**Synopsis**

**TITLE OF TRIAL**
An open-label, multi-centre, multi-national, comparative, randomised, cross-over trial evaluating preference as well as performance, acceptance, handling and safety of NovoPen 4 (MS236) versus NovoPen 3 in insulin treated diabetic patients

**INVESTIGATORS**
There were 23 investigators in this trial.

**TRIAL SITES**
There were a total of 23 trial sites in Austria, Germany, Italy, Netherlands and United Kingdom.

**PUBLICATIONS**

**TRIAL PERIOD**
19 August 2003 – 9 February 2004

**OBJECTIVES**
Primary objective:
The primary objective was to investigate which insulin delivery pen was preferred by patients with diabetes – NovoPen 4 or NovoPen 3. The patients evaluated their overall pen preference by ticking off a question after both treatment periods were completed.

Secondary objectives:
The secondary objectives were to evaluate the metabolic control as measured by:

- HbA1c at week 0, at week 6, and at week 12
- Serum Fructosamine levels at week 0, at week 6, and at week 12 (for adults only)
- Mean plasma glucose levels (7-point plasma glucose profile)(at week 6 and at week 12)(performed on normal weekday within two weeks before Visit 3 and Visit 4)
- Number/severity of hypoglycaemic episodes (at week 0, at week 6 and at week 12)

Further, the following was evaluated:
- Adverse device effects (at week 6 and week 12)
- Adverse events (at week 0, at week 6 and week 12)
- General acceptance and handling (questionnaire)(at week 6 and week 12)
- Evaluation of the user manuals for NovoPen 4 and NovoPen 3 (questionnaire)(at week 6 and week 12)

**METHODOLOGY**
The trial was an open-label, multi-centre multi-national, comparative, randomised, two-period cross-over trial in 200 insulin treated diabetic patients (planned number). Half of the patients were started on NovoPen 4 and then crossed over to NovoPen 3 with the reverse sequence being followed by the other half of the patients. This study was a non-inferiority trial. Each subject participated in the trial (screening period included) for a minimum of 14 weeks and maximally for 16 weeks.
NUMBER OF SUBJECTS PLANNED AND ANALYSED
200 patients were planned, but the protocol was amended to include 215 patients. 212 were screened, 208 were randomised, 202 completed, 197 were per protocol patients, and 208 were intention-to-treat patients (children 42/adults 155 and children 44/adults 164, respectively.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION
Type 1 or insulin using type 2 diabetic patients, aged ≥ 18, HbA1c < 11 %, who had been on basal (human isophane insulin) once or twice daily and/or bolus (rapid acting insulin analogue) insulin therapy for a minimum of 1 month, duration of diabetes ≥ 12 months.

Type 1 diabetic children/adolescents aged ≥ 9, but < 18 years, HbA1c < 11 %, who had been on basal (human isophane insulin) once or twice daily and/or bolus (rapid acting insulin analogue) insulin therapy for a minimum of 1 month, duration of diabetes ≥ 12 months.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
NovoPen 4 (half amount silver, half amount blue). Device ID #: 1001-1694
NovoRapid PenFill, 3 ml, 100 IU/ml, for s.c. injection (Insulin Aspart), Batch No.: NQ50157
Protaphane PenFill, 3 ml 100 IU/ml for s.c. injection (Human Isophane Insulin)(Germany and Italy); Batch No.: NQ50220
Insulatard PenFill, 3 ml, 100 IU/ml, for s.c. injection (Human Isophane Insulin) (The Netherlands, United Kingdom and Austria. Batch No.: NQ50220
Mixtard 30 PenFill, 3 ml, 100 IU/ml for s.c. injection (Biphasic Human Insulin 30/70) (In Italy Mixtard 30 is named Acrphane 30) (In Netherlands Biphasic Human Insulin 30/70 was not used as study medication). Batch No.: NQ50161
Ancillaries:
NovoFine G31 x 6 mm Needles (for children and thin adults)
NovoFine G30 x 8 mm Needles (for obese adults)
Patient diaries
Sharps containers
Thermo-bags
Plasma glucose meters (plasma calibrated, Lifescan)
Lancets, test strips and control solutions,
Test Media PenFill, 3 ml Novo Nordisk A/S (for demonstration use)
HCG pregnancy urine test strips

DURATION OF TREATMENT
Each subject participated in the trial (screening period included) for a minimum of 14 weeks and maximally for 16 weeks – i.e. screening visit within 2 weeks prior to inclusion in the trial and period 1: 6 weeks of injections with NovoPen 4 followed by Period 2: 6 weeks with NovoPen 3 or vice versa (+ up to 7 days for Visits 3 and 4).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER
NovoPen 3 (half amount silver, half amount blue). Device ID #: 2001-2669
NovoRapid PenFill, 3 ml, 100 IU/ml, for s.c. injection (Insulin Aspart), Batch No.: NQ50157
Protaphane PenFill, 3 ml 100 IU/ml for s.c. injection (Human Isophane Insulin)(Germany and Italy); Batch No.: NQ50220
Insulatard PenFill, 3 ml, 100 IU/ml, for s.c. injection (Human Isophane Insulin) (The Netherlands, United Kingdom and Austria. Batch No.: NQ50220
Mixtard 30 PenFill, 3 ml, 100 IU/ml for s.c. injection (Biphasic Human Insulin 30/70) (In Italy Mixtard 30 is named Acrphane 30) (In Netherlands Biphasic Human Insulin 30/70 was not used as study medication). Batch No.: NQ50161
**CRITERIA FOR EVALUATION – EFFICACY (PERFORMANCE)**

Primary endpoint: preference for NovoPen 4 over NovoPen 3.
Secondary endpoints: patient acceptance and handling, evaluation of user manual including instruction times.

**CRITERIA FOR EVALUATION – SAFETY**

HbA$_1c$, Serum Fructosamine (adults only), 7-point Plasma Glucose Profiles, body weight, vital signs, physical examination, haematology, biochemistry, hypoglycaemic episodes, adverse events, Adverse Device Effects.

**STATISTICAL METHODS**

All analyses were done separately for children and adults and were done two-sided at the 5%-significant level.

Two analysis set were used (ITT and PP) for the primary endpoint and since the results did not differ significantly only the ITT population was used for secondary and safety endpoints.

**Primary endpoint**: The 95% CI for the difference in preferences was calculated and non-inferiority was claimed if the lower limit is above -8%. Superiority was claimed if the limit is above 0%.

The primary analysis was done on the PP and the ITT population and also on the two populations ‘NovoPen 3 users’ and ‘Non NovoPen 3 users’.

**Secondary endpoints**: A total score for handling, acceptance and evaluation of the manual was calculated for each subject. These scores were compared between pens by Wilcoxon matched pairs signed rank sum test.

Instruction times from visit 2 for subjects not previously familiar with NovoPen 3 or NovoPen 3 demi were compared between pens by an ANOVA including pen, age group, sex and an interaction between age group and pen.

**Safety endpoint**: HbA$_1c$ and serum fructosamine were both analysed by an ANOVA including pen, age group (only HbA$_1c$), period, carry over, country and baseline as fixed effects and subject as random effect. Variables were removed according to type 1 sums of squares and estimates for the difference between pens were presented in the reduced model.

The 7-point profiles were presented by summary statistics and as mean graphs including measurements for both pens.

Body weight and vital signs from screening were summarised. Changes in body weight and vital signs between screening and visit 4 were summarised and compared by paired t-tests.

Physical examination, haematology and biochemistry from screening were summarised.

Hypoglycaemic episodes were summarised per severity classification. The total number of episodes was compared between pens using a log linear Poisson regression model. The ratio of incidences is presented together with a p-value and a 95% confidence interval.

All adverse device effects were listed. The total number of adverse effects was summarised per pen and presented together with the incidence rate. No statistical testing was done due to low number of adverse effects.

All treatment emerged adverse events were listed.

**DEMOGRAPHY OF TRIAL POPULATION**

Children: The trial population of 44 children/adolescents had the following characteristics: 22 girls and 22 boys, 43 white and 1 black. The mean age was 14 years. One girl dropped out of the study so 43 children completed the study.

Adults: the trial population of 159 adults had the following characteristics: 58 women and 105 men, 1 black, 1 Asian / pacific islander, 159 white and 2 with other ethnic origin. The mean age was 51 years.
Efficacy Results

Children:
- 84% of the ITT population preferred NovoPen 4, 7% preferred NovoPen 3 and 9% had no preference for any of the pens. The 95% CI for the difference in preference is 0.678 – 0.857.
- 84% of the NovoPen 3 users preferred NovoPen 4, 8% preferred NovoPen 3 and 8% had no preference. The 95% CI is 0.666 – 0.848.
- 83% of the non NovoPen 3 users preferred NovoPen 4; none preferred NovoPen 3 and 17% had no preference. The 95% CI is 0.461 – 1.206.
- The median for the patient acceptance scale was 34.5 for NovoPen 4 and 30 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.
- The median for the patient handling scale was 34 for NovoPen 4 and 30 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.
- The median for the evaluation of the manual scale was 6.5 for NovoPen 4 and 6 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.

Adults:
- 80% of the ITT population preferred NovoPen 4, 10% preferred NovoPen 3 and 10% had no preference for any of the pens. The 95% CI for the difference in preference is 0.657 – 0.753.
- 78% of the NovoPen 3 users preferred NovoPen 4, 12% preferred NovoPen 3 and 11% had no preference. The 95% CI is 0.602 – 0.715.
- 89% of the non NovoPen 3 users preferred NovoPen 4, 3% preferred NovoPen 3 and 8% had no preference. The 95% CI is 0.768 – 0.955.
- The median for the patient acceptance scale was 34 for NovoPen 4 and 30 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.
- The median for the patient handling scale was 36 for NovoPen 4 and 30 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.
- The median for the evaluation of the manual scale was 6 for NovoPen 4 and 6 for NovoPen 3. The p-value for the Wilcoxon matched pairs signed rank test is below 0.0001.

Instruction times were analysed in an ANOVA including age group, pen, sex and an interaction between age group and pen as covariates. Both the interaction and sex were removed since they were not statistically significant. Hence the difference between pens is the same for the two age groups and the estimated difference is 3.72 min with a 95% CI of 0.53 min – 6.9 min (NovoPen 3 having the longest instruction time). The p-value for this difference is 0.0234. The p-value for the difference between age group is 0.1625.
SAFETY RESULTS

- The final model for HbA1c included pen, period, age group, country and baseline value. The estimated difference in HbA1c is -0.0619% (NovoPen 4 – NovoPen 3) with a p-value of 0.1243.
- The final model for serum fructosamine included all variables pen, period, carry over, age group, country and baseline value. The estimated difference in serum fructosamine is -4.910 (NovoPen 4 – NovoPen 3) with a p-value of 0.2347.
- Changes in body weight between start and end of study was significant with a mean increase in weight of 0.79 kg for adults (p=0.0001) and mean increase in weight of 0.786 kg for children (p=0.0279).
- Changes in vital signs between start and end of study were not significant for either children or parents.
- For children the incidence rate for all hypoglycaemic events was 0.130 for NovoPen 4 and 0.144 for NovoPen 3. For adults the incidence rates were 0.0946 (NovoPen 4) and 0.104 (NovoPen 3). In a Poisson regression model a significant difference between age groups was seen with an incidence ratio of 0.364 (p=0.0006) between adults and children. The incidence ratio between pens was 0.908 (p=0.1073).
- Only one child and 8 adults experienced an adverse device effect with NovoPen 4.
- No children and 4 adults experienced an adverse device effect with NovoPen 3.
- Two additional adverse device effects occurred, but it was not possible to trace the type of device they belonged to.
- A total of 213 treatment emergent adverse events occurred during the trial. Four of these events were severe but were all rated as unlikely related to trial product. Five events were rated as probable related to trial product (back pain, mild lipodystrophy at right gluteus, arthritis in right foot, common cold and pain in abdomen (menstruation)).

CONCLUSIONS

Efficacy conclusions in children/adolescents
84% of the children preferred NovoPen 4, 7% preferred NovoPen 3 and 9% had no preference.
84% of the NovoPen 3 users preferred NovoPen 4, 8% preferred NovoPen 3 and 8% had no preference. These findings are very much in favour of NovoPen 4.
83% of the non NovoPen 3 users preferred NovoPen 4, none preferred NovoPen 3 and 17% had no preference. Also these findings are very much in favour of NovoPen 4. In all this shows that a switch from NovoPen 3 to NovoPen 4 would easily be accepted in this patient population.

The median for the patient acceptance scale was 34.5 for NovoPen 4 and 30 for NovoPen 3. The p-value is below 0.0001 showing a statistically significant preference for NovoPen 4 regarding these aspects.

Efficacy conclusions in adults
80% of the adult population preferred NovoPen 4, 10% preferred NovoPen 3 and 10% had no preference. Also for the adult population a very high preference for NovoPen 4 was shown.
78% of the NovoPen 3 users preferred NovoPen 4, 12% preferred NovoPen 3 and 10% had no preference. And also for the adults already using NovoPen 3 a very high preference for NovoPen 4 was shown. 89% of the non NovoPen 3 users preferred NovoPen 4, 3% preferred NovoPen 3 and 8 % had no preference. This shows that a switch from NovoPen 3 to NovoPen 4 would easily be accepted also for the adult population.

The median for the patient acceptance scale was 34 for NovoPen 4 and 30 for NovoPen 3. The p-value is below 0.0001 showing a statistically significant preference for NovoPen 4 regarding these aspects.
The median for the patient handling scale was 36 for NovoPen 4 and 30 for NovoPen 3. The p-value is below 0.0001 showing a statistically significant preference for NovoPen 4 regarding these aspects.

So, also regarding both the handling and acceptance aspects it is concluded that NovoPen 4 is very highly rated compared to NovoPen 3.

The median for the evaluation of the manual scale was 6 for the NovoPen 4 manual and 6 for the NovoPen 3 manual. The p-value is below 0.0001 showing that in the adult population the NovoPen 4 manual was rated high but the NovoPen 3 manual was also fully informative.

Overall, the ratings were very similar for the two patient groups and showed a superior preference for NovoPen 4.

Instruction times were analysed and the difference between the two pens are the same for the two age groups and the difference is 3.72 minutes with NovoPen 3 having the longest instruction time. The children/adolescents are faster learners than the adults regarding both devices, but this is not statistically significant – see table 1.14.

**Safety Conclusions for children/adolescents and adults**

There was no significant difference in HbA1c between the NovoPen 4 and NovoPen 3 treatment periods – neither for children/adolescents nor for adults, p=0.1243. (see histograms 1.50 and 1.51). This shows that regarding longer time metabolic control the two insulin pens are equally safe to use.

Age group was also significant in the ANOVA with a p-value of 0.0087 (see table 1.30) – i.e. the children/adolescents have a significantly less optimal diabetes regulation than the adults.

Serum Fructosamine levels were only measured in the adult population. Also here there was no significant difference between NovoPen 4 and NovoPen 3 treatment periods, see histogram 1.52. This shows that regarding medium term metabolic control the two insulin pens were equally safe in the adult population.

There were no differences between NovoPen 4 and NovoPen 3 treatment regarding the 7-point blood glucose profiles – for instance mean values for the children/adolescents were 9.96 (NP4) and 9.92 for NP3. This shows that regarding short-term metabolic control the two insulin pens were equally safe to use.

There was a statistical significant increase in body weight between start and end of the study. For adults the increase was 0.79 kg (p=0.0001) and also there was a significant increase for the children of 0.786 kg (p=0.0279). This is probably reflecting the fact that inclusion started in the late summer time where not much clothes are worn and conclusion for many patients was in the month of January – i.e. immediately after Christmas. Also for the children/adolescents who are growing a weight gain as the above lie within normal limits.

Changes in vital signs between start and end of study were not significant for either children/adolescents nor adults.

For the children/adolescents the incidence rate for all hypoglycaemic events was 0.130 for NovoPen 4 and 0.144 for NovoPen 3. For the adults the incidence rates were 0.0946 for NovoPen 4 and 0.104 for NovoPen 3. This gives a significant difference between age groups with a ratio of 0.364 (p=0.0006), corresponding to children/adolescents experiencing 2.7 times as many hypoglycaemic events as the adults. The incidence ratio between the two pens was insignificant - 0.908 (p=0.1073).

Only one child/adolescent and 8 adults experienced an adverse device effect with NovoPen 4, see table 1.5. Of these adverse device effects two (+ 2 as the observations were made for both pens by the two patients) were due to “air bubbles in the cartridges”. This is probably the same problem as what was called “blood in PenFill” internally – i.e. this prototype of NovoPen 4 had an aspirational function so that either air or blood (if the needle was situated in a vessel) was drawn into the PenFill. In the final version of NovoPen 4 this has been corrected.

There were 4 instances of blocked piston rod with NovoPen 4 and 1 with NovoPen 3. This problem has been solved.
with the new design. Finally, 2 adverse device effects related to the cap on NovoPen 3 were reported – i.e. the cap is
difficult to open. No adverse device effects were reported on NovoPen 4 regarding this issue.

No children/adolescents, but 4 adults experienced an adverse device effect with NovoPen 3, see table 1.5.

Two additional adverse device effects occurred but it was not possible to trace the type of device they belonged to.

A total of 213 treatment emergent adverse events occurred during the trial. Four of these events were severe but were
all rated as unlikely related to the trial products. Five events were rated as probably related to the trial product (back
pain, mild lipodystrophy at the gluteus, arthritis in the right foot, common cold and pain in the abdomen
(menstruation)). The monitors never query such conclusions, but from here it is definitely concluded that the above
five events could never be trial product related.

It is hereby overall concluded regarding preference as well as performance, acceptance and handling NovoPen 4 is
superior to NovoPen 3. Regarding safety both insulin delivery pens are equally safe. Regarding the adverse device
effects on NovoPen 4 both the issue of “air bubbles in the PenFill” and the blocked piston rod have been solved in the
final version of NovoPen 4.

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