis set included all participants who received at least 1 dose of M2951 or placebo and have at least 1 measured PD endpoint, not including Bruton's tyrosine kinase (BTK) occupancy, at a scheduled PD time point post-dose.

End point type	Secondary

End point timeframe:

Baseline, Day 85

End point values	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: cells per micro-liter				
arithmetic mean (standard deviation)	76 (± 242.0)	11 (± 73.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Double-Blind Period: Baseline up to 16 weeks; Open-Label Period: Baseline up to 30 weeks

Adverse event reporting additional description:

MedDRA version for the double-blind treatment period is version 20.0 and MedDRA version for the open-label extension period is version 20.1

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20 , 20.1

Reporting groups

Reporting group title	Placebo: Double-Blind Treatment Period

Reporting group description:

Participants received placebo matched to M2951 twice daily up to Day 84 during the double-blind treatment period.

Reporting group title	M2951: Double-Blind Treatment Period

Reporting group description:

Participants received M2951 50 mg M2951 orally twice daily up to Day 84 during the double-blind treatment period.

Reporting group title	Placebo/M2951: Open Label Extension Period

Reporting group description:

Participants who received placebo matched to M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.

Reporting group title	M2951/M2951: Open-Label Extension Period

Reporting group description:

Participants who received M2951 in double-blind treatment period, received 50 mg M2951 orally twice daily up to 26-weeks during the open-label extension period.

Serious adverse events	Placebo: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period	Placebo/M2951: Open Label Extension Period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 18 (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
Ear and labyrinth disorders			
Vestibular disorder			

subjects affected / exposed	0 / 32 (0.00%)	1 / 33 (3.03%)	0 / 18 (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/M2951: Open-Label Extension Period		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Vertigo CNS origin			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	0 / 21 (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: Double-Blind Treatment Period	M2951: Double-Blind Treatment Period	Placebo/M2951: Open Label Extension Period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 32 (40.63%)	17 / 33 (51.52%)	8 / 18 (44.44%)
Investigations			
Lipase increased			
subjects affected / exposed	2 / 32 (6.25%)	3 / 33 (9.09%)	0 / 18 (0.00%)
occurrences (all)	2	3	0
Blood glucose increased			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Alanine aminotransferase increased			
subjects affected / exposed	4 / 32 (12.50%)	1 / 33 (3.03%)	1 / 18 (5.56%)
occurrences (all)	4	1	1

Amylase increased			
subjects affected / exposed	3 / 32 (9.38%)	1 / 33 (3.03%)	2 / 18 (11.11%)
occurrences (all)	3	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 32 (9.38%)	0 / 33 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Neutropenia			
subjects affected / exposed	2 / 32 (6.25%)	0 / 33 (0.00%)	0 / 18 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 32 (9.38%)	3 / 33 (9.09%)	0 / 18 (0.00%)
occurrences (all)	3	3	0
Vomiting			
subjects affected / exposed	1 / 32 (3.13%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Abdominal pain upper			
subjects affected / exposed	2 / 32 (6.25%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Psychiatric disorders			

Anxiety			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 32 (12.50%)	3 / 33 (9.09%)	1 / 18 (5.56%)
occurrences (all)	4	3	1
Respiratory tract infection			
subjects affected / exposed	0 / 32 (0.00%)	2 / 33 (6.06%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Gastroenteritis			
subjects affected / exposed	2 / 32 (6.25%)	1 / 33 (3.03%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 32 (0.00%)	0 / 33 (0.00%)	0 / 18 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	M2951/M2951: Open-Label Extension Period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 21 (47.62%)		
Investigations			
Lipase increased			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Blood glucose increased			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			

subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Amylase increased			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	0 / 21 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			

subjects affected / exposed occurrences (all)	0 / 21 (0.00%) 0		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 0 / 21 (0.00%) 0		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Rheumatoid arthritis subjects affected / exposed occurrences (all)	 2 / 21 (9.52%) 2 1 / 21 (4.76%) 1		
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 0 / 21 (0.00%) 0 2 / 21 (9.52%) 2 0 / 21 (0.00%) 0 3 / 21 (14.29%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2016	To modify the text for contraceptive measures to specify "highly effective" contraception, according to the definitions provided by the Clinical Trials Facilitation Group Guideline.
02 September 2016	To include an optional open label extension period for participants to continue receiving benefit from the Investigative Medicinal Product.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported