Synopsis

Trial Registration ID-number NCT00313742 (www.clinicaltrials.gov)	**EudraCT number** 2005-003980-21
Title of Trial A Multinational, Open Label, Randomised, Three Period, Cross Over Trial Investigating The Impact Of Exercise And Type Of Basal Insulin Used On Blood Glucose Levels In Subjects With Type 1 Diabetes Treated With a Basal Bolus Regimen Using Insulin Detemir, Glargine and NPH as Comparators and Insulin Aspart as Bolus Insulin (Levemir® Exercise Study)	
Investigators Two investigators, in Germany and in the UK respectively, enrolled subjects in this study.	
Trial Sites There were two trial sites, in Germany and in the UK respectively.	
Publications None at the time of this report.	
Trial Period 06 April 2006 – 06 November 2006	**Development Phase** Phase 4

Objectives

Primary Objective:

The objective of this study was to assess the impact of three basal insulin treatments on the maximum plasma glucose decline in subjects with type 1 diabetes, managed on a basal-bolus insulin regimen, when performing physical exercise.

Secondary Objectives:

To compare the three basal insulin treatments in terms of:

- Plasma glucose profiles pre- and post-exercise.
- Minimum plasma glucose value in the period 0-150 minutes post-exercise (nadir).
- Serum bolus insulin concentration immediately prior to and post-exercise.
- Slope of decline in plasma glucose post-exercise.
- Self measured plasma glucose post-exercise and at defined time points following each exercise test (4-point profile).
- Counter-regulatory hormone response.
- Incidence of hypoglycaemic episodes (major and minor) during and post exercise.
- Time between start of the exercise test and minimum plasma glucose value (first plasma glucose value <3.0 mmol/L in case of hypoglycaemia).
- The requirement and frequency of carbohydrate treatment during and post exercise.
- Incidence of adverse events.
- Standard clinical and laboratory safety parameters.

Methodology

This was a Phase 4, three period, randomised, multinational, open label, cross over study examining the impact of physical exercise and the type of basal insulin on plasma glucose (PG) levels, in subjects with type 1 diabetes managed on a basal-bolus regimen.

All participants were actively managed before and during the trial on a basal-bolus insulin regimen using insulin aspart as the bolus. Following a 2-week screening period, eligible subjects were randomised to receive basal insulin of either insulin detemir, insulin glargine or NPH insulin. Their insulin dose was then titrated and optimised for 4 weeks to achieve a stable PG level. Subjects then underwent exercise testing and, on the day after, were crossed-over to their second randomised insulin. Subjects were then treated for another 4 weeks before performing the next exercise test. Finally subjects were then crossed-over to their third insulin and were treated for 4 weeks before their final exercise test. Insulin aspart was used as short acting insulin for the duration of the study.

PG levels were measured following blood sampling every 10 minutes during the exercise test and for the 3 hours

after the exercise test. During and in the 3 hours following the exercise test, PG measurements were taken using the subject's blood glucose meter. If PG fell to ≤ 3.0 mmol/L or the subject showed symptoms of hypoglycaemia, they were to eat/drink 10 g of carbohydrate. The procedure was to be repeated if the next PG value remained ≤3.0 mmol/L or had not increased by at least 10%. Subjects were to record self-measured PG levels at 20:00, bedtime, 02:00 and pre-breakfast following the exercise test. The potential for post-exercise PG levels to be affected by carry-over of bolus insulin aspart was assessed by monitoring its levels on exercise test days.

Number of Subjects Planned and Analysed

Planned: 50 subjects.

Analysed: 57 screened, 51 randomised to treatment. Four subjects withdrew (2 due to adverse events, 1 for personal reasons and 1 withdrew of consent). 47 subjects completed the study.

Intention to treat population: 49 subjects.

Per protocol population: 47 for exercise test 1, 46 for exercise test 2 and 47 for exercise test 3.

Diagnosis and Main Criteria for Inclusion

Subjects (male or female) with type 1 diabetes of at least 12 months duration, age ≥18 years, using a basal-bolus regimen for ≥ 3 months, HbA_{1c} ≤ 9.0%, body mass index (BMI) < 32.0 kg/m².

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir (Levemir®) 100 U/mL solution for injection, 3 mL FlexPen® (Novo Nordisk A/S), given subcutaneously in the thigh twice daily and titrated over 4 weeks prior to the exercise test to achieve a fasting PG of 6.0 mmol/L and pre-lunch PG levels of 5.0 - 7.0 mmol/L. Batch number RP51302.

Duration of Treatment

Each subject received trial medication for 12 weeks i.e. 4 weeks for each of the three treatment arms.

Reference Therapy, Dose and Mode of Administration, Batch Number

NPH insulin (UK - Insulatard®; Germany - Protaphane®) - 100 U/mL suspension for injection, 3 mL FlexPen®, (Novo Nordisk A/S) given subcutaneously in the thigh twice daily and titrated over 4 weeks prior to the exercise test to achieve a fasting PG of 6.0 mmol/L and pre-lunch PG levels of 5.0 - 7.0 mmol/L. Batch number RP51548.

Insulin glargine (Lantus®) - 100 U/mL solution for injection, 3 mL OptiSet®, (Aventis) given subcutaneously in the thigh once daily and titrated over 4 weeks prior to the exercise test to achieve a fasting PG of 6.0 mmol/L and pre-lunch PG levels of 5.0 - 7.0 mmol/L. Batch numbers 50E145 for Germany, 40E031 for the UK.

Insulin aspart (NovoRapid®) - 100 U/mL solution for injection, 3 mL FlexPen® (Novo Nordisk A/S) administered subcutaneously in the abdomen, three times a day, 0-15 minutes before breakfast, lunch and dinner. Batch number RP51129.

Criteria for Evaluation – Efficacy

Efficacy evaluation criteria comprised assessment of PG concentrations, serum insulin aspart concentrations, counter-regulatory hormone levels and the frequency of carbohydrate treatment.

Criteria for Evaluation – Safety

Safety evaluation criteria comprised the incidence of hypoglycaemic episodes, adverse events and standard clinical and laboratory safety assessments.

Statistical Methods

Two paired comparisons were performed using the null hypotheses that:

- The difference between the PG levels immediately pre-exercise and the minimum PG concentration in the 150 minutes after the end of the exercise period following detemir treatment, was or alternatively was not equal to the difference between the PG levels immediately pre-exercise and the minimum PG concentration in the 150 minutes after the end of the exercise period, following glargine treatment.
- The difference between the PG levels immediately pre-exercise and the minimum PG concentration in the 150 minutes after the end of the exercise period following detemir treatment, was or alternatively was not equal to the difference between the PG levels immediately pre-exercise and the minimum PG concentration in the 150 minutes after the end of the exercise period, following NPH treatment.

A third paired comparison (insulin glargine versus NPH insulin) was regarded as an exploratory analysis.

The primary efficacy endpoint comprised the difference between PG concentration immediately pre-exercise and the nadir concentration in the 150 minutes following the exercise test for each of the three treatment arms. Secondary efficacy endpoints comprised the PG levels immediately pre- and post-exercise, the PG profile for 150 minutes post-exercise, the time between the start of exercise and the minimum PG value post-exercise, the serum insulin aspart concentration immediately prior to and post-exercise, the post-study self-monitored PG profile, the counter-regulatory hormone response and the frequency of carbohydrate treatment and amount of carbohydrate needed. Safety evaluation endpoints comprised the incidence of hypoglycaemic episodes (major and minor) during exercise and for 150 minutes post-exercise and between 150 minutes post-exercise to 07:30 the following morning, adverse events and standard clinical and laboratory safety assessments.
Assessment of the primary efficacy endpoint was performed using the intention to treat and per protocol populations, whereas secondary efficacy endpoints used the intention to treat population only. Assessment of safety parameters used the intention to treat population. Efficacy endpoints were analysed using a mixed effects ANCOVA model with treatment, baseline value, the first order carry-over effect, period, whether or not the subject fasted between breakfast and the start of the exercise test, and study centre as main effects. The total number of hypoglycaemic episodes following exercise was tested for statistical significance using the Wilcoxon signed rank test for each treatment pair. AEs and other safety parameters were summarised.

Demography of Trial Population

The demographic characteristics of the study population are summarised below

Characteristic		**Subjects**
Age (years)	Mean ± SD	38.5 ± 9.5
	Range	21.0 – 56.0
Ethnic Origin n (%)	White	50 (98)
	Black	1 (2)
Sex n (%)	Male	34 (67)
	Female	17 (33)
Diabetes Duration (years)	Mean ± SD	28.4 ± 10.4
	Range	4.0 – 44.0
Height (m)	Mean ± SD	1.74 ± 0.08
	Range	1.57 – 1.91
Weight (kg)	Mean ± SD	76.6 ± 13.4
	Range	56.7 – 114.5
BMI (kg/m^2)	Mean ± SD	25.3 ± 3.1
	Range	18.9 – 31.7
HbA_{1c} (%)	Mean ± SD	7.4 ± 0.8
	Range	5.3 – 9.0

Efficacy Results

- The mean decreases in post-exercise PG concentration during the 150 minutes following exercise were comparable for the different basal insulin formulations, being 2.01 ± 2.01 mmol/L when subjects received insulin detemir, 2.08 ± 1.83 mmol/L when they received NPH insulin and 1.80 ± 1.88 mmol/L when they received insulin glargine.
- The mean post-exercise PG concentrations were comparable for the different formulations, being 5.71 ± 2.48 mmol/L for subjects receiving insulin detemir, 5.36 ± 2.34 mmol/L for subjects receiving NPH insulin and 5.32 ± 2.90 mmol/L for subjects receiving insulin glargine.
- As the mean pre-exercise PG concentration was slightly (non-significantly) higher when subjects were treated with insulin detemir (6.44 ± 3.03 mmol/L) as compared with when they received insulin glargine (5.74 ± 2.96 mmol/L), a post-hoc analysis was performed investigating the incidence of hypoglycaemia in relation to pre-exercise PG concentrations. For each mmol/l interval of PG, the hypoglycaemia rate was numerically higher

with insulin glargine than with insulin detemir.

- Post-exercise SMPG levels were comparable when subjects were treated with the different basal insulin formulations.
- In accordance with the data on hypoglycaemia incidence, more carbohydrate was required when subjects were treated with insulin glargine than both insulin detemir (difference 4.4 units, $p < 0.001$) and NPH insulin (difference 3.8 units, $p < 0.001$).
- Minimum and maximum post-exercise cortisol levels were lower when subjects were treated with insulin detemir compared with insulin glargine, representing a treatment difference for minimum levels of -31.1 ± 11.4 nmol/L ($p = 0.007$) and for maximum levels of –54.0 ± 16.2 nmol/L ($p = 0.001$). Minimum and maximum adrenaline levels were slightly lower when subjects were treated with NPH insulin, though the difference did not achieve statistical significance.

Safety Results

- There was a slightly higher incidence of AEs during the NPH insulin treatment period (24 events vs. 19 with insulin detemir and 14 with insulin glargine) and also in the subjects reporting AEs (31% vs. 24% with insulin detemir and 23% with insulin glargine). Most events were mild or moderate in severity.
- Three AEs were considered related to the study treatments: severe hypoglycaemia considered probably related to basal NPH insulin and insulin aspart, mild skin rash considered probably related to insulin detemir and a mild local reaction at the injection site considered probably related to insulin aspart treatment.
- No deaths occurred during the study.
- An AE of severe hypoglycaemia occurring during NPH insulin treatment that was also classified as an SAE and was considered probably related to both NPH insulin and insulin aspart administration.
- Two subjects withdrew from the study as a result of an AE: one following [redacted] epididymitis considered unlikely to be related to the insulin treatments, and the other following an AE of [redacted] local reaction at the injection site considered probably related to insulin aspart treatment.
- The highest incidence of hypoglycaemia was seen when study subjects were treated with insulin glargine (28 episodes vs. 15 with NPH insulin and 12 with insulin detemir). Differences in the incidence of hypoglycaemic episodes achieved statistical significance when comparing insulin glargine with insulin detemir ($p < 0.001$) and NPH insulin ($p = 0.02$)..
- No clinically significant changes were seen in haematology or serum chemistry parameters.
- Three subjects experienced sinus bradycardia during treatment with either NPH insulin or insulin detemir, though all such events were considered unlikely to be related to the study treatments.

Conclusions

- The different basal insulin formulations did not result in statistically significant differences in any measure of post-exercise plasma glucose concentration.
- The minimum post-exercise cortisol concentration was significantly lower when subjects were treated with insulin detemir compared with insulin glargine.
- More carbohydrate was required to compensate for hypoglycaemic episodes during treatment with insulin glargine.
- A significantly higher incidence of hypoglycaemic episodes was seen when subjects were undergoing insulin glargine treatment.
- No safety concerns were raised in association with the use of the three basal insulin formulations during this trial.

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