Synopsis

TITLE OF TRIAL
A 24-week, randomised, multi-centre, open-labelled, parallel-group trial to investigate the safety of NN304 (insulin detemir) and Neutral protamine hagedorn (NPH) human insulin in children with type 1 diabetes on a basal-bolus regimen

INVESTIGATOR(S)
A total of 17 investigators in Japan. The coordinating investigator was:
Nozomu Sasaki, Professor, Saitama Medical School Hospital, Department of Pediatrics

TRIAL SITE(S)
This was a multicentre trial; a total of 17 centres in Japan.

PUBLICATIONS
None

TRIAL PERIOD
08 June 2004 (First patient first treatment) to 23 April 2005 (Last patient last treatment)

DEVELOPMENT PHASE
Phase 3a

OBJECTIVES
Primary objective:
• To investigate the safety profile of NN304 compared to NPH human insulin during a 24-week treatment period in children with type 1 diabetes on a basal-bolus regimen.

Secondary objectives:
• To investigate the effect of NN304 compared to NPH human insulin in terms of glycaemic control as measured by glycated haemoglobin A1C (HbA1C) after a 24-week treatment period.
• To investigate the effect of NN304 compared to NPH human insulin in terms of the five-day mean Fasting plasma glucose (FPG) value during the last week of 24-week treatment period.
• To investigate the effect of NN304 compared to NPH human insulin in terms of the within-subject variation of five-day FPG during the last week of 24-week treatment period.

METHODOLOGY
• This was a multi-centre, open-labelled, asymmetrically randomised (NN304: NPH human insulin=2:1), parallel group safety trial.
• The trial included a screening visit (Visit 1) to assess the eligibility of the subjects, and a randomisation visit (Visit 2) a maximum of six weeks after the screening visit followed by a 24-week treatment period (Visits 2 to 8).
• Registration and randomisation of the subjects was made between Visits 1 and 2.

NUMBER OF SUBJECTS PLANNED AND ANALYSED
Planned number of subjects to be screened was 90. It was planned to randomise a total of 72. In total, 88 subjects were screened, of which 2 were screening failures. One subject in the NN304 group was excluded from safety population due to be judged as GCP violation. The subject disposition is shown below:

<table>
<thead>
<tr>
<th></th>
<th>NN304</th>
<th>NPH</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>57</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>Exposed</td>
<td>56(100.0)</td>
<td>27(100.0)</td>
<td></td>
</tr>
<tr>
<td>Withdrawals after receiving trial drug (Non-compliance with therapy)</td>
<td>1( 1.8)</td>
<td>0( 0.0)</td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>55( 98.2)</td>
<td>27(100.0)</td>
<td></td>
</tr>
<tr>
<td>Safety population</td>
<td>55( 98.2)</td>
<td>27(100.0)</td>
<td></td>
</tr>
<tr>
<td>Full analysis set (FAS)</td>
<td>55( 98.2)</td>
<td>27(100.0)</td>
<td></td>
</tr>
<tr>
<td>Per protocol set (PPS)</td>
<td>50( 89.3)</td>
<td>25( 92.6)</td>
<td></td>
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</tbody>
</table>

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Males and females with type 1 diabetes, age ≥ seven years and < 18 years; duration of type 1 diabetes ≥ one year,
**Current Treatment**

Current treatment with basal (once daily at bedtime or twice daily before breakfast and at bedtime) – bolus (three times a day before main meals) regimen ≥ 12 weeks using an intermediate/long-acting human insulin as basal insulin and insulin aspart and/or soluble human insulin as bolus insulin; HbA1C < 11.0%.

**Test Product, Dose and Mode of Administration, Batch Number**

**NN304 (insulin detemir):** 2400 nmol/mL (100 U/mL), 3 mL cartridge in a pre-filled pen (FlexPen®) injected subcutaneous (s.c.) in once daily at bedtime or twice daily before breakfast and at bedtime, according to the same treatment regimen for subject's pre-trial basal insulin. Start the treatment on the 70% basal insulin dose (insulin detemir unit) as their pre-trial intermediate/long-acting human insulin dose.

Batch number: NP51027 and PP50811

**Duration of Treatment**

24 weeks

**Reference Therapy, Dose and Mode of Administration, Batch Number**

**NPH human insulin (isophane human insulin):** 600 nmol/mL (100 IU/mL), 3 mL cartridge in a FlexPen® injected s.c. in once daily at bedtime or twice daily before breakfast and at bedtime, according to the same treatment regimen for subject's pre-trial basal insulin. Start the treatment on the same basal insulin dose as their pre-trial intermediate/long-acting human insulin dose.

Batch number: PP50109

**Criteria for Evaluation – Safety**

- Hypoglycaemic episodes, adverse events, haematology, biochemistry, urinalysis for micro-albuminuria, body weight/body mass index (BMI), blood pressure and funduscopy/fundusphotography.

**Criteria for Evaluation – Efficacy**

- HbA1C and five-day mean FPG (by self-monitoring blood glucose [SMBG] at home*) during the last week of 24-week treatment period

*In this trial, blood glucose was measured by the same glucose meter with which glucose in blood are converted to plasma relevant values

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

**Other Measurements:**

- Height and insulin doses (unit)

**Statistical Methods**

**Safety endpoints:**

- The incidence of hypoglycaemic episodes during the first 6 weeks and the last 18 weeks of treatment (nocturnal [23:00-06:00, inclusive] and daily [0:00-23:59, inclusive]); the incidence of hypoglycaemic episodes during the maintenance period was evaluated by estimating the relative risk of having hypoglycaemic episode in the NN304 group compared to that in the NPH human insulin group. The maintenance period was defined as the interval from 6 weeks after the first day on the trial product (excluding the day of week 6) to the last day on trial product (including the last day). In order to estimate this relative risk, all hypoglycaemic episodes reported during the maintenance period were analysed as recurrent events using a gamma frailty model. The same analyses were performed for the subsets of major hypoglycaemic episodes, minor hypoglycaemic episodes, symptoms only and biochemical hypoglycaemia [defined as asymptomatic hypoglycaemic with PG value < 3.1 mmol/L (≤ 55 mg/dL)]. Nocturnal (23:00-06:00) hypoglycaemic episodes were analysed in exactly the same way as the above. As a supplementary analysis, hypoglycaemic episodes during 22:00-07:00 were analysed in the same way in consideration of children’s bedtime.

- Adverse events (Treatment emergent adverse events [TEAE]) were summarised by the treatment groups by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and MedDRA preferred term, severity and relation to the trial product. The descriptive statistics presented for each SOC and preferred term were the number of subjects with event (N), the percent of subjects exposed with event (%), and the number of events (E).

- Laboratory assessments (haematology, biochemistry and urinalysis micro-albuminuria) 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.

- BMI after 24 weeks of treatment was analysed based on the analysis of variance (ANOVA) model with baseline BMI as a covariate and the treatment group and type of bolus insulin as fixed effects.
- Blood pressure was summarised by descriptive statistics by visit and treatment group.
- Funduscopy/fundusphotography was summarised by a shift table.

**Efficacy endpoints:**

- HbA1C after 24-week treatment; The 95% confidence interval (C.I.) for the mean difference between two treatment groups in HbA1C at 24 weeks last observation carried forward (LOCF) was constructed under the ANOVA model including the treatment group as a fixed effect and HbA1C at baseline as a covariate.
- Five-day mean FPG (SMBG) during the last week of 24-week treatment period; the mean FPG derived from the five-day FPG (SMBG) before breakfast after 24 weeks of treatment was analysed in the same way as HbA1C.
- Within-subject variation of home five-day FPG during the last week of 24-week treatment period; The within-subject variation of five-day FPG before breakfast after 24-week treatment was compared between the two treatment groups using variance component models.

**Other endpoints:**

- Height after 24 weeks of treatment was analysed in the same way as HbA1C.
- Insulin doses; Mean change of total daily insulin dose per body weight (units/kg) was graphically presented by treatment group. Total daily bolus insulin dose per body weight (units/kg) after 24-week treatment was compared between two treatment groups. Dose ratio (NN304/NPH) of total basal insulin dose per body weight (units/kg) after 24-week treatment was calculated.

### DEMOGRAPHY OF TRIAL POPULATION

Approximately 60% of the subjects in the both treatment groups were female. The subject was younger in the NN304 group than in the NPH human insulin group. Accordingly, body weight and height tended to be lower in the NN304 group than in the NPH human insulin group, but BMI was comparable in two treatment groups. These differences were not considered to affect on the result. Baseline characteristics for safety population are shown below:

<table>
<thead>
<tr>
<th></th>
<th>NN304 (N=55)</th>
<th>NPH human insulin (N=27)</th>
<th>Total (N=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>Male/Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>Mean (SD)</td>
<td>13.2 (2.5)</td>
<td>14.1 (2.5)</td>
</tr>
<tr>
<td><strong>Body weight (kg)</strong></td>
<td>Mean (SD)</td>
<td>49.09 (13.28)</td>
<td>54.20 (13.84)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>Mean (SD)</td>
<td>153.15 (11.01)</td>
<td>160.12 (12.29)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>Mean (SD)</td>
<td>20.53 (3.49)</td>
<td>20.84 (3.71)</td>
</tr>
<tr>
<td><strong>Duration of diabetes (yrs)</strong></td>
<td>Mean (SD)</td>
<td>4.72 (3.22)</td>
<td>6.51 (4.04)</td>
</tr>
<tr>
<td><strong>Baseline HbA1C (%)</strong></td>
<td>Mean (SD)</td>
<td>7.21 (0.87)</td>
<td>7.54 (1.26)</td>
</tr>
<tr>
<td><strong>Baseline total daily insulin dose (U/kg or IU/kg)</strong></td>
<td>Mean (SD)</td>
<td>1.2125 (0.2747)</td>
<td>1.1393 (0.2986)</td>
</tr>
</tbody>
</table>

### SAFETY RESULTS

- Overall, 24 hour hypoglycaemia profile was similar in the two treatment group. The incidence of hypoglycaemia during maintenance period was 96.4% (1877 episodes in 53 subjects [94.77 events/subject year]) in the NN304 group and 100% (851 episodes in 27 subjects [85.96 events/subject year]) in the NPH human insulin group. The number of episodes per year of exposure was higher in the NN304 group than in the NPH human insulin group, however the frequency of the subjects who experienced the episodes was comparable in both groups. The frequency of major hypoglycaemic episodes was similar in the two treatment group: Five subjects (9.1%) in the NN304 group reported eight episodes (0.40 events/subject year) and three subjects (11.1%) in the NPH human insulin group reported five episodes (0.51 events/subject year). No significant difference between two treatment
groups was seen in the relative risk (the NN304 group/ the NPH human insulin group) of hypoglycaemic episodes over 24 hours; 1.10 (95% C.I.: 0.43; 2.83). The risk of having symptoms only was statistically significantly lower in the NN304 group than in the NPH human insulin group (p=0.0090). There was a trend towards higher risk of biochemical hypoglycaemia in the NN304 group.

• The same trend was seen in nocturnal hypoglycaemic episodes.

• The frequency of adverse events was comparable in two treatment groups; 46 subjects (83.6%) in the NN304 group reported 156 TEAEs and 23 subjects (85.2%) in the NPH human insulin group reported 59 TEAEs. The majority of adverse events in both groups were mild. One severe hypoglycaemia was reported in the NN304 group. The most frequently classified into SOC was Infections and infestations (62 events in 29 subjects [52.7%] in the NN304 group, 22 events in 14 subjects [51.9%] in NPH human insulin group). The most frequently reported TEAEs (more than 5% of subjects in both treatment groups) were gastroenteritis, nasopharyngitis, upper respiratory tract inflammation and headache.

• Relation to treatment was considered probable or possible for five TEAEs reported in five subjects (9.1%) in the NN304 group versus one TEAE in one subject (3.7%) in the NPH human insulin group. All TEAEs that were considered probably or possibly related to the trial product were single episodes. The proportion of the subjects who experienced TEAE that was considered probably or possibly related to the trial product were low in both treatment group.

• No death occurred during the trial. Three subjects (5.5%) in the NN304 group reported three SAEs (two hypoglycaemia in two subjects, one diabetic ketoacidosis in one subject) and one subject (3.7%) in the NPH human insulin group reported one SAE (diabetic ketoacidosis). Only one severe SAE (hypoglycaemia) reported in the NN304 group was judged probably related to the trial product by the Investigator. The other SAEs were mild. All SAEs were recovered.

• After 24 weeks of treatment, the LS mean (SE) BMI adjusted for baseline value was 21.08 (0.11) kg/m² in the NN304 group and 21.40 (0.16) kg/m² in the NPH human insulin group. The estimated mean treatment difference (NN304 group – NPH human insulin group) in BMI was -0.32 (95% C.I.: -0.71; 0.08) kg/m². BMI after 24 weeks of treatment tended to be lower in the NN304 group than in the NPH human insulin group.

• The abnormal changes of clinical laboratory values reported in more than 5% of subjects was urine albumin. Urine albumin/creatinine ratio increased reported as clinical laboratory adverse event were three events in three subjects (5.5%) in the NN304 group and one event in one subject (3.7%) in the NPH human insulin group. No probably or possibly related Urine albumin/creatinine ratio increased was reported. In individual subjects, no clinically significant abnormal changes of clinical laboratory values were reported.

• With regard to blood pressures and Funduscopy/fundusphotography, no noteworthy treatment differences were observed.

**EFFICACY RESULTS**

- Mean (SD) HbA1C value at the baseline and 24 weeks of treatment were 7.21 (0.87) % and 7.54 (1.02) % for the NN304 group and 7.54 (1.26) % and 7.67 (1.02) % for the NPH human insulin group, respectively. After 24 weeks of treatment, the LS mean (SE) HbA1C adjusted for baseline value was 7.62 (0.10) % in the NN304 group and 7.52 (0.14) % in the NPH human insulin group. The estimated mean treatment difference in HbA1C adjusted for baseline value was 0.10 % (95% C.I.: -0.24; 0.45). HbA1C slightly increased after 24 weeks of treatment from baselines and no difference was seen in between the two groups.

- The mean FPG after 24 weeks of treatment was decreased from baseline in the NN304 group, whereas there was not change from baseline in the NPH human insulin group. The LS mean (SE) FPG adjusted for baseline value was 143.65 (7.52) mg/dL in the NN304 group and 163.99 (10.63) mg/dL in the NPH human insulin group. Mean FPG levels tented to be lower after 24 weeks of treatment with NN304 than with NPH human insulin but the difference was not statistically significant; the estimated mean treatment difference in FPG adjusted for baseline value was -20.34 (95% C.I.: -46.31; 5.64) mg/dL.

- Within-subjects variation as measured by CV (%) after 24 weeks of treatment were 41.0% in the NN304 group and 41.8% in the NPH human insulin group, respectively. Within-subjects variation was comparable in both groups.

- The LS mean (SE) height adjusted for baseline value was 156.94 (0.18) cm in the NN304 group and 156.93 (0.27) cm in the NPH human insulin group. The estimated mean treatment difference in height adjusted for baseline value was 0.01 (95% C.I.: -0.64; 0.67) cm. Height increased after 24 weeks of treatment and no difference was seen
between the two treatment groups.

- The dose ratio (NN304/NPH) for basal insulin was 0.853, whereas the ratio for bolus insulin was 1.127 at the end of trial. The dose ratio for total daily insulin was 1.030; therefore total daily insulin at the end of trial was comparable in the two groups.

- The estimated mean treatment difference in total daily basal insulin dose per body weight adjusted for baseline value was -0.0766 (95% C.I.: -0.1216; -0.0316) U/kg or IU/kg. The estimated mean treatment difference in total daily bolus insulin dose per body weight adjusted for baseline value was 0.0570 (95% C.I.: -0.0099; 0.1239) U/kg or IU/kg. The estimated mean treatment difference in total daily insulin dose per body weight adjusted for baseline value was -0.0225 (95% C.I.: -0.1102; -0.0652) U/kg or IU/kg. The total daily basal insulin dose per body weight was lower in the NN304 group than in the NPH human insulin group. The total daily bolus insulin dose per body weight and total daily insulin dose per body weight were comparable in the two treatment groups.

CONCLUSIONS

- There were no differences in the incidence of hypoglycaemia between NN304 and NPH human insulin groups. No difference was seen in the incidence of nocturnal hypoglycaemia.

- The overall safety profile of NN304 was similar to that of NPH human insulin on the basis of evaluation of adverse events, clinical laboratory test, blood pressures and BMI. No safety concern was raised during 24 weeks of treatment with NN304.

- Glycaemic control as measured by HbA1C after 24 weeks of treatment with NN304 was similar to that with NPH human insulin.

- Five-day FPG after 24 weeks of treatment suggested that blood glucose before breakfast tended to be lower in the NN304 group than in the NPH human insulin group.

- Within-subject variation derived from 5-day FBG was comparable in both groups.

- There were no differences in the height development after 24 weeks of treatment between the two groups.

- The dose ratio (NN304/NPH) for basal insulin was 0.853, whereas the ratio for bolus insulin was 1.127 at the end of trial. This may be partly because the starting dose of NN304 was 70% of subject’s previous basal insulin dose: some subject’s basal insulin dose may not have largely increased therefore their bolus insulin dose might have been increased. In conclusion, the total daily insulin dose was increased and total daily insulin at the end of trial was comparable in the two groups.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, except one GCP violation subject.