Clinical trial results:
A 24-Week Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Finding Study to Evaluate the Efficacy and Safety of 3 Doses of Namilumab (20 mg, 80 mg and 150 mg) in Combination with Methotrexate (MTX) in Subjects with Moderate to Severe Rheumatoid Arthritis (RA) NEXUS

Summary

EudraCT number	2013-002805-76
Trial protocol	GB DE CZ ES BG
Global end of trial date	05 December 2016

Results information

Result version number	v1 (current)
This version publication date	01 December 2017
First version publication date	01 December 2017

Trial information

Trial identification

Sponsor protocol code	M1-1188_202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02379091
WHO universal trial number (UTN)	U1111-1151-6931
Other trial identifiers	NRES: 14/SC/1252, JapicCTI: JapicCTI-152979, RNEC: 153300410A0071

Notes:

Sponsors

Sponsor organisation name	Takeda Development Center Americas Inc.
Sponsor organisation address	One Takeda Parkway, Deerfield, IL, United States, 60015
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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	05 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 2016
Global end of trial reached?	Yes
Global end of trial date	05 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to establish proof of concept and identify the optimal efficacious dose for namilumab in RA in patients with an inadequate response to methotrexate (MTX-IR) and in patients with an inadequate response to one tumor necrosis factor (TNF)-inhibitor (TNF-IR).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Czech Republic: 35
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 9
Worldwide total number of subjects	108
EEA total number of subjects	66

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	101
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 28 investigative sites in Bulgaria, Czech Republic, Japan, Poland, Russian Federation, Spain and the United Kingdom from 17 December 2014 to 05 December 2016.

Pre-assignment

Screening details:

Participants with a diagnosis of moderate to severe Rheumatoid Arthritis were enrolled equally in one of 4 treatment groups: placebo or 20, 80, 150 mg/mL namilumab.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

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

Dosage and administration details:

Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 weeks.

Arm title	Namilumab 20 mg/mL

Arm description:

Namilumab 20 mg/mL, subcutaneous (SC) injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

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

Dosage and administration details:

Namilumab 20 mg/mL, subcutaneous (SC) injection, once on Days 1, 15, 43, 71 and every 4 weeks for

12 Weeks.

Arm title	Namilumab 80 mg/mL

Arm description:

Namilumab 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

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

Dosage and administration details:

Namilumab 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks.

Arm title	Namilumab 150 mg/mL

Arm description:

Namilumab 150 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant was discontinued from the study. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

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

Dosage and administration details:

Namilumab 150 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks.

Number of subjects in period 1	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL
Started	27	28	25
Full Analysis set	26	28	24
Completed	15	18	18
Not completed	12	10	7
Pretreatment Event/Adverse Event	-	2	-
Study Termination	7	2	5
Voluntary Withdrawal	2	5	2
Principal Investigator Discretion	-	1	-

Lost to follow-up	-	-	-
Lack of efficacy	3	-	-

Number of subjects in period 1	Namilumab 150 mg/mL
Started	28
Full Analysis set	28
Completed	14
Not completed	14
Pretreatment Event/Adverse Event	1
Study Termination	8
Voluntary Withdrawal	4
Principal Investigator Discretion	-
Lost to follow-up	1
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.	
Reporting group title	Namilumab 20 mg/mL
Reporting group description:	
Namilumab 20 mg/mL, subcutaneous (SC) injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.	
Reporting group title	Namilumab 80 mg/mL
Reporting group description:	
Namilumab 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.	
Reporting group title	Namilumab 150 mg/mL
Reporting group description:	
Namilumab 150 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant was discontinued from the study. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.	

Reporting group values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL
Number of subjects	27	28	25
Age Categorical Units: Subjects			
< 45 years	9	11	7
45 to 64 years	15	16	17
65 to 74 years	1	1	1
>= 75 years	2	0	0
Age Continuous Units: years			
arithmetic mean	47.2	46.1	49.0
standard deviation	± 13.45	± 10.07	± 9.60
Gender, Male/Female Units: Subjects			
Female	23	22	17
Male	4	6	8

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	1
Not Hispanic or Latino	22	22	21
Unknown or Not Reported	4	4	3
Race/Ethnicity, Customized Units: Subjects			
Asian	6	4	3
White	21	24	22
Multiracial	0	0	0
BMI Categories Units: Subjects			
< 30 kg/m^2	24	23	16
>= 30 kg/m^2	3	5	9
Smoking classification Units: Subjects			
Participant has never smoked	16	19	18
Participant is a current smoker	6	5	5
Participant is an ex-smoker	5	4	2
Region of Enrollment Units: Subjects			
Bulgaria	2	1	1
Czech Republic	7	9	9
Japan	4	4	3
Poland	1	6	4
Russia	7	4	6
Spain	1	2	1
United Kingdom	5	2	1
Study Specific Characteristic | Height Units: cm			
arithmetic mean	164.3	167.7	167.4
standard deviation	± 10.51	± 6.65	± 8.36
Study Specific Characteristic | Weight Units: kg			
arithmetic mean	63.89	70.28	76.56
standard deviation	± 14.511	± 15.911	± 18.660
Study Specific Characteristic | Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	23.75	24.91	27.16
standard deviation	± 5.542	± 5.210	± 5.605

Reporting group values	Namilumab 150 mg/mL	Total	
Number of subjects	28	108	
Age Categorical Units: Subjects			
< 45 years	7	34	
45 to 64 years	19	67	
65 to 74 years	2	5	
>= 75 years	0	2	

Age Continuous Units: years			
arithmetic mean	51.3		
standard deviation	± 14.13	-	
Gender, Male/Female Units: Subjects			
Female	22	84	
Male	6	24	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	4	
Not Hispanic or Latino	23	88	
Unknown or Not Reported	5	16	
Race/Ethnicity, Customized Units: Subjects			
Asian	5	18	
White	22	89	
Multiracial	1	1	
BMI Categories Units: Subjects			
< 30 kg/m^2	22	85	
>= 30 kg/m^2	6	23	
Smoking classification Units: Subjects			
Participant has never smoked	18	71	
Participant is a current smoker	6	22	
Participant is an ex-smoker	4	15	
Region of Enrollment Units: Subjects			
Bulgaria	1	5	
Czech Republic	10	35	
Japan	5	16	
Poland	2	13	
Russia	9	26	
Spain	0	4	
United Kingdom	1	9	
Study Specific Characteristic | Height Units: cm			
arithmetic mean	166.5		
standard deviation	± 9.24	-	
Study Specific Characteristic | Weight Units: kg			
arithmetic mean	72.23		
standard deviation	± 19.168	-	
Study Specific Characteristic | Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	25.92		
standard deviation	± 6.313	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab 20 mg/mL

Reporting group description:

Namilumab 20 mg/mL, subcutaneous (SC) injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab 80 mg/mL

Reporting group description:

Namilumab 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant entered an open-label period and received namilumab 150 mg/mL, SC injection, every 4 Weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab 150 mg/mL

Reporting group description:

Namilumab 150 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks for 12 Weeks. Participants were assessed for response (a 20% improvement from Baseline in both swollen and tender joint counts). If the participant was a responder, the current treatment continued every 4 weeks up to Week 24. If the participant was a non-responder, the participant was discontinued from the study. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Primary: Change From Baseline in Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) at Week 12

End point title	Change From Baseline in Disease Activity Score 28 C-Reactive Protein (DAS28-CRP) at Week 12

End point description:

The DAS28-CRP score is a measure of the participant’s disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], general health: patient’s global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and acute phase response: C-Reactive Protein (CRP) for a total possible score of 0 (best) to approximately 10 (worst). Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicates improvement. A mixed model repeated measures (MMRM) model with main effects for study site, treatment, visit, and previously failed medication with interactions between visit and treatment, visit and previously failed medication, and visit and baseline value as a covariate and participant as a random effect with an unstructured covariance structure was used for analysis.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	25	22	26
Units: score on a scale				
least squares mean (standard error)	-0.77 (± 0.294)	-1.38 (± 0.288)	-1.36 (± 0.302)	-1.69 (± 0.286)

Statistical analyses

Statistical analysis title	Placebo vs Namilumab 20 mg/mL
Comparison groups	Namilumab 20 mg/mL v Placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.086 [1]
Method	ANOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.31
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.351

Notes:

[1] - MMRM model with main effects for study
site, treatment, visit, and previously failed medication with interactions between visit and treatment, visit and previously failed medication, and visit and baseline value.

