Synopsis

TITLE OF TRIAL

A 48-week, randomised, multi-centre, open-labelled, parallel-group trial to compare the efficacy and the safety of NN304 (insulin detemir) and NPH human insulin in subjects with insulin requiring diabetes mellitus on a basal-bolus regimen

INVESTIGATOR(S)

A total of 52 principal investigators in Japan

TRIAL SITE(S)

A total of 52 centres in Japan

PUBLICATIONS

None

TRIAL PERIOD	**DEVELOPMENT PHASE**
15 May 2003 (First Subject First Treatment) to 3 March 2005 (Last Subject Last Treatment)	Phase 3a

OBJECTIVES

Primary objective:

To confirm that the effect of NN304 is at least as effective in providing glycaemic control as that of Neutral Protamine Hagedorn (NPH) human insulin as measured by HbA_{1c} after 48 weeks of treatment in subjects with insulin requiring diabetes on a basal-bolus regimen.

Secondary objectives:

To compare NN304 and NPH human insulin treatment groups in terms of:

- Efficacy
  - Fasting plasma glucose (FPG) after 48 weeks of treatment (by self-monitoring at home)
  - The within-subject variation of FPG during the last 7 days of the 48-week treatment period (by self-monitoring at home)
  - The daytime 7-point plasma glucose profile within the last 12 weeks of the 48-week treatment period (by self-monitoring at home)
  - Nightly 9-hour plasma glucose profile within the last 12 weeks of the 48-week treatment period (measured by the central laboratory)
- Safety
  - Hypoglycaemic episodes profile (24-hour and nocturnal)
  - Adverse events profile
  - Standard safety parameters: clinical laboratory (haematology, biochemistry and lipids), ECG, funduscopy/fundusphotography, weight and blood pressure
- Others
  - Insulin doses (units)
  - Insulin therapy related to QoL at night (ITR-QOLN)
  - Insulin treatment satisfaction questionnaire Japan (ITSQ-J)
  - Insulin antibodies

METHODOLOGY

A multi-centre, open-labelled, asymmetrically randomised (2 NN304 : 1 NPH insulin), parallel group trial comparing the efficacy and safety of NN304 and NPH insulin in subjects with insulin requiring diabetes mellitus on a basal-bolus regimen. The trial included a screening visit to assess subject eligibility, and a randomisation visit a maximum of 6 weeks after the screening visit, followed by a 48-week treatment period. A post-trial follow-up visit was performed 2 to 9 days after the last visit.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to randomise a total of 357 subjects (NN304: 238 subjects [type 1 diabetes: 178, type 2 diabetes: 60], NPH human insulin: 119 subjects [type 1 diabetes: 89, type 2 diabetes: 30]). The subject disposition is shown below:

	Type 1		Type 2		Total
	NN304	NPH	NN304	NPH	
Screened					454
Screening failures					53
Randomised	197	99	70	35	401
Not exposed	1	1	3	0	
Exposed	196(100.0)	98(100.0)	67(100.0)	35(100.0)	
Withdrawals after receiving trial drug	13(6.6)	7(7.1)	2(3.0)	3(8.6)	
Adverse event	3(1.5)	1(1.0)	0(0.0)	1(2.9)	
Pregnancy	2(1.0)	0(0.0)	0(0.0)	0(0.0)	
Non-compliance with therapy	1(0.5)	1(1.0)	2(3.0)	0(0.0)	
Other	7(3.6)	5(5.1)	0(0.0)	2(5.7)	
Completed	183(93.4)	91(92.9)	65(97.0)	32(91.4)	
Safety population	196(100.0)	98(100.0)	67(100.0)	35(100.0)	
Full analysis set(FAS)	195(99.5)	98(100.0)	67(100.0)	35(100.0)	
Per protocol set(PPS)	180(91.8)	88(89.8)	65(97.0)	32(91.4)	

():percent

FAS: Full Analysis Set, PPS: Per Protocol Set

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Characteristics: Subjects with insulin requiring diabetes mellitus (type 1 or type 2) aged ≥ 20 years, body mass index < 30.0 kg/m^2, with HbA_{1c} < 11.0% and diabetes duration of ≥ 2 years who were being treated with a basal (once daily at bedtime or twice daily before breakfast and at bedtime) – bolus (three times a day prior to main meals) regimen for ≥ 12 weeks using an intermediate/long-acting human insulin as basal insulin and insulin aspart as bolus insulin.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

NN304 (Insulin detemir) 2400 nmol/mL (100 U/mL), 3 mL Penfill®.
Batch numbers: MW50302, NQ50409, MQ50712, PQ50348
NN304 was administered as basal insulin, s.c. once (bedtime) or twice (morning and bedtime) daily, and insulin aspart as bolus insulin 3 times daily before each main meal. All subjects in the NN304 group start treatment on approximately 70% of basal insulin dose (insulin detemir units) as their pre-trial intermediate/long-acting human insulin dose.

DURATION OF TREATMENT

48 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

NPH human insulin (Isophane human insulin) 600 nmol/mL (100 U/mL), 3 mL Penfill®.
Batch numbers: MQ50718, PQ50007
NPH human insulin was administered as basal insulin, s.c. once (bedtime) or twice (morning and bedtime) daily, and insulin aspart as bolus insulin 3 times daily before each main meal. All subjects in NPH group start the treatment on the same basal insulin dose as their pre-trial intermediate/long-acting human insulin dose.

CRITERIA FOR EVALUATION – EFFICACY

HbA_{1C}, FPG (by self-monitoring at home), 7-day FPG (by self-monitoring at home), daytime 7-point plasma glucose profile (by self-monitoring at home) and nightly 9-hour plasma glucose profile (measured by the central laboratory) (only in subgroup).

CRITERIA FOR EVALUATION – SAFETY

Hypoglycaemic episodes, adverse events, haematology, biochemistry, lipids, 12-lead ECG, funduscopy/fundusphotography, weight and blood pressure.

Other criteria: Insulin doses, Insulin treatment questionnaire (questions concerning glycaemic control, insulin therapy related QoL at night [ITR-QOLN] and insulin treatment satisfaction questionnaire Japan [ITSQ-J]) and antibodies (NN304 specific antibodies, insulin aspart [IAsp] specific antibodies, NN304-IAsp cross-reacting antibodies)

STATISTICAL METHODS

All analyses performed for the 2nd version of the integrated clinical trial report were planned after database release.

Handling of Subjects

All subjects who received at least one dose of trial product were included in the safety analysis. For all efficacy endpoints the analysis was performed on the FAS. The FAS consisted of all randomised subjects who had any available efficacy data after receiving the trial product. The analysis of the primary endpoint was also performed on the PPS.

Statistical Methods

Throughout the analyses a significance level of a two-sided 5% and a confidence coefficient of 95% were used and no multiplicity adjustment was performed.
The last observation carried forward (LOCF) approach was used for all endpoints at week 48 for subjects who had at least one valid post-baseline measurement.
All analyses were performed in subjects with type 1 and type 2 diabetes separately.

Efficacy

1) Primary endpoint

The primary endpoint, HbA_{1C} after 48 weeks of treatment, was performed based on the Analysis of Variance (ANOVA) model with baseline HbA_{1C} (week 0) as a covariate and treatment group as a fixed effect. A two-side 95% confidence interval for the difference in HbA_{1C} (NN304NPH human insulin) was constructed. The criterion for claiming non-inferiority was defined as follows: the upper limit of the confidence interval is less than 0.4%.
Superiority between treatment groups was evaluated based on the closed-testing procedure using the same confidence interval as the above.

2) Secondary endpoints

Mean FPG derived from 7-day FPG (by self-monitoring at home) after 48 weeks of treatment was analysed in the same way as the primary endpoint, i.e., using an ANOVA model with corresponding baseline (week 0) as a covariate and the treatment group as a fixed effect.
Within-subject variation of 7-day FPG (by self-monitoring at home) before week 48 was compared between the two treatment groups using variance component models as follows:

model 1: $Y_{tds(t)} = \mu + \alpha_t + \tau \cdot w_{s(t)} + \sigma \cdot u_{tds(t)}$,
model 2: $Y_{tds(t)} = \mu + \alpha_t + \tau \cdot w_{s(t)} + \sigma_t \cdot u_{tds(t)}$,

$Y_{tds(t)}$: FPG for treatment t, day d and subject s(t), and (t) means 'nest',
μ : overall mean,
α_t : treatment effect,
τ : between subject standard deviation,
σ : residual common standard deviation,
σ_t : residual standard deviation of treatment t, and all ($w_{s(t)}$) , ($u_{tsd(t)}$) being i.i.d. N(0, 1).

The test was carried out as a likelihood ratio test, comparing the model 2 to the model 1.
Daytime 7-point PG profiles within the last 12 weeks of the 48-week treatment period (by self-monitoring at home) and nightly 9-hour PG profiles within the last 12 weeks of 48-week treatment period (measured by the central laboratory) (only in subgroup) were analysed using a repeated measures ANOVA model including treatment group, time and the treatment-by-time interaction as fixed effects and subject as a random effect.

Safety

1) Hypoglycaemic episodes

The incidence of hypoglycaemic episodes during the maintenance period was evaluated by estimating the relative risk of having a hypoglycaemic episode in the NN304 group compared to that in the NPH human insulin group. The

maintenance period was defined as the interval from 4 weeks after the first date on trial product [week 4 excluded] to one day after the last doing day. In order to estimate this relative risk, all hypoglycaemic episodes occurring during the maintenance period were analysed as recurrent events using a gamma frailty model. This model is an extended Cox regression model including a random effect (following a gamma distribution), which acts multiplicatively on the baseline hazard function and describes the excess risk (or frailty) for a subject. Treatment group was included as a covariate in the model.
The same analysis was performed for each of the following subsets of hypoglycaemic episodes: major hypoglycaemic episodes, minor hypoglycaemic episodes, symptoms only hypoglycaemic episodes, biochemical hypoglycaemia defined as asymptomatic plasma glucose value < 3.1 mmol/L (≤ 55 mg/dL).
Nocturnal (23:00-06:00) hypoglycaemic episodes were also analysed in exactly the same way as the above.
2) Adverse events
Treatment emergent adverse events (TEAEs) were summarised by treatment groups by MedDRA system-organ class and MedDRA preferred term, severity and relation to trial product. TEAE was defined as an adverse event reported from the first dosing day to the post-trial visit.
3) Clinical laboratory variables, ECG, funduscopy/fundusphotography, weight and blood pressure
Clinical laboratory variables were summarised by descriptive statistics by visit and treatment group, and changes of variables were presented by figures. Shift tables relating to the reference range and showing changes from baseline were presented for each variable. All clinical laboratory values outside normal range were listed.
ECG and funduscopy/fundusphotography were summarised by shift tables. Blood pressure was summarised by descriptive statistics by visit and treatment group. Weight after 48 weeks of treatment was analysed in the same way as the primary endpoint with baseline weight (week 0) as a covariate.
Other
1) ITR-QOLN and ITSQ-J
Total score was calculated, and was analysed in the same way as the primary endpoint with corresponding baseline score as a covariate. ITR-QOLN and ITSQ-J were composed of several factors including nocturnal hypoglycaemic episodes. Total score by each factor was also analysed.
2) Insulin doses
Changes in mean daily insulin doses were graphically presented by treatment group. Mean daily insulin doses after 48 weeks of treatment were compared between the two treatment groups. Dose ratio (NN304/NPH) of mean basal insulin dose after 48 weeks of treatment was calculated.
3) Insulin antibodies
Changes of antibodies was graphically presented for each subject. Treatment group comparison at week 48 was performed by Wilcoxon rank sum test.

DEMOGRAPHY OF TRIAL POPULATION

Baseline characteristics at screening visit for all subjects included in the safety population are shown below:

Subjects with type 1 diabetes

	NN304	NPH human insulin	Total
Safety population	196	98	294
	N (%)	N (%)	N (%)
Sex			
Male	81 (41.3)	49 (50.0)	130 (44.2)
Female	115 (58.7)	49 (50.0)	164 (55.8)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	42.4 (14.2)	41.8 (13.5)	42.2 (14.0)
Body weight (kg)	58.27 (8.95)	60.02 (8.40)	58.86 (8.80)
BMI (kgm^2)	22.35 (2.65)	22.40 (2.72)	22.37 (2.67)
Duration of diabetes (years)	13.43 (8.18)	13.01 (8.47)	13.29 (8.27)
Duration of current basal-bolus regimen (months)	15.20 (17.90)	16.07 (14.50)	15.49 (16.82)
HbA_{1C} (%)[#]	7.40 (0.97)	7.42 (1.16)	7.41 (1.04)
Mean FPG (mg/dL)[#]	170.12 (51.18)	176.89 (57.61)	172.36 (53.38)

#: The data was at week 0.

Subjects with type 2 diabetes

	NN304	NPH human insulin	Total
Safety population	67	35	102
	N (%)	N (%)	N (%)
Sex			
Male	36 (53.7)	25 (71.4)	61 (59.8)
Female	31 (46.3)	10 (28.6)	41 (40.2)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)	55.2 (13.3)	58.1 (12.2)	56.2 (13.0)
Body weight (kg)	63.23 (10.98)	62.69 (11.72)	63.05 (11.18)
BMI (kgm^2)	24.21 (3.20)	23.90 (2.99)	24.10 (3.12)
Duration of diabetes (years)	14.13 (7.54)	15.26 (8.59)	14.52 (7.89)
Duration of current basal-bolus regimen (months)	11.88 (6.39)	10.14 (5.25)	11.28 (6.05)
HbA_{1C} (%)#	7.66 (1.11)	7.58 (1.11)	7.63 (1.11)
Mean FPG (mg/dL)#	167.64 (48.54)	154.20 (38.59)	163.02 (45.62)

#: The data was at week 0.

Both in subjects with type 1 and type 2 diabetes, a higher proportion of female subjects was seen in the NN304 group than in NPH human insulin group. The other demographic characteristics are similar in both groups in type 1 and type 2 subjects.

EFFICACY RESULTS

- Treatment with NN304 was non-inferior to treatment with NPH human insulin as measured by HbA_{1C} after 48 weeks of treatment in subjects with type 1 diabetes on a basal-bolus regimen in the FAS population.
  - Means (SE) adjusted for baseline HbA_{1C} were 7.33% (0.05) and 7.29% (0.07) for NN304 and NPH human insulin, respectively.
  - Mean difference (NN304-NPH human insulin) = 0.03% [95% C.I.: -0.14; 0.21]
  - Treatment with NN304 was also non-inferior to treatment with NPH human insulin in the PPS population. Mean difference (NN304–NPH human insulin) was 0.00% [95% C.I.: -0.18; 0.18]
- HbA_{1C} in subjects with type 2 diabetes was comparable for the two treatment groups, though the sample size of this subgroup was not large enough to provide statistical power in any analysis.
- The mean FPG derived from 7-day FPG by self-monitoring at home was lower after 48 weeks of treatment with NN304 than with NPH human insulin and the difference was statistically significant (p=0.0263) in subjects with type 1 diabetes.
  - Means (SE) adjusted for baseline mean FPG were 146.46 mg/dL (2.70) and 156.99 mg/dL (3.86) for NN304 and NPH human insulin, respectively.
  - Mean difference (NN304-NPH human insulin) = -10.53 mg/dL [95% C.I.: -19.81; -1.25]
- The trend that the mean FPG in the NN304 group was lower than in the NPH human insulin group was also seen in subjects with type 2 diabetes.
- Within-subject variation (CV%) derived from 7-day FPG by self-monitoring at home after 48 weeks of treatment was lower in the NN304 group than in NPH human insulin, in both subgroups of type 1 and type 2 diabetes. Statistical significance between groups was seen in the analysis of SD in both subjects with type 1 and type 2 diabetes (for both subgroups, p<0.0001).
- The overall shapes of daytime 7-point plasma glucose profile by self-monitoring at home within the last 12 weeks of 48-week treatment period were comparable for NN304 and NPH human insulin in both subjects with type 1 and type 2 diabetes. In subjects with type 1 diabetes (in subgroup of 74 subjects in the NN304 group and 39 in the NPH human insulin group), the overall shape of nightly 9-hour plasma glucose profile measured by the central laboratory within the last 12 weeks of the 48-week treatment period was different between the two treatment groups.
  - The profiles showed that fluctuation in mean plasma glucose was smaller in the NN304 group than in the NPH human insulin group.
  - Mean plasma glucose concentrations were higher in the NN304 group than in the NPH human insulin group

during the night.
- Increase in plasma glucose concentrations in the early morning was smaller in the NN304 group compared to the NPH human insulin group.
- No substantial result was obtained from nightly glucose profile in subjects with type 2 diabetes, because of the small sample size (21 subjects in the NN304 group and 11 in the NPH human insulin group).

SAFETY RESULTS

- The incidence of daily hypoglycaemic episodes during the maintenance period was comparable for the two treatment groups in subjects with type 1 diabetes.
  - A total of 8262 episodes for 178 (92.7%) subjects with NN304 treatment (50.85 events / subjects*year) and 4130 episodes for 95 (96.9%) subjects with NPH human insulin (51.53 events / subjects*year) were reported.
  - Relative risk of having a daily hypoglycaemic episode (NN304 / NPH human insulin) = 0.96 [95% C.I.: 0.65; 1.40].
- The incidence of nocturnal hypoglycaemic episodes during the maintenance period with NN304 was statistically significantly lower than with NPH human insulin (p=0.0464) in subjects with type 1 diabetes.
  - A total of 1171 episodes for 133 (69.3%) subjects with NN304 treatment (7.21 events / subjects*year) and 868 episodes for 78 (79.6%) subjects with NPH human insulin (10.83 events / subjects*year) were reported.
  - Relative risk of having a nocturnal hypoglycaemic episode (NN304 / NPH human insulin) = 0.69 [95% C.I.: 0.47; 0.99].
- In subjects with type 2 diabetes, the incidence of daily hypoglycaemic episodes and that of nocturnal hypoglycaemic episodes during the maintenance period were comparable for two treatment groups.
  - A total of 882 daily hypoglycaemic episodes for 54 (81.8%) subjects with NN304 treatment (15.57 events / subjects*year) and 435 episodes for 27 (77.1%) subjects with NPH human insulin (15.31 events / subjects*year) were reported.
  - Relative risk of having a daily hypoglycaemic episode (NN304 / NPH human insulin) = 1.02 [95% C.I.: 0.42; 2.45].
  - A total of 99 nocturnal hypoglycaemic episodes for 25 (37.9%) subjects with NN304 treatment (1.75 events / subjects*year) and 56 episodes for 11 (31.4%) subjects with NPH human insulin (1.97 events / subjects*year) were reported.
  - Relative risk of having a nocturnal hypoglycaemic episode (NN304 / NPH human insulin) = 0.85 [95% C.I.: 0.26; 2.82].
- Adverse event profile in type 1 diabetes was comparable in both treatment groups.
  - The proportion of subjects who experienced TEAEs was similar for two treatment groups. A total of 715 TEAEs were reported from 173 (88.3%) subjects in the NN304 group and 335 TEAEs were reported from 87 (88.8%) subjects in the NPH human insulin group.
  - Relation to treatment was considered probable/possible for 20 events in 13 (6.6%) subjects in the NN304 group and for 6 events in 5 (5.1%) subjects in the NPH human insulin group. These evens were sporadic and there were no differences in their pattern between the two treatment groups.
  - A total of 20 SAEs for 13 (6.6%) subjects in the NN304 group and 13 SAEs for 10 (10.2%) subjects in the NPH human insulin group were reported. The relation to treatment was considered probable/possible for hypoglycaemia (2 events for 2 subjects with NN304 treatment, 1 event for 1 subject with NPH human insulin treatment), hypoglycaemic coma (3 events for 2 subjects with NPH human insulin treatment), and amnesia and dehydration (2 events for 1 subject with NN304 treatment). Four subjects (3 in the NN304 group and 1 in the NPH human insulin group) withdrew from the trial due to the onset of adverse events.
- Adverse event profile in type 2 diabetes was also comparable in both treatment groups.
  - The proportion of subjects who experienced TEAEs was similar for the two treatment groups. A total of 249 TEAEs were reported from 61 (91.0%) subjects in the NN304 group and 124 TEAEs were reported from 29 (82.9%) subjects in the NPH human insulin group.
  - Relation to treatment was considered probable/possible for 17 events in 6 (9.0%) subjects in the NN304 group and for 5 events in 3 (8.6%) subjects in the NPH human insulin group. These evens were sporadic and there were no differences in their pattern between the two treatment groups.
  - A total of 4 SAEs (4 subjects, 6.0%) in the NN304 group and 4 SAEs (4 subjects, 11.4%) in the NPH human

insulin group were reported, but all SAEs were considered to be unlikely related to the treatment. Only one subject in the NPH human insulin group withdrew from the trial due to the onset of adverse events.

- There were no deaths during the trial.
- There were no differences in results for clinical laboratory, blood pressure, ECG and funduscopy/fundusphotography between the two treatment groups, in both subjects with type 1 and type 2 diabetes.
- Mean body weight adjusted for baseline value was lower after 48 weeks of treatment with NN304 than with NPH human insulin and statistical significant difference was seen in subjects with type 1 diabetes.
  - Means (SE) adjusted for baseline body weight were 58.99 kg (0.17) and 59.91 kg (0.24) for NN304 and NPH human insulin, respectively.
  - Mean difference (NN304-NPH human insulin) = -0.92 kg [95% C.I.: -1.51; -0.33] (p=0.0024).
- The similar trend was also found in subjects with type 2 diabetes.
  - Means (SE) adjusted for baseline body weight were 63.47 kg (0.28) and 64.29 kg (0.38) for NN304 and NPH human insulin, respectively.
  - Mean difference (NN304-NPH human insulin) = -0.82 kg [95% C.I.: -1.76; 0.11] (p=0.0847).

OTHER RESULTS

- In subjects with type 1 diabetes, the mean daily basal insulin dose at end of trial was statistically significantly lower with NN304 than with NPH human insulin, although the dose of NN304 increased toward baseline (pre-trial) level from the starting dose (70% of pre-trial basal insulin dose). The ratio (NN304 /NPH human insulin) for mean daily basal insulin dose at end of trial was 0.869. The dose of bolus insulin was slightly increased in the NN304 group; while no increase was seen in the NPH human insulin group. As a result, the ratio for total daily insulin dose at end of trial was 0.983.
  In subjects with type 2 diabetes, the mean daily basal insulin dose and the mean daily bolus insulin dose, and, as a result, total daily insulin dose at end of trial were increased from baseline in both treatment groups. All doses were slightly higher in the NN304 group than in the NPH human insulin group: the ratio (NN304/NPH human insulin) was 1.091 for mean daily basal insulin and 1.059 for total daily insulin at end of trial.
- Total scores for ITR-QOLN and ITSQ-J after 48 weeks of treatment with NN304 were higher than with NPH human insulin and the difference was statistically significant in subjects with type 1 diabetes. In general, the results of ITR-QOLN and ITSQ-J in the NN304 group were more favourable than in the NPH human insulin group. No difference between the two groups was seen in the results for subjects with type 2 diabetes, though the sample size was small.
- Subjects with type 1 diabetes in the NN304 group showed formation of NN304 specific antibodies at 49 weeks (LOCF); the change from baseline was statistically significantly larger than that in the NPH human insulin group. However, no correlation was found between change in antibodies and HbA_{1C}. The change in NN304-IAsp cross-reacting antibodies was positively correlated with basal insulin dose and total insulin dose; this is considered to be of little clinical significance.

CONCLUSIONS

Treatment with NN304 or NPH human insulin in subjects with insulin requiring diabetes (type 1 and type 2) on a basal-bolus regimen yielded the following results after 48 weeks of treatment:

- Treatment with NN304 was non-inferior to treatment with NPH human insulin as measured by HbA_{1C} after 48 weeks of treatment in subjects with type 1 diabetes.
- The mean FPG was lower in the NN304 group than in the NPH human insulin group; a statistically significant difference was seen in subjects with type 1 diabetes. Within-subject variation of FPG with NN304 was significantly lower than with NPH human insulin both in subjects with type 1 and type 2 diabetes. The overall shape of nightly 9-hour plasma glucose profiles was different between the two treatment groups; fluctuation in mean plasma glucose concentration was smaller and the increase in plasma glucose concentrations in the early morning was smaller with NN304 than with NPH human insulin.
- The incidence of daily hypoglycaemic episodes during the maintenance period was comparable for two treatment groups in both subjects with type 1 and type 2 diabetes. The incidence of nocturnal hypoglycaemic episodes during the maintenance period in the NN304 group was significantly lower than in the NPH human insulin group in subjects with type 1 diabetes.
- There were no differences between the two treatment groups for adverse events, clinical laboratory, blood pressure,

ECG and funduscopy/fundusphotography.

- Mean body weight was lower in the NN304 group than in the NPH human insulin group at end of study. The difference was statistically significant in subjects with type 1 diabetes.
- In subjects with type 1 diabetes, the mean daily basal insulin dose in the NN304 group was significantly lower than in the NPH human insulin group; the dose ratio (NN304/NPH human insulin) of basal insulin was 0.869. In subjects with type 2 diabetes, the doses of basal insulin and bolus insulin were slightly higher in the NN304 group than in the NPH human insulin group; the dose ratio of basal insulin was 1.091.
- The results of ITR-QOLN and ITSQ-J questionnaires in the NN304 group were more favourable than in the NPH human insulin group in subjects with type 1 diabetes.
- Subjects with type 1 diabetes in the NN304 group showed formation of NN304 specific antibodies at end of trial; the change from baseline was statistically significantly larger than in the NPH human insulin group. However, no correlation was found between change in antibodies and HbA_{1C}. The change in NN304-IAsp cross-reacting antibodies was positively correlated with basal insulin dose and total insulin dose; this is considered to be of little clinical significance.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.