2 Synopsis

Trial Registration ID-number NCT00503698 (ID for www.clinicaltrials.gov)	**IND Number:** 72,397 **EudraCT number:** 2006-004702-56

Title of Trial

Outcome Trial Evaluating the Efficacy and Safety of Norditropin® in Adult Patients on Chronic Haemodialysis.
A Randomised, Double-blind, Parallel group, Placebo controlled, Multi-centre trial.
This trial is also known as the OPPORTUNITY trial.

Investigator (principal)

Dr. [redacted].

Trial Sites

The trial was conducted at 202 sites in 17 countries globally (United States, Canada; United Kingdom, Sweden, Denmark, France, Germany, Poland, Hungary, Spain, Portugal, Turkey, Israel, Argentina, Brazil, Russia, South Africa). Italy was planned to participate in the trial but never randomised any patients.

Publications

Kopple et al. Opportunity™: A Randomized Clinical Trial of Growth Hormone on Outcome in Haemodialysis Patients.Clin J Am Soc Nephrol 2008;3: 1741-1751.

Trial Period		**Development Phase**
First patient first visit:	23 July 2007	Phase 3a
Last patient last visit:	19 Dec 2008	

Objectives

Primary Objective:

- To evaluate and establish the effect of Norditropin® (somatropin) on mortality in adult patients on chronic haemodialysis.

Secondary Objectives:

To evaluate the effect of Norditropin® on changes in the following parameters from randomisation to the end of trial period:

- Morbidity: number of days in hospital, in addition to normal dialysis procedures; cardiovascular events (myocardial infarction, cardiac insufficiency, stroke, other thrombo-embolic events)
- Patient Reported Outcomes (Activity of Daily Living (ADL), appetite and health related quality of life (HRQoL) Questionnaires)
- Serum Albumin
- Lean body mass and fat mass, assessed by Bioelectrical Impedance Analysis (BIA)
- Hand grip strength
- Walking test performance
- Homocysteine
- Transferrin
- Lipid profile
- Markers of inflammation, including high sensitivity C-Reactive Protein (hsCRP), Interleukin-6 (IL-6) and Tumour Necrosis Factor-ά (TNF-ά)
- Safety and tolerability of Norditropin®

Methodology

The trial was a randomised, double-blind, parallel group, placebo-controlled, multicentre, multinational trial, stratified with regard to the diabetic status at inclusion. The trial was designed to compare efficacy and safety of once daily injections of Norditropin® with placebo on time to death in adult subjects on chronic haemodialysis with low serum albumin. Each patient was planned to attend 14 visits during a 2-year trial period (104 weeks), including a screening visit to assess the subject's eligibility was performed prior to any trial related procedures, a randomisation visit, 11 treatment visits during the treatment period and an End of Treatment visit. All visits were planned to be in

connection to a dialysis session. After the treatment period was completed, subjects were followed for mortality until trial termination. Subjects who were malnourished (based on serum albumin values, assessed centrally) and had received adequate haemodialysis treatment for more than three months at time of screening, were eligible for the trial. Subjects were randomly assigned to Norditropin® 20µg/kg/day or placebo. Both subjects with and without diabetes were included.

Premature termination of the trial: The planned treatment period was scheduled to 24 months. Due to slow recruitment the trial was prematurely terminated in October 2008 by Novo Nordisk. Subjects were followed for safety until 16 January 2009 (official date of trial termination). The trial was terminated before any subjects had completed the full treatment duration of 24 months and less than 50% had completed 18 weeks of treatment (Visit 7).

Number of Subjects Planned and Analysed

Planned:	2500 subjects
Randomised:	712 subjects
Safety analysis set:	695 subjects
Full analysis set:	695 subjects
PP analysis set:	544 subjects
Completed:	0 subjects
Withdrawn:	695 subjects

The main reason for withdrawal was trial termination (66% of the patients). At time of trial termination 93 (13%) patients had been withdrawn due to adverse events (GH: 52 (15%) patients; placebo: 41 (12%) patients)).

Diagnosis and Main Criteria for Inclusion

Adult patients on chronic haemodialysis. Haemodialysis subjects with and without diabetes were included.

1. Informed consent obtained before any trial-related activities (trial-related activities are any procedure that would not have been performed during normal management of the patient).
2. Male or female in chronic (≥ 3 months prior to screening) in-centre haemodialysis (including all types of haemodialysis: e.g., short daily, nocturnal, etc.), age ≥ 18 (*updated with Amendment 6*).
3. Serum albumin < 40 g/L (median of three measurements analysed by a central laboratory).
4. Stable (≥ 3 months) and adequate haemodialysis treatment, as defined by no less than 3 consecutive monthly spKt/V ≥ 1.2 (as per KDOQI Guidelines) prior to start of screening procedures OR no less than 3 dialysis sessions per week with a total dialysis time ≥ 12 hours per week.

For subjects to be diagnosed with diabetes and considered eligible as subjects with diabetes, furthermore:

5. Current treatment with oral anti-diabetic drug (OAD) and/or insulin OR patients on dietary management with a fasting plasma glucose (FPG) ≥126 mg/dL (~ 7.0 mmol/L) (median of three measurements analysed by a central laboratory). (*changed to stratification criteria with Amendment 6*)
6. Willingness to commence insulin therapy if deemed necessary by the Investigator and/or a central assessor.

Test Product, Dose and Mode of Administration, Batch Number

Norditropin NordiFlex® 10 mg/1.5 ml. At the randomisation visit, subjects received Norditropin® 20 µg/ kg/day given as a once daily s.c. injection. Batch numbers: TY50009 and TY50020.

Duration of Treatment

The treatment period was scheduled to 24 months. Due to slow recruitment the trial was prematurely terminated in October 2008 by Novo Nordisk. Subjects were followed for safety until 16 January 2009 (official date of trial termination). The trial was terminated before any subjects had completed the full treatment duration of 24 months and less than 50% had completed 18 weeks of treatment (Visit 7). Mean trial duration was 20 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo. Mode of administration as for test drug. Batch numbers: SY50109, SY50110 and SY50117.

Criteria for Evaluation – Efficacy

Primary endpoint Mortality - Time to all-cause death for the pooled non-diabetic/diabetic population

Secondary endpoints (change in):

- Morbidity: number of days in hospital, in addition to normal dialysis procedures.
- Morbidity: cardiovascular events per year (number of myocardial infarctions, cardiac insufficiencies, strokes, other thrombo-embolic events)
- Morbidity: time from randomisation to next cardiovascular event (defined as composite of all-cause mortality, non-fatal myocardial infarction, stroke, cardiac insufficiency and other thrombo-embolic event)
- Body Composition: Lean Body Mass and Fat Mass (BIA)
- Hand Grip Strength and Walking Test
- Mortality: two-year mortality rate (*not applicable since the trial was prematurely terminated*)
- Health Related Quality of Life (HRQoL) Questionnaires

Laboratory Assessments for Efficacy:

- Serum Albumin
- Transferrin
- Homocysteine
- Lipid profile (by total cholesterol, LDL, HDL and triglycerides)
- High sensitivity C-Reactive Protein (hsCRP)
- Interleukin-6 (IL-6) and Tumour Necrosis Factor-ά (TNF-ά)
- Normalized protein nitrogen appearance (nPNA)

Criteria for Evaluation – Safety

- Adverse Events
- Physical examination
- IGF-I and IGFBP-3 (change in IGF-I, IGFBP-3, IGF-I SDS, IGFBP-3 SDS and IGF-I/IGFBP-3 molar ratio)
- Glucose metabolism (change in fasting blood glucose and insulin, self monitored blood glucose, HbA_{1C})
- Change in parathyroid hormone (PTH)
- Standard laboratory assessments (change in routine haematology and blood chemistry). Haematology: Haemoglobin (Hgb), haematocrit (Hct), and blood cells (red and white blood cells, platelet count, reticulocytes). Biochemistry: sodium (Na), potassium (K), chloride (CL), bicarbonate, urea, creatinine, phosphorus (PO_4), magnesium (Mg), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP or ALP), iron (Fe), ferritin, uric acid, vitamin B, cobalamin, foline/folate, calcium (Ca), ionised calcium (Ca^{2+}).

Additional evaluations:

- Medical events of special interest (MESIs)
- Dialysis Quality Measured as Kt/V

Statistical Methods

Analysis sets:

Full Analysis Set (FAS): Included all randomised subjects exposed to at least one dose of randomised trial medication.

Per Protocol (PP) Analysis Set: Included subjects without any major protocol violations that could affect the primary endpoint. Moreover, the subjects were to be exposed to the randomised trial medication for at least 4 weeks (28 days) and should have valid assessment necessary for deriving the primary endpoint.

Safety Analysis Set: Included all subjects exposed to at least one dose of randomised trial medication.

Primary Analysis

Death was required to be reported as a medical event of special interest (MESI). All death occurring on or before January 16th 2009 was adjudicated by an external committee. The time to all-cause death was calculated as weeks from the randomisation visit (Visit 2) to the date of death (non-censored cases) or date of the last contact (censored cases). Deaths were reported until the trial closed, whereas cardiovascular events were only reported until four weeks after last visit.

Time to all-cause death was analysed using a stratified Cox regression model with treatment and sex as fixed factors, age and time in dialysis as continuous covariates. The stratification allowed for different baseline hazard functions for non-diabetic and diabetic patients. The hypothesis of no treatment effect was tested versus the two-sided alternative, accounting for sex, age and time in dialysis.

In addition, a Cox regression model including strata as a fixed factor, but otherwise similar to the primary analysis was fitted to the data. This was made to investigate if non-diabetic and diabetic patients had different survival patterns. The influence of the baseline albumin, hsCRP, body weight, BMI and lean body mass on survival was investigated by including these one at a time as continuous covariates in the Cox model.

The treatment effect was quantified in terms of the estimated hazard ratio for death (HR=GH/placebo) together with the 95% confidence interval and p-value. The results are illustrated using Kaplan-Meier plots.

Secondary Endpoints

Lean body mass in kilos was calculated based on the corrected BIA measurements of 50 KHz using Kyles' formula. Fat mass in kilos was calculated as the difference between body weight after dialysis and lean body mass.

Cardiovascular events were defined as 'adjudicated MESIs' and these events were further categorised as myocardial infarctions, cardiac insufficiencies, strokes or other thrombo-embolic events. In addition, an adjudicated death could be cardiovascular or non-cardiovascular.

Secondary Analyses

ANOVA (analysis of variance): BIA endpoints, laboratory endpoints, nPNA, functional endpoints and summary scores for health related quality of life were analysed using ANOVA. The aim of the analysis was to compare treatment differences between hGH and placebo at the end of the trial. The ANOVA included treatment, diabetes strata and sex as fixed factors, age, time in dialysis and the baseline value as continuous covariates. For endpoints available over time mean curves were plotted to explore development over time. Time to the composite endpoint of cardiovascular event or all-cause death was analysed and presented similar to the primary endpoint.

Negative Binomial Regression: Morbidity in terms of number of cardiovascular events and number of hospitalisations was analysed using a negative binominal regression model using a log link function and the logarithm of the available collection time as offset (weeks). The model included treatment, diabetes strata and sex as fixed factors, age and time in dialysis as continuous covariates.

Additional Analyses for ANOVA Endpoints: Since the trial was prematurely terminated and less than 50% of the patients completed 18 weeks of treatment, signs of efficacy were also investigated at the earlier visits. This was done by fitting a linear mixed effect model using all post-treatment data in a joint analysis. In this approach, missing data were implicitly dealt with as part of the likelihood analysis and the specified covariance structure. For withdrawn patients the data captured at a follow-up visit were mapped to the next scheduled visit.

The model included treatment, diabetes strata, sex, visit and an interaction between treatment and visit as fixed factors, age, time in dialysis and the baseline value as continuous covariates and patient as a random effect.

Demography of Trial Population

A total of 695 adults with chronic haemodialysis were investigated. The mean age was 62 years, ranging from 19 to 96 years. The percentage of males was greater in the placebo group (60%) than in the GH group (50%). Time on dialysis varied with a median dialysis time of 2.9 years (up to 35 years). The mean BMI was 29 kg/m^2 (range: 16 to 67 kg/m^2). A total of 418 (60%) of the patients were white and 227 (33%) were black or African American. Twelve (12, 2%) patients were Asian. Most patients (71%) were from the U.S.

A total of 339 (49%) of the patients were diabetics. Of these, the majority of patients had type 2 diabetes. A total of 276 (81%) of the patients received medication to treat their diabetes. Median duration of diabetes was 18 years (range: 1 to 64 years). Patients with diabetes had a greater BMI at baseline than patients without diabetes (diabetes: 32 kg/m^2 ; without diabetes: 26 kg/m^2. The median time on dialysis was 2.3 years for patients with diabetes and 5.9 years for patients without diabetes. Main diabetes complications were diabetic retinopathy, neuropathy and nephropathy.

Efficacy Results

- There was no statistically significant difference in survival between the GH and placebo-treated groups. The hazard ratio (HR) for death for GH/placebo was 0.97 (p=0.91). The analysis included 68 deaths which were reported within the trial period (until 16 January 2009) (GH: 33, 9.5%; placebo: 35, 10%).

- Albumin and weight were strong predictors for death. An increase in albumin of 1g/L decreased the HR for death by 13%. An increase in weight of 10 kg decreased the HR for death by 16%.
- There was no statistically significant difference in time to first cardiovascular event or death between GH and placebo. The hazard ratio for event or death for GH/placebo was 0.88 (p=0.50).
- There were no statistically significant differences between GH and placebo in the number of cardiovascular events.
- There were no statistically significant differences between GH and placebo in number of hospitalisations.
- There was no statistically significant difference between GH and placebo in mean lean body mass, expressed in kg, at end-of-trial (mean difference with GH: 0.7 kg, p=0.09). Due to a reduction in body weight with GH (due to reduction in fat mass), lean body mass as percent of total body weight was statistically significantly increased with GH compared to placebo (mean difference Week 52: 2.7%, p=0.0032; End-of-trial: 1.2%, p=0.0096). The patients in the GH group had a slightly lower lean body mass percentage at baseline. With a gain in lean body mass percentage during the trial, they achieved a lean body mass percentage similar to the patients in the placebo group.
- Mean fat mass (kg) was reduced with GH compared to placebo (mean difference Week 52: 3.2 kg; End-of-trial: 1.5 kg). Mean fat mass (kg) was decreased in the GH group compared to placebo also at all other time points investigated. The differences were statistically significant.
- Mean body weight was reduced (due to reduction in fat mass) with GH compared to placebo (mean difference Week 52: 2.1 kg; End-of-trial: 1 kg). The weight decrease was apparent from Week 12 and onwards, where the differences were also statistically significant.
- There were no statistically significant differences in mean hand grip strength or speed walking between GH and placebo at end-of-trial, or during selected time points during the trial.
- Mean change in serum albumin showed an initial decrease at 4 weeks in the GH group compared to placebo. From 12 weeks of treatment albumin increased more or less parallel in both groups. There was no statistically significant difference between GH and placebo in mean albumin at end-of-trial (mean difference GH – placebo: -0.06 g/dL, 95% CI [-0.14; 0.01], p=0.09).
- Serum hsCRP decreased in the GH group relative to placebo (Week 52: 27%; End-of-trial: 24%). The decrease was already apparent at four weeks and remained lower throughout the trial. The decrease was statistically significant at all time points. No statistically significant differences between GH and placebo were observed for other inflammatory markers (IL-6 and TNF-α).
- Transferrin increased by 8% in the GH group relative to placebo. The difference between groups was already apparent at 4 weeks and remained constant throughout the trial. The increase was 5% at Week 52. The increases were statistically significant at all time points for assessment.
- Serum HDL increased by 4% in the GH group relative to placebo at end-of-trial. This difference was statistically significant. There were no differences in other lipids evaluated (total cholesterol, LDL, triglycerides).
- No differences were observed in any of the overall mean scores for quality of life between GH and placebo.

Safety Results

- A total of 3244 adverse events were reported in 549 (79%) patients during the trial. A similar number of patients experienced adverse events on GH as on placebo and there were no marked differences in the type of adverse events reported between the two groups.
- The three most frequent system organ classes reported were infections and infestations (33.7%), gastrointestinal disorders (28.6%) and injury, poisoning and procedural complications (29.4%). Cardiac and vascular disorders were reported in about 16% of the patients. The most frequent adverse events (≥5% of the patients) included nausea, diarrhoea, vomiting, pain in extremities, arthralgia, headache, cough, dyspnoea and hypotension. Most other events were one or two events in a few patients.
- Possibly/ probably drug related adverse events were primarily non-serious adverse events (139 (4%) events in 79 (11%) patients). There was no predominant preferred term or system organ classes reported. A total of 18 (3%) patients experienced possibly/ probably drug related events related to glucose metabolism (increased blood glucose: 7 (2%) patients; diabetes: 5 (1.4%) patients; hyperglycaemia: 5 (1.4%) patients; diabetes mellitus inadequate control: 1(<1%) patient). The five cases of diabetes were all reported as 'worsening of diabetes mellitus' in patients with diabetes at baseline.
- A total of 258 (37, 1%) patients experienced 586 serious adverse events. There were no major differences between

the fractions of patients with serious adverse events in the GH and placebo groups (GH: 122 (35%) patients; placebo: 136 (39%) patients). The actual number of events was greater in the placebo group (GH: 265 events; placebo: 321 events). Events within cardiovascular disorders (11.7%) and infections (12.5%) were the most frequent serious adverse events reported. The far majority of serious adverse events were considered unlikely to be related to the trial drug.

- In the GH group, 11 (3.2%) patients experienced 19 serious adverse events which were assessed as possibly drug related by the investigator. These events were single events reported in one or two patients. Three cases of hyperglycaemia (in 3 patients, 0.4%) were reported. No development of diabetes was reported or was assessed to be related to the GH treatment by investigators in this trial.
- A total of 18 (0.6%) cases of cancer were reported (GH: 10 cases; placebo: 8 cases). In 17 of the 18 cases of cancer the causality to trial drug was assessed as unlikely. One case of basal cell carcinoma in the placebo group was assessed as possibly drug related by the investigator. Three patients in the placebo group died of their cancer, [redacted]. Five patients had not yet recovered from their cancer at time of this report.
- At time of trial termination 93 (13%) patients had been withdrawn due to adverse events (GH: 52 (15%) patients; placebo: 41 (12%) patients). Four patients exposed to GH were withdrawn or died due to possibly/probably trial drug related serious adverse events (intracranial haemorrhage, congestive cardiac failure, diabetic ketoacidosis, haemoptysis).
- A total of 75 deaths were reported after exposure to the GH or placebo drugs, 69 deaths during the trial period and a further 6 deaths after trial termination (16 Jan to 21 June 2009). There was no difference in the number of deaths between GH (35 patients) and placebo (40 patients). Cardiovascular events and infections were the most frequent cause of death. Adverse events with a fatal outcome included three events of cancer (one breast cancer and two lung cancer). All three events were observed in the placebo group. The far majority of deaths were considered unlikely to be related to the trial drug. Three adverse events with fatal outcome were assessed as possibly/probably trial drug related by the investigator (pulmonary haemorrhage, staphylococcal bacteraemia and haemoptysis). The three patients died from 1 to more than 3 months after end of treatment. In all cases Novo Nordisk assessed causality as unlikely.
- Mean IGF-I SDS showed the expected rapid increase within the first weeks of GH treatment and reached values above the upper border of the reference range (baseline: -0.4; Week 4: 2.6). Thereafter, a slow and steady decline over time was observed with a value of 1.3 at end-of-trial. No changes from baseline were observed with placebo treatment. An estimated increase of 1.9 in IGF-I SDS was observed in the GH group compared to placebo at end-of-trial ($p<0.0001$). A similar pattern was observed for IGFBP-3 SDS (baseline: -0.4; Week 4: 1.1; end-of-trial: 0.5). An estimated increase of 1.2 in IGFBP-3 SDS was observed in the GH group compared to placebo at end-of-trial ($p<0.0001$).
- There were only minor changes in mean HbA_{1c}, with a slight increase from 6.0% to 6.2% during the first weeks of GH treatment. Mean HbA_{1c} was 6.0% at end-of-trial. Still, the difference between GH and placebo was statistically significantly different from zero at end-of-trial as well as for other selected time points ($p<0.0001$). No statistically significant changes were observed in insulin and glucose between GH and placebo at end-of-trial. Insulin levels increased within the reference range during the 52 Weeks evaluated. For patients without diabetes, there was a non-significant trend for insulin to increase more in the GH group than in the placebo group.
- After an initial decrease in serum PTH, PTH increased in the GH group to levels above placebo. A 13% increase was observed in PTH in the GH group as compared to the placebo group at end-of-trial. The mean GH/placebo ratio for PTH was statistically significantly different from one at end-of-trial.
- A 13% decrease was observed in serum vitamin B12 during GH treatment relative to placebo at end-of-trial. The ratio GH/placebo was statistically significantly different from one from Week 12 and at end-of-trial.
- No major clinically relevant changes were observed in other safety variables evaluated.

Conclusions

The NN1630-1453 trial is the first large-scale randomised clinical trial in adult patients undergoing maintenance haemodialysis that was aimed at evaluating the response to GH of such clinical endpoints as mortality, morbidity, body composition, serum albumin, markers of inflammation, exercise capacity, and HRQoL over an extended period of time. The trial was terminated early due to slow recruitment, and the power for showing differences was therefore

largely reduced.

- Treatment with GH did not reduce mortality compared to placebo in patients receiving maintenance haemodialysis. Neither was any difference shown in serum albumin, lean body mass, exercise capacity or HRQoL. It is possible that the short duration of this trial (mean duration of 20 weeks) or the reduced number of trial patients reduced the possibility of showing a positive effect on these parameters.
- Some improvements were observed in conventional cardiovascular risk factors. These included a reduction in fat mass and increased serum HDL-cholesterol in the GH group compared to placebo. Body weight was reduced in the GH group due to fat loss. Improvements were also observed in some non-conventional cardiovascular risk factors. These included a reduction in serum hsCRP and an increase in serum transferrin.
- Daily subcutaneous use of GH in patients with end-stage renal disease was safe and well tolerated.

The trial was conducted in accordance with the Declaration of Helsinki (2000 and 2008) and ICH Good Clinical Practice (1996).

The results presented reflect data available in the clinical database as of 19-Nov-2009 (date of database freeze).