Statistical analysis title	Placebo vs Namilumab 80 mg/mL
Comparison groups	Placebo v Namilumab 80 mg/mL
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.107 [2]
Method	ANOVA
Parameter estimate	LS Mean
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.32
upper limit	0.13
Variability estimate	Standard error of the mean
Dispersion value	0.366

Notes:

[2] - MMRM model with main effects for study
site, treatment, visit, and previously failed medication with interactions between visit and treatment, visit and previously failed medication, and visit and baseline value.

Statistical analysis title	Placebo vs Namilumab 150 mg/mL
Comparison groups	Placebo v Namilumab 150 mg/mL
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.01 [3]
Method	ANOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	-0.23
Variability estimate	Standard error of the mean
Dispersion value	0.347

Notes:

[3] - MMRM model with main effects for study
site, treatment, visit, and previously failed medication with interactions between visit and treatment, visit and previously failed medication, and visit and baseline value.

Secondary: Percentage of Participants Achieving American College of Rheumatology 20% (ACR20), 50% (ACR 50) and 70% (ACR70) Response at Weeks 12 and 24

End point title	Percentage of Participants Achieving American College of Rheumatology 20% (ACR20), 50% (ACR 50) and 70% (ACR70) Response at Weeks 12 and 24

End point description:

ACR20/50/70 response is defined as a ≥20/50/70% reduction from Baseline for both total joint count-68 joints (TJC68) and swollen joint count-66 joints (SJC66), and the following: • Patient's Assessment of Pain over the previous 24 hours using a Visual Analog Scale (VAS); left end of the line 0=no pain to right end of the line 100=unbearable pain • Patient's Global Assessment of Disease Activity • Physician's Global Assessment of Disease Activity over the previous 24 hours using a VAS where left end of the line 0=no disease activity to right end of the line 100=maximum disease activity • Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do • Acute-phase reactant: C-reactive Protein (CRP).

End point type	Secondary

End point timeframe:

Baseline and Weeks 12 and 24

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	28	24	28
Units: percentage of participants				
number (not applicable)				
ACR 20, Week 12 (n=24,25,23,26)	37.5	72.0	52.2	53.8
ACR 50, Week 12 (n=24,25,23,26)	16.7	20.0	30.4	38.5
ACR 70, Week 12 (n=24,25,23,26)	8.3	4.0	21.7	15.4

ACR 20, Week 24 (n=21,23,23,25)	33.3	65.2	47.8	56.0
ACR 50, Week 24 (n=21,23,23,25)	23.8	34.8	47.8	36.0
ACR 70, Week 24 (n=21,23,23,25)	19.0	13.0	30.4	20.0

Statistical analyses

No statistical analyses for this end point

Secondary: ACR Numeric (N) Index (ACRn) at Week 12

End point title	ACR Numeric (N) Index (ACRn) at Week 12

End point description:

ACRn is defined as the lowest % improvement for TJC68, SJC66 and the median of 5 ACR components. These are • Patient's Assessment of Pain over previous 24 hours using a VAS; left end of line 0=no pain to right end of line 100=unbearable pain • Patient's Global Assessment of Disease Activity • Physician's Global Assessment of Disease Activity over previous 24 hours using a VAS where left end of line 0=no disease activity to right end of line 100=maximum disease activity • Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do • Acute-phase reactant: CRP. A positive % change indicates improvement. MMRM model with main effects for study site, treatment, visit, and previously failed medication with interactions between visit and treatment and visit and previously failed medication and participant used as a random effect with an unstructured covariance structure.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	24	25	23	26
Units: percentage change				
least squares mean (standard error)	-17.25 (± 16.469)	3.97 (± 16.372)	19.68 (± 16.875)	17.14 (± 16.098)

Statistical analyses

No statistical analyses for this end point

Secondary: ACR Numeric (N) Index (ACRn) at Week 24

End point title	ACR Numeric (N) Index (ACRn) at Week 24

End point description:

