Clinical trial results:
A Randomized, Double-Blind, Multiple-Dose, Parallel-Group, Two-Arm Study to Evaluate the Efficacy, Safety and Immunogenicity of MSB11456 Compared to European Union approved RoActemra® in Patients with Moderately to Severely Active Rheumatoid Arthritis (APTURA I study)

Summary

EudraCT number	2019-004369-42
Trial protocol	HU SK PL BG CZ DE
Global end of trial date	06 June 2022

Results information

Result version number	v1 (current)
This version publication date	22 June 2023
First version publication date	22 June 2023

Trial information

Trial identification

Sponsor protocol code	0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04512001
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fresenius Kabi SwissBioSim GmbH
Sponsor organisation address	Route de Crassier 23, Eysins, Switzerland, 1262
Public contact	Clinical Development, Fresenius Kabi SwissBioSim GmbH, +41 793075735, clinical.development@fresenius-kabi.com
Scientific contact	Clinical Development, Fresenius Kabi SwissBioSim GmbH, +41 793075735, clinical.development@fresenius-kabi.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	06 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to demonstrate equivalent efficacy of proposed biosimilar tocilizumab MSB11456 and EU-approved RoActemra when both were administered subcutaneously to patients with moderately to severely active rheumatoid arthritis.

Protection of trial subjects:

This study was conducted in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy:

The study population comprised participants with moderately to severely active rheumatoid arthritis who had an inadequate response to at least 1 disease-modifying antirheumatic drug (either synthetic or biologic) and who were receiving a stable dose of methotrexate.

Evidence for comparator: -

Actual start date of recruitment	03 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Georgia: 94
Country: Number of subjects enrolled	Moldova, Republic of: 23
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Czechia: 44
Country: Number of subjects enrolled	Poland: 303
Country: Number of subjects enrolled	Slovakia: 6
Country: Number of subjects enrolled	Bulgaria: 34
Country: Number of subjects enrolled	Hungary: 42
Worldwide total number of subjects	604
EEA total number of subjects	429

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	499
From 65 to 84 years	105
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at research centers in Bulgaria, Czechia, Georgia, Hungary, the Republic of Moldova, Poland, Russia, Serbia and Slovakia from August 2020 to June 2022.

Pre-assignment

Screening details:

604 participants were enrolled and received treatment in the Core Treatment Period. 543 participants were re-randomized and 541 participants received treatment in the Extended Treatment Period.

Period 1

Period 1 title	Week 0 to Week 24
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Core Treatment Period: MSB11456

Arm description:

Participants received MSB11456 subcutaneously, once a week during the core treatment period (Baseline to Week 24).

Arm type	Experimental
Investigational medicinal product name	MSB11456
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection, once a week during the core treatment period (Baseline to Week 24).

Arm title	Core Treatment Period: RoActemra®

Arm description:

Participants received EU-approved RoActemra® subcutaneously, once a week during the core treatment period (Baseline to Week 24).

Arm type	Active comparator
Investigational medicinal product name	RoActemra®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection, once a week during the core treatment period (Baseline to Week 24).

Number of subjects in period 1	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®
Started	302	302
Received Treatment	302	302
Completed	267	276
Not completed	35	26
Discontinued treatment prior to Week 24	4	4
Adverse event, serious fatal	-	2
Consent withdrawn by subject	16	9
Did not meet eligibility but was randomized	-	1
Adverse event, non-fatal	14	10
Withdrawal By Sponsor`s Decision	1	-

Period 2

Period 2 title	Week 24 to Week 63
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Core Period; MSB11456; Extended Period: MSB11456

Arm description:

Participants who received MSB11456 during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to continue receiving MSB11456 subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Arm type	Experimental
Investigational medicinal product name	MSB11456
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection, once a week during the core treatment period (Baseline to Week 24) and then once a week in the extended treatment period (Week 24 to Week 52).

Arm title	Core Period: RoActemra®; Extended Period: MSB11456

Arm description:

Participants who received EU-approved RoActemra® during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to begin receiving MSB11456 subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Arm type	Experimental

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

Dosage and administration details:

Subcutaneous injection, once a week during the core treatment period (Week 0 to Week 24).

Investigational medicinal product name	MSB11456
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection, once a week during the extended treatment period (Week 24 to Week 52).

Arm title	Core Period: RoActemra®; Extended Period: RoActemra®

Arm description:

Participants who received EU-approved RoActemra® during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to continue receiving EU-approved RoActemra® subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Arm type	Active comparator
Investigational medicinal product name	RoActemra®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection, once a week during the core treatment period (Baseline to Week 24) and then once a week in the extended treatment period (Week 24 to Week 52).

Number of subjects in period 2	Core Period; MSB11456; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: RoActemra®
Started	267	139	137
Received Treatment	266	139	136
Completed	244	123	122
Not completed	23	16	15
Adverse event, serious fatal	-	1	1
Consent withdrawn by subject	6	4	6
Adverse event, non-fatal	13	8	6
Miscellaneous	3	2	1
Lost to follow-up	1	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Core Treatment Period: MSB11456
Reporting group description:	
Participants received MSB11456 subcutaneously, once a week during the core treatment period (Baseline to Week 24).	
Reporting group title	Core Treatment Period: RoActemra®
Reporting group description:	
Participants received EU-approved RoActemra® subcutaneously, once a week during the core treatment period (Baseline to Week 24).	

Reporting group values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®	Total
Number of subjects	302	302	604
Age categorical Units: Subjects			
19 to 79 years	302	302	604
Age continuous Units: years			
arithmetic mean	51.2	53.2	
standard deviation	± 12.72	± 11.33	-
Gender categorical Units: Subjects			
Female	250	248	498
Male	52	54	106
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	300	300	600
Unknown or Not Reported	1	0	1
Race Units: Subjects			
White	302	302	604
Region of Enrollment Units: Subjects			
Hungary	19	23	42
Czechia	19	25	44
Poland	156	147	303
Moldova	14	9	23
Georgia	43	51	94
Slovakia	5	1	6
Bulgaria	18	16	34
Serbia	7	11	18
Russia	21	19	40

End points

End points reporting groups

Reporting group title	Core Treatment Period: MSB11456

Reporting group description:

Participants received MSB11456 subcutaneously, once a week during the core treatment period (Baseline to Week 24).

Reporting group title	Core Treatment Period: RoActemra®

Reporting group description:

Participants received EU-approved RoActemra® subcutaneously, once a week during the core treatment period (Baseline to Week 24).

Reporting group title	Core Period; MSB11456; Extended Period: MSB11456

Reporting group description:

Participants who received MSB11456 during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to continue receiving MSB11456 subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Reporting group title	Core Period: RoActemra®; Extended Period: MSB11456

Reporting group description:

Participants who received EU-approved RoActemra® during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to begin receiving MSB11456 subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Reporting group title	Core Period: RoActemra®; Extended Period: RoActemra®

Reporting group description:

Participants who received EU-approved RoActemra® during the core treatment period (Baseline to Week 24).
Participants were then re-randomized to continue receiving EU-approved RoActemra® subcutaneously, once a week for an additional 28-week during the extended treatment period (Week 24 to Week 52).

Subject analysis set title	MSB11456
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received MSB11456 at any time in either the Core Treatment Period (Baseline to Week 24) and/or the Extended Treatment Period (Week 24 to Week 52).
Participants received MSB11456 subcutaneously, once a week.

Subject analysis set title	EU-approved RoActemra®
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who only received EU-approved RoActemra® during the Core Treatment Period (Baseline to Week 24) and/or the Extended Treatment Period (Week 24 to Week 52).
Participants received EU-approved RoActemra® subcutaneously, once a week.

Primary: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point title	Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point description:

The DAS28-ESR is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: Tender Joint Count, Swollen Joint Count, erythrocyte sedimentation rate and Patient's Global Assessment of Disease Activity.

