Clinical trial results:
A 24-week Randomized, Open-Label, Parallel-Group, Active-Controlled, Exploratory, Proof-of-Mechanism Imaging Study Investigating the Efficacy of 150 mg of Namilumab Administered Subcutaneously vs Adalimumab in Patients With Moderate to Severe Early Rheumatoid Arthritis Inadequately Responding to Methotrexate

Summary

EudraCT number	2014-002945-23
Trial protocol	GB CZ EE ES
Global end of trial date	03 November 2016

Results information

Result version number	v1 (current)
This version publication date	26 November 2017
First version publication date	26 November 2017

Trial information

Trial identification

Sponsor protocol code	MT203-2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02393378
WHO universal trial number (UTN)	U1111-1160-1791

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	One Takeda Parkway Deerfield, Unites Sates, United States, IL 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	03 November 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the effect on structural damage imaging markers measured as change from Baseline in synovitis, erosion, and bone marrow edema (osteitis), in metacarpophalangeal (MCP) joints and wrist at Week 24 on magnetic resonance imaging (MRI) using the RA-MRI scoring Outcome Measures in Rheumatoid Arthritis Clinical Trials (RAMRIS OMERACT).

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	08 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	Russian Federation: 4
Worldwide total number of subjects	7
EEA total number of subjects	3

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	4
From 65 to 84 years	3

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 5 investigative sites in Estonia and Russian Federation from 08 April 2015 to 03 November 2016.

Pre-assignment

Screening details:

Participants with a diagnosis of rheumatoid arthritis were enrolled in 2:1 ratio to receive either namilumab combined with methotrexate (MTX) or adalimumab combined with MTX.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab 40 mg

Arm description:

Adalimumab 40 mg SC injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.

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

Dosage and administration details:

Participants received Adalimumab 40 mg SC injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22.

Arm title	Namilumab 150 mg

Arm description:

Namilumab 300 mg SC injection at Week 0 followed by 150 mg SC injection at Weeks 2, 6, 10, 14, 18, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.

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

Dosage and administration details:

Participants received Namilumab 300 mg SC injection at Week 0 followed by 150 mg SC injection at Weeks 2, 6, 10, 14, 18, and 22.

Number of subjects in period 1	Adalimumab 40 mg	Namilumab 150 mg
Started	3	4
Completed	3	4

Baseline characteristics

Reporting groups	
Reporting group title	Adalimumab 40 mg
Reporting group description:	
Adalimumab 40 mg SC injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.	
Reporting group title	Namilumab 150 mg
Reporting group description:	
Namilumab 300 mg SC injection at Week 0 followed by 150 mg SC injection at Weeks 2, 6, 10, 14, 18, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.	

Reporting group values	Adalimumab 40 mg	Namilumab 150 mg	Total
Number of subjects	3	4	7
Age Categorical Units: Subjects			
45 to 64 years	1	3	4
>= 65 years	2	1	3
Age Continuous Units: years			
arithmetic mean	63.0	61.3	
standard deviation	± 7.21	± 6.90	-
Gender, Male/Female Units: Subjects			
Female	2	0	2
Male	1	4	5
Race/Ethnicity, Customized Units: Subjects			
White	3	4	7
Body Mass Index (BMI) Categories Units: Subjects			
< 30 kg/m^2	1	2	3
>= 30 kg/m^2	2	2	4
Region of Enrollment Units: Subjects			
Estonia	1	2	3
Russia	2	2	4
Study Specific Characteristic | Height Units: cm			
arithmetic mean	171.7	162.5	
standard deviation	± 8.96	± 3.00	-
Study Specific Characteristic | Weight Units: kg			
arithmetic mean	106.67	78.83	
standard deviation	± 16.197	± 16.550	-
Study Specific Characteristic | Body Mass Index (BMI)			
BMI = Weight in kg/Height in square meters.			
Units: kg/m^2			
arithmetic mean	36.77	29.68	

standard deviation	± 8.806	± 5.844	-

End points

End points reporting groups

Reporting group title	Adalimumab 40 mg
Reporting group description:	
Adalimumab 40 mg SC injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.	
Reporting group title	Namilumab 150 mg
Reporting group description:	
Namilumab 300 mg SC injection at Week 0 followed by 150 mg SC injection at Weeks 2, 6, 10, 14, 18, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.	

Primary: Change from Baseline in Synovitis, Erosion and Bone Marrow Edema (Osteitis) Score at Week 24

End point title	Change from Baseline in Synovitis, Erosion and Bone Marrow Edema (Osteitis) Score at Week 24[1]
End point description:	
A Magnetic Resonance Imaging (MRI) of Metacarpophalangeal (MCP) and Wrist of the dominant hand was performed at the baseline and at week 24. Change from the Baseline was assessed according to the Outcome Measures in Rheumatoid Arthritis (RA) Clinical Trials RA-MRI scoring (OMERACT RAMRIS) Standard. RAMRIS score is the sum of its core components: Synovitis Score, Edema Score, and Erosion Score. Synovitis is scored from 0 (normal) to 9 (maximum distension of synovial cavity). Edema is scored 0 (normal) to 69 (maximum articular bone involvement). Erosion is scored from 0 (normal) to 230 (maximum erosion of articular bone). Total RAMRIS score=0 (normal), maximum RAMRIS score=308 (severe structural damage). For Synovial Score, Edema Score, Erosion Score, and RAMRIS score, increasing number = increasing severity. Full analysis set included participants who received at least one dose of study medication. Here 'n' is the number of participants who were evaluated for specific sub-score.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not assessed for this endpoint.

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: score on a scale				
arithmetic mean (standard deviation)				
Erosion Score, Change at Week 24 (n=3,3)	0.50 (± 0.866)	0.00 (± 0.500)		
Synovitis Score, Change at Week 24 (n=3,3)	0.17 (± 0.764)	-1.50 (± 4.770)		
Osteitis Score, Change at Week 24 (n=3,2)	-0.33 (± 0.764)	-2.00 (± 3.536)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Dynamic Contrast-enhanced - Magnetic Resonance Imaging (DCE-MRI) Parameters at Week 24

End point title	Change from Baseline in Dynamic Contrast-enhanced - Magnetic Resonance Imaging (DCE-MRI) Parameters at Week 24

End point description:

DCE-MRI was used to measure synovial vascular perfusion. The change from baseline in DCE-MRI parameters of synovial vascular perfusion at Week 24 were measured. Full analysis set included participants who received at least one dose of study medication. Hence, number of participants analyzed (N) is the participants who were evaluated for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	3		
Units: mL				
arithmetic mean (standard deviation)	0.016 (± 0.0253)	-0.052 (± 0.0662)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Achieved Remission at Week 24

End point title	Number of Participants who Achieved Remission at Week 24

End point description:

Remission is defined as percentage of participants who achieved Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) score <2.6. DAS28-CRP is a composite measure of inflammation in rheumatoid arthritis (RA) and incorporates a tender and swollen joint count, CRP and patient global assessment of disease activity expressed in a gaussian distribution of variables ranging from 0 to 10. A DAS28-CRP score of <3.2 = low level of disease activity, while a score of >5.1 = high level of disease activity. Using DAS-CRP as a continuous scale allows investigators (and clinicians) to measure a clinically meaningful endpoint following institution of a therapeutic intervention. In RA, clinical remission would therefore be graded as a DAS28 score of ≤2.6 with disease flare accompanying scores of ≥5.1; well-controlled disease is best characterized as fitting in between these two scores. Full analysis set included participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 24

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: participants	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Achieved Low Disease Activity at Week 24

End point title	Number of Participants who Achieved Low Disease Activity at Week 24

End point description:

Disease Activity Score 28 based on C-reactive protein (DAS28-CRP) low disease activity is defined as a score <3.2. The DAS28-CRP is a composite measure of inflammation in RA and incorporates a tender and swollen joint count, CRP and patient global assessment of disease activity expressed in a gaussian distribution of variables ranging from 0 to 10. A DAS28-CRP score of <3.2 suggests a low level of disease activity, while a score of >5.1 suggests a high level of disease activity. Using the DAS-CRP as a continuous scale allows investigators (and clinicians) to measure a clinically meaningful endpoint following institution of a therapeutic intervention. In RA, clinical remission would therefore be graded as a DAS28 score of ≤2.6 with disease flare accompanying scores of ≥5.1; well-controlled disease is best characterized as fitting in between these two scores. Full analysis set included participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 24

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: participants	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved ACR 20, 50, and 70 at Week 24

End point title	Percentage of Participants who Achieved ACR 20, 50, and 70 at Week 24

End point description:

The American College of Rheumatology (ACR) 20 is composite index of improvement in RA proposed by the ACR. ACR20 refers to a composite improvement of 20% in swollen joint count, tender joint count, and 3 or more of the following 5 measures: Physician's Global Assessment of Disease Activity, Patient's Global Assessment of Disease Activity, Patient Pain VAS, Patient's self-addressed disability (HAQ), Acute-phase reactant (ESR or CRP) The ACR 50 and ACR 70 are similar tools, used to indicate 50% and 70% improvement, respectively. Full analysis set included participants who received at least one dose of study medication.

End point type	Secondary

End point timeframe:

Week 24

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: percentage of participants				
ACR 20	2	4		
ACR 50	2	3		
ACR 70	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in DAS28-CRP

End point title	Change from Baseline in DAS28-CRP

End point description:

The DAS28-CRP is a composite measure of inflammation in RA and incorporates a tender and swollen joint count, CRP and patient global assessment of disease activity expressed in a gaussian distribution of variables ranging from 0 to 10. A DAS28-CRP score of <3.2 suggests a low level of disease activity, while a score of >5.1 suggests a high level of disease activity. Using the DAS-CRP as a continuous scale allows investigators (and clinicians) to measure a clinically meaningful endpoint following institution of a therapeutic intervention. In RA, clinical remission would therefore be graded as a DAS28 score of ≤3.2 with disease flare accompanying scores of ≥5.1; well-controlled disease is best characterized as fitting in between these two scores. Full analysis set included participants who received at least one dose of study medication. Here 'n' is the number of participants who were evaluated at specific time point.

End point type	Secondary

End point timeframe:

Baseline Up to Week 42

End point values	Adalimumab 40 mg	Namilumab 150 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	4		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 2 (n =2,3)	-0.55 (± 0.737)	-0.78 (± 0.333)		
Week 6 (n =3,4)	-1.36 (± 1.086)	-1.58 (± 0.494)		
Week 10 (n =2,4)	-1.74 (± 1.103)	-1.83 (± 0.344)		
Week 12 (n =3,4)	-1.94 (± 1.036)	-2.12 (± 0.613)		

Week 18 (n =3,4)	-2.05 (± 1.136)	-2.72 (± 0.486)		
Week 24 (n =3,4)	-2.04 (± 1.596)	-2.99 (± 0.216)		
Week 32 (n =3,4)	-1.89 (± 1.946)	-2.38 (± 0.862)		
Week 42 (n =3,4)	-1.99 (± 1.938)	-1.57 (± 1.387)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information
Timeframe for reporting adverse events:
Baseline up to Week 42
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 150 mg

Reporting group description:

Namilumab 300 mg SC injection at Week 0 followed by 150 mg SC injection at Weeks 2, 6, 10, 14, 18, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.

Reporting group title	Adalimumab 40 mg

Reporting group description:

Adalimumab 40 mg SC injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, and 22 as an add-on to weekly existing stable MTX and folic acid as prescribed in clinical practice.

Serious adverse events	Namilumab 150 mg	Adalimumab 40 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Cellulitis streptococcal			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Namilumab 150 mg	Adalimumab 40 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	3 / 3 (100.00%)	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Forced expiratory volume decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Forced vital capacity decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Panic attack			
subjects affected / exposed	1 / 4 (25.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Joint swelling subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 3 (0.00%) 0	
Infections and infestations Streptococcal sepsis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1 1 / 4 (25.00%) 1	0 / 3 (0.00%) 0 1 / 3 (33.33%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 April 2015	• Clarified of inclusion and exclusion criteria. • Increased of the screening period from 4 weeks to 8 weeks. • Added flexibility around scheduling assessments at each visit. Allowing visits to be performed over two consecutive days. • Revised contraceptive advice.
11 February 2016	• Updated to the inclusion criteria about onset of early rheumatoid arthritis (RA). • Updated to exclusion criteria around lung function and management of associated adverse events. • Updated to the pulmonary alvelolar proteinosis (PAP) language. • Clarified and updated: Schedule of Study Procedures. • Results of the new 26-week monkey study and calculation of the new safety margin added. • Takeda made the strategic decision to stop the TELLUS study on 18 December 2015 but allow all the patients already enrolled to complete all the assessments as per protocol. The sample size and the number of sites are consequently reduced to match the recruitment status at the time of the decision.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported