Clinical trial report synopsis

Trial registration ID-number: NCT01282255	**UTN: U1111-1117-1136** **EudraCT number: 2010-021283-14**

Title of trial

Efficacy of NNC109-0012[a] in subjects with active rheumatoid arthritis.

[a]After this trial was initiated, the investigational drug was designated NNC0109-0012. Thus, this name of the investigational drug will appear in the remaining parts of the present document, except for the objectives and endpoints.

Investigators

Principal investigator: Dr. [redacted].

Trial sites

A total of 33 trial sites in 7 different countries (Czech Republic, Spain, Poland, Romania, Italy, Portugal and The United Kingdom) received approval from Ethics Committees, of which 20 sites actively enrolled patients.

Of these 20 sites, 19 sites (6 in Czech Republic, 3 in Spain, 6 in Poland and 4 in Romania) randomised and dosed at least 1 patient.

Publications

Šenolt L, Göthberg M , Valencia X, Dokoupilová E. Efficacy and safety of NNC0109-0012 (anti-IL-20 mAb) in patients with rheumatoid arthritis: results from a phase 2a trial. Ann Rheum Dis 2012;71(Suppl3):152.

Trial period	**Development phase**
Initiation date: 23 February 2011 Completion date: 3 January 2012	Phase 2

Objectives

Primary objective:

- To evaluate the change in disease activity following 12 weekly s.c. doses of NNC109-0012 3 mg/kg compared to placebo in subjects with active rheumatoid arthritis (RA) on stable background methotrexate (MTX) therapy

Secondary objectives:

- To assess signs of clinical efficacy as determined by change in disease activity (ACR scores), clinical responses (EULAR response criteria) and pharmacodynamic (PD) biomarkers during and after 12 repeated doses of NNC109-0012
- To assess safety and tolerability during and after 12 repeated doses of NNC109-0012
- To assess the pharmacokinetic (PK) profile of NNC109-0012 after 12 repeated doses of NNC109-0012
- To assess potential immunogenicity of NNC109-0012 during and after 12 repeated doses of NNC109-0012

Methodology

This was a multi-centre, randomised, double-blind, multiple-dose, placebo-controlled, two-arm phase 2a trial investigating the clinical efficacy of NNC0109-0012 in patients with active RA concomitantly treated with MTX. Patients were randomised in a 2:1 ratio, where 45 patients were allocated to active treatment and 22 patients were allocated to placebo. The patients received weekly administrations of 3 mg/kg NNC0109-0012 or placebo for a total of 12 doses per patient. All doses of NNC0109-0012 or placebo were administered subcutaneously (s.c.) to patients into the abdominal wall while they were at the trial site. All patients were closely monitored for at least 2 hours after each dosing and at regular time intervals up until 14 weeks after the last dose was given, which corresponds to a period of 5 times the expected half-life of NNC0109-0012. Thus, the entire trial period from randomisation and onwards for each of the patients was 25 weeks. An internal safety committee was established in relation to the conduct of this trial to evaluate blinded safety and pharmacokinetic data. If required, the safety committee had the mandate to request any appropriate measurements to safeguard the patients. After the safety committee had evaluated and approved blinded safety data obtained through trial Day 85 and evaluate blinded pharmacokinetic data obtained

up until trial Day 57 for the first 10 patients, trial product exposure was continued. In addition, the safety committee was constituted to perform ongoing safety surveillance during clinical development of NNC0109-0012. The primary endpoint was evaluated in an interim analysis conducted after assessments at Week 12.

Number of subjects planned and analysed

A total of 100–200 patients were planned to be screened, of whom 66 were planned to be randomised and thereafter initiated on trial product to ensure 51 completing patients. The numbers of patients randomised, exposed, withdrawn and completed are presented below. All 67 patients were included in the full and safety analysis sets and contributed therefore with data to the pharmacokinetic, pharmacodynamic, efficacy and safety endpoints. A total of 5 patients were withdrawn from treatment before 12 weeks were completed. No subject withdrew from the trial in the 13-week follow-up period.

<u>The following patients were withdrawn from the trial:</u>

- One (1) patient treated with placebo was withdrawn by the medical monitor because of [redacted] AEs reported as decreased $CD4^+$ lymphocytes and lymphopenia. This patient received [redacted] doses of placebo before withdrawal, and participated in the trial for a total of [redacted] weeks (attended [redacted] follow-up visits after withdrawal).
- One (1) patient treated with placebo was withdrawn. After the patient had received [redacted] doses of placebo, [redacted] developed cystitis on Day [redacted] and the trial product was temporarily discontinued ([redacted] doses were not given) until the trial product was permanently withdrawn on Day [redacted]. The patient was withdrawn from the trial, although the event was not reported as leading to withdrawal. The total duration of trial participation was [redacted] weeks and the patient attended [redacted] follow-up visits after withdrawal.
- Two (2) patients withdrew their informed consent after being exposed to [redacted] and [redacted] doses of NNC0109-0012. [redacted]. The total duration of their trial duration was [redacted] and [redacted] weeks, respectively. [redacted]
- One (1) patient had a positive hepatitis B surface antibody response at screening and was not eligible for inclusion as per trial protocol, but this patient was mistakenly included and received [redacted] doses of NNC0109-0012 before withdrawal. The total duration of trial participation was [redacted] weeks and the patient attended [redacted] follow-up visits after withdrawal.

Subject disposition and analysis sets	**Placebo**	**NNC0109-0012 3 mg/kg**	**Total**
Randomised	22	45	67
Exposed	22	45	67
Withdrawn	2	3	5
Adverse event	1	0	1
Subject's withdrawal of consent	0	2	2
Other reasons	1	1	2
Completed (12 weeks' treatment)	20	42	62
Completed (entire trial)	20	42	62
Full analysis set	22	45	67
Safety analysis set	22	45	67

Diagnosis and main criteria for inclusion

Patients with active RA (characterised by DAS28 (C-reactive protein; CRP) ≥ 4.5, as well as ≥5 swollen and ≥5 tender joints of the 28 joint count), diagnosed according to the American College of Rheumatology (ACR1987 classification) made at least 3 months prior to screening, aged between 18 and 75 years, except for Czech Republic (aged 18 to 65 years), and on stable MTX treatment (≥7.5 to ≤25 mg/week) for at least 4 weeks prior to randomisation. All patients had to be willing to avoid pregnancy and females to avoid breast-feeding throughout this trial and up until at least 15 weeks after last dosing. If the patient was a female, she had to be post-menopausal or surgically sterile (post-menopausal for at least 1 year, otherwise follicle-stimulating hormone [FSH] ≥ 26.72 U/L). If the patient was a female and of child-bearing potential, she had to be willing to use a highly effective method of birth control during the trial until final visit, or for 15 weeks after last dosing, if she discontinued. A highly effective method of birth control was defined as those that resulted in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomised partner. If the patient was a male and his partner was of child-bearing potential, he had to be willing to use a highly effective contraception from first dosing until final visit, or for 15 weeks after last dosing if the patient withdrew.

Main criteria for exclusion

Subjects with chronic inflammatory autoimmune disease other than RA (except secondary Sjögren's syndrome or stable hypothyroidism) or history of or current inflammatory joint disease other than RA such as gout, psoriatic arthritis, juvenile idiopathic arthritis, reactive arthritis or Lyme disease. No other disease or clinically significant abnormality in hepatic and renal parameters, or any other laboratory parameters that might compromise the safety of the subject, interfere with participation in the trial or compromise the trial objectives. Chronic or ongoing active infectious disease requiring systemic anti-infectious treatment within 2 weeks prior to randomisation. History of severe systemic bacterial, viral or fungal infections within the past 12 months prior to screening. Evidence of herpes zoster or cytomegalovirus infection that resolved less than 2 months prior to screening. Live viral or bacterial vaccinations within 4 weeks prior to screening. Past or current malignancy with the exception of: i) adequately treated and cured basal- or squamous-cell carcinoma of the skin or cervical carcinoma *in situ* occurring for more than 12 months prior to randomisation; ii) other cancer with a complete response duration of >5 years prior to randomisation, or any period of time longer than that for those malignancies that are considered as resolved after passing this duration of response. Latent or active tuberculosis. Positive tests indicating an active hepatitis B infection, hepatitis C virus antibody or human immunodeficiency virus. Any of the following concomitant medication within the last 4 weeks prior to randomisation: glucocorticoid (unless taken as a stable dose equivalent to ≤10 mg of prednisolone/day), intra-articular, intramuscular or i.v. corticosteroids, sulfasalazine, hydroxychloroquine, chloroquine, azathioprine, penicillamine, cyclosporine and other non-biologic disease-modifying anti-rheumatic drugs (DMARDs) except MTX. Any biologic DMARDs leading to failure defined at the investigator's discretion. Any of the following biologic DMARDs within the last 8 weeks prior to screening: etanercept, adalimumab, infliximab, abatacept and tocilizumab. Any of the following concomitant medication within the last 24 weeks prior to screening: i.v. immunogammaglobulins, rituximab and other B-cell-depleting biologics. If exposure occurs at any time to an anti-CD20 mAb, normal levels of $CD19^+$ B cells in the circulation are required for trial entry. Any of the following concomitant medication within the 12 weeks prior to randomisation: gold therapy or leflunomide (unless the subject has also completed oral cholestyramine active washout according to locally accepted clinical practices).

Main criteria for withdrawal

The patient could choose to withdraw at any time. The patient could withdraw from the trial at the discretion of the investigator or the sponsor as a result of any safety concern or if the patient was judged non-compliant with the trial procedures. A patient was withdrawn if any of the following applied: use of prohibited medication during trial period, withdrawal of consent, pregnancy or intention of becoming pregnant, or sponsor closure of trial.

Investigational medicinal product, dose, mode of administration and batch number

All doses of NNC0109-0012 were administered s.c. in the abdominal wall. NNC0109-0012 was provided as freeze-dried powder, which was reconstituted with sterile water to a final concentration of 100 mg/mL per vial. The batches of NNC0109-0012 utilised throughout the trial were XLDP022, YLDP012 and YLDP016.

Duration of treatment

Patients were to receive weekly doses of the trial product for 12 weeks.

Reference therapy, dose, mode of administration and batch number

Placebo was provided as a liquid formulation in single-use vials of 9 mL. Placebo was administered s.c. in the abdominal wall. The batch of placebo utilised throughout the trial was XLDP010.

Criteria for evaluation – efficacy

Primary efficacy assessments

- tender joint count (28 joints assessed) (TJC28)
- swollen joint count (28 joints assessed) (SJC28)
- C-reactive protein (CRP) level
- the subject's general health (GH) on a visual analogue scale (VAS)

Secondary efficacy assessments

- tender joint count (TJC68)
- swollen joint count (SJC66)
- CRP level
- the subject's (PtGA) and the physician's (PhGA) global assessment of disease activity on a VAS
- the subject's assessment of pain on a VAS
- the subject's assessment of physical function as measured by the health assessment questionnaire – disability index (HAQ-DI)

Secondary pharmacodynamic assessments

- CRP level
- Serum PD biomarkers, including levels of IL-20, anti-cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF) and matrix metalloproteinase-3 (MMP-3)
- Pharmacogenomic biomarkers
- PD markers in optional synovial biopsies/fluid, e.g. IL-20, IL-20R

Secondary pharmacokinetic assessment

- Serum concentrations of NNC0109-0012

Criteria for evaluation – safety

- Adverse events (AEs) and toxicity graded using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse events (CTCAE), version 4
- Vital signs: blood pressure, pulse and body temperature
- Physical examination
- Electrocardiogram (ECG)
- Haematological, biochemical, urine and lipid parameters
- Local injection-site reactions
- Antibodies against NNC0109-0012[a]

[a]*Listed in trial protocol as a PD assessment*

Statistical methods

Analysis sets

The following analysis sets were defined:

- The safety analysis set: All randomised patients exposed to at least one dose of the trial product.
- The full analysis set (FAS): All randomised patients exposed to at least one dose of the trial product and who contributed with post-dosing data.

Sample-size calculations

The sample size was based on the primary endpoint, change in DAS28 (CRP) from baseline to 12 weeks after first dose administration. The sample size was determined for a 2:1 randomisation and based on a two-sided t-test and a 5% significance level. Assuming a standard deviation of 1.3 for the change in DAS28 (CRP) and a dropout rate of 20%, a sample size of 66 subjects would give 85% power to detect a difference of 1.2 between the two treatments.

Statistical endpoints and analyses

General considerations

All tests were two-sided and a significance level of 5% was used. No adjustment for multiplicity was made since all secondary endpoints were regarded as supportive. Analyses of efficacy endpoints at other time points than 12 weeks were not specified in the trial protocol and should be regarded as descriptive. The treatment effect was quantified in terms of the estimated difference (NNC0109-0012 – placebo) or, if the endpoint was log transformed, the ratio (NNC0109-0012 /placebo), together with the 95% confidence interval and p-value. All endpoints were summarised and presented by treatment. Individual and mean time profiles were presented in addition to descriptive statistics. Individual data were listed.

Primary endpoint

- Change in DAS28 (CRP) from baseline to 12 weeks

The primary model was a mixed-effect model repeated measures (MMRM) including treatment, time and interaction between treatment and time as fixed factors; baseline DAS28 (CRP) and interaction between time and baseline DAS28 (CRP) as continuous covariates and subject as random effect. The MMRM was fitted to all post-treatment data up to Week 12 in the interim analysis. In this analysis, missing data were implicitly dealt with as part of the analysis and an unstructured covariance matrix. No attempt was made to account for differences in collection times. However, for withdrawn patients, the data captured at an end-of-trial visit were mapped to the next scheduled visit. The effect of NNC0109-0012 compared to placebo on change in DAS28 (CRP) at 12 weeks after first dose administration was estimated from this model and presented together with the 95% confidence interval and the p-value for no treatment effect. The treatment effect was also estimated at Weeks 1 to 11 to describe the effect over time (analysis not specified in the trial protocol). At the end of the trial, the MMRM model was also applied to all data to describe the effect in the follow-up period (analysis not specified in the trial protocol). Because DAS28 is a composite endpoint, the effect of the different components (TJC28, SJC28, GH and CRP) were analysed and described similarly to the primary endpoint (analyses not specified in the trial protocol).

Sensitivity analyses were carried out to investigate the effect at 12 weeks after first dose administration using different ways to account for missing values. The sensitivity analyses were based on an analysis of variance (ANOVA) model including treatment as fixed factor and baseline DAS28 (CRP) as continuous covariate. Two separate ANOVAs were fitted to the change in DAS28 (CRP) from baseline to 12 weeks after first dose administration after applying the 'last observation carried forward (LOCF)' imputation method or after including all patients who completed 12 weeks of treatment.
The interaction between the treatment effect on the change in DAS28 (CRP) from baseline to 12 weeks after first dose administration and different baseline variables (such as region, gender, duration of RA, BMI, RF, anti-CCP and CRP) were investigated by adding these as fixed factors or continuous covariates, and its interaction with treatment one at a time to the ANOVA.

Secondary efficacy endpoints

- ACR20, ACR50 and ACR70 response after 12 weeks

ACR20/50/70 at 12 weeks after first dose administration were analysed using the Fisher's exact test. ACR20/50/70 responders were separately analysed using a logistic regression model including treatment as fixed factor and baseline DAS28 (CRP) as continuous covariate. The odds ratios for achieving ACR20/50/70 for actively treated versus placebo-treated patients were calculated. Analyses not specified in the trial protocol: The time to first ACR20/50/70 response was analysed using a Cox regression model, including treatment as fixed factor and baseline DAS28 (CRP) as continuous covariate. Kaplan Meier plots were used to illustrate the results. ACR-N and the different components (TJC68, SJC66, Pain, PtGA, PhGA, HAQ-DI and CRP) were analysed and described similarly to the primary endpoint.

- EULAR response after 12 weeks

The EULAR response at 12 weeks after first dose administration was analysed using a proportional odds model with

treatment as fixed factor and baseline DAS28 (CRP) as continuous covariate. Analysis not specified in the trial protocol: The EULAR response in the two treatment arms was also compared using a Cochran-Mantel-Haenszel test.

- Change in HAQ-DI from baseline to 12 weeks

The change in HAQ-DI score from baseline to 12 weeks after first dose administration was analysed using an ANOVA including treatment as fixed factor and both DAS28 (CRP) and HAQ-DI at baseline as continuous covariates. Analyses not specified in the trial protocol: HAQ-DI responders endpoints (change in HAQ-DI ≥0.22 or ≥0.3) were defined and analysed similar to ACR20/50/70. Time to first HAQ-DI response (≥0.22 or ≥0.3 units) was described and illustrated similar to ACR20/50/70.

Secondary efficacy endpoints not specified in the trial protocol

- Remission scores
  - DAS28 (CRP) ≤2.6 and ≤2.0
  - SDAI ≤3.3 (simplified disease activity index)
  - CDAI ≤2.8 (clinical disease activity index)
  - $DA_{All\ comp \leq 1}$ (disease activity when all DAS28 components are 1 or below 1)
- Change in utility value from baseline to Week 12

Remission scores were not analysed, but presented with descriptive statistics. The utility value (calculated as a linear transformation of HAQ-DI) was defined and analysed similar to HAQ-DI.

Secondary pharmacodynamic endpoints

- Serum levels of free IL-20, CRP, anti-CCP, RF and MMP-3
- Pharmacogenomic biomarkers in peripheral blood
- Relevant markers in synovial biopsies or fluid, e.g. IL-20, IL-20R (optional)

Serum concentrations of CRP, anti-CCP, RF and MMP-3 were logarithmic-transformed before analysis. The pharmacodynamic effect was evaluated by fitting an ANOVA to the maximum (E_{max}), the minimum (E_{min}) and the mean during the dosing period (dosing $E_{mean\ Dosing}$) concentration of the respective parameter with treatment as fixed factor and baseline value as continuous covariate. Analyses not specified in the trial protocol: relative changes in CRP, anti-CCP, RF and MMP-3 at 12 weeks after first dose administration were analysed using an ANOVA including treatment as fixed factor and the baseline level of the component as continuous covariates.

No analysis was performed on biomarkers in synovial biopsies, as only one biopsy sample was obtained prior to dosing.

Secondary pharmacokinetic endpoints

- $t_{½}$ – terminal elimination half-life
- C_{max} – maximum observed serum concentration after last dose administration
- t_{max} – time to reach maximum serum concentration after last dose administration

Observed C_{max} and t_{max} was extracted from the serum concentration data. The terminal half-life was calculated as $t_{½}=\log(2)/\lambda_z$, where λ_z is the terminal rate constant. λ_z was estimated by fitting a linear function to the time versus log-concentration data using the terminal, approximately linear, part of each profile.

Secondary pharmacokinetic endpoints not specified in the trial protocol

- C_{tau} – serum concentration at the end of the dosing interval
- CL/F – total body clearance following s.c. administration
- Terminal V_z/F – apparent volume of distribution following s.c. administration based on the terminal phase

- V/F in steady-state – volume of distribution in steady-state/F
- MRT – mean residence time
- $C_{tau,\ dose\ 12}/C_{tau,\ dose\ 1}$ – accumulation of NNC0109-0012 after the 12th dose administration compared to the 1st dose administration

Secondary safety endpoints

- AEs and toxicity
- Vital signs (blood pressure, pulse and body temperature)
- Physical examination
- ECG
- Haematological, biochemical, urine and lipid parameters
- Local tolerability at injection site
- Antibodies developed against NNC0109-0012

All safety endpoints were summarised descriptively. Treatment-emergent adverse events were defined as events with an onset on or after the first day of dosing with the trial product (defined as Visit 2) and up until database lock (8 February 2012). Treatment-emergent adverse events are referred to as 'adverse events', whereas adverse events with onset prior to randomisation are referred to as 'adverse events in the screening period'. The pharmacodynamic effect for safety PD endpoints was analysed the same way as for the secondary pharmacodynamic endpoints. Antibody data were listed by dose, subject and time.

Demography of trial population

All patients but one (1) were White with a mean age of 51 years (range: 26–75 years) and a mean BMI of 28.8 kg/m^2 (range: 54–114 kg/m^2), indicating that the enrolled patients in this trial were overweight on average. The NNC0109-0012 and placebo groups were comparable with respect to mean age, body weight and BMI, as well as sex, race and ethnicity. The majority of the patients (79%) were enrolled from Poland and the Czech Republic. More females than males (51 versus 16) were included, which was expected because of the predominance of this disease in women.

Patients in this trial had been diagnosed with RA for a mean of 6.6 years (range: 0.4–17.3 years) and approximately two-thirds of the patients had at trial entrance developed antibodies against both RF and CCP. The two dose groups were comparable with respect to the number of sero-positive patients. No major differences in any of the remaining disease characteristics in terms of DAS28 (CRP) and ACR components were observed across the two dose groups. The patients were on average treated with MTX for 1.9 years (range: 0.1–14.3 years) prior to enrolment in this trial, and the lengths of MTX treatment were comparable for patients in the NNC0109-0012 and placebo groups. The patients initiated on average MTX treatment 4.7 years (range: 0–16.2 years) after the diagnosed of RA was given.

Efficacy results

Efficacy results

- A statistically significant and clinically relevant improvement in mean DAS28 (CRP) of –0.88 (95% CI: [–1.61;–0.14], p = 0.020) was observed after once-weekly treatment for 12 weeks.
- Clinical responses at Week 12 in terms of ACR20/50/70 were seen in more patients treated with NNC0109-0012 than placebo, but these differences did not reach statistical significance.

ACR response	**Placebo (N = 22)**	**3 mg/kg NNC0109-0012 (N = 45)**	**p-value[a]**
	N (%)	N (%)	
ACR20	7 (31.8%)	22 (48.9%)	0.203
ACR50	3 (13.6%)	16 (35.6%)	0.085
ACR70	1 (4.5%)	11 (24.4%)	0.086

a = p-values based on the Fisher's exact test

- Overall, a substantially higher proportion of patients with no EULAR response were observed for patients treated with placebo than with NNC0109-0012 for 12 weeks. A moderate EULAR response was achieved by a comparable proportion of patients treated with NNC0109-0012 or placebo for 12 weeks, whereas a good EULAR response was achieved by a considerably higher proportion of patients treated with NNC0109-0012 than with placebo. Overall, NNC0109-0012 induced a statistically significant improvement in EULAR response when compared to placebo (odds ratio for response versus no response in the NNC0109-0012 dose group compared to the placebo group = 3.42, 95% CI: [1.25;9.35], p = 0.017).

EULAR (CRP) response	**Placebo (N = 22)**	**3 mg/kg NNC0109-0012 (N = 45)**
	N (%)	N (%)
No	10 (46%)	11 (24%)
Moderate	11 (50%)	20 (44%)
Good	1 (4%)	14 (31%)

- A clinically relevant, but not statistically significant, mean decrease in HAQ-DI of −0.26 was obtained after 12 weeks in patients treated with NNC0109-0012 compared to placebo (95% CI: [−0.60; 0.08]; p=0.130).

Efficacy results based on endpoints and analyses not specified in the protocol

- Improvements in mean DAS28 (CRP) of −0.48 (95% CI: [−0.84;−0.11, p = 0.011) were observed in patients with RA already after 1 week of treatment and maintained for an additional 5 weeks after last dosing (−0.72, 95% CI: [−1.33;−0.10], p = 0.022). The effect was primarily driven by the change in the TJC28 (−4.0, 95% CI: [−8;−1], p = 0.021) and the patient's general health (−1.6, 95% CI.: [−2.9;−0.2], p = 0.023). Further, the improvements in DAS28 (CRP) were observed primarily in patients who were seropositive (RF-positive and/or anti-CCP−positive).
- Seropositive (RF-positive or anti-CCP positive or both) responders by ACR20 criteria at Week 12 were 59% (p=0.0275 vs placebo) and 21% (placebo); ACR50 responders were 48% (p=0.0447 vs placebo) and 14% (placebo), and ACR70 responders were 34% (p=0.0177 vs placebo) and 0% (placebo).
- Significant improvements in EULAR responses were maintained for an additional 5 weeks after last dosing (odds ratio for response versus no response in the NNC0109-0012 dose group compared to the placebo group = 2.93, 95% CI: [1.09;7.87], p = 0.033).
- Statistically significant and clinically relevant mean reductions in the following ACR-N components were observed for patients treated with NNC0109-0012 after 12 weeks' treatment, and maintained for an additional 5 to 14 weeks after last dosing:
    - TJC68: −8 (95% CI: [−14; −3], p = 0.006)
    - SJC66: −5 (95% CI: [−8; −1], p = 0.016)
    - Pain: −1.5 (95% CI: [−2.9; −0.1], p = 0.034)
    - PtGA: −1.6 (95% CI: [−3.0; −0.2]; p = 0.022)
    - PhGA: −1.4 (95% CI: [−2.4; −0.4], p = 0.008)
- Time to first ACR20, ACR50 or ACR70 response was achieved earlier in patients treated with NNC0109-0012 than in patients treated with placebo, whereas time to first HAQ-DI response was achieved simultaneously in patients treated with NNC0109-0012 or placebo.

	Placebo; NNC0109-0012 (N)	Estimated effect[a]	95% CI	p-values
Time to first ACR20 response	12;35	2.66	[1.37; 5.17]	0.004
Time to first ACR50 response	4;21	3.31	[1.13; 9.65]	0.029
Time to first ACR70 response	1;13	7.90	[1.03; 60.67]	0.047
Time to first HAQ-DI (≥0.22)	16;38	1.14	[0.63; 2.05]	0.668
Time to first HAQ-DI (≥0.30)	13;31	1.18	[0.61; 2.26]	0.622

a = estimated effect is based on the hazard ratio of 3 mg/kg NNC0109-0012 versus placebo.

- A higher proportion of patients treated with NNC0109-0012 achieved remission (SDAI ≤3.3) than placebo: 5 (11%) on NNC0109-0012 versus 0 (0%) on placebo.

Remission score	Placebo (N = 22)	3 mg/kg NNC0109-0012 (N = 45)
	N (%)	N (%)
DAS28 (CRP) ≤2.6	1 (5%)	8 (18%)
DAS28 (CRP) ≤2.0	0 (0%)	6 (13%)
SDAI ≤3.3	0 (0%)	5 (11%)
CDAI ≤2.8	1 (5%)	5 (11%)
$DA_{All\ comp\ \leq 1}$[a]	0 (0%)	5 (11%)

[a]Disease activity when all DAS28 components are 1 or below 1

- No statistically significant improvements in mean utility (0.07, 95% CI: [−0.05; 0.18], p=0.242) were observed for patients treated with NNC0109-0012 once-weekly for 12 weeks compared to placebo.

Pharmacodynamics

- The majority of the patients with RA exposed to NNC0109-0012 or placebo (91% and 96%, respectively) had free IL-20 serum concentrations below lower limit of quantification (LLOQ; 50 pg/mL) at baseline.
- No statistically significant or clinically relevant changes in the concentrations of free IL-20, RF, anti-CCP, CRP and MMP-3 were observed after once-weekly dosing with NNC0109-0012 as compared with placebo.
- [redacted]
- As only one biopsy from 1 patient was obtained prior to dosing, relevant biomarkers in synovial biopsies or fluid were not analysed.

Pharmacokinetics

Pharmacokinetic results

- Serum concentrations of NNC0109-0012 were above the LLOQ (defined as 50 ng/mL) in all patients after s.c. administration of 12 weekly doses of 3 mg/kg NNC0109-0012.
- The NNC0109-0012 serum concentrations increased following repeated dosing. NNC0109-0012 mean trough levels increased only marginally following the 11^{th} and 12^{th} dose, indicating that steady-state had not been reached in all patients.
- A slow elimination of NNC0109-0012 was observed with a mean $t_{½}$ of 23.8 days (19% CV).
- As only weekly blood sampling was scheduled C_{max} and t_{max} may not have been accurately captured and should be interpreted with caution.

Pharmacokinetic results based on endpoints and analyses not specified in the protocol

- Mean V_z/F (0.141 L/kg [20.7% CV]) was relatively small and indicated a volume of distribution that was approximately only 2-fold higher than the blood volume.
- The mean MRT was 41 days (range: 29–62 days).
- Accumulation in terms of trough concentrations of NNC0109-0012 was on average 5 times higher after administration of the 12th dose than after the 1st dose.

Safety results

- A total of 91 adverse events were reported for 31 of the 67 (46%) patients exposed in the trial. Of these, 12 events were reported for 10 (45%) patients treated with placebo and 79 were reported for 21 (47%) patients treated with NNC0109-0012.
- Local injection-site reactions constituted 42% (38/91) of all adverse events reported in this trial. All injection-site reactions were mild in severity, evaluated as probably related to the trial product and resolved within 5 days. Each symptom observed for an injection-site reaction was reported as a separate adverse event, whereas each symptom observed for all other adverse events were linked to a diagnosis (whenever possible), leading to a high number of injection-site related adverse events. Injection-site reactions were reported for 4 (9%) actively treated patients only (none for placebo-treated patients).
- The majority of the adverse events were mild (68/91) or moderate (21/91) in severity. The number of severe adverse events was low (2 in total) and comparable across the two dose groups. More mild adverse events were reported for the NNC0109-0012 group than for the placebo group (81% versus 33%) where most events were local injection-site reactions. The opposite was true for adverse event of moderate severity (18% versus 58%).
- Approximately 50% (48/91) of the adverse events were evaluated by the investigator to be possibly or probably related to the trial product and all but 2 were reported for the NNC0109-0012 group. A total of 79% (38/48) of the related events were injection-site reactions.
- No deaths or serious adverse events were reported.
- No medical events of special interest (MESIs) (defined as medication errors and suspected transmission of an infectious agent via the trial product) were reported.
- One (1) patient treated with placebo was withdrawn from the trial due to 2 adverse events (decreased $CD4^+$ lymphocytes and lymphopenia) evaluated respectively as severe and moderate in severity. Both events were evaluated as unlikely related to the trial product. This patient received [redacted] of the 12 planned doses before withdrawal.
- One (1) patient treated with placebo had an adverse event (cystitis) evaluated as mild in severity and possibly related to the trial product which led to temporary and later permanently discontinuation of the trial product. Subsequently, the patient was withdrawn from the trial due to the event.
- The number of patients who had one or more adverse events leading to temporary or permanent discontinuation of the trial product was comparable for the placebo and NNC0109-0012 groups (3 versus 2). The events (urinary tract infection and upper respiratory tract infection) reported for the 2 patients treated with NNC0109-0012 were respectively moderate and mild in severity, but both events were judged as unlikely related to the trial. [redacted].
- A higher number of adverse events in the system organ class of infections and infestations treated with NNC0109-0012 than with placebo were reported (10 versus 2) as well as a higher proportion of patients (22% versus 5%). Two (2) additional adverse events related to the immune system (decreased $CD4^+$ lymphocyte count and lymphopenia) were reported for 2 patients treated with placebo or NNC0109-0012, respectively.
- None of the changes in the haematological parameters were statistically significant or deemed clinically relevant, except for a statistically significant reduction in mean lymphocytes (of -0.18×10^9/L) observed during the 12 weeks' treatment with NNC0109-0012. However, all reductions were of mild or moderate severity in a comparable proportion of patients treated with NNC0109-0012 or placebo (19% versus 18%). The reduction in mean lymphocytes did not remain significant during the 13-week follow-up period.
- None of the changes in the biochemical parameters were statistically significant or clinically relevant, except for a statistically significant increase in mean total calcium (of 0.03 mmol/L) observed after dosing with NNC0109-0012 once weekly for 12 weeks. However, none of the patients had total calcium levels above normal range (defined as 2.6 mmol/L).

- No clinically relevant changes were observed for any of the urine parameters after treatment with NNC0109-0012 for 12 weeks.
- No clinically relevant changes were observed in body weight, body temperature, ECG, physical examination or vital signs (pulse, diastolic and systolic blood pressure) after treatment with placebo or NNC0109-0012.
- No pregnancies were reported.
- Treatment-induced ADAs were detected in 2 out of 45 (4%) patients. For both patients the NNC0109-0012 trough levels remained within the observed range for the other patients in the trial. All ADAs were cross-reactive with the IgG_4 backbone and of low titres. It was therefore considered unlikely that the ADAs were neutralising.

Conclusions

- Once-weekly s.c. treatment with NNC0109-0012 at 3 mg/kg for 12 weeks reduced disease activity in terms of change from baseline in DAS28 (CRP) in patients with RA concomitantly treated with MTX. A statistically significant reduction in disease activity versus placebo was observed already after 1 week of treatment, and was maintained for an additional 5 weeks after last dosing. Reductions in disease activity were primarily observed in patients who were seropositive (RF-positive and/or anti-CCP positive) and were maintained for an additional 14 weeks after last dosing.
- NNC0109-0012 once-weekly for 12 weeks induced a significantly higher proportion of patients with improved EULAR response than placebo, and the difference was maintained for an additional 5 weeks after the dosing period.
- No statistically significant differences in the proportion of patients achieving ACR20/50/70 responses were observed when compared to placebo.
- Treatment with NNC0109-0012 once-weekly did not induce any changes in free IL-20, RF, anti-CCP antibodies, CRP and MMP-3.
- NNC0109-0012 once-weekly was well tolerated within the context of this trial. Most adverse events were mild and the total number of events was driven primarily by local injection-site reactions observed in a few patients. NNC0109-0012 induced a statistically significant reduction in mean lymphocyte levels and increases in mean total calcium during the dosing period, but the changes did not raise any safety concerns.
- The NNC0109-0012 serum trough levels increased with repeated dosing, but continued to increase after last dosing in most patients, indicating that steady-state was not reached.
- Treatment-induced anti-drug antibodies of low titres were detected in 2 (4%) patients, but it was considered unlikely that the antibodies were neutralising.

The trial was conducted in accordance with the Declaration of Helsinki (amended 2008) and ICH Good Clinical Practice (1996). The 12-week efficacy results presented in the synopsis reflect data available in the clinical database as of 14 November 2011 (relates to partial database lock), whereas the remaining results presented reflect data available in the clinical database as of 9 February 2012 (relates to final database lock).