The DAS28-ESR score was derived using the formula: DAS28-ESR = $0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.014*GH + 0.70*Ln(ESR)$, where, TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, Ln(ESR) = natural logarithm of ESR, GH = the general health component of the DAS (i.e., Patient's Global Assessment of Disease Activity on a scale of 1 to 100 where 100 is maximal activity).

Higher values mean a higher disease activity. The level of disease activity can be interpreted as:
- Remission (score of <2.6).
- Low (score of ≤2.6 to <3.2).

- Moderate (score of ≤3.2 to ≤5.1).
- High (score of >5.1)

A negative change from baseline indicates an improvement.

End point type	Primary

End point timeframe:

Baseline; Week 24

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[1]	302[2]		
Units: Score on a scale				
least squares mean (standard error)	-3.53 (± 0.106)	-3.54 (± 0.106)		

Notes:

[1] - ITT Analysis Set: includes all randomized participants.

[2] - ITT Analysis Set: includes all randomized participants.

Statistical analyses

Statistical analysis title	Core Period: MSB11456 vs Core Period: RoActemra®
Comparison groups	Core Treatment Period: MSB11456 v Core Treatment Period: RoActemra®
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	equivalence[3]
Parameter estimate	Least squares means difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.22

Notes:

[3] - Margins for results to be considered equivalent: -0.6 to 0.6.

Secondary: Core Treatment Period: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point title	Core Treatment Period: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point description:

The DAS28-ESR is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: TJC, SJC, ESR and Patient's Global Assessment of Disease Activity. The DAS28-ESR score was derived using the formula: DAS28-ESR = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.014*GH + 0.70*Ln(ESR), where, TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, Ln(ESR) = natural logarithm of ESR, GH = the general health component of the DAS (i.e., Patient's Global Assessment of Disease Activity on a scale of 1 to 100 where 100 is maximal activity).

Higher values mean a higher disease activity. The level of disease activity can be interpreted as:
* Remission (score of <2.6)
* Low (score of ≤2.6 to <3.2)

* Moderate (score of ≤3.2 to ≤5.1)
* High (score of >5.1)

A negative change from baseline indicates an improvement.

End point type	Secondary

End point timeframe:

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

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[4]	302[5]		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2 (N: 288, 295)	-1.24 (± 1.022)	-1.21 (± 0.949)		
Week 4 (N: 294, 297)	-1.96 (± 1.184)	-1.98 (± 1.135)		
Week 8 (N: 286, 293)	-2.75 (± 1.220)	-2.69 (± 1.260)		
Week 12 (N: 282, 292)	-3.13 (± 1.249)	-3.09 (± 1.279)		
Week 16 (N: 282, 292)	-3.41 (± 1.288)	-3.32 (± 1.242)		

Notes:

[4] - Includes all randomized participants who had a result at baseline and at each specific time point.

[5] - Includes all randomized participants who had a result at baseline and at each specific time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Extended Treatment Period: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point title	Extended Treatment Period: Change From Baseline in Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR)

End point description:

The DAS28-ESR is a measure of disease activity in 28 joints that consists of a composite numerical score of the following variables: TJC, SJC, ESR and Patient's Global Assessment of Disease Activity. The DAS28-ESR score was derived using the formula: DAS28-ESR = 0.56*√(TJC28) + 0.28*√(SJC28) + 0.014*GH + 0.70*Ln(ESR), where, TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, Ln(ESR) = natural logarithm of ESR, GH = the general health component of the DAS (i.e., Patient's Global Assessment of Disease Activity on a scale of 1 to 100 where 100 is maximal activity).

Higher values mean a higher disease activity. The level of disease activity can be interpreted as:
* Remission (score of <2.6)
* Low (score of ≤2.6 to <3.2)
* Moderate (score of ≤3.2 to ≤5.1)
* High (score of >5.1)

A negative change from baseline indicates an improvement.

End point type	Secondary

End point timeframe:

Extended Period Baseline (Week 24), Week 30, Week 42, and Week 52

End point values	Core Period; MSB11456; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: RoActemra®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	267[6]	139[7]	137[8]	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 30 (N: 261, 136, 133)	-0.16 (± 0.801)	-0.13 (± 0.756)	-0.02 (± 0.863)	
Week 42 (N: 258, 134, 132)	-0.34 (± 1.042)	-0.08 (± 1.026)	-0.27 (± 1.031)	
Week 52 (N: 248, 126, 126)	-0.42 (± 1.185)	-0.31 (± 1.064)	-0.37 (± 1.086)	

Notes:

[6] - Includes all randomized participants who had a result at baseline and at each specific time point.

[7] - Includes all randomized participants who had a result at baseline and at each specific time point.

[8] - Includes all randomized participants who had a result at baseline and at each specific time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With 20% Improvement in American College of Rheumatology (ACR20) Response

End point title	Percentage of Participants With 20% Improvement in American College of Rheumatology (ACR20) Response

End point description:

ACR20 was defined as the number of participants with at least 20% improvement from baseline in number of tender and swollen joints (68/66 joint count), and at least 20% improvement from baseline in three or more of the 5 ACR Core Set measures:

* Patient's Assessment of Arthritis Pain
* Physical Function Assessment (Health Assessment Questionnaire-Disability Index)
* Acute phase reactant level (erythrocyte sedimentation rate or C-reactive protein)
* Patient's Global Assessment of Disease Activity and
* Physician's Global Assessment of Disease Activity

End point type	Secondary

End point timeframe:

Baseline; Week 24

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[9]	302[10]		
Units: Percentage of participants				
number (not applicable)	80.79	84.77		

Notes:

[9] - ITT Analysis Set: includes all randomized participants.

[10] - ITT Analysis Set: includes all randomized participants.

Statistical analyses

Statistical analysis title	Core Period: MSB11456 vs Core Period: RoActemra®
Comparison groups	Core Treatment Period: MSB11456 v Core Treatment Period: RoActemra®
Number of subjects included in analysis	604
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Difference in % Response Rate
Point estimate	-3.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.97
upper limit	2.11

Notes:

[11] - Margins for results to be considered equivalent: -15%, 15%.

Secondary: Number of Participants Who Experienced One or More Treatment-Emergent Serious Adverse Event (TESAE)

End point title	Number of Participants Who Experienced One or More Treatment-Emergent Serious Adverse Event (TESAE)

End point description:

End point type	Secondary

End point timeframe:

Baseline to end of study, up to Week 63

End point values	Core Period: RoActemra®; Extended Period: MSB11456	MSB11456	EU-approved RoActemra®	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	139[12]	302[13]	163[14]	
Units: Participants	20	51	33	

Notes:

[12] - Safety Analysis Set: all participants who received at least one dose of study drug.

[13] - Safety Analysis Set: all participants who received at least one dose of study drug.

[14] - Safety Analysis Set: all participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced One or More Treatment-Emergent Adverse Event (TEAE)

End point title	Number of Participants Who Experienced One or More Treatment-Emergent Adverse Event (TEAE)

End point description:

End point type	Secondary

End point timeframe:

Baseline to end of study, up to Week 63

End point values	Core Period: RoActemra®; Extended Period: MSB11456	MSB11456	EU-approved RoActemra®	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	139[15]	302[16]	163[17]	
Units: Participants	105	237	125	

Notes:

[15] - Safety Analysis Set: all participants who received at least one dose of study drug.

[16] - Safety Analysis Set: all participants who received at least one dose of study drug.

[17] - Safety Analysis Set: all participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Percentage of Participants With Positive Anti-Drug Antibodies (ADAs)

End point title	Core Treatment Period: Percentage of Participants With Positive Anti-Drug Antibodies (ADAs)

End point description:

Overall category includes all time points expect Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 12, and Week 24

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[18]	302[19]		
Units: percentage of participants				
number (not applicable)				
Overall (N: 299, 301)	96.0	96.3		
Baseline (N: 302, 302)	6.6	8.3		

Week 2 (N: 287, 291)	87.1	88.7		
Week 12 (N: 281, 292)	79.0	74.3		
Week 24 (N: 274, 283)	76.3	68.6		

Notes:

[18] - Participants who received study treatment and had a valid ADA result at the specific time points.

[19] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Secondary: Extended Treatment Period: Percentage of Participants With Positive Anti-Drug Antibodies (ADAs)

End point title	Extended Treatment Period: Percentage of Participants With Positive Anti-Drug Antibodies (ADAs)

End point description:

Overall category includes all time points expect for Baseline.

End point type	Secondary

End point timeframe:

Extended Period Baseline (Week 24), Week 30, Week 52, and Week 55

End point values	Core Period; MSB11456; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: RoActemra®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	266[20]	139[21]	136[22]	
Units: percentage of participants				
number (not applicable)				
Overall (N: 265, 137, 135)	97.4	97.1	94.1	
Extended Baseline (Week 24) (N: 266, 139, 136)	86.8	77.7	87.5	
Week 30 (N: 262, 134, 132)	76.7	73.1	65.9	
Week 52 (N: 246, 125, 126)	80.9	76.8	61.1	
Week 55 (N: 242, 122, 122)	81.4	82.8	77.9	

Notes:

[20] - Participants who received study treatment and had a valid ADA result at the specific time points.

[21] - Participants who received study treatment and had a valid ADA result at the specific time points.

[22] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Anti-Drug Antibodies (ADAs) Titer Levels

End point title	Core Treatment Period: Anti-Drug Antibodies (ADAs) Titer Levels

End point description:

Overall category includes all time points except Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 12, and Week 24

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[23]	302[24]		
Units: titer				
geometric mean (full range (min-max))				
Overall (N: 299, 301)	106.3 (60 to 15360)	104.0 (60 to 122880)		
Baseline (N: 302, 302)	71.4 (60 to 960)	130.4 (60 to 1920)		
Week 2 (N: 287, 291)	81.2 (60 to 1920)	88.1 (60 to 15360)		
Week 12 (N: 281, 292)	113.8 (60 to 960)	123.1 (60 to 122880)		
Week 24 (N: 274, 283)	138.4 (60 to 15360)	102.9 (60 to 1920)		

Notes:

[23] - Participants who received study treatment and had a valid ADA result at the specific time points.

[24] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Secondary: Extended Treatment Period: Anti-Drug Antibodies (ADAs) Titer Levels

End point title	Extended Treatment Period: Anti-Drug Antibodies (ADAs) Titer Levels

End point description:

Overall category includes all time points except Baseline.

End point type	Secondary

End point timeframe:

Extended Period Baseline (Week 24), Week 30, Week 52, and Week 55

End point values	Core Period; MSB11456; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: RoActemra®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	266[25]	139[26]	137[27]	
Units: titer				
geometric mean (full range (min-max))				
Overall (N: 265, 137, 135)	215.4 (60 to 15360)	166.3 (60 to 15360)	101.1 (60 to 960)	
Extended Baseline (Week 24) (N: 266, 136, 136)	127.7 (60 to 15360)	106.1 (60 to 1920)	95.6 (60 to 960)	

Week 30 (N: 262, 134, 132)	173.0 (60 to 15360)	130.6 (60 to 7680)	93.7 (60 to 960)	
Week 52 (N: 246, 125, 126)	230.9 (60 to 7680)	174.7 (60 to 15360)	96.7 (60 to 480)	
Week 55 (N: 242, 122, 122)	251.2 (60 to 15360)	200.8 (60 to 15360)	112.4 (60 to 480)	

Notes:

[25] - Participants who received study treatment and had a valid ADA result at the specific time points.

[26] - Participants who received study treatment and had a valid ADA result at the specific time points.

[27] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Secondary: Core Treatment Period: Percentage of Participants With Neutralizing Antibodies (NAb)

End point title	Core Treatment Period: Percentage of Participants With Neutralizing Antibodies (NAb)

End point description:

Overall category includes all time points except Baseline.

