Clinical trial results:
A randomised, double blind, placebo-controlled, multiple dose, phase 2b, 24 week trial followed by an open label extension of NNC0109-0012, an anti-IL-20 biologic, in patients with active rheumatoid arthritis who are inadequate responders to Methotrexate

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-000610-11
Trial protocol	BE HU CZ DE ES IT
Global end of trial date	10 November 2014

Results information

Result version number	v1 (current)
This version publication date	20 May 2016
First version publication date	20 May 2016

Trial information

Trial identification

Sponsor protocol code	NN8226-3613

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01636843
WHO universal trial number (UTN)	U1111-1127-9324

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR,1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 November 2014
Global end of trial reached?	Yes
Global end of trial date	10 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the clinical efficacy of NNC0109-0012 compared to placebo when administered as weekly repeat subcutaneous (s.c., under the skin) injections in patients with active rheumatoid arthritis (RA) with inadequate responses to methotrexate (MTX) while on a stable background of MTX therapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, October 2000, Amended 2002, 2004 and 2008, International Conference on Harmonisation (ICH) Good Clinical Practice, May 1996. Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120, and 21 CFR, parts 312, 50, and 56 were followed for United States (US) trial sites.

Background therapy:

All subjects were on a stable background treatment with methotrexate (MTX); MTX treatment for at least 16 weeks at a dose of ≥15.0 mg/week to ≤25 mg/week and at a stable dose for at least 8 weeks prior to the screening visit. Subjects could be on MTX as low as 10 mg/week only if due to documented MTX intolerance, stable dose for at least 8 weeks prior to the screening visit.
Additional background treatments could have included hydroxychloroquine/chloroquine, non-steroidal anti-inflammatory drugs (NSAIDs) or steroidal medication.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	30 October 2012
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	Poland: 12
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Argentina: 51
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Russian Federation: 35

Country: Number of subjects enrolled	Ukraine: 73
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	298
EEA total number of subjects	52

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)	252
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 80 sites in 14 countries; Argentina: 6 sites; Belgium: 1 site; Brazil: 8 sites; Czech Republic: 6 sites; France: 1 site; Germany: 1 site; Hungary: 1 site; Italy: 1 site; Mexico: 8 sites; Poland: 6 sites; Russian Federation: 9 sites; Spain: 5 sites; Ukraine: 15 sites; United States: 12 sites.

Pre-assignment

Screening details:

Of 739 subjects screened, 441 were screen failures, with 298 randomized to either placebo or one of the 3 doses of NNC0109-0012 (i.e., 60 mg/120 mg/240 mg).

Period 1

Period 1 title	Main Trial Period (week 0-24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The trial period consisted of a 24-week double-blinded and a 28-week open label extension in which investigators and subjects were still blinded. Blinding was kept for all staff involved in trial-related activities at the site and at the sponsor. After all subjects had completed the week 24 assessment, a planned week 24 partial Database Lock (DBL) was performed, and the treatment codes for all subjects released to selected individuals at the sponsor for statistical analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Main-Placebo

Arm description:

Subjects received NNC0109-0012 placebo once weekly for a duration of 24-week (double-blinded main treatment period).

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

Dosage and administration details:

NNC0109-0012 placebo was administered once weekly with NovoPen®4 by subcutaneous (s.c., under the skin) injection.

Arm title	Main-60 mg

Arm description:

Subjects received 60 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 60 mg was administered once weekly with NovoPen®4 by s.c. injection.

Arm title	Main-120 mg

Arm description:

Subjects received 120 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 120 mg was administered once weekly with NovoPen®4 by s.c. injection.

Arm title	Main-240 mg

Arm description:

Subjects received 240 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 240 mg was administered once weekly with NovoPen®4 by s.c. injection.

Number of subjects in period 1	Main-Placebo	Main-60 mg	Main-120 mg
Started	75	74	74
Completed	55	53	48
Not completed	20	21	26
Adverse event, non-fatal	3	3	1
Withdrawal criteria	13	18	25
Unclassified	1	-	-
Lost to follow-up	2	-	-
Protocol deviation	1	-	-
Lack of efficacy	-	-	-

Number of subjects in period 1	Main-240 mg
Started	75
Completed	52
Not completed	23
Adverse event, non-fatal	-
Withdrawal criteria	21
Unclassified	-
Lost to follow-up	-
Protocol deviation	-

Lack of efficacy	2

Period 2

Period 2 title	Extension Trial Period (Week 25-52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The trial period consisted of a 24-week double-blinded and a 28-week open label extension in which investigators and subjects were still blinded. After week 24 partial DBL analysis, the decision was made to discontinue the trial because of failure to reach the primary efficacy endpoint.

Arms

Are arms mutually exclusive?	Yes
Arm title	Extension-Placebo-240 mg

Arm description:

Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to placebo in the main treatment period (week 0-24), were to be switched to NNC0109-0012, 240 mg, in the 28-week open-label extension treatment period.

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 240 mg was administered once weekly with NovoPen®4 by s.c. injection.

Arm title	Extension-60-60 mg

Arm description:

Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 60 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 60 mg was administered once weekly with NovoPen®4 by s.c. injection.

