CTR synopsis

Trial registration ID-number NCT01206101	**UTN** – U1111-1114-8952 **IND number** – 14452 **EudraCT number** – 2009-013090-18

TITLE OF TRIAL

A 52-week randomised, double-blind, placebo-controlled, parallel-group, multi-centre, multinational exploratory trial in islet cell transplant subjects with type 1 diabetes mellitus to evaluate the early use of liraglutide as an adjunct to standard care regarding the percentage of subjects achieving insulin independence after first transplantation

INVESTIGATOR

There was one principal investigator for this trial: Dr. [redacted], MD, [redacted]. Dr. [redacted] was also designated signatory investigator for the trial, and was responsible for reviewing and approving the Clinical Trial Report.

TRIAL SITES

The trial was conducted at 3 sites in 3 countries, as follows: Canada: 1 site; Switzerland: 1 site; US: 1 site.

PUBLICATIONS

No publications were available at the time of this clinical trial report synopsis.

TRIAL PERIOD Initiation date: 21 March 2012 Termination date: 03 June 2013	**DEVELOPMENT PHASE** Phase 2

DATA CUT-OFF DATE

The results presented reflect the data available in the clinical database as of 03 September 2013.

OBJECTIVES

Primary objective:

- To investigate if treatment with liraglutide can increase the proportion of subjects who are insulin-independent at one year after islet cell transplant, and required only one (single-donor) islet cell transplant.

Secondary objective:

- To investigate the safety of liraglutide treatment in subjects undergoing islet cell transplantation.

METHODOLOGY

This was a randomised, double-blind, placebo-controlled, multi-centre, multinational, exploratory clinical trial that was conducted in Canada, the United States and Switzerland. Subjects were adults (men or women 18-65 years of age, both inclusive, at the time of screening) with a diagnosis of type 1 diabetes mellitus (T1DM) for at least 5 years. Approximately 60 subjects were to be enrolled in a dose titration period, and approximately 36 of those subjects were to receive islet cell transplantation. Eligible subjects were randomised in a 1:1 ratio and commenced a dose titration period with escalating doses of liraglutide or placebo (0.6 mg x 7 days, 1.2 mg x 7 days, then 1.8 mg thereafter, if tolerated). Subjects were to be given an additional 7 days at each dose level if needed to achieve tolerability. Subjects unable to tolerate the dose of 1.2 mg or 1.8 mg OD of trial drug were to be withdrawn from the study and replaced (pre-transplant period only). Subjects were to continue daily administration of trial drug throughout the run-in period while awaiting transplant. Subjects were instructed to adjust their insulin dose according to the pre-defined guidelines. The total duration of the run-in period was to be variable depending on when the subject was offered an islet cell transplant. Randomisation was provided by the Clinical Supplies System NNAS via the interactive voice/web response system (IV/WRS). An unblinded staff member at the site was responsible for contacting IV/WRS for allocation of the randomisation number (treatment assignment).

During the course of the trial, the monitor visited the trial sites to ensure that the case report forms (CRFs) were completed correctly and the protocol was adhered to, and to perform source data verification, monitor drug accountability and collect completed CRF pages. Monitoring visit intervals depended upon the recruitment rate of the trial site and the compliance of the trial site to the protocol and GCP, and were not to exceed 12 weeks.

It was planned that the Safety Committee would conduct a blinded review of severe hypoglycaemic events after the 12th

randomised subject had completed 2 months of treatment, but did not occur due to the premature termination of the trial. No other interim analyses were planned or performed for this trial.
On 03 June 2013, Novo Nordisk A/S announced the decision to discontinue the trial. At that time, 3 subjects were exposed to trial products: 2 subjects to liraglutide and 1 subject to liraglutide placebo.

NUMBER OF SUBJECTS PLANNED AND ANALYSED

The planned sample size was approximately 60 subjects to be enrolled in a dose titration period, and approximately 36 of those subjects were to receive islet cell transplantation.
A total of 9 subjects were screened, of which 6 were screening failures, and 3 subjects were randomised and exposed to trial products. One subject withdrew due to adverse events (headache, nausea and anorexia), one subject was withdrawn by the investigator due to noncompliance with required study visits, and one subject was withdrawn with the premature termination of the trial.
The trial was prematurely terminated due to a much lower than expected subject enrolment, as well as the high complexity of the trial that resulted in a trial execution timeframe of approximately 4-5 years. It was therefore unrealistic to continue the trial.
Because the trial was terminated prior to islet cell transplantation in any randomised subject, there were no subjects in the full analysis set.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

The inclusion criteria were: informed consent obtained before any trial-related activities; diagnosis of T1DM for ≥ 5 years; men or women 18-65 years (both inclusive) of age at the time of screening; involvement in intensive diabetes management defined as self-monitoring of glucose values no less than a mean of three times each day averaged over each week and by the administration of three or more insulin injections each day or insulin pump therapy; no evidence of active tuberculosis prior to screening; evidence of at least 1 episode of severe hypoglycaemia per American Diabetes Association (ADA) criteria during the 12 months prior to screening; evidence of reduced awareness of hypoglycaemia prior to randomisation; evidence of adequate pre-existing renal reserve at screening.

