Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: protocol for an investigator-initiated prospective, randomised, placebo-controlled, double-blinded, parallel intervention study

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ABSTRACT

Introduction: Diabetes is the leading cause of end-stage renal disease (ESRD). Owing to renal clearance, several antidiabetic agents cannot be used in patients with ESRD. The present protocol describes an investigator-initiated trial aiming to test safety and efficacy of treatment with the glucagon-like peptide-1 receptor agonist liraglutide in patients with type 2 diabetes and dialysis-dependent ESRD.

Methods and analysis: Twenty patients with type 2 diabetes and ESRD will be compared with 20 matched patients with type 2 diabetes and normal kidney function in a randomised, parallel, placebo-controlled, double-blinded setting. All participants will receive 12 weeks of daily treatment with liraglutide/placebo in an individually titrated dose of 0.6, 1.2 or 1.8 mg. Over nine visits, plasma liraglutide, glycaemic control, β-cell response, cardiovascular parameters, various biomarkers and adverse events will be assessed. The primary endpoint will be evaluated from dose-corrected plasma trough liraglutide concentration at the final trial visit to determine potential accumulation in the ESRD group.

Ethics and dissemination: The study has been approved by the Danish Medicines Agency, the Scientific-Ethical Committee of the Capital Region of Denmark and the Danish Data Protection Agency. An external monitoring committee (The Good Clinical Practice Unit at Copenhagen University Hospitals) will oversee the study. The results of the study will be presented at national and international scientific meetings, and publications will be submitted to peer-reviewed journals.

Trial registration: ClinicalTrials.gov Identifier: NCT01394341

ARTICLE SUMMARY

Article focus

- This study protocol describes a randomised controlled trial evaluating the safety and efficacy of treatment with the glucagon-like peptide-1 receptor agonist liraglutide in patients with type 2 diabetes and dialysis-dependent end-stage renal disease (ESRD).
- We hypothesise that patients with type 2 diabetes and ESRD will not accumulate liraglutide during treatment with recommended doses.

Key messages

- Owing to renal involvement in the elimination and degradation process, only few antidiabetic agents are suitable for the treatment of type 2 diabetes in patients with ESRD.
- Limited data exist on the pharmacokinetics, clinical effects and side effects of liraglutide in patients with moderate to severe renal impairment.
- Current knowledge does not indicate the kidneys as a major site of degradation and/or elimination of liraglutide.

Strengths and limitations of this study

- This will be the first randomised controlled trial examining the safety and efficacy of liraglutide treatment in diabetic patients with ESRD.
- The primary endpoint (plasma liraglutide) is strictly objective.
- Participants will be monitored extensively with frequent trial visits.
- The study population is limited and therefore non-representative.
- The study is not powered to conclude on most secondary endpoints.
Safety and efficacy of liraglutide in diabetic dialysis patients

INTRODUCTION
Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) and need of chronic maintenance dialysis treatment. Forty-four per cent of US ESRD patients have diabetes compared with 23% in Denmark.1, 2 Several antidiabetic drugs are cleared renally, and therefore only a limited number of antidiabetic treatment options exist for this group of patients. Insulin is the cornerstone of treatment, whereas the oral antihyperglycaemic agents biguanides, α-glucosidase inhibitors and meglitinides are not tolerable for ESRD patients. Some second-generation sulfonylureas can be used and thiazolidinediones can theoretically be used to treat diabetic ESRD patients without cardiac disease.3-4 Introduction of the newer incretin-based agents (dipeptidyl peptidase 4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists) has expanded the limited armamentarium of antidiabetic agents suitable for patients with ESRD; the DPP-4 inhibitor linagliptin can be used without dose reduction,5 and recent publications have suggested that saxagliptin, vildagliptin and sitagliptin can be used in patients with ESRD following dose reduction.6-8 GLP-1 receptor agonists, on the other hand, have been less thoroughly investigated, and therefore the vast majority of these drugs cannot at present be used in patients with ESRD. In the following, a protocol for the investigation of the safety and efficacy of the GLP-1 receptor agonist liraglutide in patients with ESRD and type 2 diabetes, including background knowledge, experimental design, planned analyses, ethics and dissemination plans, will be described.

Poor prognosis
The life expectancy of patients with type 2 diabetes and ESRD is severely reduced compared to that of patients suffering from the individual disease moieties. Thus, patients with both type 2 diabetes and ESRD have an unadjusted median survival of 2–4 years, irrespective of age and dialysis frequency.2-9 The most common cause of death in these patients is related to cardiovascular disease.10 Interventions directed towards hypertension, dyslipidaemia and other cardiovascular risk factors have, however, shown divergent and primarily negative effects on survival.11-14 Thus, there is an unmet need to find new treatments to protect diabetic ESRD patients from cardiovascular disease and premature death. Introduction of a GLP-1 receptor agonist may have the potential to meet this medical need by improving glycaemic control and reducing cardiovascular risk factors, thereby potentially reducing mortality and morbidity in the diabetic ESRD population.15-17

Liraglutide—a once-daily GLP-1 receptor agonist
GLP-1 receptor agonists stimulate insulin secretion, inhibit glucagon secretion, decrease appetite and food intake and decelerate gastric emptying, and, in consequence, reduce fasting and postprandial plasma glucose as well as body weight. Treatment with GLP-1 receptor agonists is only rarely associated with hypoglycaemia owing to the glucose-dependent effects of GLP-1 on the pancreatic hormones insulin and glucagon.18-22 Two GLP-1 receptor agonists are available for the treatment of patients with type 2 diabetes in the EU: exenatide (exists in a twice-daily and once-weekly formulation) and liraglutide. A third drug, lixisenatide, has recently been approved for treatment of type 2 diabetes by the European Medicines Agency.23 Exenatide and lixisenatide are primarily eliminated by glomerular filtration and subsequent proteolytic degradation in the tubules and are therefore unsuitable for patients with advanced stages of renal impairment.24-28 Liraglutide, on the other hand, is extensively bound to plasma proteins (>98%) and is metabolised in the same way as large proteins without a specific organ having been identified as the major site of elimination. Intact liraglutide cannot be demonstrated in the urine and only a small fraction (6%) is excreted as metabolites in the urine.25, 29 The half-life of liraglutide is approximately 13 h following a single dose injection, although with continuous once-daily injections, there is an accumulation index of 1.4–1.5 after 7 days of treatment. Furthermore, liraglutide exposure is increased proportionally with dose.25, 30 The currently available knowledge of pharmacokinetic, clinical effects and side effects in patients with moderate-to-severe renal impairment treated with liraglutide is limited.

Promising but sparse information on liraglutide treatment in ESRD patients
As indicated above, there is no indication that the kidneys represent a major route for elimination of liraglutide.25, 31 Malm-Erjefält et al31 suggest that liraglutide is degraded completely within the body, and Davidson et al32 conclude in a meta-analysis that mild renal impairment (creatinine clearance 60–89 ml/min) does not affect the efficacy or safety of liraglutide treatment. However, the number of patients with moderate or severe renal impairment in the analysis was too low to determine any significance for safety and efficacy parameters. A study by Jacobsen et al33 evaluated the pharmacokinetic properties of liraglutide following a subcutaneous injection of a single dose (0.75 mg) in patients with various degrees of renal impairment and found no signs of accumulation, even in those with ESRD. The European Medicines Agency states that there is a very limited long-term therapeutic experience regarding patients with moderate renal impairment (creatinine clearance 30–59 ml/min) and no therapeutic experience regarding patients with severe renal impairment (creatinine clearance <30 ml/min), and consequently that liraglutide cannot currently be recommended for use in patients with moderate or severe renal impairment.25 Likewise, the US Food and Drug Administration advises that liraglutide should be used with caution in patients with renal impairment owing to limited experience.34
OBJECTIVES

The primary objective of the present protocol is to evaluate the safety of liraglutide treatment in patients with type 2 diabetes and ESRD. We hypothesise that patients with type 2 diabetes and ESRD will tolerate treatment with liraglutide in doses that accord with the recommendations of the European Medicines Agency.25 Plasma liraglutide correlates with the frequency and intensity of adverse events related to treatment with liraglutide,30 and elderly patients and patients with mild renal impairment are known to be more prone to gastrointestinal side effects.25 The null hypothesis is that there will be no significant accumulation of liraglutide in terms of an increase in plasma trough liraglutide concentration, that is, the primary endpoint is trough concentration of liraglutide at the final trial visit. Secondary objectives include various clinical safety and efficacy parameters as described below.

METHODS AND ANALYSIS

Study design, randomisation and blinding

The study will be conducted as an investigator-initiated prospective, randomised, placebo-controlled, double-blinded, parallel 12-week intervention study. Two groups will be investigated: (1) patients with type 2 diabetes and ESRD (N=20) and (2) patients with type 2 diabetes and normal kidney function (N=20). Participants in both groups will be randomised into two treatment arms: liraglutide or placebo (1 : 1). An unblinded laboratory technician at the Department of Nephrology, Rigshospitalet, will be responsible for the allocation of the participants in both groups. Simple randomisation will occur consecutively in both groups according to a computer-generated randomisation list provided by Novo Nordisk A/S (Bagsvaerd, Denmark) in accordance with the randomisation ratio (1 : 1). The allocation sequence will be concealed from the investigators and healthcare staff enrolling and asssessing participants in numbered, opaque and sealed envelopes. The unblinded person will be informed in case of withdrawals or exclusion of participants, to ensure 10 completed participants in each treatment arm. The unblinded person will have no influence or knowledge of the treatment of the participants following randomisation. Participants, investigators and healthcare staff will be blinded for the allocated treatment and kept masked until the last patient’s last visit. Outcome assessors will subsequently not be blinded.

Study population and study sites

Patients in the ESRD group will be recruited among patients who receive chronic maintenance haemodialysis or peritoneal dialysis treatment at the Departments of Nephrology at Rigshospitalet, Frederiksberg Hospital or Hillerød Hospital, Denmark. The investigators will review patient charts of all dialysis patients diagnosed with diabetes. Patients who immediately meet the inclusion and exclusion criteria will be invited for screening. Eligible and amenable patients who still meet the inclusion and exclusion criteria following screening will be enrolled. Patients in the control group with type 2 diabetes and normal kidney function will be recruited from the outpatient clinic at the Department of Endocrinology, Rigshospitalet, Denmark. The groups will be matched by age, gender and body mass index. For each group, the total number of participants in the following categories will be recorded: initially assessed for eligibility, excluded before randomisation including reasons for exclusion, declined to participate, randomised, allocated for intervention, received allocated intervention, completed intervention period, withdrew/dropped out during the study period, including reasons for withdrawal/dropping out, lost to follow-up and analysed. Recruitment will proceed until 20 participants in each group have completed a minimum 6 weeks of treatment. Participants who withdraw, drop out or are excluded before 6 full weeks of treatment will be replaced. Reasons for withdrawal or exclusion will be reported in details. Participants who have been randomised will be included in the study population. Inclusion and exclusion criteria are presented in Box 1 and 2.

Experimental design

Amenable participants will receive detailed oral and written information about the study, and sufficient time for reflection will be allowed before written informed consent and authorisation are obtained. Patients and control participants will follow the same study plan unless stated otherwise; an initial screening visit will be followed by an intervention period of 12 weeks and a

Box 1 Inclusion criteria

Inclusion criteria—patients with type 2 diabetes and end-stage renal disease

- Male or female; aged 18–85 years
- End-stage renal disease treated with chronic maintenance dialysis (haemodialysis or peritoneal dialysis)
- History of type 2 diabetes (diagnosed at least 3 months prior to screening)
- Documented β-cell function (evaluated by a glucagon test)

Inclusion criteria—patients with type 2 diabetes and normal kidney function

- Male or female; aged 18–85 years
- Normal kidney function (plasma creatine <0.105 mmol/l for men and <0.090 mmol/l for women)
- History of type 2 diabetes (diagnosed at least 3 months prior to screening)
- Glycated haemoglobin ≥6.5%
- Documented β-cell function (evaluated by glucagon test)

Glycated haemoglobin significantlyunderestimates glycaemic control in haemodialysis patients.38 Accordingly, this parameter will not be used as an inclusion criterion in the group of patients with type 2 diabetes and end-stage renal disease.
follow-up visit in the week after termination of trial medication. An outline of the trial visits and examinations to be performed is shown in table 1.