Arm title	Extension-120-120 mg

Arm description:

Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 120 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 120 mg was administered once weekly with NovoPen®4 by s.c. injection.

Arm title	Extension-240-240 mg

Arm description:

Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 240 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.

Arm type	Experimental
Investigational medicinal product name	NNC0109-0012
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

NNC0109-0012, 240 mg was administered once weekly with NovoPen®4 by s.c. injection.

Number of subjects in period 2[1]	Extension-Placebo-240 mg	Extension-60-60 mg	Extension-120-120 mg
Started	53	50	45
Completed	20	24	20
Not completed	33	26	25
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	2	1	4
Withdrawal criteria	30	24	21
Protocol deviation	-	1	-

Number of subjects in period 2[1]	Extension-240-240 mg
Started	51
Completed	19
Not completed	32
Adverse event, serious fatal	-
Adverse event, non-fatal	1
Withdrawal criteria	31
Protocol deviation	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Number of subjects completed the main trial period = 208.
Number of subjects started the extension trial period = 199.
Number of subjects completed main trial period, but did not enter extension trial period = 9 (2 in placebo [1 due to protocol deviation and 1 met withdrawal criteria]; 3 [all met withdrawal criteria] in main-60 mg; 3 [1 due to AE-non fatal and 2 met withdrawal criteria] in main-120 mg; and 1 [due to AE-non fatal] in main-240 mg.

Baseline characteristics

Reporting groups	
Reporting group title	Main-Placebo
Reporting group description:	
Subjects received NNC0109-0012 placebo once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-60 mg
Reporting group description:	
Subjects received 60 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-120 mg
Reporting group description:	
Subjects received 120 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-240 mg
Reporting group description:	
Subjects received 240 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	

Reporting group values	Main-Placebo	Main-60 mg	Main-120 mg
Number of subjects	75	74	74
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	50.3	51.7	52.4
standard deviation	± 12.5	± 11.7	± 12
Gender categorical			
Units: Subjects			
Female	63	59	55
Male	12	15	19
Duration of Rheumatoid Arthritis			
Units: Years			
arithmetic mean	5.8	8.3	8.3
standard deviation	± 5.6	± 10.1	± 7.9
C-reactive protein (CRP)			
Units: mg/L			
geometric mean	14.3	20.1	15.3
full range (min-max)	0.5 to 96	0.7 to 214.9	0.7 to 123.1
Disease activity score in 28 joints (DAS28)			
Units: CRP			
arithmetic mean	6.3	6.3	6.3
standard deviation	± 0.8	± 0.7	± 0.9
Tender joint count (TJC)28			
Units: Number			
arithmetic mean	18.5	17.2	18.2
standard deviation	± 6.4	± 6.3	± 6.4

Swollen joint count (SJC)28			
Units: Number			
arithmetic mean	15.3	13.5	13.8
standard deviation	± 5.4	± 5.3	± 5.6
Tender joint count (TJC)68			
Units: Number			
arithmetic mean	33.2	28.1	30.7
standard deviation	± 14	± 14	± 15.3
Swollen joint count (SJC)66			
Units: Number			
arithmetic mean	21.8	17.7	18.5
standard deviation	± 9.8	± 8.1	± 9.1
Pain (visual analogue scale [VAS])			
Units: Centimeter			
arithmetic mean	6.5	6.8	6.8
standard deviation	± 2.3	± 1.7	± 1.9
Patient's Global Assessment of disease activity (PtGA) (VAS)			
Units: Centimeter			
arithmetic mean	6.7	6.8	6.7
standard deviation	± 2.2	± 1.7	± 2
Physician's Global Assessment of disease activity (PhGA) (VAS)			
Units: Centimeter			
arithmetic mean	7	6.9	6.9
standard deviation	± 1.5	± 1.7	± 1.4
Health Assessment Questionnaire-Disability Index (HAQ-DI)			
Units: Points			
arithmetic mean	1.8	1.8	1.7
standard deviation	± 0.5	± 0.6	± 0.6

Reporting group values	Main-240 mg	Total	
Number of subjects	75	298	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	50.4		
standard deviation	± 11	-	
Gender categorical			
Units: Subjects			
Female	60	237	
Male	15	61	
Duration of Rheumatoid Arthritis			
Units: Years			
arithmetic mean	6.5		
standard deviation	± 5.3	-	
C-reactive protein (CRP)			
Units: mg/L			
geometric mean	16.7		

full range (min-max)	0.8 to 137.8	-	
Disease activity score in 28 joints (DAS28) Units: CRP			
arithmetic mean	6.3		
standard deviation	± 0.7	-	
Tender joint count (TJC)28 Units: Number			
arithmetic mean	17.7		
standard deviation	± 6.2	-	
Swollen joint count (SJC)28 Units: Number			
arithmetic mean	13.9		
standard deviation	± 4.7	-	
Tender joint count (TJC)68 Units: Number			
arithmetic mean	30.4		
standard deviation	± 13.3	-	
Swollen joint count (SJC)66 Units: Number			
arithmetic mean	18.8		
standard deviation	± 7.6	-	
Pain (visual analogue scale [VAS]) Units: Centimeter			
arithmetic mean	6.7		
standard deviation	± 2.1	-	
Patient’s Global Assessment of disease activity (PtGA) (VAS) Units: Centimeter			
arithmetic mean	7		
standard deviation	± 1.9	-	
Physician’s Global Assessment of disease activity (PhGA) (VAS) Units: Centimeter			
arithmetic mean	6.9		
standard deviation	± 1.4	-	
Health Assessment Questionnaire-Disability Index (HAQ-DI) Units: Points			
arithmetic mean	1.7		
standard deviation	± 0.7	-	

