NN8555-3797 trial synopsis (extended; for internal use only)

Trial registration ID-number NCT01203631	**UTN number** – U1111-1116-2695 **IND number** – 107,740 **EudraCT number** – 2010-020836-21

TITLE OF TRIAL

A randomised, double-blind, parallel-group, placebo-controlled, induction trial to assess the clinical efficacy and safety of NNC0142-0000-0002[a] in subjects with moderately to severely active Crohn's disease.

[a]*hereafter referred to as NNC0142–0002*

INVESTIGATOR

One principal investigator was appointed at each of the 32 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:

Professor [redacted], [redacted].

TRIAL SITES

The trial was conducted at 32 sites in 8 countries, as follows: Belgium (1), Canada (1), France (4), Hungary (4), Israel (5), Poland (5), the Russian Federation (6), and the U.S. (6).

PUBLICATIONS

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

TRIAL PERIOD	**DEVELOPMENT PHASE**
Initiation date: 28 February 2011 Termination date: 23 May 2013	Phase 2a

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 02 July 2013.

OBJECTIVES

Primary objective:

- To compare disease activity following a single subcutaneous (s.c.) dose of NNC0142–0002 to placebo in subjects with moderately to severely active Crohn's disease (CD), measured 4 weeks after administration.

Secondary objectives:

- To compare disease activity at other time-points than Week 4, clinical response and remission, between subjects treated with NNC0142–0002 and subjects receiving placebo.
- To compare safety and tolerability of NNC0142–0002 and placebo.
- To compare health-related quality of life (HRQoL) between subjects treated with NNC0142–0002 and subjects receiving placebo.
- To compare use of concomitant medication for CD between subjects treated with NNC0142–0002 and subjects receiving placebo.
- To describe the pharmacokinetics (PK) of NNC0142–0002 during treatment.
- To compare pharmacodynamic (PD) response, by assessment of various biomarkers, between subjects treated with NNC0142–0002 and subjects receiving placebo.
- To describe the immunogenicity of NNC0142–0002.

METHODOLOGY

This was a randomised, single-dose, double-blind, placebo-controlled, parallel-group trial to assess the clinical efficacy and safety of NNC0142–0002 in subjects with moderately to severely active CD. The trial included two parallel treatment arms, and subjects were randomised in a 1:1 ratio with 40 subjects allocated to treatment with 2 mg/kg NNC0142–0002 and 38 subjects to placebo treatment. Stratification was defined as a four level categorical variable

equal to the interaction of two binary stratification factors used at randomisation: 'prior failure to a biological therapy for CD (yes/no)' and 'baseline disease activity (CDAI score < 330 vs. CDAI score ≥ 330)'. Subjects received trial product via s.c. injection into the abdominal wall. All subjects were closely monitored for 24 weeks after dosing for clinical and laboratory safety assessments, pharmacokinetics and receptor occupancy. Local tolerability was assessed before the subject left the clinic. The dosing visit was followed by regular out-patient visits for 20 weeks (at Weeks 1, 2, 4, 6, 8, 12, 16 and 20), and a final visit at 24 weeks after dosing. An internal safety committee performed on-going safety surveillance, and all safety laboratory data were reviewed at least every 3 months. Rescue medication for non-responders was allowed.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

The trial was planned for approximately 250 subjects screened, 100 randomised and exposed, and 90 to complete Week 4 of the trial. A total of 205 subjects were screened for the trial. Hereof, 78 subjects were randomised and exposed, which comprised the full analysis set (FAS) and the safety analysis set. In all, 70 subjects completed Week 4 (data not shown), and 58 subjects completed the trial (Table 1).

Table 1 – Subject disposition by treatment

	Placebo	NNC0142-0002	Total
Screened Subjects, N			205
Randomised Subjects, N (%)	38 (100.0)	40 (100.0)	78 (100.0)
Exposed Subjects, N (%)	38 (100.0)	40 (100.0)	78 (100.0)
Completed Subjects, N (%)	28 (73.7)	30 (75.0)	58 (74.4)
Withdrawn Subjects, N (%)	10 (26.3)	10 (25.0)	20 (25.6)
- Adverse event, N (%)	1 (2.6)	3 (7.5)	4 (5.1)
- Non-compliance , N (%)	0 (0.0)	1 (2.5)	1 (1.3)
- Ineffective therapy , N (%)	4 (10.5)	4 (10.0)	8 (10.3)
- Withdrawal criteria , N (%)	5 (13.2)	2 (5.0)	7 (9.0)
Random Code Broken	2 (5.3)	0 (0.0)	2 (2.6)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Main criteria for inclusion

Male and female subjects between the ages of 18–75 years diagnosed with CD for at least 3 months. Moderately to severely active CD (220 ≤ CDAI ≤ 450) confirmed by CRP ≥ 10 mg/L or endoscopic verification. Biologic-naïve subjects or subjects having failed only one biologic treatment of CD were eligible.

Main criteria for exclusion

Any of the following: Symptomatic bowel obstruction, short bowel syndrome, ileostomy or colostomy, surgical bowel resection within 6 months prior to randomisation or clinically relevant un-drained abscess. Diagnosis of indeterminate colitis, ulcerative colitis, celiac disease, or irritable bowel syndrome. Any on-going chronic or active infectious disease or microbial infection requiring systemic oral or intravenous treatment against infection within 1 month prior to randomisation. Body mass index (BMI) ≥ 38.0 kg/m^2. History of malignancy or dysplasia in the colon.

Main criteria for withdrawal

Subjects could withdraw at will at any time. The subject could have been 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, which in the clinical judgement of the investigator and/or after discussion with the sponsor may invalidate the trial; (2) sponsor closure of the trial; (3) withdrawal of informed consent; or (4) pregnancy or intention of becoming pregnant.

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

NNC0142–0002 was manufactured as a lyophilised powder in 12 mL single use vials (100 mg/vial), which was to be reconstituted with sterile water to a concentration of 100 mg/mL. The batch numbers of NNC0142–0002 used throughout the trial were VLDP031 and YLDP017. NNC0142–0002 was administered s.c. into the abdominal wall by use of a syringe.

DURATION OF TREATMENT

Subjects received a single dose of trial product.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

All doses of placebo were administered s.c. in the abdominal wall. Placebo was provided as a liquid formulation in 12 mL vials. The batch numbers of placebo used in the trial were ALDP011 and VLDP033.

CRITERIA FOR EVALUATION – EFFICACY

Clinical efficacy assessments

- Crohn's disease activity index (CDAI)
- Harvey-Bradshaw index (HBI).
- Number of draining fistulas.

HRQoL assessments

- Inflammatory bowel disease questionnaire (IBDQ).
- Short-Form Health Survey 36 (SF-36v2).

PK assessment

- NNC0142–0002 serum concentration after dose administration.

PD assessments

- CRP levels.
- Faecal calprotectin levels.
- NKG2D receptor occupancy of NNC0142–0002 on $CD8^+$ T cells and NK cells.
- Cell markers of leukocyte subsets.
- Serum biomarkers (IL-6, IL-15, TNF-α, and IL-1Ra).
- Endoscopy biopsy sub-study including histopathological assessment (Geboes criteria).

CRITERIA FOR EVALUATION – SAFETY

- Adverse events (AEs) including local tolerability.
- Physical examination including vital signs.
- Clinical laboratory safety (haematology, biochemistry, urinalysis, lipids and viral screening).
- Electrocardiogram (ECG).
- Immunogenicity (anti-NNC0142–0002 binding and neutralising antibodies).

STATISTICAL METHODS

Sample size calculation

In order ensure 80% power to detect a difference in the mean change from baseline in CDAI of 45 after 4 weeks with a standard deviation of 85 points, 90 subjects are needed, based on a two-sided t-test (significance level, α=0.10) using a 1:1 treatment ratio. Assuming a 10% drop-out rate before Week 4, 100 subjects were required to be randomised.

Definition of analysis sets

- FAS: All randomised subjects exposed to the trial product and contributed with post-dosing data to be analysed according to randomised treatment.
- Safety analysis set: All randomised subjects exposed to the dose of the trial product to be analysed according to actual treatment.
- No subjects or observations were excluded from the statistical analysis.

Statistical efficacy analyses were based on the FAS. The significance level for all CDAI endpoints was pre-specified as 10%. All comparisons for other parameters were to be tested at a significance level of 5%.

Recruitment challenges resulted in institution of a futility analysis based on the primary endpoint (CDAI change from baseline to Week 4). The purpose was to stop the trial early if it was unlikely that superiority of NNC0142-0002 over placebo could be demonstrated on the primary endpoint. The recommendation based on the futility analysis was to terminate recruitment due to a small probability that the completed trial would demonstrate superiority of active treatment over placebo on the CDAI score at Week 4.

Primary endpoint – change in CDAI from baseline to Week 4.
The primary endpoint was analysed using a mixed effects model with treatment, stratification, visit, treatment-by-visit interaction and treatment-by-stratification interaction as factors, with baseline CDAI and baseline CDAI-by-visit interaction as covariates, and subject as a random effect. The effect at Week 4 (NNC0142 0002 – placebo) was estimated from this model and presented together with the 90% confidence interval and the *p*-value for testing no treatment effect.

Secondary endpoints

- Change in CDAI from baseline to Weeks 8 and 12 was analysed as for the primary endpoint.
- Proportion of subjects in clinical remission (CDAI < 150) at Weeks 4, 8, and 12, and proportion of subjects achieving clinical response (CDAI reduction from baseline ≥ 100) at Weeks 4, 8, and 12 were analysed by Fisher's exact test and logistic regression was used as a supplemental analysis.
- HBI at Week 4: analysed by ANCOVA following LOCF imputation. The ANCOVA model included treatment and stratification as factors, and baseline HBI as covariate. HBI at Week 12 was analysed by using a mixed effects model with treatment, stratification, visit, treatment-by-visit interaction and stratification-by-visit interaction as factors, baseline HBI and baseline HBI-by-visit interaction as covariates, and subject as a random effect.
- The number of draining fistulas at Week 12 was presented using descriptive statistics.

HRQoL endpoints

- IBDQ global score at Week 12 was analysed using a mixed effects model with treatment, stratification, visit, treatment-by visit interaction and stratification-by-visit interaction as factors, baseline IBDQ and baseline IBDQ-by-visit interaction as covariates, and subject as a random effect.. The SF-36v2 health survey at Week 12 was analysed using a mixed effects model, separately for the physical and mental component summary measures. The model is analogous to the mixed effects model used for the analysis of the IBDQ data.

PK endpoints

- AUC, $C_{max,}$ t_{max} and $t_{½}$. All PK endpoints were presented using descriptively.

PD endpoints

- Levels of faecal calprotectin at Weeks 2, 4, and 12.
- Levels of CRP (mg/L) at Weeks 1, 2, 4, 8, 12, 16, 20, and 24.
- Blood cell marker assessment, including NNC0142–0002 occupancy of the NKG2D receptor on lymphocyte subsets, measured by flow cytometry at Weeks 1, 4, 8 and 12.
- Levels of selected serum and plasma biomarkers at Weeks 1, 4, 8 and 12.

Selected biomarkers were analysed using an ANCOVA model with treatment and stratification as factors, and baseline as covariate. Log-transformation of the endpoints was applied to some parameters prior to analysis when deemed necessary.
All PD endpoints were presented using descriptive statistics.

Safety endpoints
All safety endpoints were presented using descriptive statistics.

DEMOGRAPHY OF TRIAL POPULATION
Racial distribution of subjects was 75 Whites and 3 Black/Africans, and sex ratio (M/F) was 36/42. Subjects had a mean age of 35.3 years and a mean BMI of 22.8 kg/m^2, indicating that subjects were, on average, normal weight. Baseline demographic characteristics were comparable for subjects receiving NNC0142–0002 vs. placebo. Baseline disease

characteristics for subjects were similarly distributed between subjects randomised to placebo and NNC0142–0002 treatment. Mean CDAI values confirmed that the enrolled subjects had moderately to severely active Crohn's disease.

EFFICACY RESULTS

- The trial did not meet the primary endpoint as no significant difference on CDAI score (change from baseline) at Week 4 between active treatment and placebo was observed. However, a significant difference between treatment groups for CDAI score was observed at Week 12 (Figure 1A), p=0.057; 90% C.I. [-103;-8].
- For randomised subjects who were non-failures to biologics (55 out of 78, i.e. 71% of trial population): a statistically significant reduction in CDAI for NNC0142–0002 compared to placebo was observed at Weeks 1, 2, 4, 8 and 12 (Figure 1B).

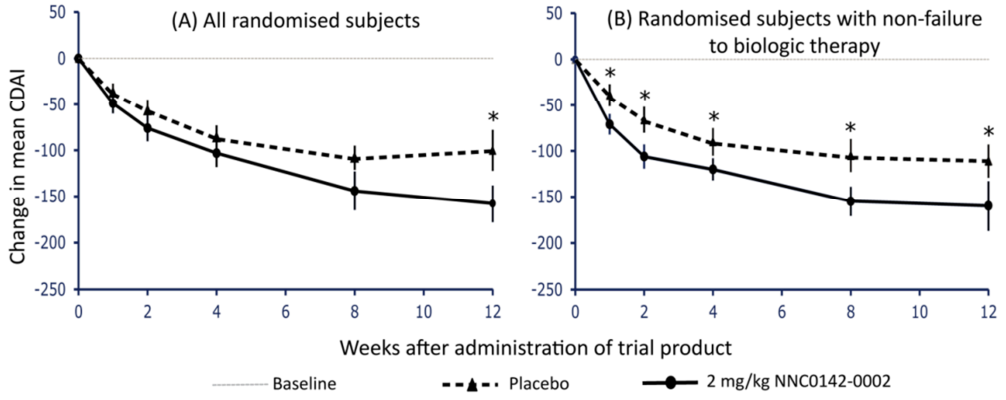

Figure 1 – Mean (±sem) CDAI over time after single-dose s.c. treatment with 2 mg/kg NNC0142–0002 or placebo in all randomised subjects (A) and subjects with non-failure to biologics only (B). For all randomised subjects (N=78), absolute mean CDAI values at baseline were 326 for placebo and 335 for NNC0142-0002. For subjects with non-failure to biologics only (N=55), absolute mean CDAI values at baseline were 329 for placebo and 338 for NNC0142–0002. *p<0.10.

- For randomised subjects who had failed biologic therapy (23 out of 78, i.e. 29%): no statistically significant reduction in CDAI between the two treatment groups was observed.
- The proportion of subjects with a clinical response (decrease in CDAI ≥ 100 from baseline) was numerically higher in the NNC0142-0002 group (43%) compared to placebo (29%) at Week 12.
- A higher proportion of subjects defined in clinical remission (CDAI < 150) were seen for the NNC0142-0002 group (10 out of 40, i.e. 25%) in contrast to placebo-treated subjects (6 out of 38, i.e. 16%),
- A statistically significant reduction in HBI (p=0.006; 95% C.I. [-4.6;-0.8]) was observed for the NNC0142–0002 group compared to placebo at Week 12.
- The numbers of draining fistulas were too few to provide for any meaningful comparison.
- No statistically significant difference in the global IBDQ score was observed between placebo and the NNC0142-0002 group.
- Improvement in the physical component summary score of the SF-36v2 was statistically significant (p= 0.044; 95% C.I. [0.09;6.84]) for the NNC0142–0002 group compared to placebo at Week 12. No statistically significant improvement was observed for the mental component summary score of the SF-36v2 for the NNC0142–0002 group compared to placebo at Week 12.
- A mean observed C_{max} of approximately13 µg/mL was reached within one week of s.c. dosing (Figure 2(i)).
- A median NKG2D receptor occupancy of 80% was observed up to 8 weeks for NNC0142–0002-treated subjects. At Week 12, median occupancy was <20% (Figure 2(ii)).

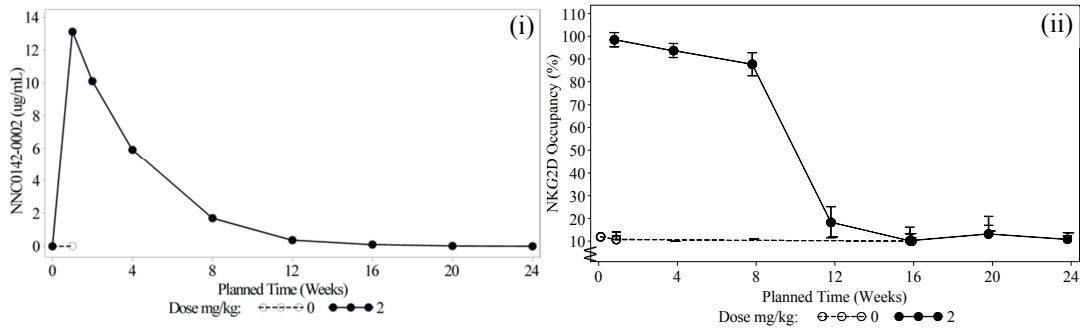

Figure 2 – (i) Mean serum concentration profiles of NNC0142–0002 after single-dose s.c. treatment with 2 mg/kg NNC0142–0002 or placebo. (ii) Median (±sem) NKG2D occupancy over time after single-dose s.c. treatment with 2 mg/kg NNC0142–0002 or placebo.

- No difference between NNC0142–0002 and placebo was detected in faecal calprotectin or CRP.
- Treatment with NNC0142–0002 significantly decreased mean percentage of NK cells and $CD8^+$ T cells expressing the NKG2D receptor compared to placebo. NKG2D receptor expression approached baseline levels at Week 24, (Figure 4).

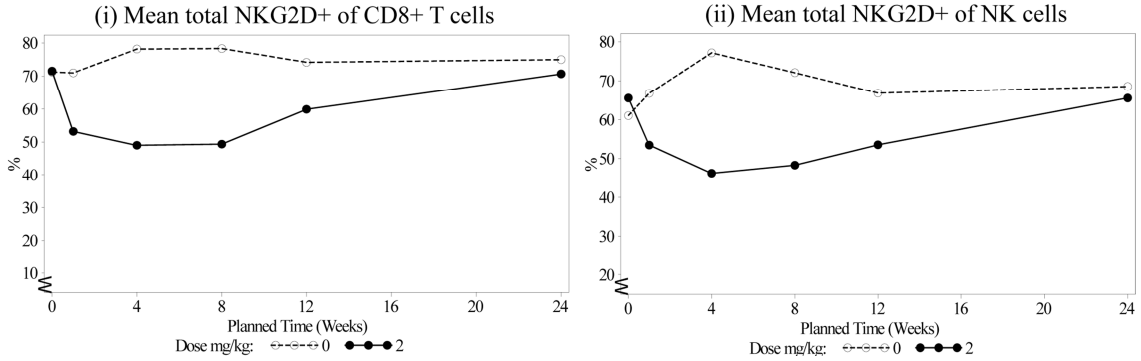

Figure 4 - Mean (±sem) expression of NKG2D on NK cells (i) and $CD8^+$ T cells (ii) after single-dose s.c. treatment with 2 mg/kg NNC0142–0002 or placebo.

- No statistically significant differences were seen for mean cytokine levels: IL-6, IL-15, TNF-α and IL-1Ra between the two treatment groups.
- No clinically relevant changes in histological score (Geboes criteria) were observed in any of the treatment groups.

SAFETY RESULTS

- A single subcutaneous administration of NNC0142–0002 at 2 mg/kg was well tolerated in subjects with moderately or severely active CD.
- A total of 180 AEs were reported for 56 (72%) subjects during the trial. Comparable proportions of subjects with AEs were observed for the two treatment groups, with 93 AEs reported for 29 (73%) NNC0142–0002-treated subjects, and 87 AEs reported for 27 (71%) placebo-treated subjects (data not shown).
- The mean time of trial participation was comparable between NNC0142–0002-treated subjects (20.7 weeks; range: 2.3 to 26.4 weeks) and placebo treated subjects (19.8 weeks; range: 1.1 to 25.7 weeks)
- In terms of AE assessed by the investigator as possibly or probably related to the trial drug, 11 subjects reported 27 AEs in the placebo group compared to only 6 subjects reporting 6 AEs in the NNC0142–0002 group. Two-thirds of AEs were attributed to general disorders/administration site conditions, gastrointestinal disorders, and infections/infestations. In absolute numbers, however, this translated into 18 out of 27 AEs in the placebo group vs. 4 out of 6 AEs in the NNC0142–0002 group.
- AEs were mainly mild (49% of events) or moderate (43% of events) in severity. A total of 14 (8% of events) events were evaluated as severe, and occurred with comparable frequencies (6 in the placebo group vs. 8 in the NNC0142–0002 group). None of the severe events were evaluated by the investigator as possibly or probably related to trial product.
- A total of 7 serious AEs were reported in 7 subjects as follows: 5 NNC0142–0002-treated (4 "exacerbation of Crohn's Disease" and 1 "*Clostridium difficile* infection"), and 2 placebo-treated subjects (1 "exacerbation of Crohn's Disease" and 1 "Nephrolithiasis"). None were judged related to trial product by the investigator.
- No deaths or medical events of special interest (such as medication errors or suspected transmission of an infectious agent via a trial product) were reported for this trial.
- A total of 4 subjects (male, aged 23–29 years) each had one AE that led to withdrawal from trial product. All withdrawals were due to exacerbation of Crohn's disease via a [redacted]. However, all of these AEs were evaluated by the investigator as having an unlikely causal relation to the trial product. One placebo-treated subject with a moderate AE did not recover by the end of the trial. The remaining 3 subjects in the NNC0142–0002 group all had AEs evaluated as severe, but they all recovered by the end of the trial.
- Of the total 6 mild or moderate injection-site reactions, 2 (5%) placebo-treated subjects reported 4 events of itching (1), pain/tenderness (1), and redness (2). In the NNC0142–0002 treated group, 2 subjects each reported one event of induration or redness.
- Infrequent and transient levels outside the normal range were observed for various cell subtypes, but there were no consistent trends indicative of relationship to treatment with NNC0142–0002.
- No safety concerns were reported throughout the trial with respect to urinalysis parameters, viral screen, physical exam, and ECG results. No statistically significant difference in lipid or cytokines, body weight, body temperature, pulse, diastolic or systolic blood pressure was observed for the NNC0142–0002treatment group when compared to placebo.
- Binding anti-drug antibodies were found in 3 samples collected prior to dosing from 2 placebo-treated subjects.

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