



## Clinical trial results:

**A randomised, double-blind, placebo-controlled, parallel-group trial to assess clinical efficacy of NNC0114-0006 in subjects with active rheumatoid arthritis**

### Summary

EudraCT number	2011-005376-42
Trial protocol	LV ES HU BG
Global end of trial date	26 August 2013

### Results information

Result version number	v1 (current)
This version publication date	15 March 2016
First version publication date	28 July 2015

### Trial information

#### Trial identification

Sponsor protocol code	NN8828-3842
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01647451
WHO universal trial number (UTN)	U1111-1125-6552

Notes:

### Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, Bagsvaerd
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	03 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2013
Global end of trial reached?	Yes
Global end of trial date	26 August 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the change in disease activity following intravenous (i.v.) administration of two doses of NNC0114-0006 compared to placebo in subjects with active rheumatoid arthritis (RA) on background methotrexate (MTX) therapy.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (amended 2008) and ICH Good Clinical Practice (1996) and 21 CFR 312.120.

Background therapy:

The trial population included subjects with active rheumatoid arthritis on concomitant treatment with MTX  $\geq 15$  mg/week for at least 4 months prior to screening, with stable dose of  $\geq 15$  mg/week and  $\leq 25$  mg/week for at least 6 weeks prior to screening (MTX doses between 7.5 and 12.5 mg/week were allowed, if the patient had intolerance to 15 mg/week).

Evidence for comparator:

not applicable

Actual start date of recruitment	20 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Serbia: 5
Worldwide total number of subjects	62
EEA total number of subjects	49

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)	55
From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 18 sites in 6 countries, as follows: Bulgaria: 4 sites; Latvia: 1; Poland: 5; Russian Federation: 4; Serbia: 2; Spain: 2 sites.

### Pre-assignment

Screening details:

Subjects with active RA who were concomitantly treated with MTX for at least 4 months prior to screening were included in the trial.

### Period 1

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

Blinding implementation details:

An unblinded monitor was responsible for monitoring the handling and preparation of the trial products during the conduct of the trial. The unblinded monitor arranged for destruction of used and unused trial products at the end of the trial.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	NNC0114-0006

Arm description:

Subjects received two doses of 12 mg/kg NNC0114-0006, administered 6 weeks apart as an i.v. infusion over a period of 30 minutes using an automated infusion pump.

Arm type	Experimental
Investigational medicinal product name	NNC0114-0006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Two doses of 12 mg/kg NNC0114-0006 were administered 6 weeks apart as an i.v. (intravenous) infusion over a period of 30 minutes using an automated infusion pump. The dose was based on body weight measured at Visit 1, and the injection volumes varied subsequently between subjects.

<b>Arm title</b>	Placebo
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Arm description:

Subjects received two doses of placebo, administered 6 weeks apart as an i.v. infusion, over a period of 30 minutes using an automated infusion pump.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Two doses of placebo, corresponding to the same volume as active drug, were administered 6 weeks apart as an i.v. (intravenous) infusion over a period of 30 minutes using an automated infusion pump. The dose was based on body weight measured at Visit 1, and the injection volumes varied subsequently between subjects.

<b>Number of subjects in period 1</b>	NNC0114-0006	Placebo
Started	41	21
Completed	37	21
Not completed	4	0
Other	1	-
Withdrawal criteria	3	-

## Baseline characteristics

### Reporting groups

Reporting group title	NNC0114-0006
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Reporting group description:

Subjects received two doses of 12 mg/kg NNC0114-0006, administered 6 weeks apart as an i.v. infusion over a period of 30 minutes using an automated infusion pump.

Reporting group title	Placebo
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Reporting group description:

Subjects received two doses of placebo, administered 6 weeks apart as an i.v. infusion, over a period of 30 minutes using an automated infusion pump.

Reporting group values	NNC0114-0006	Placebo	Total
Number of subjects	41	21	62
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	51.8	49.6	
standard deviation	± 11.1	± 8.5	-
Gender categorical			
Units: Subjects			
Female	35	16	51
Male	6	5	11
Disease activity score based on 28 joints and c-reactive protein (DAS28-CRP)			
Units: score			
arithmetic mean	5.7	5.7	
standard deviation	± 0.8	± 0.7	-
Serum levels of total IL-21			
Units: pg/mL			
geometric mean	73	85	
full range (min-max)	25 to 4834	25 to 5380	-
Health Assessment Questionnaire – Disability Index score (HAQ-DI)			
Units: score			
arithmetic mean	1.39	1.53	
standard deviation	± 0.51	± 0.49	-

## End points

### End points reporting groups

Reporting group title	NNC0114-0006
Reporting group description: Subjects received two doses of 12 mg/kg NNC0114-0006, administered 6 weeks apart as an i.v. infusion over a period of 30 minutes using an automated infusion pump.	
Reporting group title	Placebo
Reporting group description: Subjects received two doses of placebo, administered 6 weeks apart as an i.v. infusion, over a period of 30 minutes using an automated infusion pump.	

### Primary: Change in disease activity score based on 28 joints and c-reactive protein (DAS28-CRP)

End point title	Change in disease activity score based on 28 joints and c-reactive protein (DAS28-CRP)
End point description: Change in disease activity score DAS28 (CRP). DAS28 (CRP) was derived from the following formula: $\text{DAS28 (CRP)} = 0.56 \times \sqrt{\text{tender joint count [TJC28]}} + 0.28 \times \sqrt{\text{swollen joint count [SJC28]}} + 0.36 \times \ln(\text{CRP}+1) + 0.014 \times \text{PtGA} + 0.96$ TJC28 = 28 joint count for tenderness, SJC28 = 28 joint count for swelling, $\ln(\text{CRP}+1)$ = natural, logarithm of CRP+1 (mg/L), PtGA = subject's global assessment of disease activity on a visual analogue scale (VAS) recorded on a 100 mm scale.	
End point type	Primary
End point timeframe: From baseline to week 12.	

End point values	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	21		
Units: Disease activity score				
least squares mean (standard error)	-1.63 ( $\pm$ 0.18)	-0.99 ( $\pm$ 0.25)		

### Statistical analyses

Statistical analysis title	Analysis 1
Statistical analysis description: The primary model used to analyse the primary endpoint was an analysis of variance (ANOVA) model including treatment as fixed factor and the baseline level of DAS28 (CRP) as a continuous covariate. The effect at Week 12 (active – placebo) was estimated from this model and presented together with the 95% confidence interval and the p-value for no treatment effect.	
Comparison groups	NNC0114-0006 v Placebo

Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0403
Method	ANOVA
Parameter estimate	Treatment difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	-0.03

### Secondary: ACR20/50/70.

End point title	ACR20/50/70.
End point description:	
Percentage of subjects that fulfil ACR response at week 12. To calculate the ACR responses, ACR20/50/70 and ACR-N, the following were assessed: Improvement in the swollen joint count (66 joints); Improvement in the tender joint count (68 joints); Improvement in at least 3 of the following 5 assessments; Subject's assessment of pain (VAS); Subject's global assessment of disease activity (PtGA) (VAS); Physician's global assessment of disease activity (PhGA) (VAS); Subject self-assessed disability (corresponding to health assessment questionnaire-disability; index [HAQ-DI]); CRP	
Given that all three improvements occurred, patients were reported to have an ACR20, ACR50 or ACR70 response if the improvement from baseline was 20%, 50% or 70% or more, respectively.	
End point type	Secondary
End point timeframe:	
At week 12.	

End point values	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	21		
Units: Percentage of subjects				
number (not applicable)				
ACR 20 (CRP)	47.5	28.6		
ACR 50 (CRP)	25	4.8		
ACR 70 (CRP)	12.5	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of adverse events (AEs)

End point title	Incidence of adverse events (AEs)
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End point description:

The number of adverse events from the first trial-related activity, after the subject had signed the informed consent and until post treatment follow-up period (up to week 24).

End point type	Secondary
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End point timeframe:

Up to week 24.

End point values	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	21		
Units: Events	43	24		

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Incidence of antibodies against NNC0114-0006.

End point title	Incidence of antibodies against NNC0114-0006.
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End point description:

Percentage of subjects with anti-NNC0114-0006 antibodies at week 12.

End point type	Secondary
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End point timeframe:

Up to week 24.

End point values	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	21		
Units: Percentage of subjects				
number (not applicable)	2.6	0		

### Statistical analyses

No statistical analyses for this end point

#### Secondary: Terminal serum half-life (t<sub>1/2</sub>).

End point title	Terminal serum half-life (t <sub>1/2</sub> ). <sup>[1]</sup>
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End point description:

Mean terminal serum t<sub>1/2</sub> after the second dose administration.

End point type	Secondary
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End point timeframe:

After second dose administration at Week 6.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Pharmacokinetic properties are not tested for subjects in the placebo arm. Therefore the results are presented only for the treatment arm.

<b>End point values</b>	NNC0114-0006			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Days				
geometric mean (geometric coefficient of variation)	15.8 ( $\pm$ 25.9)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in serum levels of total IL-21.

End point title	Change in serum levels of total IL-21.
End point description:	Total IL-21 relative to baseline at week 12 (85 days).
End point type	Secondary
End point timeframe:	Up to Week 12.

<b>End point values</b>	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	21		
Units: pg/mL				
geometric mean (geometric coefficient of variation)	46.52 ( $\pm$ 348)	0.42 ( $\pm$ 328)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Health Assessment Questionnaire – Disability Index score (HAQ-DI)

End point title	Change in Health Assessment Questionnaire – Disability Index score (HAQ-DI)
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End point description:

Change in HAQ-DI score from baseline to Week 12.

The HAQ-DI assesses the functional status for performing activities of daily living and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that

involve both upper and lower extremities.

The HAQ-DI score ranged from 0 (0 = without any difficulty) to 3 (3 = worst functioning) and was calculated according to the HAQ manual based on the eight category scores and the use of aids/devices and/or help from another person when indicated.

End point type	Secondary
End point timeframe:	
From baseline to Week 12.	

<b>End point values</b>	NNC0114-0006	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40	21		
Units: HAQ-DI score				
arithmetic mean (standard deviation)	-0.31 (± 0.51)	-0.25 (± 0.36)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events from the first trial-related activity, after the subject had signed the informed consent and until post treatment follow-up period.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	NNC0114-0006
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Reporting group description:

Subjects received two doses of 12 mg/kg NNC0114-0006, 6 weeks apart as an i.v. infusion over a period of 30 minutes using an automated infusion pump.

Reporting group title	Placebo
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Reporting group description:

Subjects received two doses of placebo 6 weeks apart as an i.v. infusion over a period of 30 minutes using an automated infusion pump.

Serious adverse events	NNC0114-0006	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 41 (0.00%)	3 / 21 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 41 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	0 / 41 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	NNC0114-0006	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 41 (36.59%)	8 / 21 (38.10%)	
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	6 / 41 (14.63%)	4 / 21 (19.05%)	
occurrences (all)	7	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 41 (24.39%)	2 / 21 (9.52%)	
occurrences (all)	12	2	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 41 (7.32%)	0 / 21 (0.00%)	
occurrences (all)	3	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2012	1. To remove tetanus toxoid immunisations as part of this trial due to sample size limitations for this pharmacodynamic assessment and logistical challenges of implementation. Sections and sentences related to the tetanus toxoid immunisation (non-investigational medical product) have been deleted. 2. Other minor editorial revisions/changes.
04 September 2012	Included additional monitoring: 1. For tuberculosis at the end of trial. 2. For pregnancy at the second dosing visit (V5). 3. By increasing the minimum requirement post dosing follow-up at site to 4 hours, ensuring sufficient time to identify any acute reactions associated with trial product administration. A change in International Trial Manager was also updated.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Not applicable
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Notes: