2 Synopsis

Trial Registration ID-number NCT00509925	**EudraCT number** 2006-003060-59
Title of Trial A 32-week national, single-centre, open-label, randomised, crossover trial comparing energy expenditure with insulin detemir versus NPH insulin using a basal–bolus regimen with insulin aspart as mealtime insulin in subjects with type 1 diabetes.	
Investigator(s) Professor [redacted], MD, BSc, MBBS, FRCP, MRCP [redacted]	
Trial Site(s) [redacted], UK	
Publications None	
Trial Period FPFV: July 2007; LPLV: July 2008 Trial was prematurely terminated in December 2008	**Development Phase** Phase 4

This open-label study was terminated prematurely due to two unplanned interim analyses having been performed. This was subsequently reported to the UK regulatory authority, the Medicines and Healthcare products Regulatory Agency (MHRA), as a serious breach of Good Clinical Practice (GCP). As a result, the statistical analysis plan was amended and therefore not all initially planned objectives were statistically analysed. Details of these changes are provided in the Statistical Methods section.

Objectives as described in the protocol

Primary Objectives

- To measure energy expenditure before and after 16 weeks of treatment with insulin detemir in combination with insulin aspart as mealtime insulin, in comparison with energy expenditure before and after 16 weeks of treatment with NPH insulin.
- To assess and compare the effect on energy expenditure as measured by:
  - Total energy expenditure (TEE) – measured by (a) double-labelled water method and (b) dietary record method (TEE by 7-day food diary)
  - Resting energy expenditure (REE) (basal metabolic rate) and respiratory quotient – measured by indirect calorimetry
  - Diet-induced thermogenesis (DIT) – measured by indirect calorimetry
  - Physical activity thermogenesis – measured by (a) volitional exercise using Actiheart 3-D monitors, and (b) thermic efficiency (respiration during light exercise) non-exercise activity thermogenesis (NEAT)

Secondary Objectives

To assess and compare the effect on:

- Nutritional and food intake, assessed by:
  - 7-day food intake (data from 7-day food diary)
  - Calorie input during free unlimited meal
  - Response to standard meal
- Body measurements
  - Weight
  - Body composition – measured by bioelectrical impedance analysis (BIA)
  - Waist:hip ratio

- Insulin requirements
- Continued glucose monitoring system (CGMS) glucose profiles
- Hormones that affect satiety e.g., leptin, ghrelin, GLP-1, pancreatic polypeptide, peptide YY
- Hormones that affect fuel partitioning e.g., resistin, adiponectin and IGF-I
- Metabolic control
  - Achieved glycaemic control as measured by HbA_{1c} before randomisation (baseline), after treatment period 1 (16 weeks) and after treatment period 2 (32 weeks).
  - The 8-point blood glucose profiles before and after 16 weeks.
  - The effect on glycaemic control, as measured by fasting plasma glucose (FPG lab) before randomisation (baseline), after treatment period 1 (16 weeks), and after treatment period 2 (32 weeks).
  - The within-subject variation of home fasting plasma glucose (FPG home) and pre-dinner plasma glucose (PG) during the 7 days before the commencement of each 16-week treatment period and the last 7 days of each treatment period.
  - The incidence of hypoglycaemic episodes during the study (nocturnal, 23:00–06:00, and over the entire day; 24 hours).

Safety Objectives

- To assess and compare the safety profiles as measured by:
  - Occurrence of adverse events (AEs) during the duration of the study
  - Laboratory safety parameters (haematology, biochemistry, and lipids), physical examination, fundoscopy/fundosphotography, and vital signs.

Methodology

- This was a single-centre, open-label, randomised, two-period crossover trial of 32 weeks comparing insulin detemir to NPH insulin, each in conjunction with mealtime insulin aspart, in subjects with type 1 diabetes. After 16 weeks, subjects were switched over to the other basal insulin, combined with bolus mealtime insulin aspart, for the remaining 16 weeks. Results were compared at baseline, at the end of the first treatment period (16 weeks), then at the end of the second treatment period (32 weeks). Following the screening visit to assess eligibility (visit 1), subjects were randomised (1:1) at visit 2 to receive either basal insulin detemir or basal NPH insulin, each in combination with mealtime insulin aspart, for the first 16 weeks. Subjects were instructed to continue on their usual treatment until visit 2.
- Randomisation was carried out by assigning the lowest available sealed code number to each subject.
- Subjects were titrated individually with the aim of reaching and maintaining the pre-breakfast and pre-dinner plasma glucose targets of ≤6.0 mmol/L without significant hypoglycaemia.
- During the trial, subjects had to attend all eight visits, at which time various samples were taken for analyses. AEs, hypoglycaemic episodes, and insulin dose were recorded at each visit.
- Safety assessments included AEs, physical examination, vital signs, electrocardiograms (ECGs), clinical laboratory tests (haematology, biochemistry), and hypoglycaemic episodes.

Number of Subjects Planned and Analysed

A total of 40 subjects with type 1 diabetes were planned to be screened in order to randomise 30 subjects. The actual subject disposition (including analysis sets) was as follows:

	n
Planned number to be screened	40
Screened	23
Screening failures	0
Randomised	23
Exposed	23
Completed	22
Withdrawn (Reason)	1 (Other)
AEs	0
Completers	22
Intent-to-treat (ITT)	22
Per protocol (PP)	0
Safety analysis set	23

Diagnosis and Main Criteria for Inclusion

Subjects aged ≥18years, with type 1 diabetes ≥12 months, body mass index (BMI) ≤40.0 kg/m^2, HbA_{1c} between ≥7.0 and ≤11.0%, and receiving basal–bolus insulin treatment ≥3 months (i.e., at least one daily injection of long-acting insulin [including insulin glargine] and fast-acting insulin with each main meal). Subjects were to be withdrawn from the trial following the use of concomitant medication judged to affect glucose metabolism, a significant change in dietary or exercise habits, confirmed pregnancy, or the occurrence of AEs or symptoms considered unacceptable by the Investigator or Sponsor.

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir (100 U/mL) in 3-mL pen injector (batch numbers SP51226 and TP52028), injected once or twice daily according to individual need subcutaneously (sc) in the abdomen, thigh, or upper arm.

At visit 2, all eligible subjects were randomised to start on either of the basal insulins listed below for the first 16 weeks of the trial:

- Insulin detemir + insulin aspart
- NPH insulin + insulin aspart

After the first 16 weeks, subjects then switched over to the other basal insulin for the remaining 16 weeks.

Subjects were advised to inject insulin detemir or NPH insulin, and insulin aspart sc.

Duration of Treatment

Subjects administered single doses of insulin detemir or NPH insulin once or twice daily for 16 weeks, then switched over to other basal insulin for the remaining 16 weeks. Throughout the 32 weeks, subjects administered mealtime doses of insulin aspart.

Reference Therapy, Dose and Mode of Administration, Batch Number

The reference therapy was NPH insulin (100 IU/mL) in a 3-mL pen injector (batch number SP51111), injected once or twice daily according to individual need, sc.

Criteria for Evaluation – Efficacy

The following efficacy variables were assessed:

- Energy expenditure
  - TEE
  - REE
  - DIT
  - Physical activity thermogenesis
- Nutritional and food intake
  - 7-day food intake (food diary)
  - Response to standard meal
  - Calorie input during free unlimited meal
- Body measurements
  - Weight
  - Body composition
  - Waist:hip ratio
- Insulin requirements
- Hormonal assessment
- Metabolic control
  - HbA_{1c}
  - FPG
  - 8-point blood glucose profiles (self-measured)

Criteria for Evaluation – Safety

The safety evaluation was based on AEs, physical examination, vital signs, electrocardiograms (ECGs), clinical laboratory tests (haematology, biochemistry), and hypoglycaemic episodes.

Statistical Methods

As a result of two unplanned interim analyses, changes were made to the statistical analysis plan used in this study. The statistical methods used are described below.

Hypothesis

This study set out to measure energy expenditure before and after 16 weeks of treatment with insulin detemir compared with NPH insulin to explain the mechanism of weight loss association with treatment with insulin detemir.

Primary Endpoint

- TEE, as measured by both the double-labelled water method and the 7-day food diary.

Secondary Efficacy Endpoints

- REE
- DIT
- Physical activity thermogenesis
- NEAT

Safety Endpoints

- Secondary safety endpoints were the incidence of hypoglycaemic episodes and treatment-emergent AEs. The incidence of hypoglycaemic episodes were summarised by treatment, classification (major, minor, symptomatic), and time interval (diurnal, nocturnal).
- Treatment-emergent AEs were summarised by treatment, system organ class, and severity.

Other endpoints

The other endpoints assessed were:

- Body weight
- Body composition
- Waist:hip ratio
- Insulin requirements
- Hormonal assessment
- Metabolic control

These variables were summarised using descriptive statistics for each treatment group.

Unplanned Interim Analyses

- Two unplanned interim analyses were performed by the Investigator.

Changes to the Planned Analyses

- As a consequence of the unplanned interim analyses, the statistical analysis plan described in the protocol was amended to take into account the previous interim analyses. The amended statistical analysis plan was approved prior to database release.
- TEE measured by the double-labelled water method and 7-day food diary were both subject to statistical inference. All other variables were summarised using descriptive statistics only; no formal statistical testing was carried out.

Analysis Sets

ITT Analysis Set

For all endpoints the analyses were performed on an ITT analysis set. The ITT analysis set consisted of all subjects who received at least one post-treatment value of the primary endpoint.

PP Analysis Set

The analysis of the primary endpoint was also to be performed on a PP analysis set. The PP analysis set included all subjects from the ITT analysis set without any major deviations from the protocol. Since no patients fulfilled these criteria, the PP analysis was not performed.

All 22 patients who completed the trial were included in the ITT analyses. No patients were included in the PP analysis.

Statistical Methods Used to Analyse Primary and Secondary Endpoints

The primary analysis was a comparison between insulin detemir and NPH insulin treatment groups with respect to the primary endpoint, TEE, using the double-labelled water method and a 7-day food diary. A two-sided test with 5% level of significance was used. Differences between treatments were compared with an analysis of variance (ANOVA) model in which the response variable for each subject was TEE, as measured by the double-labelled water method and 7-day food diary, period and treatment were fixed effects, subject was a random effect, and a period/treatment interaction was included as a fixed effect. The treatment difference was estimated and associated 95% confidence intervals (CIs) reported. All other variables were summarised using descriptive statistics only; no formal statistical testing was carried out.

Demography of Trial Population

The population consisted of male (60.8%) and female (39.1%) subjects with type 1 diabetes. They had a mean age of 38.8 years, a mean weight of 81.9 kg, a mean BMI of 28.0 kg/m^2, and a mean waist:hip ratio of 93.5%. All subjects were white. Summary of baseline demographics were as follows:

Patient Baseline Demographic Characteristics

All exposed subjects	23
Age (years)	
N	23
Mean	38.8
SD	10.6
Median	39
Min	19
Max	56
Gender	
Male	14
Female	9
Race	
White	23
Weight (kg)	
N	23
Mean	81.9
SD	10.6
Median	81.4
Min	64
Max	106.5
BMI (kg/m^2)	
N	23
Mean	28.0
SD	3.6
Median	27.2
Min	23.7
Max	37.2

SD, standard deviation

All the values used in this table are from the screening visit.

Efficacy Results

As discussed previously, due to changes made to the statistical analysis plan only the primary endpoint of TEE by double-labelled water and 7-day food diary was subject to statistical analysis. All other variables were descriptively summarised. In addition, as all patients were excluded from the PP population, all analysis was performed in the ITT population.

Primary Endpoint

- Total energy expenditure as assessed by the double-labelled water method showed no difference between treatments. In contrast, there was a significant (*P*=0.014) difference between treatments in TEE as assessed using the 7-day food diary (163.1 [95% CI: 32.9, 293.2]).

Secondary Endpoints

- There was no difference between insulin detemir and NPH insulin with respect to the individual components of TEE assessed, with the possible exception of increased physical activity thermogenesis with insulin detemir.

Other Endpoints

- Body weight
  - In both study arms, weight was lower after treatment with insulin detemir than with NPH insulin.
- Body composition
  - Insulin detemir showed a greater tendency to reduce fat mass than to affect lean body mass compared with NPH insulin.
- Waist:hip ratio
  - No change in waist:hip ratio was observed with either treatment.
- Hormonal assessment
  - Levels of leptin tended to be lower after 16 weeks of treatment with insulin detemir than with NPH insulin. Sixteen weeks of treatment with insulin detemir or NPH insulin did not produce any consistent between-treatment differences in adiponectin, IGF-1, or resistin.
- Metabolic control endpoints
  - HbA_{1c} (mean [SD]): both treatments reduced HbA_{1c} from baseline mean of 8.2 (1.0)%. However, the reductions were slightly greater with NPH insulin. In the insulin detemir–NPH group, mean HbA_{1c} in periods 1 and 2 was 7.8 (1.3)% and 7.6 (1.4)%, respectively. In the NPH–insulin detemir group, mean HbA_{1c} in periods 1 and 2 was 7.4 (1.2)% and 8.0 (1.0)%, respectively.
  - FPG (mean [SD]): insulin detemir increased FPG from a baseline of 10.4 (3.6) mmol/L to 13.3 (5.8) mmol/L and to 13.3 (5.2) mmol/L in the insulin detemir–NPH insulin group and the NPH insulin–insulin detemir groups, respectively. In contrast, NPH insulin decreased FPG to 9.1 (7.5) mmol/L and produced no change in FPG in the insulin detemir–NPH insulin group and the NPH insulin–insulin detemir groups, respectively.

Safety Results

- AEs
  - AEs were reported by 39% (9/23) of subjects. The most frequently reported AEs were viral infections (including the common cold).
  - Twelve events were reported in seven patients when receiving insulin detemir and six events were reported in four patients during treatment with NPH insulin.
  - All AEs were mild to moderate in severity and were recovered at the end of the study.
  - One injection site induration was reported in a patient receiving insulin detemir. No change in waist:hip ratio was observed with either treatment.
  - No serious AEs were reported during the study.
- Hypoglycaemic episodes
  - The proportion of hypoglycaemic episodes overall during the trial was smaller in the insulin detemir group than in the NPH insulin group (90/199 [45%] vs. 109/199 [55%], respectively).
  - A greater percentage of events were reported as nocturnal hypoglycaemic episodes during treatment with insulin detemir (30%) than with NPH insulin (20%).

Conclusions

- The objective of this metabolic study was to try to determine why in previous studies less weight has been gained with insulin detemir than with NPH insulin. During this study the different effects of these insulins on energy balance were assessed by measuring energy expenditure (in total and as components) after 16 weeks' treatment with insulin detemir (in combination with mealtime insulin aspart), as compared with NPH insulin (in combination with mealtime insulin aspart) in subjects with type 1 diabetes. In addition, various biometrics such as weight, fat and lean body mass, and waist:hip ratio were measured to assess any measurable differences between the effects of the two study insulins.
- This open-label study was terminated prematurely due to two unplanned interim analyses having been performed. As a result of this, only 23 out of the 30 patients planned were randomised into the study, with 22 of these completing the study. The statistical analysis plan for the study was amended in light of the unplanned interim analyses. As a result of these changes, only the primary endpoint of TEE by double-labelled water and 7-day food diary was subject to statistical analysis. All other variables were descriptively summarised. All patients were excluded from the PP population and therefore all analyses were performed on the ITT population.
- TEE, as assessed by the double-labelled water method, showed no differences between insulin detemir and NPH insulin. In contrast, a statistically significant reduction in energy intake (TEE by 7 day food diary) in association with insulin detemir treatment was observed. This corresponded to a reduction in calorie intake of approximately 150 cal/day (vs. NPH insulin). The assessments of the components of TEE did not show any obvious differences between the basal insulins either, with the possible exception of NEAT, where mean energy expenditure appeared slightly higher with insulin detemir than NPH insulin. Thus, it appears that insulin detemir is associated with a reduced consumption of energy that is not balanced by reduced TEE (by the double-labelled water method).
- This study was consistent with previous studies in that it showed treatment with insulin detemir to be associated with less weight gain than NPH insulin. This was observed by lower body weight at the end of the insulin detemir treatment period. In addition, this study suggested that insulin detemir treatment (as compared to NPH insulin treatment) is associated with a reduction in fat mass. This finding is consistent with studies in rodents.
- Another finding worthy of further exploration was the observation that insulin detemir was associated with decreased levels of leptin. Secretion of leptin is generally proportional to fat mass and this hormone acts together with insulin to signal satiety. Thus, the observation that energy intake decreased with insulin detemir in the setting of reduced leptin levels (and fat mass) is unusual and potentially interesting. These observations might imply that insulin detemir is potentiating satiety directly, while independently affecting leptin secretion.
- A possible caveat to the findings of the present study was that the patients may not have had completely equivalent glycaemic control during the two treatment periods. The insulin detemir treatment periods seemed to be associated with a slight worsening of control, whereas treatment with NPH insulin appeared to improve glycaemic control. This possibly reflects inadequate titration of insulin detemir, since previous treat-to-target trials (over longer study periods) have achieved equivalent levels of glycaemic control using these insulins. Moreover, it may be that the ratio of basal–bolus insulin varied according to the basal insulin used. It should be noted that no titration guidelines were prepared for this study; instead, titration was led by the investigator, so this could have affected the trajectories of glycaemic control and might explain differences between this and previous studies. It cannot be excluded, therefore, that the findings of the present study are related to differences in glycaemic control and/or inequitable insulin regimens rather than to different influences of the two basal insulins on physiological energy balance.
- In conclusion, the study supports the broad hypothesis that a relative reduction in weight gain with insulin detemir (versus other insulin) therapy is due to a tendency for treated patients to reduce their calorie consumption without reducing their energy expenditure. Such an effect might be mediated by a direct satiety inducing effect and this hypothesis warrants further study.

The trial was conducted in accordance with the Declaration of Helsinki (October 2000, amended 2002) and ICH GCP (1 May 1996) with the exception of two unplanned interim analyses that were performed by the Investigator. This breach of GCP was reported to the UK regulatory authority, the MHRA, and the decision was subsequently taken to terminate the study.

The results presented reflect data available in the clinical database as of 20 October 2009 (date of database release).