The exclusion criteria were: body mass index >30 kg/m^2 or subject weight ≤ 45 kg; insulin requirement ≥ 1.0 U/kg/day or < 15 U/day at the time of screening; HbA_{1c} ≥ 10%; fasting C-peptide > 0.5 ng/mL; screening calcitonin ≥ 50 ng/L; ongoing active proliferative diabetic retinopathy changes or increasing macular oedema; panel-reactive anti-human leukocyte antigen antibody > 20%; female of child-bearing potential who is pregnant, breast-feeding or intend to become pregnant or is not using adequate contraceptive methods; male of reproductive age who or whose partner(s) is not using adequate contraceptive methods; active infection including hepatitis B, hepatitis C or human immunodeficiency virus; any malignancy, except for completely resected squamous or basal cell carcinoma of the skin, in the past 5 years; family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; known uncontrolled/untreated hypo/hyperthyroidism; known active alcohol abuse, substance abuse or cigarette smoking; baseline haemoglobin below lower limits of normal, lymphopaenia, neutropaenia, or thrombocytopaenia; any coagulopathy or medical condition that would require long-term anticoagulant therapy (e.g., warfarin) after transplantation (low-dose aspirin treatment is allowed) or subjects with an international normalised ratio > 1.5; severe co-existing cardiac disease; documented hepatobiliary disease or liver function tests at the time of screening; inadequately treated blood pressure elevation; untreated or inadequately treated hyperlipidaemia; severe gastroparesis; severe unremitting diarrhoea, vomiting or other gastrointestinal disorders potentially interfering with the ability to absorb oral medications; use of any medications to treat diabetes other than treatment with any basal bolus insulin regimen, including insulin pump within 4 weeks of screening; administration of live attenuated vaccine(s) within 8 weeks of screening; any previous organ transplant; history of acute idiopathic or chronic pancreatitis; any medical condition that, in the opinion of the investigator, will interfere with safe participation in the trial; known or suspected allergy or hypersensitivity to trial product(s) or related products; previous participation in this trial (participation is defined as randomised); receipt of any investigational medicinal product within 30 days of screening for this trial; any scheduled transplant in addition to the islet cell transplant.

Subjects could withdraw at will at any time. Subjects who did not meet eligibility criteria at screening or randomisation and enter the trial were withdrawn immediately. A subject must be withdrawn if any of the following situations apply and the reasons were to be documented in the medical record and CRF: the investigator judged the subject non-

compliant with relevant trial procedures; pregnancy or intent to become pregnant; any change in the subject's condition deemed clinically significant and justifying withdrawal in the investigator's opinion; unable to tolerate escalating doses of liraglutide during the run-in period; protocol deviation having influence on efficacy or safety data as judged by the investigator; idiopathic acute pancreatitis; liver function tests: serum aspartate transaminase, serum alanine transaminase, alkaline phosphate or conjugated bilirubin, with values > 1.5 times upper limit of normal at the time of transplantation; a condition that would prevent safe consideration of an islet transplant or continuation of the post-transplant treatment regimen; post-transplant lymphoproliferative disorder requiring complete withdrawal from immunosuppressive therapy; development of hypersensitisation, allergic responses, or other potentially serious drug reactions to medications specified in the protocol; participation in another clinical trial involving the use of an investigational medicinal product; primary graft failure; a diagnosis or suspicion of tuberculosis on chest X-ray; hyperglycaemia with no diagnosed treatable intercurrent cause.

INVESTIGATIONAL MEDICINAL PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Liraglutide (Victoza®), 0.6/1.2/1.8 mg. Batch numbers T011/0863 and T011/0059.

Subjects were to commence a dose escalation period with increasing doses of liraglutide (0.6 mg x 7 days, 1.2 mg x 7 days, then 1.8 mg thereafter, if tolerated). Subjects were to be given an additional 7 days at each dose level if needed to achieve tolerability. Liraglutide was to be administered once daily, irrespective of meals, by subcutaneous injections with the pen-injector either in the abdomen, thigh or upper arm. Injections could be done at any time of the day; however, administration at the same time each day was preferred. The injection sites did not need to be consistent throughout the trial.

DURATION OF TREATMENT

The planned duration of the trial was to be up approximately 32 weeks in the pre-transplant period and 52 weeks in the post-transplant period. The actual duration of treatment ranged from 1 to 19 weeks due to premature termination of the trial. Prior to the premature termination of the trial, two subjects were randomised to liraglutide and exposed to maximum doses of liraglutide [redacted] mg ([redacted]) and [redacted] mg ([redacted]).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

The reference therapy was liraglutide placebo. Subjects were to commence a similar dose titration scheme as those subjects randomised to liraglutide. Liraglutide placebo was to be administered once daily, irrespective of meals, by subcutaneous injections with the pen-injector either in the abdomen, thigh or upper arm. Injections could be done at any time of the day; however, administration at the same time each day was preferred. The injection sites did not need to be consistent throughout the trial.

CRITERIA FOR EVALUATION – EFFICACY

The primary endpoint was the proportion of subjects who were insulin-independent at 52 weeks after islet cell transplant and required only one (single-donor) islet cell transplant.

The secondary endpoints included:

- The proportion of subjects with HbA1c ≤ 6.5% at week 52 that are free from severe hypoglycaemic events from week 0 to week 52 after initial transplantation
- The proportion of insulin independent subjects who at 52 weeks after initial transplantation among all randomised subjects having one or more transplantations after randomisation.
- The average number of transplantations for all randomised subjects having one or more transplantations after randomisation
- The proportion of subjects with HbA1c ≤ 7.0% at week 52 that are free from severe hypoglycaemic events from week 0 to week 52 after initial transplantation
- Time to achievement of insulin independence after last transplant as well as after initial transplant and total time of insulin independence in the 52 weeks after initial transplantation
- Durability of insulin independence after last transplant as well as after initial transplant and total time of insulin independence in the 52 weeks after initial transplantation
- Insulin utilisation over time in the 52 weeks year after initial transplantation

- Change in fasting plasma glucose from pre-randomisation to 52 weeks after initial transplant
- Change in HbA_{1c}, and fasting C-peptide levels from pre-randomisation and pre-transplantation (for each transplant) to 52 weeks after initial transplantation
- Glucose level variability and hypoglycaemia duration derived from the continuous glucose monitoring system at baseline, weekly during liraglutide dose escalation, at 12 weeks pre-transplant, at 24 weeks post-transplant, 52 weeks post-transplant and 56 weeks (4 weeks after withdrawal of liraglutide or liraglutide placebo)
- Ryan hypoglycaemia severity score at baseline (pre-transplant), 8 weeks post-transplant, 24 weeks post-transplant and 52 weeks post-transplant
- Lability Index at baseline (pre-transplant), 8 weeks post-transplant, 24 weeks post-transplant and 52 weeks post-transplant
- Clarke score at baseline (pre-transplant), 8 weeks post-transplant, 24 weeks post-transplant and 52 weeks post-transplant
- Change in beta-cell function assessed by mixed meal test from pre-randomisation to 52 weeks after initial transplantation and to 56 weeks (4 weeks after withdrawal of liraglutide or liraglutide placebo)
- Change in beta cell function assessed by Arginine-stimulated C-peptide secretion from 4 weeks post-transplantation (for each transplantation) to 52 weeks after initial transplantation
- Change in fasting body weight at 52 weeks after initial transplantation compared with pre-transplantation weight (at randomisation and pre-transplant)
- Change in islet cell yield during culture from (0 hours) pre-culture to (24-72 hours) post-culture
- Incidence of hypoglycaemic episodes during the trial

CRITERIA FOR EVALUATION – SAFETY

The safety endpoints were the incidence of adverse events (AEs), and changes in clinical and safety parameters during the trial.

STATISTICAL METHODS

The sample size was determined such that the half-width of the two-sided 95% confidence interval for the primary endpoint was 0.25 (at most) for any possible value of the primary endpoint. Using the logistic regression method (along with the binomial distribution) gave a sample size of 15 per group. The full analysis set (FAS) were all randomised subjects who underwent one or more transplantations after randomisation. No formal statistical analyses were performed due to the premature termination of this trial.

DEMOGRAPHY OF TRIAL POPULATION

All randomised subjects in this trial were [redacted]. Two subjects resided in [redacted] and one resided in [redacted]. There were [redacted], [redacted] and [redacted] years old, and [redacted] enrolled in this trial, and their duration of diabetes ranged from [redacted] to [redacted] years.

EFFICACY RESULTS

Due to the premature termination of the trial prior to islet cell transplantation in any randomised subject, the efficacy of treating subjects with liraglutide prior to islet cell transplantation compared to liraglutide placebo, as well as adding liraglutide to the culture medium of the islet cells prior to transplantation compared to liraglutide placebo cannot be evaluated.

SAFETY RESULTS

No deaths or serious adverse events were reported during this trial. One subject withdrew from the trial due to AEs.

The incidence of AEs and changes in clinical and safety laboratory parameters were not analysed due to the premature termination of the trial.

CONCLUSIONS

The primary and secondary objectives of this trial were not fulfilled due to premature termination of the trial. Therefore, no conclusions regarding the primary and secondary objectives could be made.

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