End point type	Secondary

End point timeframe:

Baseline, Week 2, Week 12 and Week 24

End point values	Core Treatment Period: MSB11456	Core Treatment Period: RoActemra®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	302[28]	302[29]		
Units: percentage of participants				
number (not applicable)				
Overall (N: 299, 301)	8.4	11.3		
Baseline (N: 302, 302)	0	0		
Week 2 (N: 287, 291)	3.8	3.4		
Week 12 (N: 281, 292)	2.5	4.1		
Week 24 (N: 274, 283)	2.9	4.9		

Notes:

[28] - Participants who received study treatment and had a valid ADA result at the specific time points.

[29] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Secondary: Extended Treatment Period: Percentage of Participants With Neutralizing Antibodies (NAb)

End point title	Extended Treatment Period: Percentage of Participants With Neutralizing Antibodies (NAb)

End point description:

Overall category includes all time points except Baseline.

End point type	Secondary

End point timeframe:

Week 24, Week 30, Week 52 and Week 55

End point values	Core Period; MSB11456; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	Core Period: RoActemra®; Extended Period: RoActemra®	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	266[30]	139[31]	136[32]	
Units: percentage of participants				
number (not applicable)				
Overall (N: 265, 137, 135)	13.2	16.8	11.9	
Extended Baseline (Week 24) (N: 266, 139, 136)	3.8	5.8	5.9	
Week 30 (N: 262, 134, 132)	6.1	9.7	3.0	
Week 52 (N: 246, 125, 126)	1.6	2.4	1.6	
Week 55 (N: 242, 122, 122)	7.0	6.6	9.0	

Notes:

[30] - Participants who received study treatment and had a valid ADA result at the specific time points.

[31] - Participants who received study treatment and had a valid ADA result at the specific time points.

[32] - Participants who received study treatment and had a valid ADA result at the specific time points.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 63

Adverse event reporting additional description:

Safety Analysis Set: includes all participants who received at least one dose of study drug (MBS11456 or EU-approved RoActemra). The tables below only include treatment-emergent adverse events and "Other Adverse Events" only include non-serious TEAEs.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	MSB11456

Reporting group description:

All participants who received MSB11456 in the Core Treatment Period (Baseline to Week 24) and then re-randomized to continue MSB11456 in the Extended Treatment Period (Week 24 to Week 52).

Participants received MSB11456 subcutaneously, once a week.

Reporting group title	Core Period: RoActemra®; Extended Period: MSB11456

Reporting group description:

Participants received EU-approved RoActemra® subcutaneously, once a week during the core treatment period (Baseline to Week 24). Participants were then re-randomized to begin receiving MSB11456 subcutaneously, once a week during the extended treatment period (Week 24 to Week 52).

Reporting group title	EU-approved RoActemra®

Reporting group description:

All participants who received EU-approved RoActemra® in the Core Treatment Period (Baseline to Week 24) and then re-randomized to continue RoActemra® in the Extended Treatment Period (Week 24 to Week 52).

Participants received EU-approved RoActemra® subcutaneously, once a week.

Serious adverse events	MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	EU-approved RoActemra®
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 302 (16.89%)	20 / 139 (14.39%)	33 / 163 (20.25%)
number of deaths (all causes)	0	1	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Follicular thyroid cancer			

subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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
Benign ovarian tumour			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Squamous cell carcinoma of lung			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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
Pregnancy, puerperium and perinatal conditions			
Stillbirth			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Reproductive system and breast disorders			
Menorrhagia			

subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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
Uterine polyp			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Wrist fracture			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Myocardial infarction			

subjects affected / exposed	1 / 302 (0.33%)	1 / 139 (0.72%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Atrioventricular block complete			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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
Coronary artery thrombosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery disease			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Ischaemic stroke			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hilar lymphadenopathy			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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			

Cholelithiasis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Autoimmune hepatitis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic steatosis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	2 / 302 (0.66%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondyloarthropathy			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (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