End points

End points reporting groups

Reporting group title	Main-Placebo
Reporting group description:	
Subjects received NNC0109-0012 placebo once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-60 mg
Reporting group description:	
Subjects received 60 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-120 mg
Reporting group description:	
Subjects received 120 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Main-240 mg
Reporting group description:	
Subjects received 240 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).	
Reporting group title	Extension-Placebo-240 mg
Reporting group description:	
Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to placebo in the main treatment period (week 0-24), were to be switched to NNC0109-0012, 240 mg, in the 28-week open-label extension treatment period.	
Reporting group title	Extension-60-60 mg
Reporting group description:	
Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 60 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.	
Reporting group title	Extension-120-120 mg
Reporting group description:	
Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 120 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.	
Reporting group title	Extension-240-240 mg
Reporting group description:	
Subjects, who demonstrated at least a 20% improvement over baseline in TJC and SJC at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 240 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.	

Primary: ACR20 (defined as 20% improvement in American College of Rheumatology criteria measures) (i.e., responder or non-responder)

End point title	ACR20 (defined as 20% improvement in American College of Rheumatology criteria measures) (i.e., responder or non-responder)

End point description:

American College of Rheumatology (ACR)20 response was achieved at week 12, if there was an improvement equal to or greater than 20% from baseline in the following assessment:
1) Improvement in the swollen joint count (66 out of 68 joints; excludes hips)
2) Improvement in the tender joint count (68 joints; includes hips)

3) Improvement in at least 3 of the following 5 assessments:
i) Patient's assessment of pain (visual analogue scale [VAS])
ii) Patient's Global Assessment of disease activity (PtGA) (VAS)
iii) Physician's Global Assessment of disease activity (PhGA) (VAS)
iv) Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; patient reported outcomes [PRO])
v) C-reactive protein (CRP)
Analysis population: The full analysis set (FAS) included all randomised subjects. Missing data were imputed using last observation carried forward (LOCF).

End point type	Primary

End point timeframe:

At Week 12

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: Percentage of subjects				
number (not applicable)				
Responder	54.7	59.5	50	53.3
Non-responder	45.3	40.5	50	46.7

Statistical analyses

Statistical analysis title	Main-240 mg versus main-placebo

Statistical analysis description:

This binary endpoint was analysed using a logistic regression model; the model included stratum (positive or negative rheumatoid factor [RF]/anti-cyclic citrullinated protein antibodies [anti-CCP] at screening) and treatment as fixed factors and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline and duration of RA at baseline as continuous covariates. Comparison groups: main-240 mg versus main-placebo.

Comparison groups	Main-Placebo v Main-240 mg
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.9572 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.88

Notes:

[1] - The statistical analyses sought to determine which doses of NNC0109-0012 were effective, and to describe the dose-response relationship for NNC0109-0012. The dose levels of NNC0109-0012 were compared to placebo in a hierarchical manner, starting by comparing the highest dose level of NNC0109-0012 to placebo.
[2] - p-values below 5% were regarded as statistically significant.

	Main-120 mg versus main-placebo

Statistical analysis title	

Statistical analysis description:

This binary endpoint was analysed using a logistic regression model; the model included stratum (positive or negative rheumatoid factor [RF]/anti-cyclic citrullinated protein antibodies [anti-CCP] at screening) and treatment as fixed factors and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline and duration of RA at baseline as continuous covariates. Comparison groups: main-120 mg versus main-placebo.

Comparison groups	Main-Placebo v Main-120 mg
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.8453 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.81

Notes:

[3] - The statistical analyses sought to determine which doses of NNC0109-0012 were effective, and to describe the dose-response relationship for NNC0109-0012. The dose levels of NNC0109-0012 were compared to placebo in a hierarchical manner, starting by comparing the highest dose level of NNC0109-0012 to placebo.
[4] - p-values below 5% were regarded as statistically significant.

Statistical analysis title	Main-60 mg versus main-placebo

Statistical analysis description:

This binary endpoint was analysed using a logistic regression model; the model included stratum (positive or negative rheumatoid factor [RF]/anti-cyclic citrullinated protein antibodies [anti-CCP] at screening) and treatment as fixed factors and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline and duration of RA at baseline as continuous covariates. Comparison groups: main-60 mg versus main-placebo.

Comparison groups	Main-Placebo v Main-60 mg
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.353 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.67

Notes:

[5] - The statistical analyses sought to determine which doses of NNC0109-0012 were effective, and to describe the dose-response relationship for NNC0109-0012. The dose levels of NNC0109-0012 were compared to placebo in a hierarchical manner, starting by comparing the highest dose level of NNC0109-0012 to placebo.
[6] - p-values below 5% were regarded as statistically significant.

