CTR synopsis

Trial registration ID-number NCT01223911	**UTN** – U1111-1116-2430 **EudraCT number** – 2009-011791-30

TITLE OF TRIAL

A randomised, double-blind, placebo-controlled, multiple dose trial of NNC0151-0000-0000 in subjects with rheumatoid arthritis

INVESTIGATORS

One principal investigator was appointed at each of the nine trial sites that randomised subjects to treatment. The following investigator was designated signatory investigator for the trial, and was responsible for reviewing and approving the Clinical Trial Report:

[redacted], MD, PhD, [redacted]

TRIAL SITES

The trial was conducted at nine sites in four countries as follows: Czech Republic: 1 site; Denmark: 1 site; Poland: 4 sites; Romania: 3 sites.

PUBLICATIONS

No publications based on this trial were available at the time of this clinical trial report synopsis.

TRIAL PERIOD Initiation date: 10 January 2011 Termination date: 06 February 2013	**DEVELOPMENT PHASE** Phase 2a

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 22 March 2013.

OBJECTIVES

Primary objective:

- To assess the safety and tolerability, including immunogenicity, of NNC0151-0000 after four multiple doses at up to seven dose levels in subjects with active RA.

Secondary objectives:

- To assess the pharmacodynamics of NNC0151-0000 (PD) including
  - C5aR occupancy on neutrophils and monocytes
  - effect on various biomarkers, including acute phase cytokines and immunophenotyping
- To assess the PK of NNC0151-0000
- To assess the preliminary clinical improvement and efficacy of NNC0151-0000 in subjects with RA using the ACR20/50/70 and ACR-N scores and DAS28.

METHODOLOGY

This was a randomised, double-blind, placebo-controlled trial in up to 48 subjects with active RA. The subjects received multiple s.c. doses of NNC0151-0000 with one dose once weekly during a 3-week period (in total four doses) followed by a 7-week follow-up period. The trial comprised a dose escalation part of up to 7 dose levels in up to 48 subjects (4 or 8 subjects per dose level); however, the trial was terminated after the fifth dose level due to safety findings (see Safety Results section below).

The subjects were closely and regularly monitored for safety and preliminary efficacy up to 7 weeks after last dose administration. Samples for assessments of PK (serum concentration at 48 hours after dosing) and PD were collected during the same period. During the dose escalation, subjects were randomised in a 3:1 ratio, where three subjects were allocated to treatment with NNC0151-0000 and one subject to placebo treatment (3+1) at the two lowest dose levels and 8 subjects (6+2) at the next dose levels.

Safety, PK, and pharmacodynamic biomarkers such as C5aR occupancy were analysed on an on-going basis. The safety data obtained for each cohort up to Day 22 (corresponding to safety monitoring up to 4 hours after last dose

administration) of last subject in the cohort, together with available PK, PD and C5aR occupancy data up to Day 10 (corresponding to 2 days after second dose administration), were evaluated by the Study Safety Group to determine if progression to the next dose level could take place. Results of the NNC0151-0000 antibody analysis from dose level 1 were available for the Study Safety Group prior to the decision to move to dose level 3 and results of NNC015-0000 antibody analysis from dose level 2 were available for the Study Safety Group prior to the decision to move to dose level 4 and so forth until last dose level was achieved. The actual Study Safety Group meeting after each cohort was held 4-14 days after last dose administration of last subject of the cohort and the dose administration at the next dose level started, at the earliest, 5 days after the last dose administration of the last subject of the previous dose cohort.
Safety monitoring was performed continuously for 6 hours after the first dose administration and for 4 hours after the remaining dose administrations, and was followed by regular visits to the clinic up to 7 weeks after last dose administration.
The dosing frequency and route of administration was one dose weekly for three weeks (4 doses total) using s.c. administration.
Rescue therapy of intraarticular/intramuscular steroid injections equivalent to ≤ 50 mg or peroral corticosteroids ≤ 30 mg/day for ≤ 7 days and/or corticosteroids ≤ 20 mg/day were allowed after Day 29 and for the remaining duration of the trial.
First dose administration of subjects took place on separate days with an interval of at least 20 hours.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

A total of 68 subjects were planned to be screened, with 48 planned to be randomised and to complete the trial. However, the trial was terminated after the fifth dose level, with a total of 53 subjects screened, 34 randomised and 32 who completed the trial (Table 1). All 34 randomised subjects were exposed to trial product and were included in both the full analysis set (FAS) and safety analysis sets.

Table 1 – Subject disposition by treatment

	Placebo	NNC0151-0000	Total
Screened Subjects, N			53
Randomised Subjects, N (%)	9 (100.0)	25 (100.0)	34 (100.0)
Exposed Subjects, N (%)	9 (100.0)	25 (100.0)	34 (100.0)
Completed Subjects, N (%)	8 (88.9)	24 (96.0)	32 (94.1)
Withdrawn Subjects, N (%)	1 (11.1)	1 (4.0)	2 (5.9)
Non-compliance, N (%)	1 (11.1)	0 (0.0)	1 (2.9)
Adverse event, N (%)	0 (0.0)	1 (4.0)	1 (2.9)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Main criteria for inclusion

The trial included male and female subjects between the ages of 18-75 years inclusive (18-65 in Czech Republic) diagnosed with RA according to the American College of Rheumatology (ACR 1987 classification) for at least 3 months duration prior to randomisation. Subjects had to have a DAS28 (CRP) score ≥3.2 and be on stable doses of methotrexate (≤25 mg/week) for at least 4 weeks prior to dosing. Subjects with reproductive potential had to use a highly effective contraception method together with a physical barrier (e.g., condom) during sexual intercourse during participation in the trial and 10 weeks after the last dose.

Main criteria for exclusion

Subjects were excluded if they had any of the following: known or suspected allergy to trial products; previously participated in the trial; chronic inflammatory autoimmune disease other than RA (with some exceptions); history of or current inflammatory joint disease other than RA, current reactive arthritis or Lyme disease; body mass index (BMI) <18.0 or >38.0 kg/m^2 inclusive; past or current malignancy (with some exceptions); chronic or ongoing active infection disease requiring systemic anti-infectious treatment within 2 weeks before randomisation; severe systemic bacterial, viral or fungal infections within the past 12 months before randomisation; positive screening test for latent tuberculosis; clinically significant cardiac or cardiovascular disease; previous exposure to non-marketed drug substances or

experimental therapy within 4 weeks or 5 half-lives (whichever was longest) prior to screening; live virus or bacteria vaccines within 4 weeks before dosing; any of the following concomitant medication *within 4 weeks of dosing*: glucocorticoid, unless taken as a stable dose equivalent to ≤ 10 mg of prednisolone/day, intraarticular, intramuscular or intravenous corticosteroids, sulfasalazine, hydroxychloroquine, etanercept, adalimumab, cyclosporine, azathioprine, penicillamine, any other non-biologic disease-modifying anti-rheumatic drug (DMARD), except of MTX; *within 8 weeks of dosing*: infliximab, abatacept; *within 12 weeks of dosing*: gold therapy, leflunomide, unless the subject has also completed oral cholestyramine active washout according to locally accepted clinical practices; *within 24 weeks of dosing:* i.v. immunogammaglobulins, rituximab; positive hepatitis B, hepatitis C or HIV test results; donation or loss of ≥400 mL blood within 8 weeks of dosing; history of regular alcohol consumption or drug abuse; legally institutionalised subjects; or unwillingness or inability to follow procedures in the protocol; no other disease or clinically significant abnormality in hepatic or renal parameters, or any other laboratory parameters that might compromise the trial objectives; or were pregnant or breastfeeding.

Main criteria for withdrawal

Subjects could withdraw at will at any time or be withdrawn from the trial at the discretion of the investigator or the sponsor due to a safety concern or if judged non-compliant with trial procedures. A subject was withdrawn if the following applied: (1) non-compliance with protocol procedures, concurrent illness or administration of concomitant medications occurred which, in the clinical judgement of the investigator and/or after discussion with the sponsor, could have invalidated the trial; (2) adverse event of symptoms considered unacceptable by the subject or the investigator or if neutropenia caused postponement for at least one week of 2 dose administrations; (3) sponsor closure of the trial; (4) withdrawal of informed consent; or (5) pregnancy or intention of becoming pregnant.

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

NNC0151-0000 delivered as a lyophilised powder in 12 mL single use vials (100 mg/vial), which was to be reconsistuted with sterile water to 100 mg/mL and further diluted with the placebo solution. The batch number of NNC0151-0000 used throughout the trial was YLDP005. NNC0151-0000 was administered subcutaneously into the abdominal wall by use of a syringe with a needle size suitable for subcutaneous injection.

DURATION OF TREATMENT

The subjects received multiple s.c. doses of NNC0151-0000 with one dose once weekly during a 3-week period (in total 4 doses) followed by a 7-week follow-up period.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Placebo/diluent, 0 mg/mL, was delivered as a sterile solution with 9 mL in a 12 mL single use vial. The batch numbers of placebo/diluent used throughout the trial were XLDP010 and YLDP007. Placebo/diluent was administered subcutaneously into the abdominal wall by use of a syringe with a needle size suitable for subcutaneous injection.

CRITERIA FOR EVALUATION – EFFICACY

Pharmacodynamic assessments

In blood samples:

- C5aR occupancy (%) on neutrophils and monocytes
- Immunophenotyping (T, B and NK cell subsets)
- Pharmacogenomic/microarray biomarkers

In serum/plasma samples:

- Disease markers (CRP, RF and anti-CCP)
- Complement markers (C3, C5a-desArg and CH50)
- Acute phase cytokines (IL-1β, IL-6, TNF-α, INF-γ)
- C5aR activation markers and/or markers of inflammation [Assessed by VectraDA test]
- Proteomic profiling of biomarkers of inflammation [Assessed by VectraDA test]

In urine samples:

- Metabonomic or proteomic profiling (CTX-II and creatinine) [Not assessed due to change of trial design]

Pharmacokinetic assessment

- NNC0151-0000 serum concentration 48 hours after dose administration

Clinical efficacy assessments

- tender joint count (28 joints assessed) (TJC28)
- swollen joint count (28 joints assessed) (SJC28)
- CRP level
- subject's global health assessment (GH) on a visual analogue scale (VAS)
- tender joint count (68 joints assessed) (TJC68)
- swollen joint count (66 joints assessed) (SJC66)
- the subject's (PtGA) and the physician's (PhGA) global assessment of disease activity on a VAS
- the subject's assessment of pain and fatigue on a VAS
- the subject's assessment of physical function as measured by the health assessment questionnaire – disability index (HAQ-DI)

CRITERIA FOR EVALUATION – SAFETY

AEs and toxicity (by use of National Cancer Institute's CTCAE scale, version 3)

- Local injection-site reactions
- Physical examination
- Vital signs (blood pressure, pulse, ECG and body temperature) and body weight
- Haematology, biochemistry, lipids, urinalysis
- Acute phase cytokines (IL-1β, IL-6, TNF-α, INF-γ)
- Complement markers (C5a-desArg, C3, CH50)
- Antibodies against NNC0151-0000 (binding and neutralising)

STATISTICAL METHODS

Sample size calculation

The sample size was not based on any formal calculation. For the dose escalation, 4 or 8 subjects per dose level were chosen (3:1 NNC0151-0000 vs. placebo). This was a balance between exposing the smallest possible number of subjects to the new investigational drug and still being able to informally assess tolerability in order to continue with the next dose cohort.

Definition of analysis sets

The FAS was defined as all randomised subjects exposed to at least one dose of the trial product and who contributed with post-dosing data. The safety analysis set was defined as all randomised subjects exposed to at least one dose of the trial product. Since all subjects contributed with post-dosing data, the two analysis sets are the same. No subjects or observations were excluded from the statistical analysis.

Primary endpoint

AEs and toxicity (by use of National Cancer Institute's CTCAE scale, version 3) including:

- Local tolerability at injection site
- Vital signs (blood pressure, pulse, ECG and body temperature) and body weight
- Haematology, biochemistry, lipids, urinalysis
- Acute phase cytokine response (IL-1β, IL-6, TNF-α, INF-γ)
- Complement markers (e.g. C5a-desArg, C3, CH50)
- Immunogenicity (antibodies to NNC0151 0000)

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 (22 March 2013). Treatment-emergent adverse events are referred to as 'adverse events', whereas adverse events with an onset prior to randomisation are referred to as 'adverse events in the screening period'.

All safety endpoints were summarised descriptively based on all collected data.

The AEs were summarised by dose level, relation to trial product, severity, system organ class and preferred term (coded using MedDRA version 15.1). Summaries were made for all AEs and serious AEs. Descriptive statistics for AE included the number and percentage of subjects who experienced at least one AE and the total number of events. The AE reporting included clinical laboratory AEs and any clinically significant worsening in physical examinations, vital signs or ECG. All individual safety data were listed by subject and cohort.

Individual and mean time curves for the safety endpoints were presented by dose level in addition to descriptive statistics. Laboratory safety parameters were graded using CTCAE and shift tables displaying the maximum grade during the trial are presented. Laboratory safety for which no CTCAE exist were compared to the relevant reference range (when existing) and flagged as being below or above the range. Shift tables displaying the maximum severity compared to the reference ranges in laboratory safety parameters are presented.
Development of anti-drug antibodies was summarised separately for the treatment period (until week 4) and for the entire trial.

Secondary endpoints

There were no confirmatory secondary endpoints and therefore all secondary endpoints can be regarded as supportive. No statistical analysis for the secondary endpoints was pre-specified in the protocol.

Pharmacodynamic assessments

Levels of:

- C5aR-occupancy on neutrophils and monocytes
- Immunophenotyping, e.g. T, B, and NK-cell subsets
- Disease markers, e.g. CRP, RF and anti-CCP
- Complement markers, e.g. C3 and C5a
- C5aR activation markers and/or markers of inflammation [Assessed by VectraDA assay]
- Proteomic profiling of biomarkers of inflammation [Assessed by VectraDA assay]

The pharmacodynamic effect of NNC0151-0000 was evaluated by fitting an ANOVA to the maximum concentration (E_{max}) and the minimum concentration (E_{min}) of the respective parameter with dose level as fixed factor and the baseline level as continuous covariate. The pair-wise differences between the active dose groups and the placebo group were estimated and presented together with the 95% confidence intervals. If a statistically significant difference between the highest active dose level and placebo was observed, the next highest active dose level was compared to placebo according to a hierarchal test strategy. The potential cohort effect was investigated in an exploratory analysis with cohort added to the above ANOVA model as a fixed factor.
E_{max} and E_{min} were defined for vital signs and all laboratory safety and efficacy parameters as applicable. Serum/blood concentrations of CRP, T, B and NK cells and anti-drug antibodies were log-transformed before analysis.

Pharmacokinetic assessments

- Concentration at 48 hours after all dose administrations

The serum concentrations were summarised for each planned time point per dose level. The summary statistics included geometric mean, CV (%), min, median and maximum concentration.

Clinical efficacy assessments

- Change in DAS28 (CRP)
- ACR20, ACR50, ACR70 and ACR-N (CRP)

Clinical efficacy assessments not specified in the protocol

- Change in VectraDA score

DAS28 (CRP), VectraDA, ACR-N (CRP) and the DAS28 (CRP) and ACR (CRP) components were analysed by a non-parametric permutation test. The endpoints at 4 weeks were compared separately for the active dose levels and placebo using a permutation test on the actual values. The results were presented using the two-sided p-value calculated as 2 times a 1-sided p-value and the corresponding permutations. The results were illustrated in bar charts displaying the individual levels sorted by size and labelled with the dose level (Waterfall plots). The cohort effect was investigated in an explorative analysis fitting an ANOVA similar to what was fitted to the PD endpoints. ACR20/50 and 70 were summarized per visit and cohort.

DEMOGRAPHY OF TRIAL POPULATION

Demographics

All subjects were white, and the majority (70.6%) were female. The higher proportion of female subjects was expected due to the predominance of this disease in women. The mean age was 57.0 years and the mean BMI was 26.4 kg/m^2, indicating that subjects were, on average, overweight. Baseline demographic characteristics were comparable for subjects receiving NNC0151-0000 vs. placebo (Table 2), and were also similar across the different NNC0151-0000 dose groups.

Table 2 – Baseline demographic characteristics by treatment

	Placebo	NNC0151-0000	Total
Number of Subjects	9	25	34
Age (years), N	9	25	34
Mean (SD)	54.7 (11.7)	57.8 (10.5)	57.0 (10.7)
Min - Max	39.0 - 75.0	30.0 - 75.0	30.0 - 75.0
Sex, N (%)	9 (100.0)	25 (100.0)	34 (100.0)
Female	5 (55.6)	19 (76.0)	24 (70.6)
Ethnicity, N (%)	9 (100.0)	25 (100.0)	34 (100.0)
Hispanic or Latino	[redacted]		
Not Hispanic or Latino			
Race, N (%)	9 (100.0)	25 (100.0)	34 (100.0)
White	9 (100.0)	25 (100.0)	34 (100.0)
Country, N (%)	[redacted]		
Czech Republic			
Denmark			
Poland			
Romania			
Body Weight (kg), N	9	25	34
Mean (SD)	77.0 (13.8)	68.8 (11.7)	71.0 (12.6)
Min - Max	59.8 - 99.0	48.5 - 100.0	48.5 - 100.0
BMI (kg/m^2), N	9	25	34
Mean (SD)	26.8 (3.4)	26.3 (3.0)	26.4 (3.1)
Min - Max	22.7 - 33.1	20.5 - 34.2	20.5 - 34.2

Disease characteristics

Baseline disease characteristics for subjects were similarly distributed between subjects randomised to placebo and NNC0151-0000 treatment (Table 3). Subjects had been diagnosed with RA for a mean of 7.4 years and had a mean DAS28 (CRP) score of 5.5, indicating that, on average, patients had high disease activity. Erosive joint disease based on radiographic changes was detected in 67.6% of subjects (EOT Table 14.1.6). The majority of subjects were seropositive for RF or anti-CCP (79.4%). Baseline rheumatoid arthritis disease characteristics and history were similar across the NNC0151-0000 dose levels.

Table 3 – Disease characteristics by treatment

	Placebo	NNC0151-0000	Total
Number of Subjects	9	25	34
Rheumatoid Arthritis (years), N	9	25	34
Mean (SD)	7.0 (6.4)	7.6 (5.7)	7.4 (5.8)
Min - Max	0.3 - 16.9	0.9 - 26.1	0.3 - 26.1
RF, N	9 (100.0)	25 (100.0)	34 (100.0)
Positive	6 (66.7)	17 (68.0)	23 (67.6)
Negative	3 (33.3)	8 (32.0)	11 (32.4)
Anti-CCP, N	9 (100.0)	25 (100.0)	34 (100.0)
Positive	7 (77.8)	18 (72.0)	25 (73.5)
Negative	2 (22.2)	7 (28.0)	9 (26.5)
RF or anti-CCP, N	9 (100.0)	25 (100.0)	34 (100.0)
Positive	8 (88.9)	19 (76.0)	27 (79.4)
Negative	1 (11.1)	6 (24.0)	7 (20.6)
DAS28 (CRP), N	9	25	34

Mean (SD)	5.8 (0.8)	5.3 (0.6)	5.5 (0.7)
Min - Max	4.8 - 7.3	4.3 - 6.5	4.3 - 7.3
TJC28, N	9	25	34
Mean (SD)	16.1 (4.8)	12.6 (4.5)	13.5 (4.8)
Min - Max	9.0 - 26.0	6.0 - 22.0	6.0 - 26.0
SJC28, N	9	25	34
Mean (SD)	12.6 (5.1)	9.3 (3.9)	10.1 (4.4)
Min - Max	6.0 - 23.0	2.0 - 15.0	2.0 - 23.0
GH (VAS) (cm), N	9	25	34
Mean (SD)	6.3 (2.1)	6.1 (1.7)	6.2 (1.8)
Min - Max	2.8 - 8.7	2.6 - 8.9	2.6 - 8.9
CRP (mg/L), N	9	25	34
GMean (CV%)	7.1 (179)	6.2 (192)	6.5 (183)
Min - Max	0.7 - 37.2	0.3 - 66.2	0.3 - 66.2
VectraDA, N	9	25	34
Mean (SD)	48.8 (20.0)	51.8 (16.0)	51.0 (16.9)
Min - Max	14.0 - 77.0	22.0 - 79.0	14.0 - 79.0

At trial entry, subjects had been on methotrexate therapy for a mean duration of 2.2 years at a mean dose of 16.3 mg/week. All subjects continued their methotrexate regimen during the trial, and no other DMARDs were used as rescue therapy during the trial. Corticosteroid treatment was administered to 58.8% of subjects at a mean dose of 5.4 mg/day.

EFFICACY RESULTS

All efficacy endpoints were secondary endpoints in this trial.

Pharmacodynamic endpoints

C5a receptor occupancy

- Mean and maximum C5aR occupancy on neutrophils and monocytes increased in a dose-dependent manner for subjects treated with NNC0151-0000, whereas no occupancy was observed in subjects treated with placebo.

Immunophenotyping

- No statistically significant mean changes were observed in any of the lymphocyte subsets at any dose level when compared with placebo.

Pharmacogenomic/microarray markers

- At the highest dose level (0.6 mg/kg), statistically significant and biologically relevant down-regulation of one gene was observed when compared to baseline.

Disease markers

- No statistically significant changes in CRP levels were observed after NNC0151-0000 treatment compared with placebo at any of the dose levels.
- The majority of subjects (79.4%) were seropositive for RF or anti-CCP. No clear differences were observed in DAS28 (CRP) changes between seropositive and seronegative subjects.

Complement markers

- No clinically significant changes were observed in any of the complement markers assessed: C5a and C5a-desArg, C3, and CH50.

Pharmacokinetic endpoints

- The serum NNC0151-0000 concentrations were below the lower limit of quantification (LLoQ) for the majority of the subjects in the first three dose cohorts (0.05, 0.1 and 0.2 mg/kg)
- The observed concentrations appeared to be consistent with the non-linear disposition kinetics previously observed for NNC0151-0000, with no or limited systemic accumulation of NNC0151-0000 observed at measurements taken 48 hours after dose administration.

Clinical efficacy endpoints

- No statistically significant differences were seen between increasing doses of NNC0151-0000 and placebo in any of

the clinical disease measures (DAS28 [CRP], ACR 20/50/70, ACR-N, or VectraDA).

SAFETY RESULTS

Adverse events

- Forty-eight (48) AEs were reported in 16 subjects (64%) receiving NNC0151-0000 and 8 AEs were reported in 4 subjects (44%) receiving placebo.
- The most frequently reported AEs (33 out of 56 [59%]) were lymphopenia/decreased lymphocyte count, neutropenia/decreased neutrophil count and leukopenia/decreased white blood cell count; which were mostly reported in the 2 highest dose groups (0.4 and 0.6 mg/kg) and only once (lymphopenia) in the placebo group.
- Four severe AEs were reported: 3 subjects with grade [redacted] lymphopenia and one subject with grade [redacted] neutropenia, all in the two highest NNC0151-0000 dose groups (0.4 and 0.6 mg/kg). These AEs were not associated with any clinical infections and the laboratory parameters returned to normal levels within one week.
- One subject treated with 0.1 mg/kg NNC0151-0000 withdrew from the trial after experiencing an AE of hepatocellular injury that was moderate in severity and judged as unlikely related to trial product.
- No deaths, SAEs or medical events of special interest (MESIs) were reported.

Anti-drug antibodies

- Anti-NNC0151-0000 binding antibodies were detected in 80% of subjects treated with NNC0151-0000 compared with 11% treated with placebo (20 out of 25 subjects on NNC0151-0000 vs. 1 out of 9 subjects on placebo); the anti-drug antibodies were *in vitro* neutralising in a high proportion of subjects (60%).
- Dose-dependent increases in anti-drug antibody titres against NNC0151-0000 were observed.
- Anti-drug antibodies appeared to lower drug exposure and C5aR occupancy levels on neutrophils.

Local tolerability

- One subject (0.6 mg/kg NNC0151-0000) experienced injection-site rash after the second dose administration and redness after the third dose. Both events were of short duration ([redacted] and [redacted] days, respectively) and judged by the investigator as mild and possibly related to the trial product.

Other safety parameters

- Other than decreases in leukocyte, neutrophil and lymphocyte counts, no clinically relevant changes were observed in any of the other safety parameters, including vital signs, body weight, haematology, biochemistry, lipids, urinalysis, acute phase cytokines, or complement markers.

CONCLUSIONS

- Transient dose-dependent reductions in absolute neutrophil and lymphocyte counts were seen following treatment with NNC0151-0000; however, these decreases were not related to the reporting of infections.
- Anti-drug antibodies were developed in a high percentage of the subjects and had a possible neutralising effect on both PK and receptor occupancy; however, overall, no significant impact on safety was observed.
- C5aR occupancy on neutrophils and monocytes increased in a dose-dependent manner after NNC0151-0000 treatment.
- The observed NNC0151-0000 exposure showed non-linear disposition kinetics for NNC0151 0000. No or limited systemic accumulation was observed after repeated dosing.
- No differences were seen between increasing doses of NNC0151-0000 and placebo in any of the clinical disease measures.

The trial was conducted in accordance with the Declaration of Helsinki (2004) and ICH Good Clinical Practice (1996) and 21 CFR 312.12