Spondylolisthesis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic inflammatory disease			
subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asymptomatic COVID-19			
subjects affected / exposed	2 / 302 (0.66%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	38 / 302 (12.58%)	12 / 139 (8.63%)	19 / 163 (11.66%)
occurrences causally related to treatment / all	3 / 38	1 / 12	0 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	1 / 302 (0.33%)	0 / 139 (0.00%)	0 / 163 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			

subjects affected / exposed	0 / 302 (0.00%)	1 / 139 (0.72%)	0 / 163 (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
Arthritis bacterial			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 302 (0.00%)	0 / 139 (0.00%)	1 / 163 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

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

Non-serious adverse events	MSB11456	Core Period: RoActemra®; Extended Period: MSB11456	EU-approved RoActemra®
Total subjects affected by non-serious adverse events			
subjects affected / exposed	163 / 302 (53.97%)	82 / 139 (58.99%)	92 / 163 (56.44%)
Investigations			
Mycobacterium tuberculosis complex test positive			
subjects affected / exposed	14 / 302 (4.64%)	4 / 139 (2.88%)	4 / 163 (2.45%)
occurrences (all)	14	4	4
Alanine aminotransferase increased			
subjects affected / exposed	36 / 302 (11.92%)	22 / 139 (15.83%)	22 / 163 (13.50%)
occurrences (all)	48	28	28
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 302 (6.29%)	9 / 139 (6.47%)	10 / 163 (6.13%)
occurrences (all)	20	9	10
Blood bilirubin increased			
subjects affected / exposed	11 / 302 (3.64%)	8 / 139 (5.76%)	3 / 163 (1.84%)
occurrences (all)	16	11	3
Blood pressure increased			
subjects affected / exposed	6 / 302 (1.99%)	4 / 139 (2.88%)	6 / 163 (3.68%)
occurrences (all)	6	4	6

Blood bilirubin unconjugated increased			
subjects affected / exposed	5 / 302 (1.66%)	5 / 139 (3.60%)	4 / 163 (2.45%)
occurrences (all)	5	7	5
Low density lipoprotein increased			
subjects affected / exposed	5 / 302 (1.66%)	4 / 139 (2.88%)	2 / 163 (1.23%)
occurrences (all)	6	5	4
Blood cholesterol increased			
subjects affected / exposed	4 / 302 (1.32%)	4 / 139 (2.88%)	3 / 163 (1.84%)
occurrences (all)	6	4	5
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 302 (1.66%)	2 / 139 (1.44%)	4 / 163 (2.45%)
occurrences (all)	7	3	6
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 302 (0.66%)	0 / 139 (0.00%)	4 / 163 (2.45%)
occurrences (all)	2	0	4
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 302 (4.30%)	6 / 139 (4.32%)	4 / 163 (2.45%)
occurrences (all)	13	6	4
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 302 (5.63%)	2 / 139 (1.44%)	4 / 163 (2.45%)
occurrences (all)	25	2	6
Dizziness			
subjects affected / exposed	4 / 302 (1.32%)	2 / 139 (1.44%)	4 / 163 (2.45%)
occurrences (all)	5	3	4
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	22 / 302 (7.28%)	8 / 139 (5.76%)	12 / 163 (7.36%)
occurrences (all)	50	17	22
Thrombocytopenia			
subjects affected / exposed	11 / 302 (3.64%)	2 / 139 (1.44%)	7 / 163 (4.29%)
occurrences (all)	26	2	11
Neutropenia			

subjects affected / exposed	19 / 302 (6.29%)	8 / 139 (5.76%)	10 / 163 (6.13%)
occurrences (all)	43	17	14
Anaemia			
subjects affected / exposed	5 / 302 (1.66%)	6 / 139 (4.32%)	2 / 163 (1.23%)
occurrences (all)	5	6	2
Lymphopenia			
subjects affected / exposed	5 / 302 (1.66%)	1 / 139 (0.72%)	4 / 163 (2.45%)
occurrences (all)	6	1	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	9 / 302 (2.98%)	0 / 139 (0.00%)	6 / 163 (3.68%)
occurrences (all)	9	0	7
Diarrhoea			
subjects affected / exposed	7 / 302 (2.32%)	3 / 139 (2.16%)	4 / 163 (2.45%)
occurrences (all)	7	3	4
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 302 (1.32%)	4 / 139 (2.88%)	1 / 163 (0.61%)
occurrences (all)	12	4	1
Rash			
subjects affected / exposed	3 / 302 (0.99%)	2 / 139 (1.44%)	4 / 163 (2.45%)
occurrences (all)	3	3	4
Dermatitis allergic			
subjects affected / exposed	1 / 302 (0.33%)	3 / 139 (2.16%)	0 / 163 (0.00%)
occurrences (all)	1	3	0
Renal and urinary disorders			
Cystitis noninfective			
subjects affected / exposed	2 / 302 (0.66%)	4 / 139 (2.88%)	1 / 163 (0.61%)
occurrences (all)	2	4	2
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	7 / 302 (2.32%)	4 / 139 (2.88%)	4 / 163 (2.45%)
occurrences (all)	8	5	4
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	9 / 302 (2.98%)	5 / 139 (3.60%)	9 / 163 (5.52%)
occurrences (all)	10	5	12
Upper respiratory tract infection			
subjects affected / exposed	17 / 302 (5.63%)	6 / 139 (4.32%)	10 / 163 (6.13%)
occurrences (all)	20	7	11
Urinary tract infection			
subjects affected / exposed	5 / 302 (1.66%)	4 / 139 (2.88%)	3 / 163 (1.84%)
occurrences (all)	8	5	3
Bronchitis			
subjects affected / exposed	7 / 302 (2.32%)	0 / 139 (0.00%)	3 / 163 (1.84%)
occurrences (all)	7	0	3
Pharyngitis			
subjects affected / exposed	2 / 302 (0.66%)	1 / 139 (0.72%)	4 / 163 (2.45%)
occurrences (all)	2	1	4
COVID-19			
subjects affected / exposed	38 / 302 (12.58%)	12 / 139 (8.63%)	19 / 163 (11.66%)
occurrences (all)	39	12	19
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	10 / 302 (3.31%)	5 / 139 (3.60%)	6 / 163 (3.68%)
occurrences (all)	13	7	6
Hyperlipidaemia			
subjects affected / exposed	10 / 302 (3.31%)	5 / 139 (3.60%)	5 / 163 (3.07%)
occurrences (all)	10	5	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 May 2020	The following updates were implemented: * Due to the COVID-19 pandemic, measures were implemented to increase safeguarding for the patients, including: - Implementation of risk minimization and the mitigation plan for COVID-19. - Provision of a separate ICF to inform patients of the nature and impact of COVID-19. - Updates to the exclusion criteria to exclude patients with confirmed or suspected active COVID-19 infection and to ensure that the investigator specifically evaluated the patient's eligibility taking into consideration COVID-19 risk factors and situation. - Provided details of action to take with the IMP due to COVID-19 and confirmed details of COVID-19 AE/SAE reporting. - Permitted the inclusion of local laboratories (with preapproval of the Sponsor) instead of central laboratories, if required due to the COVID-19 situation. * Provided fuller details of injection site reactions and reporting, and instructions for the investigator to ask the patient if any such reaction had occurred since the last assessment. * Replaced predefined AESIs with a statement that any AEs that lead to interruption of IMP, permanent discontinuation of IMP, or withdrawal from the study would be considered predefined AESIs.
01 February 2021	The following changes were implemented: * Added that COVID-19 vaccination was not allowed from 4 weeks prior to randomization until the completion of the Week 30 visit (COVID-19–related protocol deviation); noted that COVID-19 vaccination was not recommended thereafter until the completion of the Week 55 visit and provided guidance regarding the timing of any such vaccination. * Removed details regarding North America, Asia, and the Rest of the World, including stratification by geographical region, as the study was being conducted in Europe only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported