Synopsis

TITLE OF TRIAL A one-year, multi-national, open-labelled, parallel-group, 2:1 randomised treat-to-target trial comparing efficacy and safety of insulin detemir with insulin glargine using a basal-bolus regimen with insulin aspart as mealtime insulin in subjects with type 2 diabetes
INVESTIGATORS Fifty-six (56) principal investigators in 5 countries. Signatory investigators were: Dr [redacted], [redacted] and Dr [redacted]
TRIAL SITES A total of 56 trial sites participated in the trial: 7 in Finland, 7 in France, 6 in Norway, 10 in Sweden and 26 in the United States
PUBLICATIONS None

TRIAL PERIOD	**DEVELOPMENT PHASE**
29 September 2004 – 27 December 2005	Phase 3b

OBJECTIVES

Primary Objective:

- To compare the glycaemic control of insulin detemir with that of insulin glargine as measured by HbA_{1c} in subjects with type 2 diabetes on a basal-bolus regimen with insulin aspart as bolus insulin after a 52 week treatment period.

Secondary Objectives:

- Proportion of subjects with HbA_{1c} ≤7.0% after 52 weeks of treatment.
- Proportion of subjects with HbA_{1c} ≤7.0% without symptomatic hypoglycaemia confirmed by a plasma glucose value <4.0 mmol/l (<72 mg/dL) or any single plasma glucose value <3.1 mmol/l (<56 mg/dL) in the last 3 months of treatment.
- Glycaemic control as measured by fasting plasma glucose (FPG, central laboratory) during the trial.
- Within-subject variation of self-measured plasma glucose (SMPG) before breakfast and dinner during the trial.
- Glycaemic control as measured by 10-point SMPG profiles during the trial.
- Incidence of hypoglycaemic episodes during the trial; nocturnal (11 pm – 6 am) and over the entire day (24 hours).
- The safety profile as measured by occurrence of adverse events during the trial.
- The safety profile as measured by laboratory safety parameters (haematology, biochemistry and lipids), physical examination, fundoscopy/fundusphotography and vital signs.
- Weight change during the trial.
- Basal and bolus insulin doses after 52 weeks of treatment.
- Insulin treatment satisfaction assessed by the Insulin Treatment Satisfaction Questionnaire (ITSQ) during the trial.

In addition:

- Time to change of basal insulin treatment regimen, from once to twice daily, in the insulin detemir treated group.
- Proportion of insulin detemir treated subjects on once daily basal insulin at the end of the trial after 52 weeks of treatment.
- Possible correlation between endogenous insulin production (serum insulin and C-peptide) and insulin requirements in insulin naïve subjects.
- Serum adiponectin levels as a marker for insulin sensitivity and weight change after 52 weeks of treatment.

METHODOLOGY

This was a 52 week, multi-national, open-labelled, parallel-group, randomised 2:1 (insulin detemir:insulin glargine) treat-to-target trial in subjects with type 2 diabetes currently on any oral antidiabetic drug (OAD) therapy or on any insulin in any regimen with or without OADs >4 months. Subjects were randomised 2:1 to insulin detemir or insulin glargine with insulin aspart as mealtime insulin in combination with their current OAD treatment (except for insulin secretagogues and α-glucosidase inhibitors, which were to be discontinued and thiazolidinediones which was only allowed in the US and should be discontinued in all other countries). Randomisation was stratified according to current treatment regimen (OAD monotherapy, OAD combination therapy, insulin with OADs or insulin without OADs). Insulin detemir was initially administered once-daily, but subjects could be changed to a twice-daily treatment regimen if the average PG before breakfast was ≤6.0 mmol/L but the average plasma glucose (PG) before dinner remained >6.0 mmol/L after titration of the evening dose and optimisation of the bolus doses. Insulin glargine was administered once daily throughout the trial according to the labelling. The trial included a screening visit to assess the subjects´ eligibility and a randomisation visit (maximum 2 weeks after the screening visit) followed by a 52-week titration and treatment period. During this titration and treatment period, plasma glucose levels were intensively monitored through a number of visits and telephone contacts and basal insulin treatment was individually titrated according to a pre-defined titration algorithm. The target values for plasma glucose before breakfast and dinner were ≤6.0 mmol/L (108 mg/dL).

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to include a total of 300 subjects with type 2 diabetes in order to obtain 255 subjects for evaluation, assuming a drop out rate of approximately 15%. In total, 460 subjects were screened, of which 137 were screening failures.

The subject disposition is shown below:

	Detemir N (%)	Glargine N (%)	All N (%)
Screened			460
Randomised	216 (100.0)	107 (100.0)	323 (100.0)
Exposed	214 (99.1)	105 (98.1)	319 (98.8)
Withdrawals	43 (19.9)	23 (21.5)	66 (20.4)
Adverse Event	12 (5.6)	3 (2.8)	15 (4.6)
Ineffective therapy	1 (0.5)	1 (0.9)	2 (0.6)
Non-compliance with protocol	17 (7.9)	10 (9.3)	27 (8.4)
Other	13 (6.0)	9 (8.4)	22 (6.8)
Completers	173 (80.1)	84 (78.5)	257 (79.6)
ITT analysis set	214 (99.1)	105 (98.1)	319 (98.8)
PP analysis set	159 (73.6)	78 (72.9)	237 (73.4)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

Male and female subjects with type 2 diabetes aged ≥18 years, with a BMI ≤40.0kg/m^2 and HbA_{1c} between 7.0% and 11.0% both inclusive. The subjects had a history of diabetes of at least 1 year, were on any OAD therapy or on any insulin treatment regimen with or without OADs for at least 4 months prior to screening.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin detemir (Levemir®) 100 U/mL (2400 nmol/L) FlexPen® 3 mL solution for injection in a pre-filled pen. Batch numbers PP50227and RP50752.

Insulin aspart (NovoRapid®) 100 U/mL FlexPen® 3 mL solution for injection in a pre-filled pen. Batch numbers PP50493 and RP50402.

DURATION OF TREATMENT

Treatment for 52 weeks with insulin detemir or insulin glargine as basal insulin and insulin aspart as bolus insulin in combination with the subjects' current OAD therapy.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Insulin glargine (Lantus®) 100 IU/mL OptiPen Pro1® for use with 3mL cartridges in EU and in 10 mL vials in the United States, Aventis, Germany/United States. Batch numbers 40L427, 41D067, 40D073, 40D074 and 40D054.

Insulin aspart (NovoRapid®) 100 U/mL FlexPen® 3mL solution for injection in a pre-filled pen, Novo Nordisk A/S, Denmark. Batch numbers PP50493 and RP50402.

CRITERIA FOR EVALUATION – EFFICACY

$HbA_{1c,}$ FPG, SMPG, 10-point SMPG profiles, body weight, serum adiponectin, basal and bolus insulin doses, insulin treatment satisfaction questionnaire, serum insulin and C-peptide in insulin naïve subjects at baseline .

CRITERIA FOR EVALUATION – SAFETY

Hypoglycaemic episodes, adverse events, laboratory analysis of haematology, biochemistry, lipids, pregnancy, vital signs, physical examination and fundusphotography/fundoscopy.

STATISTICAL METHODS

Two analysis sets were defined: the modified Intention-To-Treat (ITT) analysis set consisting of all randomised subjects exposed to at least one dose of trial product and the Per Protocol (PP) analysis set consisting of all exposed subjects, who completed the trial and who did not violate the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the efficacy results.

Efficacy analyses were performed on the basis of the ITT analysis sets, except for $HbA_{1c,}$ FPG and body weight. For these three endpoints, only subjects who were exposed to trial products for at least 12 weeks and had at least one measurement after randomisation were included. Safety analyses were only performed on the ITT analysis. Confirmatory efficacy and analyses on hypoglycaemic episodes were repeated for the PP analysis set as the number of subjects in the ITT and PP analysis sets differed by more than 10%. For comparison with previous trials, body weight analyses were also performed on all end-of-trial completers.

For the primary endpoint, the null hypothesis (non-inferiority) was that glycaemic control (HbA_{1c}) achieved at the end of treatment with insulin detemir plus insulin aspart was as good as that achieved with insulin glargine plus insulin aspart. The alternative hypothesis was that glycaemic control was inferior with insulin detemir. The criterion claiming non-inferiority was defined as follows: the upper limit of the two-sided 95% confidence-interval for the difference in HbA_{1c} ((insulin detemir + insulin aspart) – (insulin glargine + insulin aspart)) is less than 0.4%.

HbA1c after 52 weeks were analysed using an analysis of variance with a baseline value as covariate (ANCOVA) model with treatment, pre-trial treatment, as defined by pre-trial stratification and country, as fixed effects and baseline HbA_{1c} as a covariate. Proportion of subjects achieving HbA1c ≤7.0% after 52 weeks of treatment and proportion of subjects achieving HbA1c ≤7.0% without symptomatic hypoglycaemia in the last 3 months of treatment, was compared between treatment groups using Fisher's exact test. Mean FPG(lab) after 52 weeks of treatment was compared between the groups by fitting an ANCOVA as for HbA_{1c}. The within-subject variation in self-measured pre-breakfast and pre-dinner plasma glucose was evaluated after 24 and 52 weeks of treatment by use of a likelihood ratio test.

The 10-point plasma glucose profiles were analysed for parallelism using a repeated measurements analysis of variance (ANOVA), dependent on treatment, country, time and time by treatment interaction as fixed effects. If the time-by-treatment interaction could be assumed non-significant, the difference between treatments was estimated and tested for significance using the same model.

The change in body weight adjusted by serum adiponectin levels was analysed by an ANCOVA model after 52 weeks of treatment, as for HbA_{1c}. Insulin doses were summarised in units and units per kg body weight for basal and bolus separately as well as dose ratios between treatment groups in the basal and bolus insulin dose. Mean and median basal and bolus insulin doses were analysed by descriptive statistics.

The proportion of insulin detemir treated subjects maintained on once-daily basal insulin after 52 weeks could be estimated from the survival distribution. To account for subjects who changed regimen at several occasions, the regimen used at end of trial (the last visit) was defined and used when the doses were summarised. The number of subjects who changed regimen and the number of changes was summarised. The change in insulin treatment satisfaction questionnaire (ITSQ) score was analysed by fitting an ANCOVA model with treatment

and country as fixed factors and the baseline score as a covariate. A separate analysis was performed for the change to week 24 and 52. Descriptive statistics of serum insulin and C-peptide measurement at baseline were presented and insulin resistance was estimated by the homeostasis model assessment, the HOMA index. The correlation of serum insulin, C-peptide and the HOMA index with total basal dose at end of trial was investigated graphically by means of scatter plots.
Hypoglycaemic episodes during the treatment period were classified by severity (all, major, minor and symptoms only) and time of occurrence (24 hr and nocturnal, i.e. 23:00 – 6:00) and were analysed as recurrent events in a Cox regression analysis using a gamma frailty model.
Overall incidence of treatment emergent adverse events (TEAEs) was compared by descriptive statistics. AEs were defined as treatment emergent if the onset were on or after the first day of trial product and no later than 7 days after the last day of the trial product. Adverse events occurring from trial drug discontinuation until 7 days after were included in definition of TEAEs but the reporting might be incomplete as no active follow-up period was defined for the study. Laboratory values were compared to the relevant reference range and flagged as being below or above the range. Clinical laboratory abnormalities regarded as clinically significant were reported and handled as AEs. No formal statistical analyses were planned for the laboratory safety parameters. Vital signs, physical examination and fundoscopy/fundusphotography were presented using summary statistics.

DEMOGRAPHY OF TRIAL POPULATION

Baseline characteristics for all exposed subjects are shown in the table below. A slight variation was observed between sex and ethnic origin, but overall the subjects were similar in the two groups at baseline. About 80% of the subjects were on insulin treatment prior to trial entry, with approx. 50% on a basal-bolus regimen and approx. 20% on premix insulin with or without basal and/or bolus insulin treatment. In addition to the insulin treatments, approx. 46% of all subjects were treated with both insulin and one or more OADs prior to the trial.

	Detemir	Glargine	All
N	214 (100.0)	105 (100.0)	319 (100.0)
Males, N (%)	130 (60.7)	55 (52.4)	185 (58.0)
Females, N (%)	84 (39.3)	50 (47.6)	134 (42.0)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)	59 (11)	58 (11)	58 (11)
Weight (kg)	93.3 (17.5)	91.5 (17.9)	92.8 (17.6)
BMI (kg/m^2)	31.5 (4.7)	31.7 (4.7)	31.5 (4.7)
Diabetes duration (yrs)	13.6 (8.1)	13.4 (7.8)	13.6 (8.0)
HbA_{1c} (%) D)	8.6 (1.0)	8.8 (1.1)	8.7 (1.0)
FPG (mmol/L)	9.5 (3.0)	9.8 (2.9)	9.6 (3.0)

The last available value before randomisation is presented for weight, HbA_{1c} and FPG.

EFFICACY RESULTS

Primary Endpoint:

- Treatment with insulin detemir plus insulin aspart as mealtime insulin with or without OAD treatment was non-inferior to insulin glargine plus insulin aspart as mealtime insulin with or without OAD treatment after 52 weeks. Mean difference (insulin detemir – insulin glargine) = 0.17, 95% confidence interval (CI): [-0.07, 0.40]. The criterion for superiority was not fulfilled.
- HbA_{1c} decreased by an average of 1.52 and 1.68 percent point with insulin detemir and insulin glargine, respectively.
  - HbA_{1c} after 52 weeks was estimated to 7.19% with insulin detemir and 7.03% with insulin glargine.

Secondary Endpoints:

- The proportion of subjects achieving an HbA_{1c} below or equal to 7.0% in the absence of hypoglycaemia during the last 3 months was similar with insulin detemir (17%) and insulin glargine (21%), (p=0.43). About 36% of the subjects in both groups achieved an HbA_{1c} below or equal to 7.0% with or without hypoglycaemia.
- $FPG_{(lab)}$ after 52 weeks of treatment from baseline were similar for the two treatment groups with concentrations of 7.05 mmol/mL with insulin detemir and 6.68 mmol/mL with insulin glargine. The mean difference (insulin detemir – insulin glargine) = 0.36 mmol/mL, 95% CI: [-0.26, 0.99].
- Within-subject variation in self-measured pre-breakfast and pre-dinner plasma glucose after 52 weeks of treatment was similar in the two groups.
  - After 52 weeks, standard deviations in pre-breakfast and pre-dinner plasma glucose were 1.36 mmol/mL and 1.99 mmol/mL with insulin detemir and 1.39 and 2.06 mmol/mL with insulin glargine (p=0.661 and 0.559, respectively).
- The overall shape of the 10-point self-measured plasma glucose profiles was similar with the two treatments after 24 weeks (p=0.229) and 52 weeks (p=0.208).

Other Endpoints:

- Body weight gain was lower with insulin detemir than with insulin glargine after 52 weeks of treatment (p=0.049). On average, subjects in the insulin detemir group gained 2.8 kg, while subjects in the insulin glargine group gained 3.8 kg over the 52 weeks of treatment.
  - The results based on the PP analysis set and the subset of subjects completing the trial did not confirm this statistical significant difference between the two treatment groups based on the ITT analysis set. The mean body weight gain based on both the PP analysis set and on subjects completing the trial was 3.3 kg with insulin detemir and 4.3 kg with insulin glargine after 52 weeks (p= 0.090 for PP; p=0.109 for trial completers).
  - To some extent, the difference in body weight gain between insulin detemir and insulin glargine could be explained by HbA_{1c}, but not by adiponectin or insulin resistance.
- Daily median basal insulin doses per kg body weight were 0.88 U/kg (range 0.15 - 3.86 U/kg) with insulin detemir administered once or twice daily vs. 0.65 IU/kg (range 0.11 - 1.65 IU/kg) with insulin glargine administered once daily. Daily median bolus insulin doses per kg body weight were 0.36 U/kg (range 0.04 - 1.63 U/kg) vs. 0.33 IU/kg (range 0.04 - 1.56 IU/kg) in the insulin detemir and insulin glargine group, respectively.
  - A positive correlation was observed between insulin resistance in insulin naïve subjects at baseline and insulin requirements at end of trial in both treatment groups.
  - No correlation was observed between change in serum adiponectin levels and basal insulin doses after 52 weeks in either treatment group.
- Median time to change to a twice daily insulin detemir regimen was 28.4 weeks of treatment.
- The proportion of subjects completing the trial on a once daily insulin detemir regimen was 43%.
- Total mean ITSQ score after 24 and 52 weeks of treatment was similar with insulin detemir and insulin glargine (p=0.08 and 0.25, respectively). The total mean ITSQ score increased from baseline in both treatment groups after 24 and 52 weeks of treatment, indicating a general increase in treatment satisfaction.

SAFETY RESULTS

- In general, 52 weeks of treatment with insulin detemir resulted in a safety profile similar to that of insulin glargine.
- The proportion of subjects who experienced AEs as well as the number of AEs per subject was similar for the two treatment groups.
  - The most frequently reported AEs were: nasopharyngitis, upper respiratory tract infections and headache. The vast majority of AEs were considered unrelated to trial products and were mild or moderate in severity.
  - SAEs were reported for 14.5% subjects in the insulin detemir group and 13.3% subjects in the insulin glargine group. With the exception of two subjects in the insulin glargine group who reported more than one AE at the same day, all the SAEs reported were single episodes occurring in a single subject.
  - One (1) subject treated with insulin detemir for [redacted] days died from myocardial infarction and 1 subject treated with insulin glargine for [redacted] days died from lung cancer. Both deaths were considered unrelated to trial products.
  - The proportion of subjects with AEs considered as having a possible or probable relation to basal trial product was higher with insulin detemir (21%, most frequently general disorders and administration site conditions, nervous system disorders and skin a nd subcutaneous tissue disorders) than with insulin glargine (13%, most frequently general disorders and administration site conditions, investigations and nervous system disorders).
  - Relations to treatment were considered possible or probable for 5 of the serious adverse events in the insulin detemir group (three events of hypoglycaemia, one event of accidental overdose and one event of cerebellar infarction) and for 2 of the SAEs in the insulin glargine group (1 event of hypoglycaemic coma and 1 event of loss of consciousness).
  - Twelve (12, 5.6%) subjects from the insulin detemir group were withdrawn due to the onset of 6 unlikely related (hypersensitivity, hypotension, injection site induration, vasculitis and two events of myocardial infarction), 4 probably related (injection site mass, urticaria, pruritus and rash) and 3 possibly related (insomnia, cerebellar infarction and headache) AEs, whereas 3 (2.8%) subjects from the insulin glargine group were withdrawn from the trial due to the onset of 4 unlikely related AEs (lung cancer, anxiety and hypertension plus chest pain).
  - Application disorders were reported in 9% of subjects with insulin detemir and 4% of subjects with insulin glargine.
- The relative risk of having hypoglycaemia was similar in the two treatment groups as was the proportion of subjects who experienced hypoglycaemia and nocturnal hypoglycaemia. Major hypoglycaemic episodes were reported by 5% of the subjects with insulin detemir and 6% of the subjects with insulin glargine.
- No clinically relevant findings were observed for any of the clinical laboratory variables, vital signs or fundoscopy or fundusphotograpy results.

CONCLUSIONS

After 52 weeks of treatment with insulin detemir or insulin glargine in combination with insulin aspart with or without OAD treatment, the following was observed:

- non-inferiority of insulin detemir was established regarding glycaemic control as measured by HbA_{1c} after 52 weeks of treatment compared with insulin glargine.
- the proportion of subjects with HbA_{1c} ≤7.0% with or without hypoglycaemia was similar with insulin detemir and insulin glargine (approx. 36%).
- the proportion of subjects who achieved an HbA_{1c} below or equal to 7.0% in the absence of hypoglycaemia was similar with insulin detemir (17%) and insulin glargine (21%).
- $FPG_{(lab)}$ was similar with insulin detemir and insulin glargine
- within-subject variation in self-measured pre-breakfast and pre-dinner plasma glucose was similar with insulin detemir and insulin glargine.
- the overall shape of the 10-point self-measured plasma glucose profiles was similar with the two treatments.
- the relative risk of having a hypoglycaemic event was similar in the two treatment groups as well as the proportion of subjects having hypoglycaemia.
- the occurrence of adverse events during the trial was similar for the two treatments.
  - Insulin detemir gave rise to more AEs considered as having a possible or probable relation to basal trial product compared with insulin glargine (21% vs. 13%).
  - More subjects were withdrawn due to AEs with insulin detemir than with insulin glargine (5.6% vs. 2.8% of subjects).
- no difference was observed for vital signs and fundoscopy/fundusphotography between insulin detemir and insulin glargine
- the safety profiles as measured by laboratory safety variables were similar between insulin detemir and insulin glargine.
- body weight gain was lower with insulin detemir (2.8 kg) than with insulin glargine (3.8 kg) after 52 weeks of treatment.
- daily median basal insulin doses were 0.88 U/kg (range 0.15 - 3.86 U/kg) with insulin detemir administered once and twice daily vs. 0.65 IU/kg (range 0.11 - 1.65 IU/kg) with insulin glargine administered once daily and daily median bolus insulin doses were 0.36 U/kg (range 0.04 - 1.63 U/kg) vs. 0.33 IU/kg (range 0.04 - 1.56 IU/kg) in subjects treated with insulin detemir compared to subjects treated with insulin glargine.
- total mean ITSQ score after 24 and 52 weeks of treatment was similar with insulin detemir and insulin glargine.
- median time to change to a twice daily insulin detemir regimen was 28.4 weeks of treatment.
- the proportion of subjects completing the trial on a prescribed once daily insulin detemir regimen was 43%.
- a positive correlation was observed between insulin resistance in insulin naïve subjects at baseline and insulin requirements at end of trial in both treatment groups.
- no correlation was observed between change in serum adiponectin levels and basal insulin doses after 52 weeks in either treatment group.

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