2 Synopsis

Trial Registration ID-number	**EudraCT number**
NCT00274274	2005-000319-87

Title of Trial

A 52 Week, Open Labelled, Randomised Multi-Centre 2 Arm Parallel Group Trial Comparing Efficacy and Safety of Insulin Aspart, Given in a Fixed Dose Regimen or in a Flexible Regimen, with or without Insulin Detemir in Subjects with Type 2 Diabetes

Investigator(s)

71 Principal Investigators were involved in the trial. Coordinating and Signatory Investigator was Professor Dr. med. [redacted]

Trial Site(s)

In total, 71 centres in Germany were involved, 62 of them were active and screened subjects in the trial, and 58 of them randomised subjects in the trial.

Publications

None

Trial Period	**Development Phase**
First subject screened: 06 Sep 2005 Last subject completed: 20 Nov 2006	Phase 4

Objectives

Primary Objective:

- To compare the glycaemic control, measured as HbA_{1c} after 52 weeks of treatment, in patients with type 2 diabetes treated with a supplementary insulin therapy (SIT) being randomized either to a SIT with fixed dose regimen or to a SIT with flexible dose regimen including more intensive education and therapy control.

Secondary Objectives:

To compare the two treatments in terms of:

- 9-point self-measured glucose profiles after 12, 26, 39 and 52 weeks
- HbA_{1c} after 12, 26 and 39 weeks
- Percentage of subjects with $HbA_{1c} < 7\%$ after 52 weeks
- Duration of education
- Changes of quality of life to baseline after 26 and 52 weeks
- Insulin doses per day
- Frequency of blood glucose measurements
- Weight development
- Incidence of hypoglycaemic episodes
- Incidence of adverse events
- Standard safety

Methodology

The trial was a 52 weeks multi-centre, open-labelled, randomised, controlled, two-armed, parallel group trial in short acting insulin naïve patients with type 2 diabetes. For all subjects a supplementary insulin therapy (SIT) was initiated and subjects were randomised either to a SIT with fixed dose insulin aspart regimen (FIX) or a SIT with flexible dose insulin aspart regimen (FLEX) which included advanced education, insulin dose adjustment on a regular basis and more frequent blood glucose measurements. All previous diabetes therapies (insulins as well as OADs) were stopped prior to randomisation with exception of metformin. The two regimens were compared in terms of efficacy, safety and quality of life. At a screening visit (Visit 1) within 3 weeks before randomisation, the eligibility of the subjects was assessed. After randomisation (Visit 2), an education and titration period of 12 weeks took place where the subjects were introduced to a supplementary insulin therapy with preprandial insulin aspart. Insulin detemir could be added when needed. During this period, frequent visits (Visit 3 till Visit 10, two of them optionally as telephone

contacts) at one or two weeks intervals were scheduled in order to achieve the blood glucose targets in both groups. Thereafter, a treatment period of 40 weeks followed which included 3 visits (Visits 11, 12 and 13) at the site and 3 additional scheduled contacts by telephone, fax or e-mail. At Visit 13, an end-of-trial examination was performed 52 weeks after randomisation.

Number of Subjects Planned and Analysed

Under the assumption of an approximately 15% general drop-out rate, 320 subjects were planned to be randomised in order to yield a sufficient power (90%) to test the primary hypotheses. Actually, 431 subjects were screened for participation in this trial and 373 were randomised to one of the two treatment arms (183 to the fixed and 190 to the flexible insulin aspart dose regimen). One randomised subject (fixed dose regimen) was not exposed to trial medication. In total 323 subjects (86.6%), 158 subjects (86.3%) on the fixed and 165 (86.8%) on the flexible regimen, completed the trial. The ITT analysis population comprised 372 subjects (182 FIX and 190 FLEX), the PP analysis population 312 subjects (152 FIX and 160 FLEX).

Diagnosis and Main Criteria for Inclusion

Key characteristics of the trial population were: type 2 diabetes ≥ 6 months, age ≥ 18 years, BMI ≤ 40 kg/m^2 and HbA_{1c} ≥ 7.0% and ≤ 11%. Subjects had to be able and willing to perform self-monitoring of blood glucose and use multiple daily injections regimens during the entire study. Fertile females had to use acceptable methods of contraception. Subjects with frequent hypoglycaemia, previous treatment with short-acting insulin(s) for > 10 days, severe diabetic retinopathy or significant concomitant diseases among others were excluded from the trial.

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir (Levemir®), supplied in 3 mL pre-filled disposable FlexPen® containing 2400 nmol/mL (100 U/mL), batch nos. RP50754 (expiry date: 10/2006) and SP50274 (expiry date: 11/2007). Administered subcutaneously once or twice daily if needed, with a fixed regimen during the 40 weeks treatment period of the trial.

Insulin aspart (NovoRapid®), supplied in 3 mL pre-filled disposable FlexPen® containing 600 nmol/mL (100 U/mL), batch no. RH70144 (expiry date: 04/2007). Administered subcutaneously immediately before each meal, with a fixed regimen during the 40 weeks treatment period of the trial.

All trial products were manufactured and supplied by Novo Nordisk A/S, Denmark.

Duration of Treatment

52 weeks (12 weeks in education / titration period and 40 weeks in treatment period)

Reference Therapy, Dose and Mode of Administration, Batch Number

Insulin detemir (Levemir®), supplied in 3 mL pre-filled disposable FlexPen® containing 2400 nmol/mL (100 U/mL), batch nos. RP50754 (expiry date: 10/2006) and SP50274 (expiry date: 11/2007). Administered subcutaneously once or twice daily if needed, with a flexible regimen during the 40 weeks treatment period of the trial.

Insulin aspart (NovoRapid®), supplied in 3 mL pre-filled disposable FlexPen® containing 600 nmol/mL (100 U/mL), batch no. RH70144 (expiry date: 04/2007). Administered subcutaneously immediately before each meal, with a flexible regimen during the 40 weeks treatment period of the trial

All trial products were manufactured and supplied by Novo Nordisk A/S, Denmark.

Criteria for Evaluation – Efficacy

HbA_{1c} after 12, 26, 39 and 52 weeks (primary efficacy parameter), percentage of subjects with HbA_{1c} < 7% after 52 weeks, 9-point self-measured blood glucose profiles after 12, 26, 39 and 52 weeks, impact of usage of insulin detemir and metformin.

Criteria for Evaluation – Safety

Incidence of adverse events, weight development, incidence of hypoglycaemic episodes, haematology, biochemistry, fundoscopy, vital signs.

Other Criteria for Evaluation

Other criteria were duration of education, insulin doses per day, frequency of blood glucose measurements and changes in quality of life after 26 and 52 weeks, as measured by the WHO (Five) Well Being Index and the 8-Item Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Statistical Methods

The primary endpoint was the change of HbA_{1c} (%) after 52 weeks of treatment. Analysis of the primary endpoint was performed on both the ITT and PP population. Analysis of secondary endpoints was based on the ITT population. The primary hypotheses were:

H_0: Δ_{52} HbA_{1c} SIT Fix – Δ_{52} HbA_{1c} SIT Flex > 0.4% vs. H_1: Δ_{52} HbA_{1c} SIT Fix – Δ_{52} HbA_{1c} SIT Flex ≤ 0.4%

Δ_{52} HbA_{1c} SIT Flex = difference in HbA_{1c} after 52 weeks of treatment with SIT with a flexible dose regimen

Δ_{52} HbA_{1c} SIT Fix = difference in HbA_{1c} after 52 weeks of treatment with SIT with fixed dose regimen

d=0.4% was considered the clinically meaningful margin for non-inferiority with the FDA for registration trials for insulin detemir.

The primary endpoint was analysed using an ANCOVA model with HbA_{1c} at baseline as covariate and treatment regimen as fixed effect. A one-sided test was used to demonstrate non-inferiority of the fixed regimen and the alpha level of the test was adjusted to 2.5% to account for this. Secondary endpoints were analysed by means of exploratory and descriptive statistical methods. Throughout the analyses a significance level of 5% was used.

Demography of Trial Population

The FIX group consisted of 98 (53.8%) male and 84 (46.2%) female subjects, the FLEX group of 108 (56.8%) male and 82 (43.2%) female subjects. All trial participants were white (i.e. having origins in any of the original people of Europe, North Africa or the Middle East). The following table summarises numeric baseline characteristics of the ITT population (mean, SD).

Variable	FIX (N=182)	FLEX (N=190)
Age (years)	63.4 (9.2)	61.8 (8.7)
Weight (kg)	90.4 (15.5)	91.4 (16.4)
Height (m)	1.7 (0.1)	1.7 (0.1)
BMI (kg/m^2)	31.6 (4.5)	31.4 (4.6)
Duration of diabetes (years)	10.1 (7.0)	10.1 (7.0)
HbA_{1c} (%)	8.20 (0.81)	8.24 (0.95)*

* N=189

Regarding demographic and baseline characteristics both treatment groups were comparable.

Efficacy Results and Results of Other Evaluation Criteria

- Both treatment regimens resulted in a clinically relevant lowering of mean (±SD) HbA_{1c} after 52 weeks of treatment, from 8.20±0.81% to 6.96±0.90% in the FIX and from 8.24±0.94% to 6.72±0.95% in the FLEX group (ITT population). The baseline-corrected mean difference (least square mean) Fixed-Flexible was 0.250 percentage points with a 95% confidence interval of 0.067 to 0.433 and a p-value of 0.0074. Since the upper confidence limit of the difference exceeded the value of 0.4% (absolute), the criterion for non-inferiority was not met.
- The majority (78.0% of the FIX and 75.3% of the FLEX group) of the subjects in the ITT group were treated with once daily insulin detemir in order to reach the treatment targets. Insulin aspart at mealtime only was effective in about 15% of the subjects. More than once daily insulin detemir was only used in three subjects of the FIX group and one single subject in the FLEX group, i.e. insulin detemir was used once daily in 98% of the subjects with additional basal insulin therapy.
- For the PP population the mean difference (least square mean) Fixed-Flexible was 0.207 percentage points with a 95% confidence interval of 0.034 to 0.379 and a p-value of 0.0191. Since the upper confidence limit of the difference remained below the value of 0.4% (absolute), the criterion for non-inferiority was met in this population.
- The baseline-corrected treatment difference (least square mean, ITT) Fixed-Flexible after 12 weeks of treatment was 0.139 percentage points (95% CI: -0.020 to 0.297; p=0.087), and the respective differences after 26 and 39 weeks were 0.216 percentage points (95% CI: 0.044 to 0.389; p=0.014) and 0.203 percentage points (95% CI: 0.019 to 0.386; p=0.031), respectively.
- Both treatment regimens resulted in a clinically relevant shift of the mean self-measured 9-point blood glucose profiles towards lower values by about 20-30%. This effect was achieved already after 12 weeks and during the

remainder of the study no further relevant improvements could be observed. The FLEX regimen generally showed slightly lower BG values than the FIX regimen but statistically significant differences between the regimens were not observed.

- A target of $HbA_{1c} \leq 6.5\%$ after 52 weeks of treatment reached 62 subjects (34.4%) of the FIX and 79 subjects (43.4%) of the FLEX group. For the target ≤ 7.0% the respective figures were 110 (61.1%) and 126 (69.2%), and for the target ≤ 7.5% 139 (77.2%) and 156 (85.7%). Only for the latter target the difference between the treatment regimens was statistically significant with an odds ratio Fixed/Flexible of 0.5650, a 95% confidence interval of 0.3148 to 1.003 and a p-value of 0.04.
- Mean daily insulin aspart doses increased in the FIX group from 25.0±12.8 U (start dose) to 46.2±25.2 U at the end of the 12-week titration period, and in the FLEX group from 23.5±15.2 U to 42.4±29.5 U. Mean daily insulin detemir doses increased accordingly from 9.9±5.3 U to 21.9±12.0 U (FIX) and from 10.2±6.1 U to 20.8±11.6 U (FLEX). After titration, in both treatment groups, mean daily insulin doses showed a further steady but less pronounced rise towards the end of treatment. After 52 weeks mean daily insulin aspart dose was 48.6±27.9 U in the FIX and 45.2±34.4 U in the FLEX group, and the respective figures for insulin detemir were 27.1±16.4 U (FIX) and 25.4±17.2 U (FLEX). Except for the insulin detemir start dose, mean daily doses were slightly but consistently higher in the FIX than in the FLEX group.
- There was no statistically significant factor by treatment group interaction regarding the impact of insulin detemir and metformin on HbA_{1c}-values after 52 weeks of treatment (i.e. there was no influence of insulin detemir and/or metformin on the primary endpoint).
- In the FIX group mean (±SD) duration of education was 6.70±4.14 hours and in the FLEX group 11.40±6.29 hours with medians of 5.5 and 11.0 hours, respectively.
- In the FIX group, the mean number of recommended self-measured blood glucose profiles per week was about 4-5 during the titration period, decreased thereafter to about 2 and remained at that level until the end of the trial. In the FLEX group, the mean number of recommended self-measured blood glucose profiles per week was about 6-7 during the titration period titration and remained at that level until the end of the trial. In both groups the actually performed blood glucose self-measurements followed the patterns of the recommendations. However, there was a slight but consistent trend to higher numbers of actually performed than of recommended measurements.
- In both treatment groups, the mean recommended numbers of blood glucose measurements per profile were consistently about 4-5 during the whole trial. A median of 4 measurements per profile was most common, the minimum number recommended was 2 and the maximum 9. In both groups the number of actually performed blood glucose measurements per profile corresponded well to the numbers of recommended measurements.
- The WHO (Five) Well Being Index remained fairly unchanged. Neither the scores of any of the five statements nor the total score showed a treatment-related statistically significant difference between the two regimens after 52 weeks.
- Mean scores of DTSQ items and questions indicated for both regimen groups an improvement after 52 weeks. However, ANCOVA of the three items "Treatment satisfaction", "Perceived frequency of hyperglycaemia" and "Perceived frequency of hypoglycaemia" showed for none of the respective scores a treatment-related statistically significant difference between the two regimens.

Safety Results

- There were 138 subjects (75.8%) of the FIX and 132 (69.5%) of the FLEX group who experienced at least one treatment-emergent adverse event and the respective numbers of single events were 483 and 457.
- The majority of AEs was of mild or moderate intensity. Adverse events with an intensity rated as "severe" were experienced by 17 subjects (9.3%) of the FIX and by 22 subjects (11.6%) of the FLEX group.
- Adverse events with an assessment of a "probable" or "possible" relation to insulin aspart occurred in 8 subjects (4.4%) of the FIX and in 2 subjects (1.1%) of the FLEX group.
- Adverse events with an assessment of a "probable" or "possible" relation to insulin detemir occurred in 9 subjects (4.9%) of the FIX and in 2 subjects (1.1%) of the FLEX group.
- Most common were AEs due to infections and infestations, followed by musculoskeletal / connective tissue disorders and gastrointestinal disorders, and the incidence rates were fairly comparable in the two treatment

groups. The most frequent single adverse events were nasopharyngitis, occurring in 36 subjects (19.8%) with the FIX and 47 subjects (24.7%) with the FLEX regimen, and headache, occurring in 17 subjects (9.3%) with the FIX and 21 subjects (11.1%) with the FLEX regimen.

- Adverse events rated "possibly" or "probably" related to the trial drugs affected various organ systems without showing any preferences.
- In total 88 subjects (48.4%) of the FIX and 89 (46.8%) of the FLEX group experienced at least one treatment-emergent hypoglycaemic episode during the trial (the first 6 weeks of study treatment not included). The total number of hypoglycaemic episodes in the FIX group was 611, one of them major, 323 minor and 287 "symptoms only". The total number of hypoglycaemic episodes in the FLEX group was 846, one major, 517 minor and 328 "symptoms only".
- The vast majority of hypoglycaemic episodes (85.4% in the FIX and 91.6% in the FLEX group) was diurnal. The proportion of nocturnal hypoglycaemic episodes in the FIX group was about twice that observed in the FLEX group (13.7% vs. 7.1%).
- The incidence rate of all hypoglycaemic episodes was lower under the FIX than under the FLEX regimen (0.080 vs. 0.106 events per subject week). Further analysis indicated a higher relative risk particularly of minor and diurnal hypoglycaemic episodes for the FLEX regimen while for nocturnal hypoglycaemic episodes the relative risk appeared higher for the FIX regimen. However, statistical significance could not be demonstrated for these differences.
- Three cases of death occurred during this trial: One subject died from cancer, a second from acute coronary syndrome and a third from urothel carcinoma. All three subjects belonged to the FLEX group and in all cases the relationship to the trial medication was assessed as "unlikely" by the Investigator.
- Treatment-emergent adverse events classified as "serious" by the Investigator (SAEs) were experienced by 30 subjects (16.5%) of the FIX and by 37 subjects (19.5%) of the FLEX group and the number of single events was 40 and 52, respectively.
- Cardiovascular events were the most frequent SAEs with angina pectoris as the most frequent disorder, with an incidence of 0.5% in the FIX and of 1.6% in the FLEX group.
- Four SAEs, experienced by 3 subjects of the FIX and by one subject of the FLEX group, were severe hypoglycaemias which resulted in hospitalisation.
- The vast majority of SAEs was assessed as being "unlikely" related to the trial drug and the majority of subjects with SAEs recovered from the events.
- Eleven subjects were withdrawn from the trial due to adverse events (including three cases of death), 5 of the FIX and 6 of the FLEX regimen.
- There were slight and in both treatment groups similar changes in some laboratory parameters which, although statistically significant, were not considered as clinically relevant findings.
- There were no clinically relevant changes in vital signs (blood pressure, pulse rate).
- For the majority of subjects in both treatment groups ocular fundus findings remained unchanged during the trial. However, subjects with worsened findings slightly outweighed those showing improvement.
- Mean body weight increased in the FIX group by 2.4 kg (from 90.4 kg at screening to 92.8 kg after 52 weeks of treatment) and in the FLEX group by 1.7 kg (from 91.4 to 93.1 kg). The corresponding increase in BMI was 0.9 kg/m^2 in the FIX (from 31.6 to 32.5 kg/m^2) and 0.7 kg/m^2 in the FLEX group (from 31.4 to 32.1 kg/m^2). Most of the weight gain was achieved during the first 26 weeks of treatment. Body weight and BMI after 52 weeks showed no treatment-related statistically significant differences between the two regimen groups.

Conclusions

- Both supplementary insulin treatment regimens investigated in this trial (FIX and FLEX) were effective and safe treatment alternatives for subjects with type 2 diabetes insufficiently controlled with one or more OAD(s), premixed insulin, intermediate-acting insulin, long-acting insulin or a combination of these drugs.
- With regard to the primary efficacy endpoint HbA_{1c} after 52 weeks, both treatment regimens were similarly effective with a slightly but significantly greater HbA_{1c}-lowering effect under the FLEX compared to the FIX regimen, as demonstrated for both the ITT and the PP analysis population. For the ITT population non-inferiority of

the FIX vs. the FLEX regimen could not be demonstrated while this was the case for the PP population.

- Regarding the other secondary efficacy endpoints such as HbA_{1c} after 12, 26 and 39 weeks, 9-point self-measured glucose profiles after 12, 26, 39 and 52 weeks and achievement of metabolic targets, both treatment regimens appeared similarly effective with a trend in favour of the FLEX regimen.
- There was a trend towards higher percentages of subjects reaching the HbA_{1c} targets in the FLEX vs. the FIX group with a significant difference with regard to the category $HbA_{1c} \leq 7.5\%$. 61.1% of the FIX group and 69.2% of the FLEX group reached an $HbA_{1c} \leq 7.0\%$.
- Pre-prandial administration of insulin aspart ensured an effective control of postprandial glucose regulation in both study arms.
- The combination of insulin aspart and once daily insulin detemir ensured near normoglycaemic prandial glucose regulation and HbA_{1c} reduction below 7.0% in the majority of the subjects.
- The trial supports that insulin detemir should generally be used once daily in combination with insulin aspart in type 2 diabetes. Just about 15% of the subjects could be treated sufficiently with short-acting insulin only. Daytime basal insulin in typical type 2 diabetes is subject to exceptional use due to lack of necessity.
- The better efficacy of the FLEX regimen was achieved at the price of prolonged education and more frequent blood glucose self-measurements. However, both treatment groups showed an equal trend towards increased treatment satisfaction with regard to baseline.
- Subjects showed a high compliance in following the Investigator's instructions with regard to blood glucose measurements.
- Both regimens resulted in a moderate weight and BMI gain of comparable extent which seems to be acceptable with respect to HbA_{1c} improvement.
- The incidence of hypoglycaemic events was generally low with respect to the achievement of HbA_{1c} targets. Half of the subjects did not experience hypoglycaemia at all.
- A trend towards a higher relative risk in particular of minor and of diurnal hypoglycaemic episodes was evident under the FLEX regimen, while for nocturnal hypoglycaemic episodes the relative risk appeared higher under the FIX regimen.
- The incidence of treatment-emergent adverse events was similar for both regimens.
- Regarding clinical laboratory values, vital signs and ocular fundus findings both regimens appeared comparably safe.

The trial was conducted in accordance with the Declaration of Helsinki(Edinburgh 2000, with amendments Washington 2002 and Tokyo 2004) and ICH Good Clinical Practice (1996).