Secondary: ACR20

End point title	ACR20

End point description:

ACR20 response was achieved at week 24, if there was an improvement equal to or greater than 20% from baseline in the following assessment:
1) Improvement in the swollen joint count (66 out of 68 joints; excludes hips)
2) Improvement in the tender joint count (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
i) Patient's assessment of pain (VAS)
ii) Patient's Global Assessment of disease activity (PtGA) (VAS)
iii) Physician's Global Assessment of disease activity (PhGA) (VAS)
iv) Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; PRO)
v) C-reactive protein (CRP)
Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF. Due to the premature termination of this study, this endpoint was analysed only at the pre-planned week 24 time point, but could not be analysed at the pre-planned week 52 time point.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: Percentage of subjects				
number (not applicable)				
Responder	60	58.1	47.3	52
Non-responder	40	41.9	52.7	48

Statistical analyses

No statistical analyses for this end point

Secondary: ACR50

End point title	ACR50

End point description:

ACR50 response was achieved at week 24, if there was an improvement equal to or greater than 50% from baseline in the following assessment:
1) Improvement in the swollen joint count (66 out of 68 joints; excludes hips)
2) Improvement in the tender joint count (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
i) Patient's assessment of pain (VAS)
ii) Patient's Global Assessment of disease activity (PtGA) (VAS)
iii) Physician's Global Assessment of disease activity (PhGA) (VAS)
iv) Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; PRO)
v) C-reactive protein (CRP)
Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF. Due to the premature termination of this study, this endpoint was analysed only at the pre-planned week 24 time point, but could not be analysed at the pre-planned week 52 time point.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: Percentage of subjects				
number (not applicable)				
Responder	40	31.1	27	25.3
Non-responder	60	68.9	73	74.7

Statistical analyses

No statistical analyses for this end point

Secondary: ACR70

End point title	ACR70

End point description:

ACR70 response was achieved at week 24, if there was an improvement equal to or greater than 70% from baseline in the following assessment:
1) Improvement in the swollen joint count (66 out of 68 joints; excludes hips)
2) Improvement in the tender joint count (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
i) Patient's assessment of pain (VAS)
ii) Patient's Global Assessment of disease activity (PtGA) (VAS)
iii) Physician's Global Assessment of disease activity (PhGA) (VAS)
iv) Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI; PRO)
v) C-reactive protein (CRP)
Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF. Due to the premature termination of this study, this endpoint was analysed only at the pre-planned week 24 time point, but could not be analysed at the pre-planned week 52 time point.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: Percentage of subjects				
number (not applicable)				
Responder	14.7	10.8	10.8	12
Non-responder	85.3	89.2	89.2	88

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DAS28-CRP (defined as Disease Activity Score for 28 joints with C-reactive protein measure) from baseline

End point title	Change in DAS28-CRP (defined as Disease Activity Score for 28 joints with C-reactive protein measure) from baseline

End point description:

The 28 joints assessed for this measurement are the proximal interphalangeal (PIP) joints of the fingers, the interphalangeal (IP) joints of the thumbs, the 10 metacarpophalangeal (MCP) joints plus the wrists, elbows, shoulders and knees. In order to calculate the DAS28, each of the 28 joints was to be evaluated for tenderness and swelling.
Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At weeks 12 and 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	73	75
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-1.6 (± 1.2)	-1.6 (± 1.2)	-1.5 (± 1.2)	-1.6 (± 1.1)
Week 24	-2 (± 1.5)	-1.9 (± 1.1)	-1.8 (± 1.3)	-2 (± 1.4)

Statistical analyses

No statistical analyses for this end point

Secondary: Simplified Disease Activity Index (SDAI) remission (SDAI of 3.3 or below) (At week 12)

End point title	Simplified Disease Activity Index (SDAI) remission (SDAI of 3.3 or below) (At week 12)

End point description:

Simplified Disease Activity Index (SDAI) remission was achieved when the SDAI was below or equal to 3.3. The SDAI is the simple sum of the TJC (using 28 joints), SJC (using 28 joints), patient global assessment (PtGA) (0-10 cm scale, recorded on a 100 mm visual analogue scale), physician global assessment (PhGA) (0-10 cm scale, recorded on a 100 mm visual analogue scale), and CRP level (mg/dL). Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At week 12

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	71	71	74
Units: Percentage of subjects				
number (not applicable)				
Responder	0	4.1	1.4	1.3
Non-responder	100	95.9	98.6	98.7

Statistical analyses

No statistical analyses for this end point

Secondary: Simplified Disease Activity Index (SDAI) remission (SDAI of 3.3 or below) (At week 24)

End point title	Simplified Disease Activity Index (SDAI) remission (SDAI of 3.3 or below) (At week 24)

End point description:

SDAI remission was achieved when the SDAI was below or equal to 3.3. The SDAI is the simple sum of the TJC (using 28 joints), SJC (using 28 joints), patient global assessment (PtGA) (0-10 cm scale, recorded on a 100 mm visual analogue scale), physician global assessment (PhGA) (0-10 cm scale, recorded on a 100 mm visual analogue scale), and CRP level (mg/dL). Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	71	73	69	72
Units: Percentage of subjects				
number (not applicable)				
Responder	5.3	1.4	4.2	4
Non-responder	94.7	98.6	95.8	96

Statistical analyses

No statistical analyses for this end point

Secondary: European League Against Rheumatism (EULAR) criteria response (At week 12)

End point title	European League Against Rheumatism (EULAR) criteria response (At week 12)

End point description:

The EULAR response criteria (no response, moderate response and good response) were calculated using the present and observed changes in DAS28-CRP. Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At week 12

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	73	75
Units: Percentage of subjects				
number (not applicable)				
No response	32	28.4	31.5	28
Moderate response	61.3	58.1	60.3	60
Good response	6.7	13.5	8.2	12

Statistical analyses

No statistical analyses for this end point

Secondary: European League Against Rheumatism (EULAR) criteria response (At week 24)

End point title	European League Against Rheumatism (EULAR) criteria response (At week 24)

End point description:

The EULAR response criteria (no response, moderate response and good response) were calculated using the present and observed changes in DAS28-CRP. Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	73	75
Units: Percentage of subjects				
number (not applicable)				
No response	30.7	29.7	38.4	36
Moderate response	46.7	52.7	42.5	44
Good response	22.7	17.6	19.2	20

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the overall scores of Health Assessment Questionnaire – Disability Index (HAQ-DI)

End point title	Change from baseline in the overall scores of Health Assessment Questionnaire – Disability Index (HAQ-DI)

End point description:

The HAQ-DI assesses the functional status for performing activities of daily living and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in 8 categories of functioning which represent dressing, rising, eating walking, hygiene, reach, grip, and usual activities. For each of these categories, the subjects reported the amount of difficulty in performing two or three specific activities. The HAQ-DI score ranges from 0-3 (3=worst functioning) and was calculated according to the HAQ manual based on the 8-category scores and the use of aids/devices and/or help from another person when indicated. Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At weeks 12 and 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	73	75
Units: Score				
arithmetic mean (standard deviation)				
At week 12	-0.48 (± 0.63)	-0.47 (± 0.54)	-0.42 (± 0.47)	-0.46 (± 0.67)
At week 24	-0.57 (± 0.66)	-0.5 (± 0.61)	-0.47 (± 0.5)	-0.52 (± 0.74)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the overall scores of Short Form Health Survey (SF-36v2 6D) - Physical Component

End point title	Change from baseline in the overall scores of Short Form Health Survey (SF-36v2 6D) - Physical Component

End point description:

The SF-36v2 Health Survey is a survey which assesses the functional status and well-being of the subject utilising 36 questions covering selected concepts. The concepts cover physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health over the prior 4 weeks. Scores for each concept and overall scores for the physical and the mental components were calculated according to the SF-36 manual. The scores were transformed to a 100-point scale with higher scores indicating a better health state. Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At weeks 12 and 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74	73	73	75
Units: Score				
arithmetic mean (standard deviation)				
At week 12	7.7 (± 8.3)	6.2 (± 6.4)	6 (± 7.4)	5.8 (± 7.2)
At week 24	8.7 (± 7.5)	7 (± 7.7)	7.7 (± 8)	6.9 (± 9.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the overall scores of Short Form Health Survey (SF-36v2 6D) - Mental Component

End point title	Change from baseline in the overall scores of Short Form Health Survey (SF-36v2 6D) - Mental Component

End point description:

The SF-36v2 Health Survey is a survey which assesses the functional status and well-being of the patient utilising 36 questions covering selected concepts. The concepts cover physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health over the prior 4 weeks. Scores for each concept and overall scores for the physical and the mental components were calculated according to the SF-36 manual. The scores were transformed to a 100-point scale with higher scores indicating a better health state. Analysis population: The FAS included all randomised subjects. Missing data was imputed using LOCF.

End point type	Secondary

End point timeframe:

At weeks 12 and 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	74	73	73	75
Units: Score				
arithmetic mean (standard deviation)				
At week 12	3.4 (± 11)	4.5 (± 9.7)	4.7 (± 10.7)	5.7 (± 11.8)
At week 24	5.5 (± 13.1)	6 (± 9.6)	3.7 (± 10.9)	6.5 (± 11.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Safety endpoint: Incidence and type of adverse events (AEs) - Upto week 24

End point title	Safety endpoint: Incidence and type of adverse events (AEs) - Upto week 24

End point description:

All AEs presented in this report are treatment-emergent AEs (TEAEs). A TEAE was defined as an event

that has onset date on or after the first day of dose administration, and no later than the end of the entire trial.
Analysis population: The safety analysis set (SAS) consisted of all subjects randomised and exposed to at least one dose of trial product. For the SAS, AE data are presented for the main treatment period (week 0-24) plus follow-up period (12-week) for subjects who withdrew during the main treatment period.

End point type	Secondary

End point timeframe:

Upto week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	75	74	74	75
Units: Number of events				
All AEs	115	164	122	160
Serious AEs (SAEs)	4	4	3	1
Non-serious AEs (nSAEs)	111	160	119	159

Statistical analyses

No statistical analyses for this end point

Secondary: Safety endpoint: Incidence and type of adverse events (AEs) - Upto week 52

End point title	Safety endpoint: Incidence and type of adverse events (AEs) - Upto week 52

End point description:

Analysis population: The extension trial set (ETS) consisted of subjects who entered the open-label extension treatment period (week 25-52). For the ETS, the data analyses included measurements starting at week 0 through week 52 plus the 12-week follow-up, and could therefore overlap with AE data reported for the SAS (i.e., for the main treatment period [week 0-24]).

End point type	Secondary

End point timeframe:

Upto week 52

End point values	Extension-Placebo-240 mg	Extension-60-60 mg	Extension-120-120 mg	Extension-240-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	50	45	51
Units: Number of events				
All AEs	170	169	97	161
Serious AEs (SAEs)	8	5	6	4
Non-serious AEs (nSAEs)	162	164	91	157

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic assessments - Change from baseline in van der Heijde sharp score.

End point title	Radiographic assessments - Change from baseline in van der Heijde sharp score.

End point description:

Change from baseline at week 24 in the van der Heijde modified Total Sharp Score (mTSS) and 2 subdomains of the van der Heijde Sharp score (i.e., erosion score and joint-space narrowing score [JSN]) was ranked for the subjects. The van der Heijde modified Sharp scoring system assesses changes in structural damage, assigning scores for erosions of 0–5.0 from 16 areas in the hands and wrists, and from the feet, each side of the 10 metatarsophalangeals (MTPs) and two intraphalangeal joints of the big toe. For Joint Space Narrowing (JSN) scores of 0–5 were assigned to 15 areas from the hands and wrists and six areas from the feet. The total van der Heijde radiographic score ranged from 0-448. Analysis population: The FAS included all randomised subjects. Missing data were imputed using LOCF.
Change from baseline in van der Heijde sharp score was planned to be analysed only at the pre-planned week 24; hence, no data for week 12 are available.

End point type	Secondary

End point timeframe:

At week 24

End point values	Main-Placebo	Main-60 mg	Main-120 mg	Main-240 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	60	63	65
Units: Score				
arithmetic mean (standard deviation)				
Total Erosion Score	0.8 (± 1.9)	0.6 (± 1.7)	0.8 (± 2.5)	0.3 (± 1.8)
Joint space narrowing (JSN)	0.3 (± 0.6)	0.3 (± 1.2)	0.1 (± 0.8)	0.1 (± 0.8)
modified Total Sharp Score (mTSS)	1.1 (± 2.2)	0.8 (± 2.6)	0.9 (± 2.9)	0.4 (± 2.2)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For main trial period: treatment period (week 0-24) + follow-up period (12-week) for subjects who withdrew during the main treatment period.
Extension trial period: treatment period (week 25-52) + follow-up period (12-week).

Adverse event reporting additional description:

AEs are reported for the SAS and for the ETS.
For the ETS, the data analyses included measurements starting at week 0 through week 52 plus the 12-week follow-up, and could therefore overlap with AE data reported for the SAS (i.e., for the main treatment period [week 0-24]).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Main-placebo

Reporting group description:

Subjects received NNC0109-0012 placebo once weekly for a duration of 24-week (double-blinded main treatment period).

Reporting group title	Main-120 mg

Reporting group description:

Subjects received 120 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Reporting group title	Main-240 mg

Reporting group description:

Subjects received 240 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Reporting group title	Main-60 mg

Reporting group description:

Subjects received 60 mg of NNC0109-0012, once weekly for a duration of 24-week (double-blinded main treatment period).

Reporting group title	Main-total NNC0109-0012

Reporting group description:

This reporting group is the combination of 3 reporting groups, i.e., main-60 mg + main-120 mg + main-240 mg.

Reporting group title	Extension-Placebo-240 mg

Reporting group description:

Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to placebo in the main treatment period (week 0-24), were to be switched to NNC0109-0012, 240 mg, in the 28-week open-label extension treatment period.

Reporting group title	Extension-60-60 mg

Reporting group description:

Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 60 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extentsion treatment period.

Reporting group title	Extension-120-120 mg

Reporting group description:

Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and

swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 120 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.

Reporting group title	Extension-240-240 mg

Reporting group description:

Subjects, who demonstrated at least a 20% improvement over baseline in tender joint count (TJC) and swollen joint count (SJC) at week 24 (i.e., after main treatment period), were allowed to enter the 28-week open-label extension period. Subjects randomised to active product, "NNC0109-0012, 240 mg" in the main treatment period (week 0-24), were to maintain their same dose regimen in the 28-week open-label extension treatment period.

Serious adverse events	Main-placebo	Main-120 mg	Main-240 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 75 (5.33%)	3 / 74 (4.05%)	1 / 75 (1.33%)
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 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Cervix carcinoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 75 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Mononeuropathy multiplex			

subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 75 (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
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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			
Abdominal hernia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Colitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Dyspepsia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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

Gastritis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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 haemorrhage			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 75 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Bronchospasm			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Pulmonary embolism			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Renal and urinary disorders			
Glomerulonephritis chronic			

subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 75 (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			
Back pain			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 75 (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 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Pneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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
Visceral leishmaniasis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 74 (0.00%)	0 / 75 (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	Main-60 mg	Main-total NNC0109-0012	Extension-Placebo-240 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 74 (5.41%)	8 / 223 (3.59%)	5 / 53 (9.43%)
number of deaths (all causes)	0	0	1

number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 74 (1.35%)	1 / 223 (0.45%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
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			
Ankle fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Mononeuropathy multiplex			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 223 (0.45%)	0 / 53 (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
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 74 (1.35%)	1 / 223 (0.45%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 223 (0.45%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 223 (0.45%)	0 / 53 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Gastritis			
subjects affected / exposed	1 / 74 (1.35%)	1 / 223 (0.45%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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