**Trial visits and examinations**

On an initial screening day, a fasting 6 min glucagon-stimulated C-peptide test will be performed for documentation of preserved pancreatic β-cell function. A fasting C-peptide level >350 pmol/l and/or an increase in C-peptide concentration of >300 pmol/l 6 min following the glucagon injection will be considered sufficient for documentation of preserved β-cell function in accordance with local guidelines. Also, blood samples will be collected (table 2), medical history will be recorded and a full physical examination will be performed. All female participants of childbearing potential will be tested for pregnancy, and assurance will be obtained of adequate use of anticonceptive methods throughout the study period. During the intervention period, all participants will attend eight planned visits: randomisation (week 0), weeks 1, 2, 4, 6, 8, 10 and 12. At each visit, blood sampling will be performed (table 2) and trial medication will be dispensed. Furthermore, used packaging will be collected to estimate compliance, adverse events will be assessed and glycaemic control will be evaluated at each visit from week 1. Participants will attend in a fasting state (8 h overnight) for the randomisation visit (week 0) and the weeks 6 and 12 visits. After fasting, blood samples will be collected and a 4 h liquid meal test will be performed. The meal (250 ml Renilon 4.0 (Nutricia, Allerød, Denmark); 500 kcal: 58.8 g carbohydrate, 25 g fat and 10 g protein) will be mixed with 1.5 g paracetamol dissolved in 50 ml water (for documentation of gastric emptying) and ingested over 10 min. Repeated blood samples for measurements of plasma glucose, insulin, C-peptide, glucagon, GLP-1, glucose-dependent insulino tropic polypeptide (GIP) and paracetamol will be drawn throughout the 4 h meal test. Owing to an already extensive amount of time spent in hospital care by dialysis patients, the meal tests have been made optional for ESRD patients. A blood glucose meter (Contour; Bayer HealthCare, Copenhagen, Denmark) will be handed out on the day of randomisation, and participants will be asked to measure blood glucose three times daily (fasting in the morning, before dinner and late evening) throughout the following 12 weeks. Furthermore, a 24 h continuous glucose monitoring system will be used to assess glycaemic control (iPro2 device with Enlite glucose sensors; Medtronic Denmark A/S, Copenhagen, Denmark). The device estimates blood glucose 288 times per day over six successive days and will be attached at the randomisation, weeks 2, 6 and 10 visits. The patients treated with haemodialysis will have the following additional analyses performed: (1) plasma liraglutide will be measured three times weekly during the first 2 weeks after randomisation, (2) plasma liraglutide will be measured continuously on either side of the dialysis filter and in the dialysis water during a 4 h dialysis session at the week 2 visit and (3) plasma liraglutide will be measured two times during the 1-week period between termination of trial medication and follow-up.

**Intervention**

Trial medication will be initiated on the randomisation day in a dosage of 0.6 mg subcutaneously once daily. All participants will be requested to get the medicine injected in the abdomen before breakfast. Depending on glycaemic control and side effects, the dose can be increased to 1.2 mg after a minimum of 1 week of treatment and to a maximum of 1.8 mg following another week of treatment. The dose can be adjusted at all trial visits. Trial medication will be delivered in boxes of two prefilled, disposable pen-injectors, each containing 3 ml of a premixed colourless solution. The active pens will contain liraglutide (6 mg/ml) mixed with sterile water, disodium phosphate dihydrate, propylene glycol and phenol. Pens containing placebo will be visually identical to those with the active component and be composed of the same elements as the active pens except for liraglutide. The dose of the usual antidiabetic medication will be individually adjusted parallel with the dose adjustment of trial medication to ensure optimal glycaemic control. If sufficient glycaemic control is not achieved

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**Box 2 Exclusion criteria**

**Exclusion criteria—both groups**

- Type 1 diabetes
- Chronic pancreatitis or previous acute pancreatitis
- Known or suspected hypersensitivity to trial product(s) or related products
- Treatment with oral glucocorticoids, calcineurin inhibitors, dipeptidyl peptidase 4 inhibitors or other drugs, which in the investigator’s opinion could interfere with glucose or lipid metabolism 90 days prior to screening
- Cancer (except basal cell skin cancer or squamous cell skin cancer) or any other clinically significant disorder, which in the investigator’s opinion could interfere with the results of the trial
- Inflammatory bowel disease
- Cardiac disease defined as heart failure (New York Heart Association Class III–IV) and/or diagnosis of unstable angina pectoris and/or myocardial infarction within the last 6 months
- Body mass index ≤18.5 or ≥50.0 kg/m²
- Women of childbearing potential who are pregnant, breastfeeding, intend to become pregnant or are not using adequate contraceptive methods
- Clinical signs of diabetic gastroparesis
- Impaired liver function (alanine aminotransferase > twice upper reference level)
- Use of any investigational product 90 days prior to this trial
- Known or suspected abuse of alcohol or narcotics
- Screening plasma calcitonin ≥50 ng/l
- Participants with a personal or family history of medullary thyroid carcinoma or a personal history of multiple endocrine neoplasia type 2
on the maximum tolerable dose of trial medication in combination with ongoing antidiabetic treatment, insulin detemir will be added as rescue therapy.

Outcome measures and analysis methods

Primary endpoint

The primary endpoint is the dose-corrected plasma trough liraglutide concentration at the final trial visit (week 12); plasma liraglutide levels in the liraglutide-treated ESRD group and the liraglutide-treated control group will be compared to assess the level of any accumulation of liraglutide in ESRD patients. Plasma trough liraglutide concentration is dose-dependent and is expected to increase if the kidneys play a significant role in the degradation and elimination process of intact liraglutide. The primary endpoint will be reported based on a modified per protocol analysis; thus, it will be restricted to participants who have completed a minimum of 6 weeks of intervention with a compliance >80% of the prescribed trial medication. In case the full intervention period has not been completed, we will use the ‘last observation carried forward’ method.

Secondary endpoints

Secondary pharmacodynamic parameters include glycaemic control (assessed from 24 h glucose profile, daily blood glucose measurements and glycated haemoglobin, postprandial plasma glucose (assessed by mean and peak plasma glucose values and area under the curve (AUC) for plasma glucose during meal tests), pancreatic β-cell function (assessed from postprandial insulin and C-peptide responses), cardiovascular parameters (heart rate, blood pressure, lipid profile, electrocardiogram and proBNP), dose of antidiabetic agents other than liraglutide, and body weight.

Secondary safety parameters include adverse events such as gastrointestinal side effects and hypoglycaemic episodes registered by blood glucose metres and from questioning during trial visits (divided into minor (blood glucose <3.1 mmol/l, and no need for assistance) and major (requiring assistance from third person)), liver and kidney function and markers of inflammation and endothelial function (Von Willebrand factor, C-reactive protein and urate).

Secondary pharmacokinetic parameters will be evaluated from all participants attending haemodialysis treatment. The influence of haemodialysis on liraglutide treatment will be evaluated in relation to reduction in the ratio of liraglutide before and after dialysis treatment, clearance of liraglutide during dialysis treatment, concentration of liraglutide in dialysis fluid and time to steady state during continuous daily treatment. Furthermore, plasma liraglutide concentrations from all trial visits will be evaluated as time-dependent differences in excursions and as total responses during the study period in both groups.

Secondary endpoints will be reported based on the intention-to-treat analysis, thus including all randomised

Table 1 Trial visits and examinations

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<th>Electrocardiogram</th>
<th>Adverse event assessment</th>
<th>Blood glucose profile</th>
<th>Continuous 24 h glucose measurement (CGM)</th>
<th>Dose adjustment of trial medication</th>
<th>Dose adjustment of ongoing antidiabetic medication</th>
<th>Glucagon test</th>
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*, Will be affected if >6 weeks of treatment has been completed.
#, Only haemodialysis patients; liraglutide samples will be collected 3 times/week.
§, Optional for dialysis patients.
f, Fasting.

The number of participants in each group has been chosen based on a power calculation on the primary endpoint. On the basis of previous trials with liraglutide, the trough value is estimated to be 20 000 pmol/l during steady state and the SD is estimated to be 8000 pmol/l in participants with normal kidney function. With 10 patients with normal kidney function and 10 dialysis patients treated with liraglutide, it will be possible to show a difference of 10 600 pmol/l, corresponding to 53% of the steady state trough level, using a significance level of 5% (α=0.05) and a power of 80% (1−β=0.80). Further power will be gained by analysing data from all visits using a linear mixed model.

**Data analysis**

To address our primary objective, we shall use a linear mixed model which will elucidate differences in concentrations of plasma liraglutide. We will use group, trial visit day and dose administered since the last trial visit as explanatory variables and apply a model with interaction between the group and trial visit day to model two different trajectories. The primary endpoint will be calculated as the difference between the estimated, dose-corrected plasma trough liraglutide concentrations in the two groups treated with liraglutide, at the final trial visit (week 12). Furthermore, differences at each trial visit will be estimated along with the 95% confidence limits to assess excursions, and data will be evaluated as total responses during the study period using AUC (calculated by the trapezoidal rule) for the estimated and dose-corrected plasma liraglutide (secondary endpoints).

Secondary endpoint data will be compared between the two arms in the ESRD group (active vs placebo) and between the two active liraglutide groups (type 2 diabetes with ESRD vs type 2 diabetes with normal kidney function). Distribution of data will be assessed using a graphical evaluation of residuals from the linear mixed model and Kolmogorov-Smirnov tests. Homogeneity of variance will be assessed using Levene’s test. Normally distributed data will be evaluated using parametric testing and for data that do not follow a normal distribution or that exhibit unequal variances, non-parametric testing will be preferred. The χ² or Fisher’s exact tests will be used for group comparisons between categorical data. All tests will be two-tailed and p values less than 0.05 will be considered significant. When interpreting multiple comparisons of the two groups, for example, for data compared at each visit, the Benjamini-Hochhberg procedure will be used to control the type I error rate.

**ETHICS AND DISSEMINATION**

This investigator-initiated trial has the potential to evaluate safety parameters of vital importance, before further and more extensive testing of efficacy and long-term safety and before potential addition of the GLP-1 receptor agonist liraglutide to the limited armamentarium of antidiabetic drugs used to treat type 2 diabetes in ESRD patients. The limited knowledge available does not...
suggest renal involvement in the elimination and degradation of liraglutide. A positive outcome for the primary endpoint of the trial, that is, no significant accumulation of liraglutide in ESRD patients during continuous treatment, may pave the way for the use of liraglutide in the treatment of type 2 diabetes in ESRD patients and thus potentially increase their chances of obtaining good glycemic control. This will, however, require larger trials including ESRD patients with a wider spectrum of antidiabetic treatment regimens and comorbidities and longer intervention periods, thereby being able to test hard clinical outcomes. A negative result, that is, a significant accumulation of liraglutide in ESRD patients, will also be of clinical and scientific interest, since it will indicate renal involvement in the clearance of liraglutide, which is contradictory to current knowledge.25–30 31 33 34 The potential side effects and risks will be minimised by close monitoring of glycaemic control, individual dose adjustments of both trial medication and ongoing antidiabetic medication and frequent study visits. The individual dose adjustment of trial medication and ongoing antidiabetic treatment will ensure that randomisation to the two placebo groups will not cause deterioration of glycaemic control during intervention. The potential disadvantages, including expense of time, potential adverse events and discomfort related to fasting, are expected to be overshadowed by the knowledge and possible clinical importance that the trial outcome will produce. The results of the study will be presented at national and international scientific meetings, and manuscripts will be written in accordance with the CONSORT 2010 Statement37 and submitted to peer-reviewed journals.

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Contributors TI, FKK, TJ, JJH, MH and BFR conceived and designed the study. BFR sponsored the trial. TJ was the coordinating investigator and principal investigator at the Department of Nephrology, Rigshospitalet. TJ was the principal investigator at the Department of Endocrinology, Rigshospitalet. PMH was the principal investigator at the Department of Internal Medicine, Hillerød Hospital. MJ and MR were the sub-investigators. KBC contributed to statistical consultancy and drafted the statistical part of the manuscript. TI, FKK and BFR drafted the remaining part of the manuscript. All authors have read and approved the final version of the manuscript.

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Ethics approval The study has been approved by the Danish Medicines Agency (EudraCT number: 2010-021922-36), the Scientific-Ethical Committee of the Capital Region of Denmark (H-3-2011-032) and the Danish Data Protection Agency (2007-58-0015). The study is registered at ClinicalTrials.gov (NCT01394341) and will be carried out under the surveillance and guidance of the GCP unit at Copenhagen University Hospital in compliance with the ICH-GCP guidelines. The study was launched in September 2011 and will be conducted in accordance with the Helsinki Declaration.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES
Safety and efficacy of liraglutide in diabetic dialysis patients


Safety and efficacy of liraglutide in patients with type 2 diabetes and end-stage renal disease: protocol for an investigator-initiated prospective, randomised, placebo-controlled, double-blinded, parallel intervention study

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