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 1 diabetes
INVESTIGATORS A total of 38 investigators in 7 countries. Signatory investigators were [redacted], MD and [redacted], MD.
TRIAL SITES A total of 38 trial sites in 7 countries (the United States, the United Kingdom, Germany, France, the Netherlands, Finland and Sweden)
PUBLICATIONS None

TRIAL PERIOD	**DEVELOPMENT PHASE**
04 Oct 2004 – 20 Dec 2005	Phase 3b

OBJECTIVES

The primary objective of this trial is:

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

The secondary objectives of this trial are to compare the two treatments (insulin detemir versus insulin glargine) in terms of:

- Proportion of subjects with $HbA_{1c} \leq 7.0$ % after 52 weeks of treatment.
- Proportion of subjects with $HbA_{1c} \leq 7.0$ % without any episodes of major hypoglycaemia (as defined in section 8.3.4) during the last month of treatment.
- Glycaemic control as measured by fasting plasma glucose (FPG, central laboratory analysis) 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.
- Change in snacking during the trial.
- Basal and bolus insulin doses after 52 weeks of treatment.
- 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 daily to twice daily, in the insulin detemir treated group.
- Proportion of insulin detemir-treated subjects on once daily basal insulin after 52 weeks of treatment.
- Serum activity of Angiotensin-Converting-Enzyme (serum-ACE) as a biomarker for susceptibility to hypoglycaemic episodes.
- Serum-adiponectin levels as a marker for insulin sensitivity and weight change after 52 weeks of treatment.

METHODOLOGY

This was a multi-national, open-labelled, parallel-group treat-to-target trial with a 52-week treatment period, comparing the efficacy and safety of insulin detemir and insulin glargine in subjects with type 1 diabetes on a basal-bolus treatment regimen with insulin aspart at meals. Subjects were randomised 2:1 (insulin detemir:insulin glargine) to the two treatment groups.

Subjects were treated according to a pre-defined algorithm with the aim of reaching and maintaining a plasma glucose target of ≤ 6.0 mmol/L (108 mg/dL) before breakfast and dinner without significant hypoglycaemia. The investigator was to ensure appropriate dose adjustments throughout the trial using the insulin titration guideline. A central Insulin Titration Committee daily reviewed the information from the investigator after each contact and followed up on significant deviations from the algorithm.

All subjects were initiated on a once-daily basal treatment regimen and were asked to inject their basal insulin dose in the evening at approximately the same time each day. For subjects randomised to insulin detemir, a second daily dose in the morning could be added if the pre-dinner plasma glucose target was not reached despite titration according to the insulin titration guideline.

The trial included a screening visit to assess the eligibility of the subjects and a randomisation visit within 2 weeks of the screening visit, followed by a 52-week treatment period. In order to reach and maintain glycaemic control, frequent contacts between subjects and investigators were mandatory.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

It was planned to allocate 435 subjects to randomised treatment.

The number of subjects actually screened, randomised, exposed and included in the intent-to-treat and the per-protocol analysis sets is shown in the table below.

	Detemir N (%)	Glargine N (%)	All N (%)
Screened			515
Randomised	300 (100.0)	147 (100.0)	447 (100.0)
Exposed	299 (99.7)	144 (98.0)	443 (99.1)
Withdrawals	37 (12.3)	25 (17.0)	62 (13.9)
Adverse Event	6 (2.0)	4 (2.7)	10 (2.2)
Ineffective therapy	6 (2.0)	5 (3.4)	11 (2.5)
Non-compliance with protocol	15 (5.0)	4 (2.7)	19 (4.3)
Other	10 (3.3)	12 (8.2)	22 (4.9)
Completers	263 (87.7)	122 (83.0)	385 (86.1)
ITT analysis set	299 (99.7)	144 (98.0)	443 (99.1)
PP analysis set	254 (84.7)	120 (81.6)	374 (83.7)

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

A total of 447 male and female subjects with type 1 diabetes on a basal-bolus regimen for at least 3 months were randomly allocated to the two treatment groups. At trial entry, the subjects were ≥ 18 years of age, had had type 1 diabetes for at least 12 months and had $HbA_{1c} \leq 11.0\%$.