ACRn is defined as the lowest % improvement for TJC68, SJC66 and the median of 5 ACR components. These are • Patient's Assessment of Pain over previous 24 hours using a VAS; left end of line 0=no pain to right end of line 100=unbearable pain • Patient's Global Assessment of Disease Activity • Physician's Global Assessment of Disease Activity over previous 24 hours using a VAS where left end of line 0=no disease activity to right end of line 100=maximum disease activity • Health Assessment Questionnaire: 20 questions, 8 components: dressing/grooming, arising, eating, walking, hygiene, reach, grip and activities, 0=without difficulty to 3=unable to do • Acute-phase reactant: CRP. A positive % change indicates improvement. MMRM model with main effects for study site, treatment, visit, and previously failed medication with interactions between visit and treatment and visit and previously failed

medication and participant used as a random effect with an unstructured covariance structure.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	28	24	28
Units: percentage change				
arithmetic mean (standard deviation)	34.04 (± 40.248)	35.35 (± 50.191)	44.66 (± 38.203)	36.57 (± 38.709)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS28-CRP at Weeks 2, 6, and 10

End point title	Change From Baseline in DAS28-CRP at Weeks 2, 6, and 10

End point description:

The DAS28-CRP score is a measure of the participant's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], general health: patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and acute phase response: C-Reactive Protein (CRP) for a total possible score of 0 (best) to approximately 10 (worst). Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicates improvement. A MMRM model with main effects for study site, treatment, visit, and previously failed medication with interactions between visit and treatment, visit and previously failed medication, and visit and baseline value as a covariate and participant as a random effect with an unstructured covariance structure was used for analysis.

End point type	Secondary

End point timeframe:

Baseline and Weeks 2, 6 and 10

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	28	24	28
Units: score on a scale				
least squares mean (standard error)				
Change at Week 2 (n=26,28,23,28)	-0.33 (± 0.236)	-0.58 (± 0.222)	-0.84 (± 0.245)	-0.95 (± 0.224)
Change at Week 6 (n=25,26,23,27)	-0.70 (± 0.268)	-1.13 (± 0.256)	-1.37 (± 0.275)	-1.42 (± 0.257)
Change at Week 10 (n=25,25,22,27)	-0.75 (± 0.280)	-1.19 (± 0.273)	-1.39 (± 0.289)	-1.51 (± 0.269)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in DAS28-CRP at Week 24

End point title	Change From Baseline in DAS28-CRP at Week 24

End point description:

The DAS28-CRP score is a measure of the participant's disease activity calculated using the tender joint count (TJC) [28 joints], swollen joint count (SJC) [28 joints], general health: patient's global assessment of disease activity [visual analog scale: 0=no disease activity to 100=maximum disease activity] and acute phase response: C-Reactive Protein (CRP) for a total possible score of 0 (best) to approximately 10 (worst). Scores below 2.6 indicate best disease control and scores above 5.1 indicate worse disease control. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	18	16	17
Units: score on a scale				
arithmetic mean (standard deviation)	-1.75 (± 1.401)	-2.37 (± 1.083)	-2.20 (± 1.219)	-2.26 (± 0.962)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Reduction of Pain as Measured Using a Visual Analog Scale (VAS) at Weeks 2, 12 and 24

End point title	Percentage of Participants with a Reduction of Pain as Measured Using a Visual Analog Scale (VAS) at Weeks 2, 12 and 24

End point description:

Reduction of Pain, defined as a ≥40% change from Baseline as measured using a 100 mm Visual Analog Scale (VAS); left end of the line 0=no pain to right end of the line 100=unbearable pain at weeks 2, 12 and 24.

End point type	Secondary

End point timeframe:

Baseline and Week 2, 12 and 24

End point values	Placebo	Namilumab 20 mg/mL	Namilumab 80 mg/mL	Namilumab 150 mg/mL
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	28	24	28
Units: percentage of participants				
number (not applicable)				
Week 2 (n=26,28,23,28)	7.7	14.3	8.7	3.6
Week 12 (n=24,25,23,26)	20.8	44.0	39.1	30.8
Week 24 (n=22,23,23,25)	22.7	43.5	47.8	24.0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to 30 days after last dose of study drug (Up to 46.4 Weeks)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Namilumab 20 mg/mL

Reporting group description:

Namilumab 20 mg/mL, subcutaneous (SC) injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Placebo

Reporting group description:

Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab 150 mg/mL

Reporting group description:

Namilumab 150 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Placebo to Namilumab 150 mg/mL

Reporting group description:

Namilumab placebo-matching, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 12; followed by Namilumab 150 mg/mL, SC injection, every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab 80 mg/mL

Reporting group description:

Namilumab 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Reporting group title	Namilumab to Namilumab 150 mg/mL

Reporting group description:

Namilumab 20 or 80 mg/mL, SC injection, once on Days 1, 15, 43, 71 and every 4 weeks up to Week 12; followed by namilumab 150 mg/mL, SC injection, every 4 weeks up to Week 24. All participants were on a stable dose of methotrexate tablets (15-25 mg weekly) and folic acid (at least 5 mg/week) orally throughout the duration of the study.

Serious adverse events	Namilumab 20 mg/mL	Placebo	Namilumab 150 mg/mL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	1 / 28 (3.57%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo to Namilumab 150 mg/mL	Namilumab 80 mg/mL	Namilumab to Namilumab 150 mg/mL
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	1 / 25 (4.00%)	4 / 24 (16.67%)

number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 12 (0.00%)	1 / 25 (4.00%)	0 / 24 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
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			
Asthma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Namilumab 20 mg/mL	Placebo	Namilumab 150 mg/mL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 28 (46.43%)	9 / 27 (33.33%)	12 / 28 (42.86%)
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 28 (3.57%)	1 / 27 (3.70%)	0 / 28 (0.00%)
occurrences (all)	2	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	3 / 28 (10.71%)
occurrences (all)	1	0	3
Hepatobiliary disorders			
Drug-induced liver injury			

subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	2 / 28 (7.14%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	3	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 28 (25.00%)	5 / 27 (18.52%)	5 / 28 (17.86%)
occurrences (all)	8	6	5
Bronchitis			
subjects affected / exposed	1 / 28 (3.57%)	2 / 27 (7.41%)	1 / 28 (3.57%)
occurrences (all)	1	2	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	3
Laryngitis			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 28 (0.00%)	0 / 27 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Placebo to Namilumab 150 mg/mL	Namilumab 80 mg/mL	Namilumab to Namilumab 150 mg/mL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 12 (41.67%)	12 / 25 (48.00%)	6 / 24 (25.00%)
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Forced expiratory volume decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
White blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 12 (0.00%)	3 / 25 (12.00%)	0 / 24 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	2 / 25 (8.00%)	0 / 24 (0.00%)
occurrences (all)	1	2	0
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	2 / 24 (8.33%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue			

disorders			
Rheumatoid arthritis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 25 (8.00%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 25 (8.00%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Bronchitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	2 / 25 (8.00%)	1 / 24 (4.17%)
occurrences (all)	0	2	1
Laryngitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 25 (8.00%)	0 / 24 (0.00%)
occurrences (all)	0	2	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Oral herpes			
subjects affected / exposed	1 / 12 (8.33%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2014	The protocol was amended to clarify the study populations, secondary and exploratory endpoints, statistical analysis, biomarker analyses, and blood sample collection time points. The following summarizes the significant changes made in the amendment: 1) Updated the nonclinical and clinical background sections; 2) Updated the objectives and endpoints sections; 3) Clarified the study design and description sections; 4) Updated the TNF-IR and MTX population balance 5) Addition of language for screening subjects in Asia; 6) Changed the inclusion and exclusion criteria; 7) Clarified the excluded medications and treatments sections; 8) Amended the blood sample collection, laboratory test and lung function test parameters to exclusion criteria; 9) Changed the statistical analysis section; 10) Addition of information regarding management of AEs.
02 April 2015	The protocol was amended to include Japan in the study. The following summarizes the significant changes made in the amendment: 1) Updated the sponsorship for the study; 2) Changed the Takeda representative's approval; 3) Updated the MTX-IR population; 4) Clarified regarding statistical considerations, especially in regard to modeling and Stratification; 5) Addition of Japan; 6) Japan specific visit, and procedures and processes; 7) Updated the biomarker sampling; 8) Revised contraception and pregnancy avoidance counselling; 9) Updated sponsor supplied companion medication.
21 January 2016	The primary purpose of this amendment was to remove the extension period of the study and reduce the overall sample size to approximately 100 subjects. The following summarizes the significant changes made in the amendment: 1) Reduced the minimum number of subjects assigned to each treatment group; 2) Removed the minimum number requirement for TNF-IR subjects; 3) Included a primary analysis once all subjects had completed 12 weeks of treatment; 4) Revised the section for sample size justification; 5) Updated timing of the PGx analysis; 6) Allowed prior treatment with 1 immunomodulatory biological agent or kinase inhibitor; 7) Updated exclusion criteria around lung function and management of associated AEs; 8) Clarified excluded medications and treatments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported