2 Synopsis

Trial Registration ID-number NN304-1808	**EudraCT number – 2006-006589-41**
Title of Trial A seven-month open-labelled randomised multi-centre two-group parallel trial comparing administration of insulin detemir once daily in the morning versus NPH insulin once daily in the morning in ageing subjects with type 2 diabetes. The 3L Study (Levemir® in Later Life)	
Investigator(s) - Professor [redacted] Study Coordinator/Principal Investigator France [redacted] - Professor [redacted] Principal Investigator United Kingdom [redacted]	
Trial Site(s) 25-35 Investigational sites were planned in both France and UK Actual number of sites in France: 35 Actual number of sites in UK: 22	
Publications None.	
Trial Period Planned FPFV: 01 Sept 2007 Planned LPLV: 01 June 2008 Actual FPFV: 12 Jul 2007 (21 Jan 2008 for UK) Actual LPLV: 29 Dec 2008 (The amendment 5 extended the recruitment period)	**Development Phase** Phase IV
Objectives The aim of the study was to compare two -basal insulin regimens as insulin therapy initiation in ageing type 2 diabetic patients with insulin detemir versus NPH insulin given once daily in the morning **Primary Objective:** • To investigate if once daily insulin detemir was non inferior compared with once daily NPH insulin as measured by HbA1c in ageing subjects with type 2 diabetes naive to previous insulin therapy after 7 months of treatment (including a one-month titration period). Insulin detemir and NPH insulin were both to be administered before breakfast **Secondary Objectives:** • To compare insulin detemir to NPH insulin therapy, measured at 4 and 7 months (except for Quality of Life only measured after 7 months) o Quality of Life (treatment satisfaction, health status, behavioural and psychological scoring) o Efficacy objectives o Safety objectives o Insulin dose requirements	
Methodology This was a bi-national, multicentre, randomised, open-label, controlled, parallel group study with a two week screening period, followed by a seven-month treatment period which included a one month period of intensive titration. The trial was conducted using a "treat to target" design, with a first month of forced dose titration and	

thereafter an active dose adjustment following the same guidelines in the 2 groups, addressing basal doses. Insulin detemir was administered in Innolet® 100 U/L, solution for injection in a pre-filled pen, 3 mL and Isophane (NPH) insulin was administered in Innolet® 100 IU/L, solution for injection in a pre-filled pen, 3 mL. All trial products were administered subcutaneously, and were dosed according to the insulin titration guideline prepared for this trial. Subjects attended the study site at screening (V0) and randomisation (V1), and at 1 (V2), 4 (V3) and 7 months (V4). Subjects were also contacted by telephone on 11 occasions between V1 and V4, and in the event of any premature discontinuation of the trial, were asked to attend the study site for a final visit.

Number of Subjects Planned and Analysed

A total of 286 aging (≥ 70 years; range, 70–94 years) subjects with type 2 diabetes (143 subjects in France and 143 subjects in the UK) were planned to be included in this trial.

Despite the extension of the recruitment period, it has been impossible to recruit enough patients in the study. The decision has then been made to prematurely discontinue the trial.

A total of 124 subjects were screened (56 in France 68 in UK), 86 subjects were enrolled and treated, 38 were randomised to insulin detemir and 48 to NPH insulin, and 41 subjects completed (21 insulin detemir, 20 NPH insulin) the trial. All 86 subjects who received at least one dose of study medication were included in the analyses.

Withdrawals: In total 45 patients were withdrawn, 17 from the insulin detemir group and 28 from the NPH insulin group. Reasons for withdrawal were; adverse events (0 insulin detemir, 2 NPH insulin); non-compliance (2 insulin detemir, 4 NPH insulin); ineffective therapy (1insulin detemir, 0 NPH insulin); other (10 insulin detemir, 16 NPH insulin); not recorded (4 insulin detemir, 6 NPH insulin).

Diagnosis and Main Criteria for Inclusion

A total of 286 insulin naive male or female ageing subjects with type 2 diabetes who were currently treated with oral antidiabetic drugs (OADs), but were considered to benefit from insulin treatment, were to be randomly allocated to the 2 treatment groups. At trial entry the subjects must have been ≥70 years of age, with a defined therapeutic target set between 7.0–8.0 %. They must have type 2 diabetes with HbA1c ≥8.0% and ≤10.5% at screening, be insulin naïve and optimally treated by oral antidiabetic drugs (OAD) at maximum tolerated doses for at least 3 months and considered able to comply with the requirements of the trial.

Test Product, Dose and Mode of Administration, Batch Number

Insulin detemir was supplied in Innolet® 100 U /L, solution for injection in a pre-filled pen, 3 mL All trial products were for subcutaneous administration and were dosed according to the insulin titration guideline prepared for this trial. Insulin detemir was to be given once-daily before breakfast.

Batch numbers:TV63I139

Duration of Treatment

Seven months (including a one month intensive treatment titration period).

Reference Therapy, Dose and Mode of Administration, Batch Number

Isophane (NPH) insulin was supplied in Innolet® 100 IU/L, solution for injection in a pre-filled pen, 3 mL. Dosing was once daily before breakfast.

Batch numbers: TV63I140

Criteria for Evaluation – Efficacy

Efficacy was assessed by the following endpoints:

- Percentage of subjects with HbA1c ≤8.0%
- Percentage of subjects with HbA1c ≤8.0% without hypoglycaemia

HbA1c measurement was performed within a maximum of 3 days following V0 and V1 and within a maximum of 7 days preceding V3 and V4.

- Glycaemic control as measured by 3-point Self Measured Plasma glucose (SMPG [fasting, pre-lunch and pre-dinner plasma glucose])

SMPG was performed by the subject throughout the study, and data was recorded on the case report form (CRF) for assessment of efficacy on the following periods:

- Every day during the last 7 days before V3
- Every day during the last 7 days before V4

Daily insulin doses were recorded in the diary by the subject and recorded on the CRF.

- Within-subject variation of body weight during the trial
- Percentage of patients achieving Fasting Plasma Glucose ≤8.8 mmol/L (160 mg/dL)
- Within-subject variation of Plasma Glucose during the trial
- Incidence of hyperglycaemic events (>300 mg/dL)

Criteria for Evaluation – Safety

Safety was assessed by the following secondary endpoints:

- Physical examination
- Vital signs
- Hypoglycaemic episodes
- Adverse events

Statistical Methods

A non-inferiority criterion was defined prior to the study as a difference in HbA1c between groups lower than 0.4%. For 80% power and 5% significance level with a baseline-adjusted standard deviation of 1.1, a total of 238 completers (119 per group) was required. Owing to a 20% maximal expected frequency of patients lost for follow up, 286 patients were to have been included, 143 patients in each group. Randomisation of patients between groups was stratified on trial site, using blocks of defined value. All the analysis was to be conducted on an intention to treat (ITT) basis. Per protocol (PP) analysis was also to be conducted for description purposes. Results were to be presented as mean ± SD and 95% confidence intervals. For HbA1c, adjusted difference between groups was to be presented with observed power calculated on trial real sample size. Patient withdrawal was to be analysed separately, especially for failure purposes (all, glycaemia, HbA1c). Quantitative variables, including HbA1c, plasma glucose level and insulin doses were to be analysed using a baseline-adjusted ANOVA, with insulin group as fixed effect centre country, significant baseline difference between groups and interactions were to be used as fixed effects. Percentages and quantitative variables were to be analysed using Chi-square test or Fisher's exact test if necessary. Incidence of events such as hypoglycaemia or hyperglycaemia was to be evaluated with relative risk, and analysed using a Cox regression. Explorative analysis was to be conducted to look for factors associated to responders, HbA1c and glucose values within target, hypoglycaemias and hyperglycaemias, adverse events. Missing data was to be replaced in ITT analysis by the last value obtained in regular evaluation according to the protocol.

Since the trial was prematurely discontinued the required number of completers was not achieved in order to obtain the required statistical power to be able to do between-group comparisons. Instead only descriptive statistics at baseline and a safety analysis were performed for the trial results

Demography of Trial Population

A total of 86 subjects with Type 2 diabetes were investigated: 46 men and 40 women. The mean age at baseline was

76.8 (range 70 to 94) years. Mean weight at baseline was 79.0 (range 42.0 to 121.5) kg. Mean BMI at baseline was 29.5 (range 19.0 to 44.3). Mean systolic blood pressure at baseline was 141.2 (range 109.0 to 196.0) and mean diastolic blood pressure at baseline was 73.6 (range 49.0 to 94.0). The mean duration of diabetes at trial onset was 14.6 (range 0.9 to 42.9) years and mean duration of oral antidabetic (OAD) treatment at trial onset was 6.9 (range 0.1 to 39.0) years.

Baseline glycaemic characteristics were as follows: (Values shown as mean (SD):

- Mean baseline HbA1c: insulin detemir 9.26 (0.87); NHP insulin 9.12 (0.78)
- Baseline FCG (mg/dL): insulin detemir 166.0 (44.5); NHP insulin 174.8 (42.2)
- Pre-lunch CG (mg/dL): insulin detemir 182.8 (55.7); NHP insulin 188.2 (66.2)
- Predinner CG (mg/dL): insulin detemir 182.7 (53.6); NHP insulin 174.0 (59.9)
- Baseline insulin dose (IU): insulin detemir 15.7 (5.6); NHP insulin 16.2 (4.8)

Efficacy Results

- Not applicable due to the small number of patients in each group.

Safety Results

- **Mean (sd) number of total hypoglycaemic episodes per patient expressed as rate per week by visit**

	Insulin detemir	**NPH insulin**
Screening (-2 to 0 weeks)	0.039 (0.179)	0.073 (0.372)
Month 1	0.026 (0.097)	0.120 (0.282)
Difference (Month 1– Screening) (p-value)	-0.013 (0.209) (p=0.94)	0.047 (0.446) (p=0.46)
Screening*	0.039 (0.179)	0.076 (0.380)
Months 2–4*	0.015 (0.051)	0.072 (0.167)
Difference (Months 2–4 – Screening) (p-value)	-0.024 (0.177) (p=0.81)	-0.004 (0.394) (p=0.11)
Screening**	0.039 (0.179)	0.058 (0.381)
Months 5-7**	0.018 (0.078)	0.041 (0.099)
Difference (Months 5–7 – Screening)	-0.022 (0.131) (p=0.50)	-0.017 (0.400) (p=0.052)

* Excludes subjects removed prior to Visit 2 ** excludes subjects removed prior to Visit 3

The percentage of subjects with at least one episode of hypoglycaemia was lower with insulin detemir than with NPH insulin during all time periods assessed: Month 1, 8% vs 21% Months 2–4, 11% vs. 28% ; Months 5–7, 5% vs. 23%

- **Nocturnal hypoglycaemic episodes by visit (Rate/week)**

	Insulin detemir	**NPH insulin**
Screening*	0.000 (0.000)	0.000 (0.000)
Months 2–4	0.002 (0.014)	0.002 (0.012)
Difference (Months 2–4 – Screening) (p-value)	0.002 (0.014) (p=1.0)	0.002 (0.012) (p=1.0)

***** Excludes subjects removed prior to Visit 2

No nocturnal hypoglycaemic episodes were reported for month 1 or months 5-7.

- During months 2–4 one patient in each of the insulin detemir and NPH insulin groups reported at least one episode of nocturnal hypoglycaemia (3% and 2%, respectively).

- **Major Hypoglycaemic episodes by visit (Rate/week)**

	Insulin detemir	**NPH insulin**
Screening (-2 to 0 weeks)	0.000 (0.000)	0.000 (0.000)
Month 1	0.000 (0.000)	0.005 (0.036)
Difference (Month 1– Screening)	0.000 (0.000)	0.005 (0.036)

- No major hypoglycaemic episodes were reported during months 2-4 or 5-7.

- During Month 1, no patient on insulin detemir and one patient (2%) on NPH insulin experienced a major hypoglycaemic event.

- **Minor hypoglycaemic episodes by visit (Rate/week)**

	Insulin detemir	**NPH insulin**
Screening (-2 to 0 weeks)	0.000 (0.000)	0.063 (0.366)
Month 1	0.013 (0.057)	0.042 (0.119)
Difference (Month 1– Screening)	0.013 (0.057)	-0.021 (0.378)
Screening*	0.000 (0.000)	0.064 (0.370)
Months 2–4	0.007 (0.023)	0.024 (0.060)
Difference (Months 2–4 – Screening)	0.007 (0.023)	-0.042 (0.368)
Screening**	0.000 (0.000)	0.058 (0.381)
Months 5-7	0.007 (0.041)	0.021 (0.052)
Difference (Months 5–7 – Screening)	0.007 (0.041)	-0.037 (0.388)

***** Excludes subjects removed prior to Visit 2 ** excludes subjects removed prior to Visit 3

- When expressed as percentage of subjects with at least one episode, there was a lower proportion of patients with events on insulin detemir than on NPH insulin during each time period; Month 1: 5 % vs. 13% ; Months 2–4: 8% vs. 20%; Months 5–7 3% vs. 19%.

- **Symptoms only hypoglycaemic episodes by visit (Rate/week)**

	Insulin detemir	**NPH insulin**

Screening (-2 to 0 weeks)	0.039 (0.179)	0.010 (0.072)
Month 1	0.013 (0.081)	0.073 (0.199)
Difference (Month 1– Screening)	-0.026 (0.200)	0.063 (0.175)
Screening*	0.041 (0.182)	0.011 (0.073)
Months 2–4	0.009 (0.032)	0.047 (0.163)
Difference (Months 2–4 – Screening)	-0.031 (0.172)	0.036 (0.135)
Screening**	0.039 (0.179)	0.000 (0.000)
Months 5-7	0.011 (0.068)	0.016 (0.069)
Difference (Months 5–7 – Screening)	-0.029 (0.123)	0.016 (0.069)

* Excludes subjects removed prior to Visit 2 ** excludes subjects removed prior to Visit 3

- Fewer (%) patients on insulin detemir than on NPH insulin experienced symptoms only hypoglycaemia during each time period: Month 1: 3% vs. 17%; Months 2-4: 8% vs. 9%; Months 5–7: 3% vs. 7%.

- **Hypoglycaemic episodes with SMCG >3.1 mmol/L (Rate/week)**

	Insulin detemir	**NPH insulin**
Screening (-2 to 0 weeks)	0.000 (0.000)	0.063 (0.366)
Month 1	0.013 (0.057)	0.042 (0.119)
Difference (Month 1– Screening)	0.013 (0.057)	-0.021 (0.378)
Screening*	0.000 (0.000)	0.065 (0.374)
Months 2–4	0.007 (0.023)	0.024 (0.060)
Difference (Months 2–4 – Screening)	0.007 (0.023)	-0.042 (0.368)
Screening**	0.000 (0.000)	0.058 (0.381)
Months 5-7	0.007 (0.041)	0.025 (0.072)
Difference (Months 5–7 – Screening)	0.007 (0.041)	-0.042 (0.385)

* Excludes subjects removed prior to Visit 2 ** excludes subjects removed prior to Visit 3.

Adverse events

- A total of 48 subjects in the study reported treatment emergent adverse events, 20 in the insulin detemir treatment group and 28 in the NPH insulin treatment group.
- A total of 127 adverse events were reported (50 in insulin detemir group, 77 in NPH insulin group),
  - 14 (11%) (4 in insulin detemir group, 10 in NPH insulin group) of these events were classed as serious. Only one was considered possibly related to the study drug, and all the others were considered unrelated to the study drug. One additional SAE occurred in a patient that has not received any study drug.
  - In the insulin determir group: the 4 SAE were considered unlikely; [redacted] (angina unstable and cellulitis) and [redacted] (hiatus hernia and Barrett's oesophagus).
  - In the NPH insulin group: 1 SAE was considered possibly related to the study drug and [redacted] (fall); 9 were considered unlikely: [redacted] (streptococcal sepsis, carotid artery stenosis, disorientation,

tachycardia, campylobacter intestinal infection and bradycardia), [redacted] (prostate cancer) and 2 were fatal (breast cancer metastatic and brain neoplasm).

- The majority of reported adverse effects were mild (68%) or moderate (25%) with 34 mild and 14 moderate adverse events in the insulin detemir treatment group and 52 mild and 18 moderate in the NPH insulin group.
- Of 9 severe adverse events reported, 7 were in the NPH insulin treatment group and 2 in the insulin detemir group.
- In the insulin detemir group 4 adverse events were probably linked to treatment and 2 possibly. In the NPH insulin group there were no probable linked adverse events and 3 possible.
- The most frequent treatment emergent adverse effects in the insulin detemir treatment group were: nasopharyngitis (4 subjects reported 5 events); constipation (3 subjects reported 3 events); headache (2 subjects reported 4 events); oropharyngeal pain (2 subjects reported 2 events)
- The most frequent treatment emergent adverse effects in the NPH insulin treatment group were: nasopharyngitis (4 subjects reported 6 events); headache (3 subjects reported 3 events); arthralgia (3 subjects reported 3 events).

Conclusions

- Due to the small number of patients recruited in the study, the efficacy comparisons were not possible
- Insulin detemir was safe and well-tolerated when administered once-daily in the morning to elderly patients with type 2 diabetes.
- No major hypoglycaemic events were reported in insulin detemir-treated patients.
- A lower proportion of patients on insulin detemir than on NPH insulin reported minor, symptoms only, and hypoglycaemic events confirmed by SMCG <3.1 mmol/L.
- A similar proportion of patients on insulin detemir and NPH insulin experienced nocturnal hypoglycaemic events.
- The adverse event profile was similar between insulin detemir and NPH insulin.
- Most adverse events were mild to moderate in severity.
- Fewer serious adverse events were reported in patients on insulin detemir than in patients on NPH insulin.

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).

The results presented reflect data available in the clinical database as of 02 December 2009.