Subjects with proliferative retinopathy or maculopathy requiring acute treatment within 6 months prior to study start, recurrent major hypoglycaemia, anticipated change in medication known to interfere with glucose metabolism, impaired hepatic or renal function, cardiac problems or uncontrolled hypertension believed to interfere with study participation were not included in the trial.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Levemir® (insulin detemir) 100 U/mL (2400 nmol/mL) FlexPen® 3 mL solution for injection in a pre-filled pen (Novo Nordisk A/S, Denmark). The dose was individually titrated and administered as subcutaneous injections. Batch numbers were: RP50752 and PP50227.

As **meal-related insulin,** the following was supplied:

NovoRapid® (insulin aspart), 100 U/mL FlexPen® 3 mL solution for injection in a pre-filled pen (Novo Nordisk, Denmark). The dose was individually titrated and administered as subcutaneous injections. Batch numbers were: RP50402 and PP50493.

DURATION OF TREATMENT

52 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Lantus® (insulin glargine) 100 IU/mL in 3 mL cartridges in Europe and in 10 mL vials in the United States (Aventis, Germany/United States). An OptiPen Pro 1 device registered for use with insulin glargine cartridges was supplied in the EU while syringes were supplied in the US. The dose was individually titrated and administered as subcutaneous injections. Batch numbers were: 40D054, 40D073, 40D074, 40L427 and 41D067.

As **meal-related insulin**, the following was supplied:

NovoRapid® (insulin aspart), 100 U/mL FlexPen® 3 mL solution for injection in a pre-filled pen (Novo Nordisk, Denmark). The dose was individually titrated and administered as subcutaneous injections. Batch numbers were: RP50402 and PP50493.

CRITERIA FOR EVALUATION – EFFICACY

$HbA_{1c,}$ FPG, SMPG and 10-point SMPG profiles. Other: body weight, number of snacks, serum adiponectin, basal and bolus insulin doses and insulin treatment satisfaction questionnaire.

CRITERIA FOR EVALUATION – SAFETY

Adverse events, hypoglycaemic episodes, laboratory analyses (haematology, biochemistry and lipids), pregnancy, vital signs, physical examination and fundusphotography/fundoscopy. Other: serum ACE.

STATISTICAL METHODS

Analyses were made according to the intention-to-treat (ITT) principle and the safety population comprises all randomised and exposed subjects. Per Protocol (PP) analyses were made on all efficacy endpoints and on hypoglycaemic episodes as supportive evidence. All tests, except the primary analysis for the primary endpoint, were two-sided. P-values below or equal to 0.05 were considered as statistically significant. Summary statistics and 95% confidence intervals (CI) are presented based on the estimates from the statistical models that were used.

Primary Endpoint

- HbA_{1c} (%) after 52 weeks of treatment.

Secondary Efficacy Endpoints:

- The proportion of subjects achieving $HbA_{1c} \leq 7.0$ % after 52 weeks of treatment
- Proportion of subjects achieving $HbA_{1c} \leq 7.0$ % without any episodes of major hypoglycaemia (as defined in protocol section 8.3.4) during the last month of treatment
- Fasting plasma glucose during the trial (central laboratory analysis)
- Within-subject variation of SMPG before breakfast and dinner during the trial
- 10-point SMPG profiles during the trial.

Other Efficacy Endpoints:

- Body weight measured after 52 weeks of treatment
- Total daily snacking after 52 weeks of treatment
- Serum-adiponectin after 52 weeks of treatment
- Basal and bolus insulin doses after 52 weeks of treatment
- Time to start insulin detemir twice daily
- Proportion of insulin detemir-treated subjects on once daily basal insulin after 52 weeks of treatment.
- Treatment satisfaction measured by the ITSQ during the trial.

STATISTICAL METHODS – CONTINUED

Safety Endpoints

- Incidence of hypoglycaemic episodes (all, major, minor and symptoms only) during the trial; nocturnal (11 pm - 6 am) and over the entire day (24 hours)
- Incidence of adverse events during the trial
- Physical examination after 52 weeks of treatment
- Vital signs after 52 weeks of treatment
- Fundoscopy/fundusphotography after 52 weeks of treatment
- Clinical laboratory tests (haematology, biochemistry and lipids) after 52 weeks of treatment

Other Safety Endpoints:

- Serum-ACE activity measured at baseline (Visit 2)

Efficacy Analyses

The aim of the analysis of the **primary endpoint** was to investigate if glycaemic control, measured as HbA_{1c}, after 52 weeks of treatment with insulin detemir+ insulin aspart, was non-inferior to insulin glargine + insulin aspart using a non-inferiority margin of 0.4%. If non-inferiority was established, superiority of insulin detemir treatment over insulin glargine treatment was to be investigated. The non-inferiority hypothesis was evaluated by fitting an analysis of covariance (ANCOVA) model to the primary endpoint with treatment and country as fixed factors and baseline HbA_{1c} as covariate. A two-sided 95% confidence interval for the treatment difference (insulin detemir- insulin glargine) was calculated based on the above model and the ITT analysis set. Insulin detemir was shown non-inferior to insulin glargine if the upper confidence limit was below 0.4% (absolute). If non-inferiority were established, it was concluded that insulin detemir was superior to insulin glargine if the complete confidence interval was below 0%. Non-inferiority for the primary endpoint was also evaluated for the PP analysis set. The result of this analysis was used as supportive evidence to the primary analysis.

The proportion of **subjects achieving an HbA_{1c} below or equal to 7%** (with or without having any major hypoglycaemic episodes) was compared between the two groups using Fisher's exact test. **FPG** after 52 weeks, **weight**, **snacking** and **insulin treatment satisfaction** were compared between the groups by fitting an ANCOVA model, similar to that used for the primary efficacy endpoint, with treatment and country as fixed factors and baseline value as covariate. **The within-subject variation** after 24 and 52 weeks were evaluated separately for the pre-breakfast and the pre-dinner values, respectively. The within-subject variation for each treatment was estimated by fitting a mixed effect model with subject as a random effect, treatment and country as fixed factors. The within-subject variation for the two groups was compared using the likelihood ratio test where the above model was compared to a model where a common residual variance was fitted. The **10-point SMPG profiles** were compared after 24 and 52 weeks of treatment separately. The between group comparison was made by investigating the treatment-by-time interaction, which assessed if the treatment effect was constant over time, i.e. if the profiles could be regarded as parallel. A mixed effect model was fitted to the data with subject as a random effect, treatment, country, time and treatment · time as fixed factors. The residual variance structure was modelled as 'unstructured' for each subject whereas independence was assumed across subjects. If the treatment-by-time interaction was statistically significantly different from zero, the profiles could not be regarded as parallel. **Duration of exposure** to trial product, **time to switch from a once to a twice daily insulin regimen**, **time to meeting the self-measured pre-breakfast** and **pre-dinner PG targets** were estimated and described using the Kaplan-Meier estimate. Pre-specified exploratory analyses were made on **weight** and **serum adiponectin**. No correction for multiple endpoints was performed.

STATISTICAL METHODS – CONTINUED

Safety Analyses

Treatment emergent adverse events were compared between treatment groups by means of descriptive statistics. **Treatment emergent hypoglycaemic episodes** were compared between the treatment groups by estimating the hazard (instantaneous risk) ratio for having a hypoglycaemic episode in the insulin detemir group compared to the insulin glargine group. The hypoglycaemic episodes were analysed as recurrent events using a gamma frailty model. This model is an extended Cox regression model with treatment as covariates extended with a random effect (following a gamma distribution), which acts multiplicatively on the baseline hazard function describing the excess risk (or frailty) for a subject. In consistency with the project, the hazard ratio will be referred to as a relative risk ratio. **Vital signs** and **fundoscopy/fundusphotography** were summarised using descriptive statistics for each treatment group and in total. If applicable, the change from baseline were summarised for each treatment group. Any clinically relevant deterioration in **physical examination** since Visit 1 was only reported as an adverse event and not presented separately. Exploratory analyses were made to investigate the **relationship between the baseline ACE activity and major and minor hypoglycaemic episodes**. **Event rates for hypoglycaemic episodes** were compared between the groups using a negative binomial regression model with the logged exposure time as an offset and the appropriate baseline characteristics as fixed factors or continuous covariates.

DEMOGRAPHY OF TRIAL POPULATION

The two treatment groups were very similar with respect to demographic data and baseline characteristics. In both treatment groups, there were more males than females and the vast majority of subjects were White. The majority of subjects (54%) were on an insulin regimen with 1 basal and 3 bolus injections daily, while 15% of the subjects were on a regimen with 2 basal and 3 bolus injections daily and 13% of the subjects were on a regimen with 1 basal and 4 bolus injections daily. No subjects used pre-mixed insulin.

	Detemir	Glargine	All
N	299 (100.0)	144 (100.0)	443 (100.0)
Males, N (%)	167 (55.9)	81 (56.3)	248 (56.0)
Females, N (%)	132 (44.1)	63 (43.8)	195 (44.0)
	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)	42 (13)	41 (12)	42 (12)
Weight (kg)	79.6 (14.9)	78.9 (15.4)	79.4 (15.1)
BMI (kg/m^2)	26.5 (4.0)	26.3 (3.9)	26.5 (4.0)
Diabetes duration (yrs)	17.2 (11.7)	17.3 (10.7)	17.2 (11.4)
HbA_{1c} (%) D)	8.1 (1.1)	8.1 (1.2)	8.1 (1.1)
FPG (mmol/L)	10.3 (4.3)	10.1 (4.6)	10.2 (4.4)

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

EFFICACY RESULTS

Primary Endpoint

- Treatment with insulin detemir was non-inferior to insulin glargine as measured by the primary endpoint, HbA_{1c} after 52 weeks of treatment and the pre-specified criteria of 0.4%, for the ITT analysis set (detemir: 7.57%, glargine: 7.56% (estimated means), mean difference: 0.01; 95% confidence interval: [-0.13; 0.16]) as well as for the PP analysis set. Superiority was not shown.

Secondary Endpoints

- A total of 33% of subjects with insulin detemir and 30% of subjects with insulin glargine reached an HbA_{1c} level ≤ 7% after 52 weeks of treatment, with or without episodes of major hypoglycaemia during the last month of treatment (p=0.655).
- A total of 32% of subjects with insulin detemir and 29% of subjects with insulin glargine reached an $HbA_{1c} \leq 7.0$ % after 52 weeks of treatment without any major hypoglycaemic episodes during the last month of treatment (p=0.573).
- There was no statistically significant difference in FPG between insulin detemir and insulin glargine after 52 weeks (detemir: 8.58 mmol/L, glargine: 8.81 mmol/L (estimated means), mean difference: -0.23; 95% confidence interval: [-1.04; 0.58]; p=0.577).
- The within-subject variation in pre-breakfast (p=0.103) and pre-dinner (p=0.586) PG, as estimated by the within-subject standard deviation, was comparable for insulin detemir and insulin glargine after 52 weeks of treatment.
- The overall shapes of the mean 10-point PG profiles after 52 weeks with insulin detemir and insulin glargine were similar except for a lower value after lunch and a higher value pre-dinner with insulin detemir compared to insulin glargine (the treatment-by-time interaction was statistically significant (p=0.009) meaning that the profiles could not be regarded as parallel).

Other Efficacy Endpoints

- There was no statistically significant difference between insulin detemir and insulin glargine treatment groups with respect to change in body weight after 52 weeks of treatment (detemir: 0.36 kg, glargine: 0.42 kg (estimated means), mean difference: -0.06; 95% confidence interval: [-0.84; 0.73]; p=0.888).
- There was no statistically significant difference between insulin detemir and insulin glargine treatment groups with respect to change in mean snacking after 52 weeks of treatment (p=0.278).
- No statistically significant difference was found between the treatment groups in change of adiponectin levels after 52 weeks of treatment (estimated difference was 0.54 [95% confidence interval: [-1.23; 0.16] ug/mL, p=0.113). Both baseline BMI and adiponectin have a statistically significant effect on the change of adiponectin after 52 weeks.
- The median daily basal insulin dose per kg body weight was 0.44 (range: 0.12 - 1.70) U/kg in the insulin detemir group and 0.34 (0.09 - 0.95) U/kg in the insulin glargine group after 52 weeks of treatment, while the median daily bolus insulin dose per kg body weight were 0.33 U/kg in both treatment groups after 52 weeks of treatment.
- The median number of days to change from a once-daily to a twice-daily regimen in the insulin detemir group was 107 days.
- After 52 weeks of treatment, 90 (34%) subjects out of 263 completing subjects were on a once-daily insulin detemir regimen and 173 (66%) subjects were on a twice-daily insulin detemir regimen.
- After 52 weeks of treatment, the total mean ITSQ score was similar for insulin detemir and insulin glargine (p=0.823).

SAFETY RESULTS

- In the insulin detemir group, 277 (93%) subjects reported 1511 adverse events and in the insulin glargine group, 129 (90%) subjects reported 550 adverse events. The most frequently reported adverse events in both treatment groups were 'nasopharyngitis', 'headache', 'influenza' and 'pharyngolaryngeal pain'. The vast majority of adverse events were considered to be unlikely related to trial products and were mild or moderate in severity.
- One (1) subject, treated with insulin glargine for [redacted], died due to acute myocardial infarction and coronary artery atherosclerosis.
- In the insulin detemir group, 34 (11%) subjects reported 51 serious adverse events and in the insulin glargine group, 7 (5%) subjects reported 9 serious adverse events. Relation to trial product was considered probable or possible for 12 of the serious adverse events reported in the insulin detemir group versus 1 event in the insulin glargine group; all these events were hypoglycaemic episodes.
- Six (2%) subjects in the insulin detemir group and 4 (3%) subjects in the insulin glargine group were withdrawn from the trial due to adverse events.
- The overall risk of having a hypoglycaemic episode during the treatment period was similar between the insulin detemir and the insulin glargine groups with a relative risk (insulin detemir/insulin glargine) of 0.94 (p=0.571). The risk of having a nocturnal hypoglycaemic episode during the treatment period was similar in the two groups with a relative risk of 1.12 (p=0.375).
- No clinically relevant differences between treatment groups were observed for clinical laboratory tests, vital signs, physical examination or fundoscopy/fundusphotography after 52 weeks of treatment.

Other Safety Endpoints

- For 24h minor hypoglycaemic episodes, sex, BMI, baseline HbA_{1c}, serum ACE and duration of diabetes were indicated as risk factors and for nocturnal minor episodes, sex and duration of diabetes were indicated as risk factors. No risk factors could be found for major hypoglycaemic episodes.

CONCLUSIONS

After 52 weeks of treatment with insulin detemir or insulin glargine in combination with insulin aspart in subjects with type 1 diabetes:

- Treatment with insulin detemir was non-inferior to insulin glargine as measured by the primary endpoint, HbA_{1c} after 52 weeks of treatment and the pre-specified criteria of 0.4%, for the ITT analysis set (detemir: 7.57%, glargine: 7.56% (estimated means), mean difference: 0.01; 95% confidence interval: [-0.13; 0.16]) as well as for the PP analysis set. Superiority was not shown.
- A total of 33% of subjects with insulin detemir and 30% of subjects with insulin glargine reached an HbA_{1c} level ≤ 7% with or without episodes of major hypoglycaemia (p=0.66), while 32% and 29% of subjects, respectively, reached an HbA_{1c} ≤ 7.0 % without any major hypoglycaemic episodes during the last month of treatment (p=0.57).
- There was no statistically significant difference between insulin detemir and insulin glargine in FPG, within-subject variation in pre-breakfast and pre-dinner PG, body weight, mean snacking, total mean ITSQ score or adiponectin levels.
- The overall shapes of the mean 10-point PG profiles with insulin detemir and insulin glargine were similar except for a lower post-lunch and a higher pre-dinner value with insulin detemir compared to insulin glargine.
- The median daily basal insulin dose per kg body weight was 0.44 U/kg with insulin detemir and 0.34 U/kg with insulin glargine, while the median daily bolus insulin dose per kg body weight were 0.33 U/kg in both treatment groups.
- The median number of days to change from a once-daily to a twice-daily regimen in the insulin detemir group was 107 days, and 34% of the completing subjects were on a once-daily insulin detemir regimen and 66% were on a twice-daily insulin detemir regimen.
- The percentage of subjects reporting adverse events was similar for insulin detemir (93%) and insulin glargine (90%)s. The vast majority of adverse events were mild or moderate and unlikely related to trial products. One subject (on insulin glargine for [redacted]) died due to acute myocardial infarction and coronary artery atherosclerosis. Serious adverse events were reported for 11% and 5% of subjects, respectively. Six (2%) subjects on insulin detemir and 4 (3%) subjects on insulin glargine withdrew from the trial due to adverse events.
- The overall risk of having a hypoglycaemic episode during the treatment period was similar between the insulin detemir and the insulin glargine groups with a relative risk (insulin detemir/insulin glargine) of 0.94 (p=0.571). The risk of having a nocturnal hypoglycaemic episode during the treatment period was similar in the two groups with a relative risk of 1.12 (p=0.375).
- No clinically relevant differences between treatment groups were observed for clinical laboratory tests, vital signs, physical examination or fundoscopy/fundusphotography.

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