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 anti-TNF biologics.

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	2012-000609-58
Trial protocol	BE HU GB CZ DE ES IT
Global end of trial date	11 November 2014

Results information

Result version number	v1 (current)
This version publication date	24 June 2016
First version publication date	24 June 2016

Trial information

Trial identification

Sponsor protocol code	NN8226-3612

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01636817
WHO universal trial number (UTN)	U1111-1127-9273

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	11 November 2014
Global end of trial reached?	Yes
Global end of trial date	11 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 s.c. injections in patients with active rheumatoid arthritis (RA) who are inadequate responders to anti-TNFα biologics and are on a stable background of methotrexate (MTX) therapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki, October 2000, Amended 2002, 2004 and 2008, ICH Good Clinical Practice, May 1996. FDA 21 CFR 312.120, and 21 Code of Federal Regulations, parts 312, 50, and 56 were followed for US trial sites.

Background therapy:

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

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 August 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	Argentina: 46
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 36
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Mexico: 39
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	United States: 83
Worldwide total number of subjects	239
EEA total number of subjects	35

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)	205
From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 79 sites in 12 countries : Argentina: 5 sites; Belgium: 1 site; Brazil: 9 sites; Czech Republic: 2 sites; France: 1 site; Germany: 1 site; Hungary: 1 site; Italy: 1 site; Mexico: 8 sites; Poland: 2 sites; Spain: 4 sites; United States: 44 sites.

Pre-assignment

Screening details:

Of 654 subjects screened, 415 were screen failures and 239 were randomised 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 period and a 28-week open-label extension during which investigators and patients remained blinded. Blinding was kept for all staff involved in trial-related activities at the site and at the sponsor. After the failure of the NN8226-3613 (EudraCT no: 2012-000610-11) trial with NNC0109-0012 in RA to achieve its primary efficacy endpoint in a partial data base lock (DBL) analysis, this trial was prematurely terminated.

Arms

Are arms mutually exclusive?	Yes
Arm title	Main-Placebo

Arm description:

All subjects in this arm received NNC0109-0012 placebo once weekly for a period of 24-weeks (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, 0 mg/mL was administered into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Arm title	Main-60 mg

Arm description:

All subjects in this arm received 60 mg of NNC0109-0012, once weekly for a period of 24-weeks (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 into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Arm title	Main-120 mg

Arm description:

All subjects in this arm received 120 mg of NNC0109-0012, once weekly for a period of 24-weeks (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, 120mg was administered into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Arm title	Main-240 mg

Arm description:

All subjects in this arm received 240 mg of NNC0109-0012, once weekly for a period of 24-weeks (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 into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Number of subjects in period 1	Main-Placebo	Main-60 mg	Main-120 mg
Started	61	61	58
Exposed	61	61	58
Completed	29	31	31
Not completed	32	30	27
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	3	3	1
Withdrawal criteria	27	26	24
Unclassified	-	-	-
Lost to follow-up	-	-	2
Lack of efficacy	1	1	-
Protocol deviation	-	-	-

Number of subjects in period 1	Main-240 mg
Started	59
Exposed	57
Completed	32
Not completed	27
Adverse event, serious fatal	-

Adverse event, non-fatal	1
Withdrawal criteria	24
Unclassified	1
Lost to follow-up	-
Lack of efficacy	-
Protocol deviation	1

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 consisted of a 24-week double-blinded period and a 28 week open-label extension during which investigators and patients remained blinded.

Arms

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

Arm description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to placebo in the main treatment period were to be switched to receive 240 mg of NNC0109-0012 subcutaneous (s.c.), once-weekly in the 28-week 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 into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Arm title	Extension-60-60 mg

Arm description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 60 mg in the main treatment period were to maintain their same dosage regimen during the 28-week 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 into either the abdomen or thigh once weekly with NovoPen®

4 by subcutaneous (s.c., under the skin) injection.

Arm title	Extension-120-120 mg

Arm description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 120 mg in the main treatment period were to maintain their same dosage regimen during the 28-week 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, 120mg was administered into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Arm title	Extension-240-240 mg

Arm description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 240 mg in the main treatment period were to maintain their same dosage regimen during the 28-week 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 into either the abdomen or thigh once weekly with NovoPen® 4 by subcutaneous (s.c., under the skin) injection.

Number of subjects in period 2[1]	Extension-Placebo-240 mg	Extension-60-60 mg	Extension-120-120 mg
Started	28	27	28
Completed	5	9	11
Not completed	23	18	17
Adverse event, serious fatal	1	-	-
Adverse event, non-fatal	1	1	-
Withdrawal criteria	19	15	17
Unclassified	-	1	-
Lack of efficacy	2	-	-
Protocol deviation	-	1	-

Number of subjects in period 2[1]	Extension-240-240 mg
Started	29
Completed	9
Not completed	20
Adverse event, serious fatal	-
Adverse event, non-fatal	1
Withdrawal criteria	19
Unclassified	-
Lack of efficacy	-
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 by 24 week : 123
Number of subjects started the open-label extension period : 112
A total of 11 subjects completed the main trial, but did not enter the extension trial due to trial withdrawals as follows: 1 in placebo (adverse event); 4 (all met withdrawal criteria) in main-60 mg; 3 subjects each in main -120 mg and main- 240 mg arms for meeting the withdrawal criteria respectively.

Baseline characteristics

Reporting groups	
Reporting group title	Main-Placebo
Reporting group description:	
All subjects in this arm received NNC0109-0012 placebo once weekly for a period of 24-weeks (double-blinded main treatment period).	
Reporting group title	Main-60 mg
Reporting group description:	
All subjects in this arm received 60 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).	
Reporting group title	Main-120 mg
Reporting group description:	
All subjects in this arm received 120 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).	
Reporting group title	Main-240 mg
Reporting group description:	
All subjects in this arm received 240 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).	

Reporting group values	Main-Placebo	Main-60 mg	Main-120 mg
Number of subjects	61	61	58
Age categorical Units: Subjects			
Age continuous			
Baseline characteristics for age values were collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: years arithmetic mean standard deviation	 51.1 ± 12	 51.9 ± 11.6	 53.2 ± 11.9
Gender categorical Units: Subjects			
Female	53	54	49
Male	8	7	9
Duration of Rheumatoid Arthritis (RA)			
Baseline characteristics for duration of RA data was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Years arithmetic mean standard deviation	 10 ± 6.8	 11.8 ± 8.1	 12.6 ± 8.8
C-reactive protein (CRP)			
Baseline data for CRP was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: mg/ L geometric mean full range (min-max)	 21.4 2.9 to 299.5	 18.9 1 to 184.6	 18.2 0.3 to 123.5

Disease activity score in 28 joints (DAS28)			
Baseline data for DAS28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	6.3	6.3	6.5
standard deviation	± 0.8	± 0.8	± 0.8
Tender joint count (TJC) 28			
Baseline data for TJC28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	16.8	16.7	18.7
standard deviation	± 6.4	± 5.8	± 5.4
Swollen joint count (SJC) 28			
Baseline data for SJC28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to total of 57 number of subjects in 240 mg group.			
Units: Number			
arithmetic mean	13.5	13.3	13.8
standard deviation	± 4.6	± 5.5	± 4.8
Tender joint count (TJC) 68			
Baseline data for TJC68 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total of 57 number of subjects in 240 mg group.			
Units: Number			
arithmetic mean	30.5	29.4	31.1
standard deviation	± 15.7	± 15.5	± 13.3
Swollen joint count (SJC) 66			
Baseline data for SJC 66 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	18.4	18.7	18.4
standard deviation	± 8.4	± 10.7	± 9.2
Pain (visual analogue scale [VAS])			
Baseline data for pain on VAS was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	7	6.7	7.3
standard deviation	± 1.9	± 1.9	± 2
Patient’s Global Assessment of disease activity (PtGA) (VAS)			
Baseline data for PtGA was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	7	6.9	7.5
standard deviation	± 2.2	± 1.7	± 1.8

Physician's Global Assessment of disease activity (PhGA) (VAS)			
Baseline data for PhGA was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	6.7	6.8	7.3
standard deviation	± 1.7	± 1.7	± 1.5
Health Assessment Questionnaire-Disability Index (HAQ-DI)			
Baseline data for HAQ-DI was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Points			
arithmetic mean	1.9	1.9	2
standard deviation	± 0.6	± 0.6	± 0.6

Reporting group values	Main-240 mg	Total	
Number of subjects	59	239	
Age categorical			
Units: Subjects			

Age continuous			
Baseline characteristics for age values were collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: years			
arithmetic mean	52.4		
standard deviation	± 11.1	-	
Gender categorical			
Units: Subjects			
Female	54	210	
Male	5	29	
Duration of Rheumatoid Arthritis (RA)			
Baseline characteristics for duration of RA data was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Years			
arithmetic mean	10		
standard deviation	± 6.8	-	
C-reactive protein (CRP)			
Baseline data for CRP was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: mg/ L			
geometric mean	17		
full range (min-max)	1.1 to 87.4	-	
Disease activity score in 28 joints (DAS28)			
Baseline data for DAS28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial			

product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	6.5		
standard deviation	± 0.7	-	
Tender joint count (TJC) 28			
Baseline data for TJC28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	19.7		
standard deviation	± 6.2	-	
Swollen joint count (SJC) 28			
Baseline data for SJC28 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to total of 57 number of subjects in 240 mg group.			
Units: Number			
arithmetic mean	15.7		
standard deviation	± 5.2	-	
Tender joint count (TJC) 68			
Baseline data for TJC68 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total of 57 number of subjects in 240 mg group.			
Units: Number			
arithmetic mean	34.7		
standard deviation	± 15.8	-	
Swollen joint count (SJC) 66			
Baseline data for SJC 66 was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Number			
arithmetic mean	20.7		
standard deviation	± 9.1	-	
Pain (visual analogue scale [VAS])			
Baseline data for pain on VAS was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	6.5		
standard deviation	± 1.9	-	
Patient’s Global Assessment of disease activity (PtGA) (VAS)			
Baseline data for PtGA was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	6.9		
standard deviation	± 1.7	-	
Physician’s Global Assessment of disease activity (PhGA) (VAS)			
Baseline data for PhGA was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial			

product leading to a total number of 57 subjects in 240 mg group.			
Units: Centimeter			
arithmetic mean	7.1		
standard deviation	± 1.7	-	
Health Assessment Questionnaire-Disability Index (HAQ-DI)			
Baseline data for HAQ-DI was collected and reported for exposed subjects as full analysis set (FAS). Two subjects randomised to the 240 mg group (N=59) were withdrawn before receiving trial product because of inclusion/exclusion criteria violations, however they were not exposed to the active trial product leading to a total number of 57 subjects in 240 mg group.			
Units: Points			
arithmetic mean	2		
standard deviation	± 0.5	-	

End points

End points reporting groups

Reporting group title	Main-Placebo

Reporting group description:

All subjects in this arm received NNC0109-0012 placebo once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-60 mg

Reporting group description:

All subjects in this arm received 60 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-120 mg

Reporting group description:

All subjects in this arm received 120 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-240 mg

Reporting group description:

All subjects in this arm received 240 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Extension-Placebo-240 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to placebo in the main treatment period were to be switched to receive 240 mg of NNC0109-0012 subcutaneous (s.c.), once-weekly in the 28-week extension treatment period.

Reporting group title	Extension-60-60 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 60 mg in the main treatment period were to maintain their same dosage regimen during the 28-week extension treatment period.

Reporting group title	Extension-120-120 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 120 mg in the main treatment period were to maintain their same dosage regimen during the 28-week extension treatment period.

Reporting group title	Extension-240-240 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 240 mg in the main treatment period were to maintain their same dosage regimen during the 28-week 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 assessed at week 12, if there was an improvement equal to or greater than 20% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)

3) Improvement in at least 3 of the following 5 assessments
– Patient's assessment of pain by visual analogue scale (VAS)
– Patient's Global Assessment of disease activity (PtGA) (VAS)
– Physician's Global Assessment of disease activity (PhGA) (VAS)
– Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The full analysis set (FAS) included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	44.3	47.5	50	50.9
Non-responder	55.7	52.5	50	49.1

Statistical analyses

Statistical analysis title	Main-240 mg versus main-placebo

Statistical analysis description:

The binary endpoint was analysed using a logistic regression model. This model included prior use of anti-TNF biologic therapy and seropositivity strata at screening and treatment as fixed factors, and duration of RA and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline as covariates.

Comparison groups	Main-Placebo v Main-240 mg
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.4473 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	2.76

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 0.05 indicate statistical significance for a two-sided test following the testing sequence.

Statistical analysis title	Main-120 mg versus main-placebo

Statistical analysis description:

The binary endpoint was analysed using a logistic regression model. This model included prior use of anti-TNF biologic therapy and seropositivity strata at screening and treatment as fixed factors, and duration of RA and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline as covariates.

Comparison groups	Main-Placebo v Main-120 mg
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4901 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	2.7

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 0.05 indicate statistical significance for a two-sided test following the testing sequence.

Statistical analysis title	Main-60 mg versus main-placebo

Statistical analysis description:

The binary endpoint was analysed using a logistic regression model. This model included prior use of anti-TNF biologic therapy and seropositivity strata at screening and treatment as fixed factors, and duration of RA and disease activity score in 28 joints based on C-reactive protein (DAS28-CRP) at baseline as covariates.

Comparison groups	Main-Placebo v Main-60 mg
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.7018 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.36

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 0.05 indicate statistical significance for a two-sided test following the testing sequence.

Secondary: ACR20

End point title	ACR20

End point description:

ACR 20 response achieved at week 24, if there was an improvement equal to or greater than 20% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
– Patient's assessment of pain by visual analogue scale (VAS)
– Patient's Global Assessment of disease activity (PtGA) (VAS)
– Physician's Global Assessment of disease activity (PhGA) (VAS)
– Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes (PRO))
– C-reactive protein (CRP)
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	31.1	36.1	36.2	38.6
Non-responder	68.9	63.9	63.8	61.4

Statistical analyses

No statistical analyses for this end point

Secondary: ACR50

End point title	ACR50

End point description:

ACR 50 response achieved at week 12, if there was an improvement equal to or greater than 50% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
– Patient's assessment of pain by visual analogue scale (VAS)
– Patient's Global Assessment of disease activity (PtGA) (VAS)
– Physician's Global Assessment of disease activity (PhGA) (VAS)
– Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	19.7	26.2	19	33.3
Non-responder	80.3	73.8	81	66.7

Statistical analyses

No statistical analyses for this end point

Secondary: ACR20

End point title	ACR20

End point description:

ACR 20 response achieved at week 52, if there was an improvement equal to or greater than 20% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
- Patient's assessment of pain by visual analogue scale (VAS)
- Patient's Global Assessment of disease activity (PtGA) (VAS)
- Physician's Global Assessment of disease activity (PhGA) (VAS)
- Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
- C-reactive protein (CRP)

Analysis population: The extension trial set (ETS) included all patients who entered the open-label extension from week 25 to 52. The ETS was not defined in the protocol, but was defined before the DBL on 21-Jan-2015. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At 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	28	27	28	29
Units: Percentage of subjects				
number (not applicable)				
Responder	17.9	18.5	25	24.1
Non-responder	82.1	81.5	75	75.9

Statistical analyses

No statistical analyses for this end point

Secondary: ACR50

End point title	ACR50

End point description:

ACR 50 response achieved at week 24, if there was an improvement equal to or greater than 50% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
– Patient's assessment of pain by visual analogue scale (VAS)
– Patient's Global Assessment of disease activity (PtGA) (VAS)
– Physician's Global Assessment of disease activity (PhGA) (VAS)
– Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	14.8	19.7	19	19.3
Non-responder	85.2	80.3	81	80.7

Statistical analyses

No statistical analyses for this end point

Secondary: ACR50

End point title	ACR50

End point description:

ACR 50 response achieved at week 52, if there was an improvement equal to or greater than 50% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
– Patient's assessment of pain by visual analogue scale (VAS)
– Patient's Global Assessment of disease activity (PtGA) (VAS)
– Physician's Global Assessment of disease activity (PhGA) (VAS)
– Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The extension trial set (ETS) included all patients who entered the open-label extension from week 25 to 52. The ETS was not defined in the protocol, but was defined before the DBL

on 21-Jan-2015. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At 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	28	27	28	29
Units: Percentage of subjects				
number (not applicable)				
Responder	7.1	0	17.9	13.8
Non-responder	92.9	100	82.1	86.2

Statistical analyses

No statistical analyses for this end point

Secondary: ACR70

End point title	ACR70

End point description:

ACR 70 response achieved at week 12, if there was an improvement equal to or greater than 70% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
– Patient’s assessment of pain by visual analogue scale (VAS)
– Patient’s Global Assessment of disease activity (PtGA) (VAS)
– Physician’s Global Assessment of disease activity (PhGA) (VAS)
– Patient’s assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	3.3	1.6	8.6	5.3
Non-responder	96.7	98.4	91.4	94.7

Statistical analyses

No statistical analyses for this end point

Secondary: ACR70

End point title	ACR70

End point description:

ACR 70 response achieved at week 24, if there was an improvement equal to or greater than 70% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments
- Patient's assessment of pain by visual analogue scale (VAS)
- Patient's Global Assessment of disease activity (PtGA) (VAS)
- Physician's Global Assessment of disease activity (PhGA) (VAS)
- Patient's assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
- C-reactive protein (CRP)

Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	61	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	6.6	9.8	8.6	5.3
Non-responder	93.4	90.2	91.4	94.7

Statistical analyses

No statistical analyses for this end point

Secondary: ACR70

End point title	ACR70

End point description:

ACR 70 response achieved at week 52, if there was an improvement equal to or greater than 70% from baseline for the below parameters.
1) Improvement in the SJC (66 out of 68 joints; excludes hips)
2) Improvement in the TJC (68 joints; includes hips)
3) Improvement in at least 3 of the following 5 assessments

– Patient’s assessment of pain by visual analogue scale (VAS)
– Patient’s Global Assessment of disease activity (PtGA) (VAS)
– Physician’s Global Assessment of disease activity (PhGA) (VAS)
– Patient’s assessment of physical function as measured by the Health Assessment Questionnaire-Disability Index (HAQ-DI, patient reported outcomes(PRO))
– C-reactive protein (CRP)
Analysis population: The extension trial set (ETS) included all patients who entered the open-label extension from week 25 to 52. The ETS was not defined in the protocol, but was defined before the DBL on 21-Jan-2015. Missing data were imputed using LOCF.

End point type	Secondary

End point timeframe:

At 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	28	27	28	29
Units: Percentage of subjects				
number (not applicable)				
Responder	0	0	7.1	3.4
Non-responder	100	100	92.9	96.6

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 were 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 subjects randomised and exposed to at least one dose of trial product. 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	61	60	57	57
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-1.3 (± 1.3)	-1.6 (± 1.3)	-1.8 (± 1.3)	-1.7 (± 1.3)
Week 24	-1.4 (± 1.4)	-1.7 (± 1.3)	-1.9 (± 1.1)	-1.7 (± 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:

The Simplified Disease Activity Index (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). The SDAI was assessed based on the responders (SDAI <= 3.3) and non-responders to the trial product.
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	60	57	57
Units: Percentage of subjects				
number (not applicable)				
Responder	0	0	1.7	0
Non-responder	100	100	98.3	100

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:

The Simplified Disease Activity Index (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). The SDAI was analysed at week 24 and assessed based on the responders (SDAI <= 3.3) and non-responders to the trial product.
Analysis population: The FAS included all randomised subjects and exposed to at least one dose of trial product. 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	60	57	58	57
Units: Percentage of subjects				
number (not applicable)				
Responder	1.6	5	0	0
Non-responder	98.4	95	100	100

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 was categorised as no response, moderate and good response. The responses were calculated using the present and observed changes in DAS28-CRP.
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	60	57	57
Units: Percentage of subjects				
number (not applicable)				
No response	47.5	46.7	36.8	43.9
Moderate response	44.3	43.3	49.1	43.9
Good response	8.2	10	14	12.3

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 was categorised as no response, moderate and good response. The responses were calculated using the present and observed changes in DAS28-CRP.
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	61	60	57	57
Units: Percentage of subjects				
number (not applicable)				
No response	59	61.7	50.9	52.6
Moderate response	32.8	25	40.4	36.8
Good response	8.2	13.3	8.8	10.5

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

The HAQ-DI assessed the functional status for performing activities of daily living and included questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involved both upper and lower extremities. There were 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 patient reported the amount of difficulty in performing two or three specific activities. The HAQ-DI score ranges from of 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 subjects randomised and exposed to at least one dose of trial product. 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	61	60	57	57
Units: Score				
arithmetic mean (standard deviation)				
Week 12	-0.26 (± 0.62)	-0.45 (± 0.56)	-0.43 (± 0.53)	-0.42 (± 0.47)
Week 24	-0.41 (± 0.61)	-0.43 (± 0.62)	-0.41 (± 0.57)	-0.46 (± 0.52)

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 covered 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 are transformed to a 100-point scale with higher scores indicating a better health state.
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	60	59	56	57
Units: Score				
arithmetic mean (standard deviation)				
Week 12	5.5 (± 8.9)	3.8 (± 10.9)	5.9 (± 13.2)	4.2 (± 7.4)
Week 24	5.1 (± 8.2)	1.3 (± 12.5)	6.2 (± 11.8)	4.3 (± 9)

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 patient utilising 36 questions covering selected concepts. The concepts covered 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 are transformed to a 100-point scale with higher scores indicating a better health state.
Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. 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	60	59	56	57
Units: Score				
arithmetic mean (standard deviation)				
Week 12	4.1 (± 8.6)	5.4 (± 7.7)	4.3 (± 7.9)	5.3 (± 6.8)
Week 24	4.8 (± 7.7)	7.1 (± 9.4)	4.4 (± 9.1)	5.7 (± 7.4)

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE was defined as any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. A treatment emergent adverse events (TEAEs) 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. All AEs presented in this report are TEAEs.
Analysis population: The safety analysis set (SAS) included all patients randomised and exposed to at

least one dose of trial product. The AE data was presented for main treatment period (week 0-24) plus the follow-up period (12 weeks) for subjects who withdrew during the main treatment period.

End point type	Secondary

End point timeframe:

Up to 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	61	58	57
Units: Number of events				
All Adverse events	129	116	131	126
Serious adverse events	5	6	2	2
Non-serious adverse events	124	110	129	124

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety endpoint: Incidence and type of adverse events (AEs) - Up to 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:

Up to 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	28	27	28	29
Units: Number of events				
All adverse events	133	112	159	155
Serious adverse events	4	6	4	3
Non-serious adverse events	129	106	155	152

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:

Radiographic assessment was performed by obtaining posterior anterior projections of hands, wrists and feet and were scored using the van der Heijde (VDH) modified Sharp criteria. Change from baseline in VDH for total erosion score, Joint Space Narrowing (JSN) and modified Total Sharp Score (mTSS) were assessed at week 24. The VDH modified Sharp scoring system assesses the 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 JSN, scores of 0–5 were assigned to 15 areas from the hands and wrists and 6 areas from the feet. Analysis population: The FAS included all subjects randomised and exposed to at least one dose of trial product. Missing data were imputed using LOCF. Change from baseline in VDH 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 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	45	37	36	42
Units: Score				
arithmetic mean (standard deviation)				
Total Erosion Score	1.1 (± 2.4)	0.8 (± 1.5)	1 (± 4.1)	0.5 (± 1.3)
Joint space narrowing (JSN)	0.5 (± 1.1)	0.3 (± 1.1)	0.5 (± 2)	0.5 (± 2.1)
modified Total Sharp Score (mTSS)	1.6 (± 3.2)	1.1 (± 2.3)	1.5 (± 5.9)	1 (± 3)

Statistical analyses

No statistical analyses for this end point

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 were collected and reported for both safety analysis set (SAS) and extension trial set (ETS).
The ETS data analyses included measurements starting at week 0 through week 52 plus the 12-week follow-up, and could therefore overlap with the SAS data analyses reported for main treatment period from 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:

All subjects in this arm recieved NNC0109-0012 placebo once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-60 mg

Reporting group description:

All subjects in this arm recieved 60 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-120 mg

Reporting group description:

All subjects in this arm recieved 120 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-240 mg

Reporting group description:

All subjects in this arm recieved 240 mg of NNC0109-0012, once weekly for a period of 24-weeks (double-blinded main treatment period).

Reporting group title	Main-total NNC0109-0012

Reporting group description:

This reporting group comprises of all 3 reporting groups: Main-60 mg, Main-120 mg and Main-240 mg for a trial period of 0 to 24-weeks.

Reporting group title	Ext-placebo-240 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to placebo in the main treatment period were to be switched to receive 240 mg of NNC0109-0012 subcutaneous (s.c.), once-weekly in the 28-week extension treatment period.

Reporting group title	Ext-60-60 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 60 mg in the main treatment period were to maintain their same dosage regimen during the 28-week extension treatment period.

Reporting group title	Ext-120-120 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 120 mg in the main treatment period were to maintain their same dosage regimen during the 28-week extension treatment period.

Reporting group title	Ext-240-240 mg

Reporting group description:

The subjects in this arm who demonstrated 20% or more improvement in tender and swollen joint counts in the main treatment period (at week 24) were eligible to enter the 28 week open-label extension treatment period. Subjects randomised to NNC0109-0012, 240 mg in the main treatment period were to maintain their same dosage regimen during the 28-week extension treatment period.

Serious adverse events	Main-placebo	Main-60 mg	Main-120 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 61 (6.56%)	5 / 61 (8.20%)	2 / 58 (3.45%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Investigations			
Weight decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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			
Patella fracture			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Toxicity to various agents			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Vascular disorders			
Peripheral embolism			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Inguinal hernia			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Pancreatitis acute			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (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
Lung infiltration			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Foot deformity			

subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Muscle spasms			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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			
Disseminated tuberculosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (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
Extradural abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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
Osteomyelitis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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 tract infection			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (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-240 mg	Main-total NNC0109-	Ext-placebo-240 mg

		0012	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 57 (1.75%)	8 / 176 (4.55%)	4 / 28 (14.29%)
number of deaths (all causes)	0	1	2
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight decreased			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Patella fracture			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Vascular disorders			
Peripheral embolism			

subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Small intestinal obstruction			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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

Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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
Foot deformity			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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
Rotator cuff syndrome			

subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Disseminated tuberculosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (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
Extradural abscess			
subjects affected / exposed	1 / 57 (1.75%)	1 / 176 (0.57%)	0 / 28 (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
Osteomyelitis			
subjects affected / exposed	1 / 57 (1.75%)	1 / 176 (0.57%)	0 / 28 (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
Pneumonia			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ext-60-60 mg	Ext-120-120 mg	Ext-240-240 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 27 (18.52%)	3 / 28 (10.71%)	3 / 29 (10.34%)
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)			
Bladder transitional cell carcinoma			

subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Cholangiocarcinoma			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Papillary thyroid cancer			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Investigations			
Weight decreased			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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			
Patella fracture			
subjects affected / exposed	0 / 27 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Toxicity to various agents			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Vascular disorders			
Peripheral embolism			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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			
Anaemia			

subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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 / 27 (0.00%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
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 / 27 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Inguinal hernia			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Pancreatitis acute			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Small intestinal obstruction			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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			
Acute respiratory failure			

subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Lung infiltration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Foot deformity			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Muscle spasms			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	0 / 29 (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
Rotator cuff syndrome			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Disseminated tuberculosis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Extradural abscess			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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
Osteomyelitis			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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 / 27 (0.00%)	1 / 28 (3.57%)	0 / 29 (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
Respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	0 / 29 (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

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

Non-serious adverse events	Main-placebo	Main-60 mg	Main-120 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 61 (44.26%)	24 / 61 (39.34%)	24 / 58 (41.38%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	1 / 58 (1.72%)
occurrences (all)	2	1	1
Body temperature increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			

Hypertension			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	2 / 58 (3.45%)
occurrences (all)	2	2	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 61 (6.56%)	2 / 61 (3.28%)	2 / 58 (3.45%)
occurrences (all)	4	2	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	3 / 58 (5.17%)
occurrences (all)	0	2	3
Injection site erythema			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	3 / 58 (5.17%)
occurrences (all)	1	1	6
Injection site reaction			
subjects affected / exposed	2 / 61 (3.28%)	9 / 61 (14.75%)	4 / 58 (6.90%)
occurrences (all)	8	16	6
Pyrexia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	2 / 58 (3.45%)
occurrences (all)	0	2	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	3 / 61 (4.92%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences (all)	3	0	1
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	2 / 58 (3.45%)
occurrences (all)	0	2	3
Nausea			
subjects affected / exposed	2 / 61 (3.28%)	3 / 61 (4.92%)	4 / 58 (6.90%)
occurrences (all)	2	3	5
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 61 (1.64%)	2 / 61 (3.28%)	2 / 58 (3.45%)
occurrences (all)	1	2	2
Oropharyngeal pain			
subjects affected / exposed	0 / 61 (0.00%)	2 / 61 (3.28%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Productive cough			
subjects affected / exposed	0 / 61 (0.00%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Back pain			
subjects affected / exposed	2 / 61 (3.28%)	0 / 61 (0.00%)	2 / 58 (3.45%)
occurrences (all)	2	0	3
Muscle spasms			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Osteoarthritis			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	2 / 58 (3.45%)
occurrences (all)	0	0	2
Pain in extremity			

subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Rheumatoid arthritis			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	2 / 58 (3.45%)
occurrences (all)	2	5	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 61 (8.20%)	2 / 61 (3.28%)	0 / 58 (0.00%)
occurrences (all)	5	2	0
Furuncle			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 61 (0.00%)	1 / 58 (1.72%)
occurrences (all)	2	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 61 (1.64%)	2 / 61 (3.28%)	1 / 58 (1.72%)
occurrences (all)	1	2	1
Influenza			
subjects affected / exposed	3 / 61 (4.92%)	1 / 61 (1.64%)	3 / 58 (5.17%)
occurrences (all)	3	1	3
Nasopharyngitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	2 / 61 (3.28%)	1 / 61 (1.64%)	0 / 58 (0.00%)
occurrences (all)	2	1	0
Sinusitis			
subjects affected / exposed	2 / 61 (3.28%)	2 / 61 (3.28%)	3 / 58 (5.17%)
occurrences (all)	2	3	3
Tooth abscess			
subjects affected / exposed	0 / 61 (0.00%)	0 / 61 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 61 (4.92%)	2 / 61 (3.28%)	3 / 58 (5.17%)
occurrences (all)	3	2	3

Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)	2 / 61 (3.28%)	3 / 58 (5.17%)
occurrences (all)	1	3	4

Non-serious adverse events	Main-240 mg	Main-total NNC0109-0012	Ext-placebo-240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 57 (47.37%)	75 / 176 (42.61%)	18 / 28 (64.29%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 57 (1.75%)	3 / 176 (1.70%)	1 / 28 (3.57%)
occurrences (all)	1	3	1
Body temperature increased			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 57 (1.75%)	5 / 176 (2.84%)	1 / 28 (3.57%)
occurrences (all)	1	5	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 57 (1.75%)	5 / 176 (2.84%)	3 / 28 (10.71%)
occurrences (all)	2	6	6
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 57 (0.00%)	5 / 176 (2.84%)	0 / 28 (0.00%)
occurrences (all)	0	5	0
Injection site erythema			
subjects affected / exposed	4 / 57 (7.02%)	8 / 176 (4.55%)	3 / 28 (10.71%)
occurrences (all)	19	26	3
Injection site reaction			
subjects affected / exposed	3 / 57 (5.26%)	16 / 176 (9.09%)	2 / 28 (7.14%)
occurrences (all)	17	39	5
Pyrexia			

subjects affected / exposed	2 / 57 (3.51%)	6 / 176 (3.41%)	0 / 28 (0.00%)
occurrences (all)	2	6	0
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 57 (1.75%)	2 / 176 (1.14%)	1 / 28 (3.57%)
occurrences (all)	1	2	1
Diarrhoea			
subjects affected / exposed	3 / 57 (5.26%)	4 / 176 (2.27%)	2 / 28 (7.14%)
occurrences (all)	3	4	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 57 (0.00%)	3 / 176 (1.70%)	0 / 28 (0.00%)
occurrences (all)	0	5	0
Nausea			
subjects affected / exposed	0 / 57 (0.00%)	7 / 176 (3.98%)	2 / 28 (7.14%)
occurrences (all)	0	8	2
Vomiting			
subjects affected / exposed	1 / 57 (1.75%)	4 / 176 (2.27%)	2 / 28 (7.14%)
occurrences (all)	3	6	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 57 (1.75%)	5 / 176 (2.84%)	0 / 28 (0.00%)
occurrences (all)	1	5	0
Oropharyngeal pain			
subjects affected / exposed	0 / 57 (0.00%)	2 / 176 (1.14%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Productive cough			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	0 / 28 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	1 / 28 (3.57%)
occurrences (all)	0	1	1

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 57 (3.51%)	2 / 176 (1.14%)	1 / 28 (3.57%)
occurrences (all)	2	2	1
Back pain			
subjects affected / exposed	0 / 57 (0.00%)	2 / 176 (1.14%)	2 / 28 (7.14%)
occurrences (all)	0	3	2
Muscle spasms			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Osteoarthritis			
subjects affected / exposed	0 / 57 (0.00%)	2 / 176 (1.14%)	0 / 28 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	0 / 57 (0.00%)	1 / 176 (0.57%)	1 / 28 (3.57%)
occurrences (all)	0	1	1
Rheumatoid arthritis			
subjects affected / exposed	1 / 57 (1.75%)	5 / 176 (2.84%)	3 / 28 (10.71%)
occurrences (all)	1	8	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 57 (1.75%)	3 / 176 (1.70%)	2 / 28 (7.14%)
occurrences (all)	1	3	2
Furuncle			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis			
subjects affected / exposed	1 / 57 (1.75%)	2 / 176 (1.14%)	1 / 28 (3.57%)
occurrences (all)	1	2	2
Gastroenteritis viral			
subjects affected / exposed	0 / 57 (0.00%)	3 / 176 (1.70%)	2 / 28 (7.14%)
occurrences (all)	0	3	3
Influenza			
subjects affected / exposed	2 / 57 (3.51%)	6 / 176 (3.41%)	3 / 28 (10.71%)
occurrences (all)	2	6	3
Nasopharyngitis			

subjects affected / exposed	1 / 57 (1.75%)	2 / 176 (1.14%)	1 / 28 (3.57%)
occurrences (all)	2	3	1
Pharyngitis			
subjects affected / exposed	1 / 57 (1.75%)	2 / 176 (1.14%)	2 / 28 (7.14%)
occurrences (all)	1	2	2
Sinusitis			
subjects affected / exposed	4 / 57 (7.02%)	9 / 176 (5.11%)	1 / 28 (3.57%)
occurrences (all)	5	11	1
Tooth abscess			
subjects affected / exposed	0 / 57 (0.00%)	0 / 176 (0.00%)	0 / 28 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 57 (1.75%)	6 / 176 (3.41%)	2 / 28 (7.14%)
occurrences (all)	1	6	2
Urinary tract infection			
subjects affected / exposed	6 / 57 (10.53%)	11 / 176 (6.25%)	3 / 28 (10.71%)
occurrences (all)	7	14	3

Non-serious adverse events	Ext-60-60 mg	Ext-120-120 mg	Ext-240-240 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 27 (62.96%)	24 / 28 (85.71%)	21 / 29 (72.41%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	0	2	1
Body temperature increased			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 27 (11.11%)	2 / 28 (7.14%)	2 / 29 (6.90%)
occurrences (all)	3	2	2
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	3 / 29 (10.34%)
occurrences (all)	1	2	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	2	1	0
Injection site erythema			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	4 / 29 (13.79%)
occurrences (all)	0	6	39
Injection site reaction			
subjects affected / exposed	7 / 27 (25.93%)	3 / 28 (10.71%)	3 / 29 (10.34%)
occurrences (all)	19	4	18
Pyrexia			
subjects affected / exposed	3 / 27 (11.11%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences (all)	3	1	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 27 (3.70%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	0	2	1
Diarrhoea			
subjects affected / exposed	1 / 27 (3.70%)	1 / 28 (3.57%)	4 / 29 (13.79%)
occurrences (all)	1	1	4
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	2	3	0
Nausea			
subjects affected / exposed	2 / 27 (7.41%)	4 / 28 (14.29%)	0 / 29 (0.00%)
occurrences (all)	2	5	0
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	0 / 29 (0.00%)
occurrences (all)	0	3	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Oropharyngeal pain			
subjects affected / exposed	2 / 27 (7.41%)	1 / 28 (3.57%)	0 / 29 (0.00%)
occurrences (all)	2	1	0
Productive cough			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	1 / 29 (3.45%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 27 (7.41%)	2 / 28 (7.14%)	3 / 29 (10.34%)
occurrences (all)	2	2	3
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	0 / 29 (0.00%)
occurrences (all)	0	4	0
Muscle spasms			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Osteoarthritis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	0	2	0
Pain in extremity			
subjects affected / exposed	2 / 27 (7.41%)	0 / 28 (0.00%)	0 / 29 (0.00%)
occurrences (all)	2	0	0
Rheumatoid arthritis			
subjects affected / exposed	2 / 27 (7.41%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	8	3	1
Infections and infestations			
Bronchitis			

subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	1 / 29 (3.45%)
occurrences (all)	1	3	1
Furuncle			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	5 / 28 (17.86%)	1 / 29 (3.45%)
occurrences (all)	0	5	1
Gastroenteritis viral			
subjects affected / exposed	2 / 27 (7.41%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	2	2	0
Influenza			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	1 / 29 (3.45%)
occurrences (all)	0	3	1
Nasopharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 28 (7.14%)	0 / 29 (0.00%)
occurrences (all)	1	2	0
Pharyngitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 28 (3.57%)	1 / 29 (3.45%)
occurrences (all)	1	1	1
Sinusitis			
subjects affected / exposed	0 / 27 (0.00%)	3 / 28 (10.71%)	5 / 29 (17.24%)
occurrences (all)	0	3	7
Tooth abscess			
subjects affected / exposed	0 / 27 (0.00%)	0 / 28 (0.00%)	2 / 29 (6.90%)
occurrences (all)	0	0	2
Upper respiratory tract infection			
subjects affected / exposed	4 / 27 (14.81%)	5 / 28 (17.86%)	2 / 29 (6.90%)
occurrences (all)	4	6	2
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	5 / 28 (17.86%)	6 / 29 (20.69%)
occurrences (all)	1	7	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2012	Added definition of highly effective contraception methods; added joint count assessments at V32, V38, V44, and V50; added pregnancy test at V16 and V20; and the correction of other inconsistencies.
30 July 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	Novo Nordisk A/S, decided to terminate phase 2b trial NN8226-3612 in rheumatoid arthritis (RA) on 7-Aug-2014 following the failure of the NN8226-3613 trial (EudraCT no: 2012-000610-11) with NNC0109-0012 in RA to achieve its primary efficacy endpoint in a partial database lock (DBL) analysis. The trial failed to demonstrate any statistically significant difference between NNC0109-0012 and placebo on the primary endpoint, ACR20, and showed no effect on disease activity after 12 weeks of treatment in the randomised subjects.	-

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 on 07-Aug-2014.

Notes: