2 Synopsis

Trial Registration ID-number	**EudraCT number – EU only**
NCT00795600	2008-003739-19

Title of Trial

A multi-centre, open-labelled, randomised, two-group parallel trial comparing the change in fat distribution in overweight and obese subjects with type 2 diabetes after 26 weeks of treatment with insulin detemir once daily versus insulin NPH once daily, both with insulin aspart at mealtimes.

Investigators

There were five principal investigators: Dr. [redacted], Dr. [redacted], Dr. [redacted], Dr. [redacted] and Dr. [redacted].

Trial Sites

There were five active centres in Spain where the trial was conducted: [redacted]

Publications

None at this moment.

Trial Period	**Development Phase**
29 April 2009 – 10 August 2010	IV

Objectives

Primary Objective:

To compare the change in trunk fat mass, assessed by DEXA (Double Energy X-ray Absorptiometry), after 26 weeks of treatment with insulin detemir or insulin NPH [Neutral Protamine Hagedorn] (both with insulin aspart in the main meals) in overweight and obese type 2 diabetic subjects.

Secondary Objectives:

- **Efficacy:**
  - Additional for DEXA: Whole Body Fat Mass (g), Whole Body Lean Mass (g), Trunk Lean Mass (g), Calculated Whole Body Fat Percentage and Calculated Trunk Fat Percentage.
  - CT scan: Visceral Adipose Tissue Area (cm^2), Subcutaneous Adipose Tissue Area (cm^2), Calculated Visceral/Subcutaneous Adipose Tissue Ratio and Liver/Spleen Attenuation Ratio (L/S).
  - Change in HbA_{1c} from baseline to 12 and 26 weeks of treatment.
  - Change in Fasting plasma glucose from baseline to 12 and 26 weeks of treatment.
  - To quantify the relationship between BMI (Body Mass Index) and required daily dose of insulin detemir.
  - Change in cytokine in the adipose tissue (adiponectin) from baseline to 26 weeks of treatment.
  - Change of inflammatory parameters (hsCRP and PAI-1) from baseline to 26 weeks of treatment.
  - Change of weight from baseline to 26 weeks of treatment.
  - Change in waist and hip circumference from baseline to end of treatment.

- **Safety:**
  - Incidence of hypoglycaemia in the 26 weeks of treatment.
  - Change of lipid profile from baseline to 26 weeks of treatment.
  - Incidence of Adverse events during the trial.
  - Safety profile as measured by laboratory safety parameters (haematology, biochemistry) and physical examination/vital signs before and at the end of treatment.

Methodology

This was a phase 4, multi-centre, local, open-labelled, randomised, two parallel groups clinical trial comparing the change in trunk fat mass of subjects with type 2 diabetes who were obese or overweight treated either with insulin

detemir or NPH in intensive insulin regimens.

Number of Subjects Planned and Analysed

As the primary objective was to demonstrate a difference of 5% in the primary endpoint, using an ANCOVA (analysis of covariance) model with 3 factors and 1 covariate and with a standard deviation of 5%, the number of patients needed would be of 23 patients per group. Assuming a withdrawal rate of 20%, the total number of randomised patients would be 58. With a planned screening failure of 20%, the total number of patients planned to be screening would be 73.The number of subjects screened and the populations conformed by them are presented as follows:

Population	Insulin Detemir	Insulin NPH	Overall
Screened			81
Screen failures			21
Randomised	25 (100.0%)	35 (100.0%)	60 (100.0%)
Safety	24 (96.0%)	35 (100.0%)	59 (98.3%)
Intent-to-treat	24 (96.0%)	35 (100.0%)	59 (98.3%)
Per protocol	21 (84.0%)	31 (88.6%)	52 (86.7%)

Percentages calculated over the randomised population.

Diagnosis and Main Criteria for Inclusion

Male and female subjects with type 2 diabetes who had been treated with 2 or 3 doses of insulin for at least 3 months prior to inclusion were randomly allocated to the two treatment groups. At trial entry, the subjects were required to be at least 18 years of age and have a BMI ≥ 27.5 kg/m^2 and ≤ 40 kg/m^2. They should have an HbA_{1c} ≥ 7% and ≤ 11.0% at screening based on analysis from central laboratory.

Test Product, Dose and Mode of Administration, Batch Number

FlexPen insulin detemir® 100 U/mL subcutaneously with batch number VP52055 with expiry date 22 February 2011.

Duration of Treatment

The duration of treatment was of 26 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Isophane (NPH) Insulin FlexPen® 100 IU/mL subcutaneously with batch number VP51913 with expiry date 26 December 2010.

Criteria for Evaluation – Efficacy

- The change in trunk fat mass (g), assessed by DEXA scan at baseline and at week 26, was the primary endpoint.

The following were considered secondary variables:

- Additional to DEXA scan:
  - Whole Body Fat Mass (g)
  - Whole Body Lean Mass (g)
  - Trunk Lean Mass (g)
  - Calculated Whole Body Fat Percentage
  - Calculated Trunk Fat Percentage
- CT (Computerised Tomography) scan:
  - Visceral Adipose Tissue Area (cm^2)
  - Subcutaneous Adipose Tissue Area (cm^2)
  - Calculated Visceral/Subcutaneous Adipose Tissue Ratio
  - Liver/Spleen Attenuation Ratio (L/S)
- Change in HbA_{1c} (Glycosylatyed Haemoglobin) from baseline to 12 and 26 weeks
- Change of Fasting plasma glucose from baseline to 12 and 26 weeks
- Change of Adiponectin from baseline to 26 weeks
- Change of inflammatory parameters (hsCRP [highly sensitive C reactive protein] and PAI-1) from baseline to 26 weeks
- Change of weight from baseline to 26 weeks

- Change in waist and hip circumference from baseline to end of treatment

Criteria for Evaluation – Safety

- Incidence of hypoglycaemia in the 26 weeks of treatment
- Change of lipid profile (Total Cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides and free fatty acids) from baseline to 26 weeks
- Incidence of Adverse events during the trial
- Haematology (haemoglobin, haematocrit, thrombocytes, erythrocytes, leucocytes, differential cell count) before and at the end of treatment
- Biochemistry (creatinine, creatine phosphokinase (CPK), urea, albumin, bilirubin (total), alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (ALP), sodium, potassium) before and at the end of treatment
- Vital signs
- Physical examination

Statistical Methods

All efficacy analyses were performed on the full analysis set. Additionally, primary efficacy variable was also analysed for the per protocol population.

ANCOVA model, to determine differences between treatment groups, was used in which was included the treatment group, treatment with metformin (as ordinal variable) and gender as fixed effects, and baseline values as covariate to analyse the primary efficacy variable and the following secondary variables: additional for DEXA and CT scans, HbA_{1c}, fasting plasma glucose, cytokine levels in the adipose tissue and inflammatory parameters. For body weight and waist-hip circumference variables were analysed using an ANOVA model including the two stratification criteria (metformin use and gender), and the corresponding baseline value as a covariate. Finally, the relation between the BMI and the required daily dose of Detemir insulin was analysed by using the Pearson correlation coefficient or the Spearman rho value when appropriate. All statistical tests were performed as two-sided and with a level of significance of 95%.

For safety parameters, descriptive statistics were done for AEs, vital signs and physical examination. Hypoglycaemic episodes would be analysed using the Poisson regression model if a sufficient number of episodes was provided. Otherwise, only descriptive statistics would be done.

Demography of Trial Population

Variable	Insulin Detemir n=24	Insulin NPH N=35
Age (years)[A]	60.63 (8.87)	63.74 (9.39)
Gender (males)[B]	13 (54.2%)	16 (45.7%)
Race (white)[B]	24 (100.0%)	35 (100.0%)
Systolic blood pressure(mmHg)[A]	145.17 (18.87)	139.97 (18.14)
Diastolic blood pressure (mmHg)[A]	81.04 (11.01)	75.34 (10.68)
Pulse (beats/min)[A]	77.38 (10.89)	76.26 (12.38)
Height (cm)[A]	1.60 (0.09)	1.59 (0.10)
Weight (kg)[A]	83.05 (13.74)	85.99 (14.29)
BMI (kg/m^2)[A]	32.21 (4.10)	34.03 (3.96)
Waist circumference (cm)[A]	107.73 (9.93)	110.04 (9.31)
Hip circumference cm)[A]	108.79 (7.56)	112.74 (8.89)
Duration of diabetes (years)[A]	13.58 (6.68)	17.43 (9.00)
Diabetes complications		
Diabetic nephropathy (yes)[B]	4 (16.7%)	5 (14.3%)
Diabetic neuropathy (yes)[B]	5 (20.8%)	7 (20.0%)
Diabetic retinopathy (yes)[B]	11 (45.8%)	16 (45.7%)
Macroangiopathy (yes)[B]	4 (16.7%)	12 (34.3%)
Fundoscopy (abnormal CS)		
Left eye (yes)[B]	0 (0.0%)	2 (5.7%)
Right eye (yes)[B]	0 (0.0%)	2 (5.7%)

[A] mean (s.d.); [B] n (%)

Efficacy Results

Primary efficacy variable

- Insulin Detemir did not show statistically significant differences when compared to Insulin NPH for the change (percentual and relative) in trunk fat mass throughout the study.
- The analysis for the PP population showed similar results with no differences as for the ITT population.

Secondary efficacy variables

- No statistically significant differences were found between treatment groups as far as the additional DEXA scan secondary variables were concerned (Whole Body Fat Mass, Whole Body Lean Mass, Trunk Lean Mass, Calculated Whole Body Fat Percentage and Calculated Trunk Fat Percentage).
- The same happened with the variables for the CT scan (Visceral Adipose Tissue Area, Subcutaneous Adipose Tissue Area, Calculated Visceral/Subcutaneous Adipose Tissue Ratio, and Liver/Spleen Attenuation Ratio) where no statistically significant differences were found.
- The changes of HbA_{1c}, Fasting Plasma Glucose, Adiponectin Levels, and hsCRP and PAI-1 inflammatory parameters from the end of the trial when compared to the baseline values did not show any statistically significant difference between treatment groups.
- There were not statistically significant differences between treatment groups regarding the change in weight and BMI during the study.
- Statistically significant differences in favour of Insulin Detemir group were found for the change in waist circumference at visits 4 and 5, although these differences were not reported at the end of the study. Changes in hip circumference were not statistically significant throughout the study.

Safety Results

- A total of 21 (87.5%) patients in the Insulin Detemir group and 30 (85.7%) patients in the Insulin NPH group

reported at least one treatment emergent adverse event.

- The most frequently reported TEAEs for both groups were: *Nasopharyngitis* (29.2% in the Detemir group vs. 20.0% in the NPH group) , *Headache* (16.7% vs.20.0%), and *Back pain* (12.5% vs. 11.4%) respectively.
- All adverse events in the Insulin Detemir group were of mild and moderate intensity.
- A total of 6 patients reported at least one related TEAE in the Insulin Detemir group and one patient in the Insulin NPH group. The most frequently related TEAE reported was *Injection site reaction.*
- Three patients in each group reported at least one serious adverse event, although none of them were considered related to the study medication either Insulin Detemir or Insulin NPH.
- Both groups showed a similar profile when comparing the change from baseline at 26 weeks of treatments except for total cholesterol where Insulin Detemir decreased that parameter at the end of the study.
- Finally, although there were not statistically significant differences a low rate in hypoglycaemic episodes in the Insulin Detemir group was reported (70.8% vs. 91.4%).

Conclusions

- Insulin Detemir did not reach the pre-established difference of 5% in trunk fat mass at 26 weeks of treatment, neither showed significant differences when compared to Insulin NPH.
- No significant differences were found for any of the secondary efficacy variables between the two treatment groups.
- Insulin Detemir group showed less hypoglycaemic episodes than Insulin NPH group.
- For both groups the most frequently reported adverse events were Nasopharyngitis, Headache and Back pain.
- None of the serious adverse events were considered as related to the study medication, confirming the good safety profile of Insulin Detemir.

The trial was conducted in accordance with the Declaration of Helsink Tokyo 2004i and ICH Good Clinical Practice 01 May 1996.

The results presented reflect data available in the clinical database as of 26 November 2010.