Bronchospasm			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Pulmonary embolism			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 74 (1.35%)	1 / 223 (0.45%)	0 / 53 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Renal and urinary disorders			
Glomerulonephritis chronic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Infections and infestations			
Bronchopneumonia			

subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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
Pneumonia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 223 (0.45%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Urosepsis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	1 / 53 (1.89%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visceral leishmaniasis			
subjects affected / exposed	0 / 74 (0.00%)	0 / 223 (0.00%)	0 / 53 (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	Extension-60-60 mg	Extension-120-120 mg	Extension-240-240 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 50 (8.00%)	5 / 45 (11.11%)	3 / 51 (5.88%)
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 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Cervix carcinoma			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 51 (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
Nervous system disorders			
Embolic stroke			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mononeuropathy multiplex			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 51 (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
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Colitis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Dyspepsia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 51 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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 / 50 (0.00%)	1 / 45 (2.22%)	0 / 51 (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
Bronchospasm			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 51 (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
Pulmonary embolism			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Hepatobiliary disorders			

Cholecystitis acute			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	0 / 51 (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
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
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			
Glomerulonephritis chronic			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Rheumatoid arthritis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 45 (2.22%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Urosepsis			

subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	0 / 51 (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
Visceral leishmaniasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 45 (2.22%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
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	Main-placebo	Main-120 mg	Main-240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 75 (37.33%)	19 / 74 (25.68%)	32 / 75 (42.67%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 75 (4.00%)	2 / 74 (2.70%)	2 / 75 (2.67%)
occurrences (all)	3	2	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 75 (2.67%)	1 / 74 (1.35%)	1 / 75 (1.33%)
occurrences (all)	2	1	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 75 (4.00%)	2 / 74 (2.70%)	0 / 75 (0.00%)
occurrences (all)	3	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 75 (4.00%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	3	0	1
General disorders and administration site conditions			
Injection site erythema			

subjects affected / exposed	1 / 75 (1.33%)	3 / 74 (4.05%)	4 / 75 (5.33%)
occurrences (all)	1	3	6
Injection site reaction			
subjects affected / exposed	1 / 75 (1.33%)	6 / 74 (8.11%)	12 / 75 (16.00%)
occurrences (all)	1	7	21
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 75 (1.33%)	1 / 74 (1.35%)	0 / 75 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	2 / 75 (2.67%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 75 (0.00%)	2 / 74 (2.70%)	3 / 75 (4.00%)
occurrences (all)	0	2	4
Rheumatoid arthritis			
subjects affected / exposed	4 / 75 (5.33%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	4	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	1 / 75 (1.33%)	2 / 74 (2.70%)	2 / 75 (2.67%)
occurrences (all)	1	2	2
Influenza			
subjects affected / exposed	3 / 75 (4.00%)	0 / 74 (0.00%)	3 / 75 (4.00%)
occurrences (all)	3	0	3
Nasopharyngitis			
subjects affected / exposed	2 / 75 (2.67%)	2 / 74 (2.70%)	3 / 75 (4.00%)
occurrences (all)	3	2	3
Pharyngitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 74 (1.35%)	3 / 75 (4.00%)
occurrences (all)	0	1	4
Respiratory tract infection			

subjects affected / exposed	3 / 75 (4.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences (all)	4	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 75 (4.00%)	1 / 74 (1.35%)	4 / 75 (5.33%)
occurrences (all)	3	1	5
Urinary tract infection			
subjects affected / exposed	2 / 75 (2.67%)	1 / 74 (1.35%)	3 / 75 (4.00%)
occurrences (all)	2	1	3

Non-serious adverse events	Main-60 mg	Main-total NNC0109-0012	Extension-Placebo-240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 74 (45.95%)	85 / 223 (38.12%)	33 / 53 (62.26%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 74 (5.41%)	8 / 223 (3.59%)	2 / 53 (3.77%)
occurrences (all)	4	8	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 74 (2.70%)	4 / 223 (1.79%)	3 / 53 (5.66%)
occurrences (all)	2	4	3
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 74 (1.35%)	3 / 223 (1.35%)	3 / 53 (5.66%)
occurrences (all)	1	3	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 74 (2.70%)	2 / 223 (0.90%)	1 / 53 (1.89%)
occurrences (all)	2	2	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 74 (5.41%)	5 / 223 (2.24%)	4 / 53 (7.55%)
occurrences (all)	4	5	4
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	2 / 74 (2.70%)	9 / 223 (4.04%)	2 / 53 (3.77%)
occurrences (all)	2	11	16
Injection site reaction			

subjects affected / exposed	4 / 74 (5.41%)	22 / 223 (9.87%)	7 / 53 (13.21%)
occurrences (all)	6	34	12
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 74 (2.70%)	3 / 223 (1.35%)	2 / 53 (3.77%)
occurrences (all)	2	3	3
Gastritis			
subjects affected / exposed	3 / 74 (4.05%)	4 / 223 (1.79%)	4 / 53 (7.55%)
occurrences (all)	3	4	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 74 (4.05%)	8 / 223 (3.59%)	0 / 53 (0.00%)
occurrences (all)	3	9	0
Rheumatoid arthritis			
subjects affected / exposed	4 / 74 (5.41%)	5 / 223 (2.24%)	3 / 53 (5.66%)
occurrences (all)	6	7	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 74 (2.70%)	3 / 223 (1.35%)	3 / 53 (5.66%)
occurrences (all)	3	4	3
Gastroenteritis			
subjects affected / exposed	1 / 74 (1.35%)	5 / 223 (2.24%)	2 / 53 (3.77%)
occurrences (all)	1	5	2
Influenza			
subjects affected / exposed	4 / 74 (5.41%)	7 / 223 (3.14%)	5 / 53 (9.43%)
occurrences (all)	4	7	5
Nasopharyngitis			
subjects affected / exposed	1 / 74 (1.35%)	6 / 223 (2.69%)	2 / 53 (3.77%)
occurrences (all)	1	6	3
Pharyngitis			
subjects affected / exposed	1 / 74 (1.35%)	5 / 223 (2.24%)	4 / 53 (7.55%)
occurrences (all)	2	7	4
Respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	1 / 223 (0.45%)	4 / 53 (7.55%)
occurrences (all)	1	1	6
Upper respiratory tract infection			

subjects affected / exposed	4 / 74 (5.41%)	9 / 223 (4.04%)	2 / 53 (3.77%)
occurrences (all)	7	13	3
Urinary tract infection			
subjects affected / exposed	3 / 74 (4.05%)	7 / 223 (3.14%)	1 / 53 (1.89%)
occurrences (all)	3	7	1

Non-serious adverse events	Extension-60-60 mg	Extension-120-120 mg	Extension-240-240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 50 (46.00%)	15 / 45 (33.33%)	29 / 51 (56.86%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 50 (6.00%)	2 / 45 (4.44%)	2 / 51 (3.92%)
occurrences (all)	4	3	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 50 (4.00%)	1 / 45 (2.22%)	0 / 51 (0.00%)
occurrences (all)	2	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 50 (6.00%)	1 / 45 (2.22%)	2 / 51 (3.92%)
occurrences (all)	3	1	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 50 (6.00%)	0 / 45 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 50 (6.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences (all)	3	0	1
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	3 / 51 (5.88%)
occurrences (all)	2	0	12
Injection site reaction			
subjects affected / exposed	3 / 50 (6.00%)	5 / 45 (11.11%)	7 / 51 (13.73%)
occurrences (all)	22	5	13
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 45 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Gastritis			
subjects affected / exposed	2 / 50 (4.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 50 (6.00%)	1 / 45 (2.22%)	3 / 51 (5.88%)
occurrences (all)	3	1	4
Rheumatoid arthritis			
subjects affected / exposed	2 / 50 (4.00%)	1 / 45 (2.22%)	1 / 51 (1.96%)
occurrences (all)	2	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 50 (2.00%)	2 / 45 (4.44%)	3 / 51 (5.88%)
occurrences (all)	1	2	3
Gastroenteritis			
subjects affected / exposed	1 / 50 (2.00%)	3 / 45 (6.67%)	4 / 51 (7.84%)
occurrences (all)	1	3	4
Influenza			
subjects affected / exposed	3 / 50 (6.00%)	1 / 45 (2.22%)	2 / 51 (3.92%)
occurrences (all)	3	3	2
Nasopharyngitis			
subjects affected / exposed	3 / 50 (6.00%)	0 / 45 (0.00%)	3 / 51 (5.88%)
occurrences (all)	3	0	3
Pharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 45 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	4
Respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	0 / 45 (0.00%)	4 / 51 (7.84%)
occurrences (all)	3	0	4
Urinary tract infection			

subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 5	2 / 45 (4.44%) 2	4 / 51 (7.84%) 6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2012	Added deviation of highly effective contraception methods; added joint count assessments at Visit (V)32, V38, V44, V50; Added pregnancy test at V16 and V20 and the correction of other inconsistencies.
10 November 2012	Added 1 and 2 hours post dose Vital Signs to week 24; Added Biochemistry, Haematology, Urinalysis and Vital Signs to week 30; reduced frequency of antinuclear antibodies (ANA) testing to Screening visit, week 24 and end of trial; increased intra-articular (IA) injection dose from 40 mg/week to 80 mg/week and the correction of other inconsistencies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
07 August 2014	On 07-Aug-2014, Novo Nordisk A/S announced the decision to terminate the phase 2a Trial NN8226-3613 for the development of NNC0109-0012 for rheumatoid arthritis (RA). This occurred as a consequence of the planned partial database lock (pDBL) and analysis (01-July-2014) which showed no significant differences in primary endpoint achievement (ACR20 at week 12) comparing NNC0109-0012 treatment with placebo. This analysis included all randomised subjects in Trial NN8226-3613. The decision by Novo Nordisk to discontinue dosing in the trial as of 07-Aug 2014 was based on the finding of no statistically significant differences in changes in disease activity after treatment with NNC0109-0012 compared with placebo.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was terminated prematurely.

Notes: