



Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial

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Summary

Background The combination of insulin and glucagon-like peptide-1 (GLP-1) receptor agonist therapy improves glycaemic control, induces weight loss, and reduces insulin dose needed in type 2 diabetes. We assessed the efficacy and safety of the GLP-1 receptor agonist liraglutide as an add-on therapy to insulin for overweight adult patients with type 1 diabetes.

Methods We did a randomised, double-blind, placebo-controlled trial at Steno Diabetes Center (Gentofte, Denmark). Patients aged 18 years or older with type 1 diabetes, insufficient glycaemic control ($HbA_{1c} >8\%$ [64 mmol/mol]), and overweight (BMI >25 kg/m²) were randomly assigned (1:1) to receive insulin treatment plus either liraglutide or placebo (saline solution) by subcutaneous injection once per day. Randomisation was done in blocks of four. Treatment assignment was masked to investigators and patients. Treatment lasted 24 weeks and liraglutide was started at a dose of 0.6 mg per day, escalated to 1.2 mg per day after 1 week, and then again to 1.8 mg per day after another week. Intervals between dose increments could be extended at the discretion of the investigator. The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were changes in hypoglycaemic events, glycaemic variability, glycaemic excursions, insulin dose, bodyweight, postprandial plasma concentrations of glucagon and GLP-1, gastric emptying, blood pressure, heart rate, patient-reported outcome measures, time spent in hypoglycaemia, near-normoglycaemia, and hyperglycaemia, plasma fasting glucose, mean glucose, and cholesterol. Efficacy analyses were calculated by use of a mixed model, whereby a patient's data are used as long as the patient is in the study. The safety analyses were done in the intention-to-treat population, which consisted of all patients who received at least one dose of their randomly assigned study drug. This study is registered with ClinicalTrials.gov, number NCT01612468.

Findings Between July 10, 2012, and May 30, 2014, we enrolled 100 patients with type 1 diabetes, with 50 patients allocated liraglutide and 50 to placebo. Four patients from the liraglutide group and six patients from the placebo group discontinued treatment before 24 weeks. At the end of treatment, change in HbA_{1c} from baseline did not differ between groups (-0.5% , 95% CI -0.8 to -0.4 [-6.0 mmol/mol, 95% CI -8.7 to -4.4] with liraglutide vs -0.3% , -0.6 to -0.2 [-4.0 mmol/mol, -6.6 to -2.3] with placebo; between-group difference -0.2% [-0.5 to 0.1 ; 2.2 mmol/mol, -5.5 to 1.1], $p=0.1833$). The number of hypoglycaemic events was reduced with liraglutide, with an incident rate ratio of 0.82 (95% CI 0.74 to 0.90). However, we detected no changes in glycaemic variability (continuous overall net glycaemic action per 60 min from 10.3 [95% CI 9.8 to 10.8] to 9.9 [9.2 to 10.6] in the liraglutide treated patients vs 10.2 [9.7 to 10.7] to 9.7 [9.1 to 10.3] in the placebo treated patients). Both bolus insulin (difference -5.8 IU, 95% CI -10.7 to -0.8 , $p=0.0227$) and bodyweight (difference -6.8 kg, 95% CI -12.2 to -1.4 , $p=0.0145$) decreased with liraglutide treatment compared with placebo. Heart rate increased with liraglutide, with a difference between groups of 7.5 bpm (95% CI 2.8–12.2, $p=0.0019$). Postprandial plasma glucagon and GLP-1 concentrations did not differ between groups (difference between groups at end of treatment: -408 mmol/L per 240 min [95% CI -941 to 125, $p=0.1309$] for glucagon and -266 mmol/L per 240 min [-1034 to 501, $p=0.4899$] for GLP-1). Gastric emptying was delayed after 3 weeks of treatment with liraglutide (19.9 min, 95% CI 0.8 to 39.0, $p=0.0412$), but we detected no difference after 24 weeks of treatment (-1.5 min, -20.5 to 17.6, $p=0.8793$). Patient-reported outcome measures differed between groups only with respect to perceived frequency of hypoglycaemia, which was higher with placebo, with a difference between groups of -0.6 (95% CI -1.1 to -0.07 , $p=0.0257$). Liraglutide was associated with more frequent nausea (29 [58%] patients with liraglutide vs five [10%] with placebo), dyspepsia (11 [22%] patients with liraglutide vs one [2%] with placebo), diarrhoea (ten [20%] patients with liraglutide vs one [2%] with placebo), decreased appetite (seven patients [14%] with liraglutide vs none with placebo), and vomiting (seven [14%] patients with liraglutide vs one [2%] with placebo).

Interpretation In patients with type 1 diabetes, overweight, and insufficient glycaemic control, the reduction in HbA_{1c} did not differ between insulin plus placebo and insulin plus liraglutide treatment. Liraglutide was associated with reductions in hypoglycaemic events, bolus and total insulin dose, and bodyweight, and increased heart rate.

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See [Comment](#) page 190

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Panel: Research in context**Evidence before this study**

We searched Cochrane library, MEDLINE, and Embase with the terms “glucagon-like peptide-1” or “GLP-1” in combination with “type 1 diabetes” or “IDDM” or “T1DM” or “T1D”. We also searched the reference lists of articles identified by this search strategy. Additionally, we did a systemic search for abstracts from major international scientific meetings (American Diabetes Association, European Association for the Study of Diabetes, and International Diabetes Federation). We applied no publication date or language restrictions or specific criteria for assessment of quality and the final search was done on July 20, 2015. Data from previous non-randomised clinical studies of the addition of a GLP-1 receptor agonist to existing insulin treatment in type 1 diabetes suggest that the combination reduces bodyweight, postprandial glucose excursions, and daily insulin dose, with improved or unaltered glycaemic control. Only one of these studies, a non-published interim analysis, had a randomised, placebo-controlled design. In October, 2015, our group reported the first randomised, placebo-controlled trial investigating the efficacy and safety of liraglutide for normal-weight patients with insufficient controlled type 1 diabetes.

Added value of this study

This study is the largest to date to investigate the efficacy and safety of a GLP-1 receptor agonist adjunct to insulin treatment in patients with type 1 diabetes with a randomised, placebo-controlled, double-blind design. In our study, we identified a reduction in both bodyweight and daily insulin dose compared with placebo. Hypoglycaemia was less frequent in the liraglutide group. Our findings provide valuable information about the advantages and disadvantages associated with combination therapy with insulin and GLP-1 receptor agonist in patients with type 1 diabetes.

Implications of all the available evidence

We do not currently recommend the combined treatment for the general population of patients with type 1 diabetes. However, the combination might be useful for a sub-population of patients with type 1 diabetes. Further studies are needed to define the therapeutic potentials of different GLP-1 receptor agonists.

Introduction

Guidelines for the management of type 1 diabetes recommend near-normalisation of blood glucose by intensification of insulin therapy with multiple daily injections of insulin or continuous subcutaneous insulin infusion to delay the onset and slow progression of diabetic complications.¹⁻³ However, achieving and maintaining strict glycaemic control is a demanding task for many patients, and is associated with an increased risk of hypoglycaemia, which can interrupt daily activities, result in inappropriate countermeasures, and increase risk for accidents. Strict glycaemic control can also result in substantial weight gain,¹ which is a growing clinical problem. In industrialised parts of the world, 50% of adult patients with type 1 diabetes are estimated to be overweight or obese.⁴

In insulin-treated overweight patients with type 2 diabetes, treatment with glucagon-like peptide-1 (GLP-1) receptor agonist stimulates glucose-dependent insulin secretion, suppresses glucagon secretion, slows gastric emptying, and reduces appetite.⁵⁻⁸ This treatment results in improved glycaemic control and weight loss, with concomitant reductions in necessary insulin dose, but without increased risk of hypoglycaemia.⁹

Results from small-scale, open-label, and non-randomised clinical studies suggest that the addition of GLP-1 receptor agonist to insulin treatment for type 1 diabetes is associated with weight loss, smaller postprandial glucose excursions, and reduced insulin requirements, with improved or unaltered glycaemic control.¹⁰⁻¹⁷ We aimed to assess the efficacy and safety of liraglutide, a GLP-1 receptor agonist, as an addition to

insulin therapy for overweight patients with insufficiently controlled type 1 diabetes.

Methods**Study design and participants**

The study was a single-centre, parallel, randomised, double-blind, placebo-controlled intervention study done at Steno Diabetes Center (Gentofte, Denmark). The study was approved by the Scientific-Ethical Committee of the Capital Region of Denmark (H-1-2012-031), the Danish Medicines Authority (EudraCT: 2012-001150-26), and the Data Protection Agency. The study was done under the surveillance and guidance of the Good Clinical Practise unit, University of Copenhagen (Copenhagen, Denmark), in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practise guidelines. A trial protocol was reported previously.¹⁸

We recruited participants from among patients attending four outpatient clinics in the Capital Region of Denmark. Patients were eligible if they had been diagnosed with type 1 diabetes in accordance with WHO criteria for more than 1 year, were aged 18 years or older, and had a BMI more than 25 kg/m² and HbA_{1c} more than 8% (64 mmol/mol). Exclusion criteria were insulin pump treatment (because the investigators did not have sufficient expertise with this treatment), hypoglycaemia unawareness, gastroparesis, impaired kidney function (estimated glomerular filtration rate <60 mL/min/1.73 m²), liver disease with raised alanine aminotransferase more than three times the upper normal range, history of pancreatitis, pregnancy, lactation, inadequate contraception

(ie, single-layer contraception) in women of childbearing potential, cancer (unless in complete remission for >5 years), history of alcohol or drug misuse, or any medical or psychological disorder that made the patient unsuitable for study participation as judged by the investigators' assessment. There was no criteria with respect to what kind of insulin the patient was treated with or how many times per day it was injected. However, after randomisation type of insulin was not allowed to change. The ability to count carbohydrates was also not a criterion for participation and no data were recorded about this. Written informed consent was obtained from all participants.

Randomisation and masking

Participants were randomly assigned (1:1) in blocks of four to receive either liraglutide (Novo Nordisk, Måløv, Denmark) or placebo (saline injection) once per day, as an add-on to existing insulin treatment, by use of a computer-generated randomisation list generated by a third-party organisation (Trial Partner, Aarhus, Denmark). The personnel who did the randomisation had no further involvement in the trial. Masking of allocation was achieved by use a website generated by Trial Partner. The study staff logged on to the website, to identify patients by a unique patient ID. The computer then automatically enrolled the patient into one of the two groups. A specific number that was identical to a number on a box of three pens was generated, so the study staff were able to hand out the correct investigational medical product to the patient. Treatment masking was achieved by the placebo pen being indistinguishable from the liraglutide pen and all participants and study staff were masked to treatment allocations.

Procedures

Liraglutide (6.0 mg/mL) and placebo were given as self-administered subcutaneous injections. Treatment with liraglutide began at 0.6 mg per day (0.1 mL injection), was increased to 1.2 mg per day (in 0.2 mL injection) after 1 week, and increased again to 1.8 mg per day (in 0.3 mL injection) after another week. Intervals between dose increments could be extended at the discretion of the investigator and on the basis of the patient's tolerance to the treatment. To reduce the risk of hypoglycaemia, doses of bolus and basal insulin were reduced by 33% and 25%, respectively, at the time of randomisation.¹² Patients were not allowed to change the type of insulin (bolus or basal) during the study period. Insulin dose was adjusted in accordance with self-measured blood glucose (SMBG) and continuous glucose monitoring (CGM). Treatment targets were preprandial glucose concentrations of 4–7 mmol/L and postprandial concentrations less than 10 mmol/L, in accordance with national and international guidelines.^{2,19} Before randomisation, patients did not receive any structured education about the treatment of hyperglycaemia or

hypoglycaemia. However, they had all participated in a mandatory educational program offered by their respective outpatient clinics.

Five visits to the study centre were scheduled (weeks 0, 3, 12, 23, and 24) at which we collected information about concomitant medication, basal and bolus insulin doses, number of hypoglycaemic events, bodyweight, blood pressure, and heart rate. We also collected blood samples. During weeks 0, 12 and 23, patients wore a blinded continuous glucose monitor (Ipro2, Medtronic, Minneapolis, MN, USA) for 6 consecutive days. After each period of continuous glucose monitoring, the results were discussed with the patient to optimise glycaemic control. We assessed patient outcome measures with the Diabetes Treatment and Satisfaction Questionnaire, version s (DTSQs) and the Problem Area In Diabetes questionnaire (PAID). The DTSQs was subdivided into three sections: total treatment satisfaction (questions 1, 4, 5, 6, 7, and 8), perceived frequency of hyperglycaemia (question 2), and perceived frequency of hypoglycaemia (question 3).

At weeks 0 (randomisation), 3, and 24 (end of treatment) the first 40 participants (40 was deemed to provide sufficient power with 25% dropouts, appendix p 1) enrolled in the trial underwent a 4 h standardised liquid mixed meal test (Nutridrink Protein [Nutricia, Schiphol, Netherlands]; 200 mL containing 300 kcal, 31.2 g carbohydrate, 20 g protein, and 10.6 g fat) with 1500 mg of paracetamol added to the meal (appendix). We used the paracetamol absorption test to measure the Gastric emptying rate.²⁰

See Online for appendix

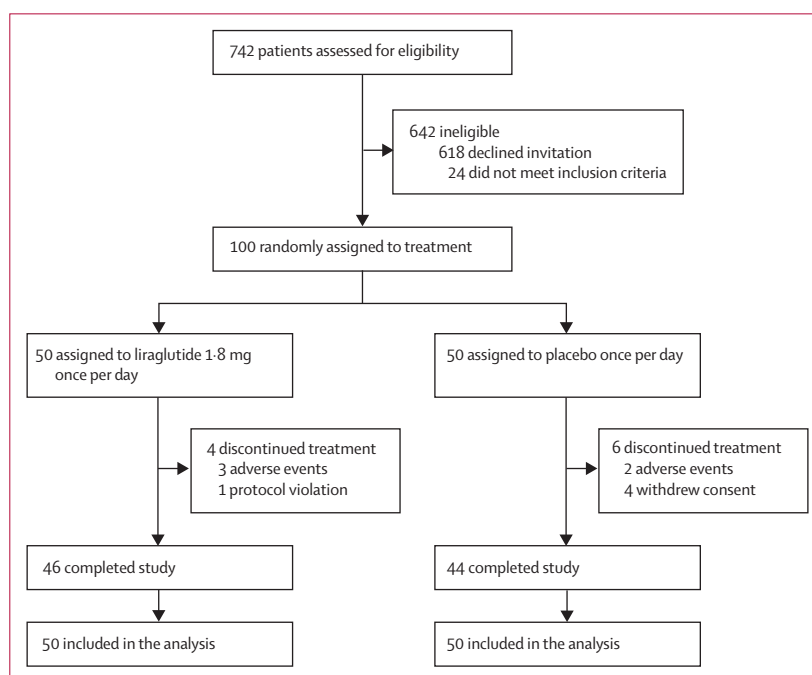


Figure 1: Trial profile

	Liraglutide (n=50)	Placebo (n=50)
Sex		
Male	30 (60%)	35 (70%)
Female	20 (40%)	15 (30%)
Age (years)	47 (13)	49 (12)
White ethnic origin	50 (100%)	50 (100%)
HbA _{1c} (%)	8.7 (0.7)	8.7 (0.7)
HbA _{1c} (mmol/mol)	71.6 (7.7)	71.8 (7.6)
Bodyweight (kg)	93.4 (14.2)	94.0 (12.5)
BMI (kg/m ²)	30.3 (3.5)	29.8 (3.1)
Duration of diabetes (years)	20 (12)	25 (12)
C-peptide >30 pmol/L	12 (24%)	9 (18%)
C-peptide (pmol/L)	11 (72)	22 (30)
GAD-65 positive (>5 pmol/L)	35 (70%)	29 (58%)
Dose of basal insulin (IU/day)	32 (16)	33 (15)
Type of basal insulin		
Glargine, qd	14 (28%)	9 (18%)
Glargine, bid	15 (30%)	4 (8%)
Detemir, qd	11 (22%)	8 (16%)
Detemir, bid	10 (20%)	26 (52%)
NPH, qd	0	3 (6%)
Dose of bolus insulin (IU/day)	27 (12)	27 (10)
Type of bolus insulin		
Insulin aspart	50 (100%)	50 (100%)
Total cholesterol (mmol/L)	4.5 (1.0)	4.7 (1.0)
HDL cholesterol (mmol/L)	1.3 (0.4)	1.3 (0.3)
LDL cholesterol (mmol/L)	2.7 (0.9)	2.8 (0.9)
VLDL cholesterol (mmol/L)	0.5 (0.3)	0.6 (0.3)
Triglycerides (mmol/L)	1.2 (0.6)	1.3 (0.7)
Systolic blood pressure (mmHg)	131 (15)	130 (16)
Diastolic blood pressure (mmHg)	82 (9)	81 (8)
Heart rate (beats/min)	77 (10)	75 (13)
Data are mean (SD) or n (%). NPH=neutral protamine hagedorn. qd=once daily administration. bid=twice daily administration.		
Table 1: Baseline characteristics		

Outcomes

The primary endpoint was change in HbA_{1c} from baseline to week 24. Secondary endpoints were change from baseline to week 24 in insulin dose (IU/day for both bolus and basal); number of hypoglycaemic events (defined as blood glucose ≤ 3.9 mmol/L); glycaemic variability assessed by CGM estimated as the mean amplitude of glycaemic excursions (MAGE) continuous overall net glycaemic action 60 min (CONGA_{60 min}), and SD of mean glucose; bodyweight; ambulatory blood pressure, gastric emptying; patient-reported outcome measures; time spent in hypoglycaemia, near-normoglycaemia (4.0–9.9 mmol/L), or hyperglycaemia (≥ 10.0 mmol/L); glycaemic excursions; plasma fasting glucose; heart rate, cholesterol; and adverse events. Additionally, we calculated changes in total area under the curve (AUC_{0–240 min}) for postprandial plasma concentrations of glucose, glucagon, and total GLP-1. To focus on glycaemic

control and safety, not all of the secondary endpoints from the protocol are included in this report (lean body mass and fat mass composition as determined by DXA scan, food preferences, VAS score for appetite, carotid intima media thickness, pulse wave velocity, and 24 h ambulatory blood pressure monitoring are not reported). We assessed safety by recording and grading adverse events at each patient visit in accordance with Good Clinical Practice guidelines.

Statistical analysis

We based our sample size calculation on data from a randomised controlled trial done in patients with type 1 diabetes treated with insulin injection therapy versus insulin pump therapy²¹ because there were no relevant data about GLP-1 receptor agonist treatment for type 1 diabetes available when the study was initiated. To detect a difference between groups of 0.5% (6 mmol/mol) in change from baseline in HbA_{1c} with 80% power at a 5% significance level and a presumed SD of 0.8% (9 mmol/mol), we needed 37 participants in each study group (two-sided test). To allow for a 25% drop-out rate, we aimed to enrol 100 participants in the trial, with 50 in each group. Before the end of the trial, a statistician reviewed the planned statistical methods for the trial. To obtain a higher efficacy in the statistical analysis, the statistician recommended use of a linear mixed model to compare our longitudinal data, instead of the unpaired two-sample *t* test described in the protocol.

We present baseline demographics as mean with standard deviation (SD) for continuous variables (age, duration of diabetes, BMI, and HbA_{1c}), and as numbers for sex. We did efficacy analyses with linear mixed-effect models with visit, treatment, and their interaction as fixed factors and a random intercept on the patient level. We did the efficacy analyses with a mixed model, whereby the patients' data were used as long as the patient was in the study (eg, if a patient dropped out after 7 weeks, his or her data counted at week 6, but not at week 8). We included all 100 patients in the efficacy analysis. We assessed the overall effect of treatment with a likelihood ratio test against a model that included only visit (ie, which day the visit was) as a fixed effect. For the insulin dose outcomes (basal, bolus, and total insulin dose), we also included bodyweight as a continuous fixed effect, and its two-way interactions with visit and treatment, respectively, and the three-way interaction with visit and treatment. To assess self-reported events of hypoglycaemia, we used an incidence rate ratio (IRR) test. We deemed a CI with both the lower and upper limit less than one to show significance at a 5% significance level. We calculated areas under curves with the trapezoidal method. The safety analyses were based on the intention-to-treat population and consisted of all patients who received at least one dose of the study drug. We used the R statistical software package (version 3.2.2) to do the analyses. All statistical analyses were done blinded to treatment allocation.

	Randomisation			Week 3			Week 12			Week 24		
	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo
Hb _{A1c} (%)	8.7 (8.5 to 8.9)	8.7 (8.5 to 8.9)	-0.02 (-0.3 to 0.3) [0.9112]	8.1 (7.9 to 8.3)	8.5 (8.3 to 8.7)	-0.4 (-0.7 to -0.1) [0.0073]	8.2 (7.9 to 8.4)	8.4 (8.1 to 8.6)	-0.2 (-0.5 to 0.1) [0.1833]
HbA _{1c} (mmol/mol)	71.6 (69.4 to 73.9)	71.8 (69.5 to 74.1)	-0.2 (-3.4 to 3.0)	65.2 (62.9 to 67.5)	69.7 (67.4 to 72.0)	-4.5 (-7.7 to -1.2)	65.6 (63.3 to 67.9)	67.8 (65.5 to 70.1)	-2.2 (-5.5 to 1.1)
Total insulin (IU/day)	58.7 (51.7 to 65.8)	60.6 (53.5 to 67.6)	-1.8 (-11.8 to 8.2) [0.7185]	59.9 (52.8 to 66.9)	68.1 (61.0 to 75.2)	-8.3 (-18.3 to 1.7) [0.1043]	61.9 (54.9 to 69.0)	72.1 (65.0 to 79.2)	-10.1 (-20.0 to -0.1) [0.0479]	62.8 (55.7 to 69.9)	74.0 (66.9 to 81.1)	-11.2 (-21.2 to -1.2) [0.0291]
Bolus insulin (IU/day)	26.6 (23.1 to 30.1)	27.4 (24.0 to 30.9)	-0.8 (-5.7 to 4.1) [0.7415]	25.7 (22.2 to 29.2)	30.8 (27.3 to 34.3)	-5.0 (-10.0 to -0.1) [0.0455]	26.5 (23.0 to 30.0)	32.0 (28.5 to 35.5)	-5.5 (-10.5 to -0.6) [0.0292]	27.1 (23.6 to 30.6)	32.8 (29.3 to 36.3)	-5.8 (-10.7 to -0.8) [0.0227]
Basal insulin (IU/day)	32.1 (27.4 to 36.9)	33.1 (28.4 to 37.9)	-1.0 (-7.7 to 5.7) [0.7692]	34.1 (29.4 to 38.9)	37.8 (33.0 to 42.6)	-3.7 (-10.4 to 3.1) [0.2859]	35.5 (30.7 to 40.3)	40.1 (35.3 to 44.9)	-4.6 (-11.4 to 2.2) [0.1817]	35.9 (31.1 to 40.7)	41.2 (36.4 to 46.0)	-5.3 (-12.0 to 1.5) [0.1257]
Weight-adjusted total insulin (IU/kg/day)	0.6 (0.6 to 0.7)	0.7 (0.6 to 0.7)	-0.02 (-0.1 to 0.1) [0.6394]	0.7 (0.6 to 0.7)	0.7 (0.7 to 0.7)	-0.06 (-0.2 to 0.03) [0.1636]	0.7 (0.6 to 0.8)	0.8 (0.7 to 0.8)	-0.1 (-0.2 to 0.02) [0.1485]	0.7 (0.7 to 0.8)	0.8 (0.7 to 0.9)	-0.1 (-0.2 to 0.02) [0.1162]
Weight-adjusted bolus insulin (IU/kg/day)	0.3 (0.3 to 0.3)	0.3 (0.3 to 0.3)	-0.01 (-0.1 to 0.04) [0.6679]	0.3 (0.3 to 0.3)	0.3 (0.3 to 0.4)	-0.04 (-0.1 to 0.01) [0.0813]	0.3 (0.3 to 0.3)	0.3 (0.3 to 0.4)	-0.04 (-0.1 to 0.01) [0.0976]	0.3 (0.3 to 0.3)	0.4 (0.3 to 0.4)	-0.04 (-0.1 to 0.01) [0.0905]
Weight-adjusted basal insulin (IU/kg/day)	0.3 (0.3 to 0.4)	0.4 (0.3 to 0.4)	-0.01 (-0.1 to 0.1) [0.7256]	0.4 (0.3 to 0.4)	0.4 (0.4 to 0.4)	-0.02 (-0.2 to 0.03) [0.4255]	0.4 (0.4 to 0.4)	0.4 (0.4 to 0.5)	-0.03 (-0.1 to 0.04) [0.4160]	0.4 (0.4 to 0.5)	0.4 (0.4 to 0.5)	-0.03 (-0.1 to 0.03) [0.3582]
Continuous glucose monitoring												
Hypoglycaemia (h/day)	1.2 (0.3 to 2.1)	1.1 (0.7 to 1.6)	0.1 (-0.9 to 1.1) [0.8652]	1.0 (0.5 to 1.6)	1.6 (0.8 to 2.3)	-0.5 (-1.4 to 0.4) [0.2551]	1.3 (1.0 to 1.8)	1.8 (0.8 to 2.8)	-0.5 (-1.5 to 0.6) [0.3970]
Near normoglycaemia (h/day)	9.3 (8.3 to 10.5)	10.0 (8.9 to 11.1)	-0.6 (-2.2 to 0.9) [0.4244]	11.1 (9.8 to 12.5)	9.5 (8.3 to 10.6)	1.7 (-0.1 to 3.4) [0.0572]	10.3 (9.0 to 11.5)	10.8 (9.4 to 12.1)	-0.5 (-2.3 to 1.3) [0.5838]
Hyperglycaemia (h/day)	13.4 (11.9 to 14.8)	12.8 (11.5 to 14.1)	0.5 (-1.4 to 2.4) [0.5760]	11.8 (10.2 to 13.4)	13.0 (11.4 to 14.7)	-1.2 (-3.4 to 1.0) [0.2810]	12.4 (10.9 to 13.9)	11.4 (9.8 to 13.0)	1.0 (-1.2 to 3.2) [0.3583]

(Table 2 continues on next page)

	Randomisation		Week 3		Week 12		Week 24		Liraglutide vs placebo		
	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo			
(Continued from previous page)											
MAGE	8.7 (8.1 to 9.3)	9.2 (8.5 to 10.0)	-0.6 (-1.5 to 0.4) [0.2301]	8.5 (7.7 to 9.2)	9.0 (8.2 to 9.7)	-0.5 (-1.5 to 0.5) [0.3421]	8.4 (7.9 to 8.9)	9.1 (8.3 to 10.0)	-0.7 (-1.7 to 0.3) [0.1549]
CONGA _{60 min}	10.3 (9.8 to 10.8)	10.2 (9.7 to 10.7)	0.1 (-0.6 to 0.8) [0.7835]	9.4 (8.7 to 10.0)	9.9 (9.4 to 10.5)	-0.6 (-1.4 to 0.2) [0.1529]	9.9 (9.2 to 10.6)	9.7 (9.1 to 10.3)	0.2 (-0.7 to 1.1) [0.7171]
SD of mean glucose	4.3 (4.1 to 4.6)	4.5 (4.2 to 4.8)	-0.1 (-0.5 to 0.3) [0.5077]	4.1 (3.8 to 4.4)	4.3 (4.1 to 4.6)	-0.2 (-0.6 to 0.2) [0.2536]	4.3 (4.0 to 4.6)	4.3 (4.0 to 4.6)	-0.03 (-0.5 to 0.4) [0.8650]
Bodyweight (kg)	92.4 (88.6 to 96.2)	93.1 (89.3 to 96.9)	-0.8 (-6.1 to 4.6) [0.7823]	89.8 (86.0 to 93.6)	93.0 (89.2 to 96.8)	-3.1 (-8.5 to 2.2) [0.2496]	87.4 (83.6 to 91.2)	-5.6 (-11.0 to -0.2) [0.0424]	86.5 (82.7 to 90.3)	93.3 (89.5 to 97.1)	-6.8 (-12.2 to -1.4) [0.0145]
Systolic blood pressure (mmHg)	131 (127 to 135)	130 (126 to 135)	0.2 (-5.6 to 6.0) [0.9435]	126 (122 to 131)	129 (125 to 134)	-3.1 (-9.0 to 2.9) [0.3156]	125 (120 to 129)	-2.7 (-8.8 to 3.3) [0.3697]	125 (121 to 130)	130 (125 to 134)	-4.2 (-10.2 to 1.8) [0.1720]
Diastolic blood pressure (mmHg)	82 (80 to 84)	81 (78 to 83)	-1.2 (-2.1 to 4.6) [0.4638]	81 (79 to 83)	79 (77 to 81)	2.0 (-1.4 to 5.4) [0.2553]	81 (79 to 84)	-0.9 (-4.3 to 2.6) [0.6204]	81 (78 to 83)	81 (78 to 83)	-0.1 (-3.6 to 3.3) [0.9317]
Heart rate (beats/min)	77 (73 to 80)	75 (72 to 78)	-1.6 (-3.0 to 6.2) [0.4896]	79 (76 to 83)	73 (70 to 77)	6.0 (1.3 to 10.7) [0.0121]	82 (79 to 85)	8.6 (3.9 to 13.3) [0.0004]	80 (76 to 83)	72 (69 to 75)	7.5 (2.8 to 12.2) [0.0019]
Total cholesterol (mmol/L)	45 (4.3 to 4.8)	47 (4.4 to 4.9)	-0.2 (-0.5 to 0.2) [0.3917]	4.3 (4.0 to 4.5)	-0.5 (-0.9 to -0.1) [0.0078]	4.2 (4.0 to 4.5)	4.5 (4.2 to 4.8)	-0.3 (-0.7 to 0.1) [0.1157]
HDL (mmol/L)	1.3 (1.2 to 1.4)	1.3 (1.2 to 1.4)	0.02 (-0.1 to 0.2) [0.7101]	1.3 (1.2 to 1.4)	-0.1 (-0.2 to 0.1) [0.3432]	1.3 (1.2 to 1.4)	1.3 (1.2 to 1.4)	0.03 (-0.1 to 0.2) [0.7101]
LDL (mmol/L)	2.7 (2.5 to 2.9)	2.8 (2.6 to 3.0)	-0.1 (-0.5 to 0.2) [0.4309]	2.5 (2.2 to 2.7)	-0.4 (-0.7 to -0.1) [0.0233]	2.4 (2.2 to 2.7)	2.7 (2.5 to 3.0)	-0.3 (-0.6 to 0.1) [0.1074]
VLDL (mmol/L)	0.5 (0.5 to 0.6)	0.6 (0.5 to 0.7)	-0.1 (-0.2 to 0.1) [0.2887]	0.5 (0.4 to 0.6)	-0.04 (-0.2 to 0.1) [0.5207]	0.5 (0.4 to 0.5)	0.5 (0.4 to 0.6)	-0.1 (-0.2 to 0.1) [0.3354]
Triglycerides (mmol/L)	1.2 (1.0 to 1.3)	1.3 (1.1 to 1.5)	-0.1 (-0.4 to 0.1) [0.3273]	1.2 (1.0 to 1.3)	-0.1 (-0.3 to 0.2) [0.5950]	1.0 (0.8 to 1.2)	1.1 (1.0 to 1.3)	-0.1 (-0.4 to 0.1) [0.3626]

Data are mean (95% CI) or mean (95% CI) [p value] for between-group differences. Hypoglycaemia was defined as ≤ 3.9 mmol/L, near normoglycaemia as 4.0–9 mmol/L and hyperglycaemia as ≥ 10.0 mmol/L. MAGE=mean amplitude of glycaemic excursions. CONGA_{60 min}=continuous overall net glycaemic action (60 min).

Table 2: Primary and secondary outcomes.

This trial is registered with ClinicalTrials.gov, number NCT01612468.

Role of the funding source

The funder provided an unrestricted research grant and supplied the identical liraglutide and placebo pens for the trial, but had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The data are owned by the investigators, and the corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We assessed 742 patients with type 1 diabetes for eligibility to enter the study (figure 1), of which 24 patients did not meet inclusion criteria, 618 declined the invitation, and 100 agreed to participate. We identified no differences in baseline characteristics with respect to sex, age, disease duration, HbA_{1c}, cholesterol, blood pressure, and BMI between individuals who did or did not agree to participate. From July 10, 2012, to May 30, 2014, participants were randomly assigned 50 to receive liraglutide and 50 to receive placebo. During the 24 weeks of intervention, four patients assigned to receive liraglutide discontinued the trial: three patients withdrew because of treatment-related gastrointestinal adverse events (one patient after 3 weeks and two patients after 12 weeks) and one because of a protocol violation (after 12 weeks). Six patients assigned to receive placebo discontinued the trial: four patients withdrew consent because of missing treatment effect (one patient after 3 weeks and three patients after 12 weeks), one discontinued because of an allergic reaction not related to the assigned treatment (after 3 weeks), and one discontinued because of nausea (after 3 weeks). All 100 patients were included in the efficacy analysis. Baseline characteristics were similar between groups except for diabetes duration, which was longer in patients assigned to receive placebo, although both groups had a long duration of type 1 diabetes (table 1). Additionally, more patients randomly assigned to liraglutide were treated with glargine than with detemir compared with the patients who received placebo.

After 24 weeks of treatment, HbA_{1c} fell in both the liraglutide and placebo groups, but there were no significant differences between groups (table 2). However, at 12 weeks of treatment, the difference between groups was significant ($p=0.0073$), in favour of liraglutide (figure 2).

In the SMBG analysis, significantly fewer episodes of biochemically verified hypoglycaemia were reported in the liraglutide group compared with placebo. During 26 weeks (hypoglycaemia events were recorded from the time of informed consent, which was two weeks prior to randomisation), 736 events (0.010 events/patient/day) occurred in the liraglutide group (incidence rate (IR) 0.61) and 884 events (0.015 events/patient/day) occurred

in the placebo group (IR 0.75), giving an IRR of 0.81 (95% CI 0.74 to 0.90). However, during the three 6 day CGM periods, we detected no significant differences between groups in time spent in hypoglycaemia, near-normoglycaemia, or hyperglycaemia (table 2). Furthermore, glycaemic variability, estimated as the MAGE, CONGA_{60 min}, and SD of mean glucose, did not differ between groups at any timepoint (table 2)

After 24 weeks of treatment, bodyweight decreased with liraglutide, but remained unchanged with placebo. The difference between groups at the end of treatment was -6.8 kg (95% CI -12.2 to -1.4 ; $p=0.0145$; figure 3 and table 2). We detected no association between bodyweight at baseline and change in bodyweight during the trial ($p=0.1760$).

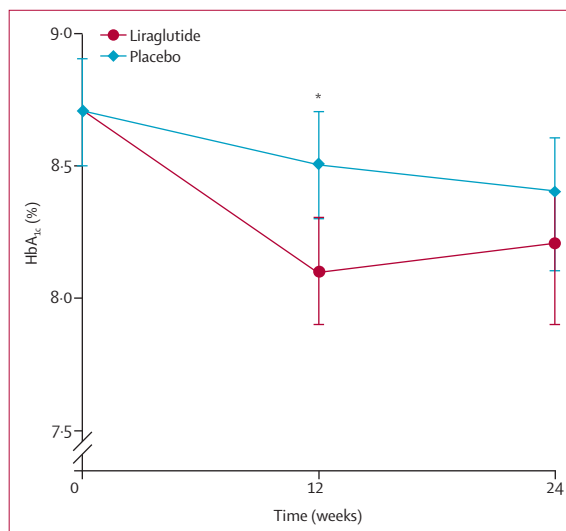


Figure 2: HbA_{1c}

Data are mean (95% CI). HbA_{1c} (mmol/mol) = (10.93 × HbA_{1c} [%]) - 23.5. * $p<0.05$.

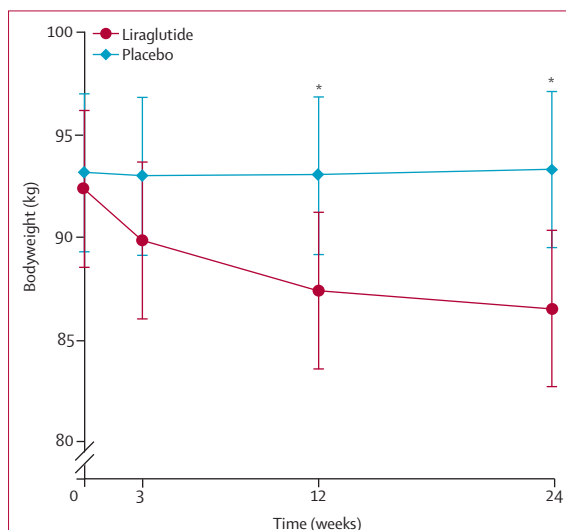


Figure 3: Bodyweight

Data are mean (95% CI). * $p<0.05$.

The insulin dose was increased during the 24 week trial period in both groups because of insufficient glycaemic control before study entry (table 2). However, after 3 weeks of treatment, the bolus insulin dose was significantly lower in the liraglutide group than in the placebo group. The difference between groups was sustained throughout the trial, corresponding to a difference of 21·3% at week 24. At 24 weeks, the difference between basal insulin dose for patients who received liraglutide and those who received placebo was 16·5%. When adjusted for bodyweight, we detected no significant differences in insulin doses at any timepoint

(table 2 and appendix p 3). Neither GAD nor C-peptide status affected the response to treatment in terms of HbA_{1c}, insulin dose, hypoglycaemic events, or weight.

We used a gastric emptying test to assess postprandial plasma concentrations of glucose, glucagon, and GLP-1, and gastric emptying (table 3, appendix). Fasting plasma glucose values were similar between groups at baseline, after 3 weeks, and after 24 weeks of treatment (table 3). We detected no treatment effect of liraglutide on the postprandial responses (ie, total AUC_{0-240 min}) of plasma glucose, glucagon, or GLP-1, but we noted that postprandial glucose and glucagon in both groups

	Randomisation			Week 3			Week 24		
	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo
Fasting plasma glucose (mmol/L)	13·0 (10·5 to 15·5)	14·4 (12·7 to 16·2)	-1·4 (-4·4 to 1·5) [0·3303]	11·3 (9·2 to 13·3)	12·4 (10·5 to 14·4)	-1·2 (-3·9 to 1·6) [0·3956]	11·3 (9·2 to 13·3)	12·4 (10·5 to 14·4)	-1·6 (-3·8 to 2·5) [0·6734]
Total AUC _{0-240 min} (mmol/L per 240 min)									
Postprandial plasma glucose	4208 (3800 to 4616)	4684 (4251 to 5117)	-476 (-1071 to 119) [0·1152]	3987 (3579 to 4395)	4311 (3878 to 4744)	-324 (-919 to 271) [0·2815]	3668 (3259 to 4076)	3942 (3509 to 4375)	-275 (-870 to 320) [0·3606]
Glucagon	2382 (2017 to 2748)	2583 (2195 to 2970)	-200 (-733 to 332) [0·4540]	2031 (1665 to 2397)	2310 (1922 to 2697)	-279 (-812 to 254) [0·2990]	1872 (1507 to 2238)	2280 (1892 to 2668)	-408 (-941 to 125) [0·1309]
GLP-1	3914 (3388 to 4441)	3786 (3228 to 4344)	129 (-639 to 896) [0·7387]	3288 (2762 to 3814)	3434 (2876 to 3992)	-146 (-913 to 621) [0·7050]	3290 (2764 to 3817)	3557 (2999 to 4115)	-266 (-1034 to 501) [0·4899]
Plasma paracetamol	17·6 (15·9 to 19·2)	15·9 (14·1 to 17·7)	1·7 (-0·8 to 4·1) [0·1750]	18·3 (16·7 to 20·0)	15·7 (13·9 to 17·4)	2·7 (0·2 to 5·1) [0·0332]	18·5 (16·8 to 20·1)	15·4 (13·6 to 17·2)	3·1 (0·6 to 5·5) [0·0152]
Plasma paracetamol time to peak (min)	95·0 (81·9 to 108·1)	79·1 (65·2 to 92·9)	15·9 (-3·1 to 35·0) [0·1002]	103·3 (90·2 to 116·4)	83·4 (69·6 to 97·3)	19·9 (0·8 to 39·0) [0·0412]	84·2 (71·1 to 97·3)	85·6 (71·7 to 99·5)	-1·5 (-20·5 to 17·6) [0·8793]

Data are mean (95% CI) or mean (95% CI) [p value] for between-group differences. AUC=area under the curve.

Table 3: Meal test results

	Randomisation			Week 3			Week 24		
	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo	Liraglutide	Placebo	Liraglutide vs placebo
DTSQs score									
Treatment Satisfaction scale total	27·3 (25·7 to 28·9)	26·6 (25·1 to 28·2)	0·7 (-1·6 to 2·9) [0·5663]	29·4 (27·8 to 31·0)	28·2 (26·7 to 29·8)	1·1 (-1·1 to 3·4) [0·3135]	29·9 (28·2 to 31·5)	29·8 (28·1 to 31·4)	0·1 (-2·2 to 2·5) [0·9265]
Perceived frequency of hyperglycaemia	3·5 (3·1 to 3·9)	3·8 (3·4 to 4·2)	-0·2 (-0·8 to 0·3) [0·4307]	2·9 (2·5 to 3·3)	3·4 (3·0 to 3·8)	-0·6 (-1·1 to 0·003) [0·0512]	3·0 (2·6 to 3·4)	3·2 (2·8 to 3·6)	-0·2 (-0·8 to 0·4) [0·5914]
Perceived frequency of hypoglycaemia	1·9 (1·6 to 2·3)	1·9 (1·6 to 2·3)	0·03 (-0·5 to 0·5) [0·9163]	1·9 (1·6 to 2·3)	1·7 (1·3 to 2·1)	0·2 (-0·3 to 0·7) [0·4073]	1·7 (1·3 to 2·1)	2·3 (1·9 to 2·7)	-0·6 (-1·1 to -0·07) [0·0257]
PAID score	24·5 (19·9 to 29·1)	24·2 (19·5 to 28·9)	0·3 (-6·3 to 6·9) [0·9258]	19·7 (15·1 to 24·4)	21·8 (17·1 to 26·4)	-2·1 (-8·6 to 4·5) [0·5372]	20·7 (15·9 to 25·4)	23·1 (18·3 to 27·9)	-2·4 (-9·1 to 4·3) [0·4797]

Data are mean (95% CI) or mean (95% CI) [p value] for between-group differences. DTSQs=Diabetes Treatment and Satisfaction Questionnaire version s. PAID=Problem Areas In Diabetes.

Table 4: Patient-reported outcome measures

decreased significantly with time. Gastric emptying of the meal (total AUC_{0-240min} for plasma paracetamol) did not differ at baseline, but was significantly affected by liraglutide treatment. Total AUC_{0-240min} increased in patients who received liraglutide, and significant differences existed between groups after 3 weeks and 24 weeks of treatment. Time-to-peak of plasma paracetamol was initially shorter in patients who received placebo than in those who received liraglutide and, at 3 weeks of treatment, we noted that gastric emptying was significantly slower for patients treated with liraglutide than for those treated with placebo (table 3 and appendix p 3). Although emptying seemed to be faster with placebo, even at baseline, there was no significant difference between groups, except at 3 weeks of treatment (table 3).

Systolic blood pressure decreased in patients who received liraglutide, but did not change in patients who received placebo after 24 weeks of treatment (table 2). Diastolic blood pressure did not change with time and did not differ between groups (table 2). In patients receiving liraglutide, ambulatory heart rate increased from baseline to week 24. In patients who received placebo, heart rate decreased from baseline to week 24. Differences between groups were significant at weeks 3, 12, and 24 (table 2).

After 12 weeks, total cholesterol differed significantly between groups (table 2). However, after 24 weeks, the difference between groups was no longer significant. LDL cholesterol, triacylglycerol, and VLDL cholesterol did not differ between groups at any timepoints (table 2). We noted a significant reduction during the intervention in the liraglutide-treated patients for LDL cholesterol (-0.3 mmol/L, 95% CI -0.4 to -0.1 , $p=0.0131$), triglycerides (-0.2 mmol/L, 95% CI -0.3 to -0.02 , $p=0.0259$), and VLDL cholesterol (-0.1 mmol/L, -0.3 to -0.02 , $p=0.0141$). For the placebo-treated patients, only VLDL cholesterol changed with time (-0.1 mmol/L, -0.001 to -0.2 , $p=0.0481$). HDL cholesterol did not change over time in any of the groups.

Total treatment satisfaction scores as assessed with DTSQs improved in both groups during the trial (table 4). DTSQs did not differ between groups at any timepoint. Perceived frequency of hyperglycaemia decreased in both groups during the trial, with no differences between groups at any timepoint. Perceived frequency of hypoglycaemia was significantly different between groups at the end of treatment, because of increased perceived frequency of “unacceptable” low blood glucose events in patients who received placebo (table 3).

In patients who received liraglutide, PAID scores decreased significantly with time, suggesting that fewer problems were perceived as being associated with diabetes. The difference in PAID scores of patients who received liraglutide between randomisation and the end of treatment was 3.8 (95% CI 0.5 to 7.1; $p=0.0225$), whereas we detected no significant change with placebo (difference of 1.1, 95% CI -2.2 to 4.4, $p=0.5042$).

	Liraglutide (n=50)	Placebo (n=50)
≥1 adverse event*	45 (90%)	23 (46%)
Nausea	29 (58%)	5 (10%)
Dyspepsia	11 (22%)	1 (2%)
Diarrhoea	10 (20%)	1 (2%)
Decreased appetite	7 (14%)	0
Vomiting	7 (14%)	1 (2%)
Constipation	3 (6%)	1 (2%)
Allergic reaction not related to investigational medicinal product	3 (6%)	3 (6%)
Upper respiratory-tract infection	4 (8%)	4 (8%)
Pneumonia	2 (4%)	3 (6%)
Influenza	2 (4%)	3 (6%)
Dizziness	2 (4%)	2 (4%)
Headache	2 (4%)	2 (4%)
Vitamin D deficiency	1 (2%)	1 (2%)
Injection-site erythema	1 (2%)	1 (2%)
Herpes labialis infection	1 (2%)	1 (2%)
Tachycardia	0	2 (4%)
≥1 serious adverse events	3 (6%)	2 (4%)
Pneumonia	2 (4%)	0
Atrial fibrillation	1 (2%)	0
Multiple sclerosis	0	1 (2%)
Severe hypoglycaemia	0	1 (2%)

*Hypoglycaemia events are described separately.

Table 5: Adverse events

However, the groups did not significantly differ at any timepoints (table 4).

Liraglutide and placebo were both well tolerated (table 5). Gastrointestinal adverse events (eg, nausea, dyspepsia, and vomiting) were more common in the liraglutide group than in the placebo group. Although gastrointestinal adverse events were transient, seven patients who received liraglutide had their dose temporarily reduced to 1.2 mg per day shortly after escalation of the dose to 1.8 mg per day (range 3–35 days). Two patients were unable to tolerate 1.8 mg per day and completed the trial on 1.2 mg per day. Five severe adverse events occurred (three in the liraglutide group vs two in the placebo group), including one case of severe hypoglycaemia, which occurred in a patient who received placebo (table 5).

Discussion

Our findings show that liraglutide plus insulin had no significant effect on HbA_{1c} compared with placebo plus insulin after 24 weeks of treatment. However, patients receiving liraglutide had significantly reduced bodyweight and total daily and bolus insulin doses, although the weight-adjusted changes in total and bolus insulin doses were not significant. In the liraglutide group, fewer episodes of SMBG-verified hypoglycaemia occurred than in the placebo group. Gastric emptying

was delayed with liraglutide treatment at 3 weeks, but we identified no effect of liraglutide on plasma glucagon or GLP-1 concentrations. Adverse events were mild, mostly gastrointestinal, and were more frequent in patients who received liraglutide than in those who received placebo, with transient nausea being the most common event.

So far, seven studies have assessed the addition of a GLP-1 receptor agonist to insulin treatment for type 1 diabetes.^{10–16} The results of these studies differ in terms of glycaemic control, as measured by HbA_{1c}. Four non-placebo-controlled studies have reported reductions in HbA_{1c} of 4–9 mmol/mol during 10 to 24 weeks of treatment, compared with insulin alone.^{11,13,15,16} Three other studies reported similar improvements in HbA_{1c} during 4 to 26 weeks of treatment with either insulin alone, or with concomitant insulin and GLP-1 receptor agonist treatment.^{12,14,22} Notably, none of the previous studies had a randomised, double-blind, placebo-controlled design.

In our study, the similar effect on HbA_{1c} in the two groups after 24 weeks of treatment might be a result of the study design. We treated patients' blood glucose towards a target in accordance with clinical guidelines, although without the intensive monitoring done in a classic treat-to-target design. Thus, the treatment effect in our study is shown in terms of reduced insulin doses in the liraglutide group, rather than in reductions in HbA_{1c}. However, when adjusted for weight the differences in bolus and total insulin dose were no longer significant. Although we accept that our treat-to-target approach to insulin titration might have some limitations, we nevertheless consider the present design as being close to the potential future real-world daily clinical use of liraglutide.

Bodyweight decreased progressively with time in patients with type 1 diabetes who received liraglutide, in accordance with the findings of the scientific literature about GLP-1 receptor agonist treatment in type 1 diabetes.^{10–14,16,22} We detected a reduction in bodyweight of 6.4%, which is likely to be important to most patients with type 1 diabetes.⁴ Weight loss, in combination with unaltered or improved glycaemic control, has been reported to improve quality of life,²³ improve insulin sensitivity,²⁴ and reduce cardiovascular risk factors for patients with type 1 diabetes.²⁵

Findings from previous studies of GLP-1 receptor agonist therapy in type 1 diabetes have consistently shown reductions in total, basal, and bolus insulin doses.^{11–14,16} Our results are consistent with these findings, although both groups needed more insulin than was given at randomisation to improve glycaemic control. We judged this need for an increase to be a consequence of insufficient glycaemic control before study entry, and the absence of a run-in period in the study design.

The frequency of SMBG-verified hypoglycaemic events decreased in patients who received liraglutide, whereas the CGM findings showed no differences

between groups in time spent in hypoglycaemia, near-normoglycaemia, or hyperglycaemia. However, the CGM was done three times for 6 consecutive days, which is a short time period compared with the 24 week intervention. Additionally, food intake and exercise were not standardised during the CGM period, which could affect the overall results. In analysis of CGM data, we expected that a delay in gastric emptying, combined with suppression of postprandial glucagon secretion, would decrease glycaemic fluctuations. However, we detected no changes in glycaemic variability, which have been reported in other studies of GLP-1 receptor agonists for type 1 diabetes.^{12,16} One reason for substituting part of the insulin dose for a GLP-1 receptor agonist for the treatment of type 1 diabetes is to suppress glucagon secretion, which was reported in a previous study.¹² However, both GLP-1 receptor agonist and insulin suppress glucagon secretion, and as a consequence of the increased insulin dose, it may be difficult to detect an additional suppressive effect of liraglutide.

We only included overweight or obese patients in this study. We have also done a randomised, placebo-controlled, double-blind trial to investigate the efficacy and safety of 1.2 mg liraglutide once per day as an add-on to insulin in normal weight adults with inadequately controlled type 1 diabetes.²⁶ In that study, during 12 weeks of intervention, we saw no additional effect of liraglutide therapy on HbA_{1c}, but we did detect a significant reduction in bodyweight and insulin requirements in patients who received liraglutide compared with those who received placebo. These results are in accordance with those of our present study, and we speculate that the effect on glycaemic endpoints does not differ significantly between 1.2 mg and 1.8 mg liraglutide in lean and obese patients, respectively. However, as previously described, 1.8 mg liraglutide seems to reduce bodyweight more than does 1.2 mg.⁵

We chose liraglutide 1.8 mg, the highest dose approved for the treatment of type 2 diabetes, to bring about the largest effect on both glycaemic outcomes and bodyweight. Previously, we have reported that the tolerability of liraglutide in type 1 diabetes is rather poor.¹² However, we anticipated that patients with a higher BMI would have greater tolerance than did the lean patients in the earlier study. In accordance with this increased tolerance, we had a very low drop-out rate in this study. In our study²⁶ of normal-weight patients, two (10%) of 20 patients treated with liraglutide dropped out of the study, compared with four (8%) of 50 patients in the present study.

In type 2 diabetes, the addition of a GLP-1 receptor agonist to normal therapy has been reported to improve patient-reported outcomes in clinical trials.²⁷ In type 1 diabetes there is a little evidence for this effect. In the present trial, patient-reported overall treatment satisfaction improved in both the liraglutide and placebo groups, with reduced perceived frequency of both hyperglycaemia and hypoglycaemia. We only identified a

difference between groups with respect to the perceived frequency of hypoglycaemia after 24 weeks of treatment. Furthermore, scores on the PAID questionnaire decreased during the trial in both groups, showing fewer problems being perceived to be associated with diabetes. We speculate that this reduction is a consequence of the patients participating in a clinical trial, whereby increased focus on both the patient and their diabetes compared with normal care led to improved treatment satisfaction in both the liraglutide and placebo groups. This effect, combined with a natural tendency to report satisfaction with the current treatment to make the best of the situation (ceiling effect)²⁸ means that detection of a difference between groups might be difficult. The fact that only DTSQs was used with PAID is a limitation of the trial. We would be interested to also assess the DTSQ change version (DTSQc), because it assesses the current treatment in relation to the previous treatment, rather than the overall treatment satisfaction.

Another limitation of this trial is that the randomisation was done with fixed-size blocks of four, which could make the allocation of patients predictable to some extent, and might result in selection bias. Nevertheless, the study was double blinded and the investigators were not involved in the randomisation. A strength of the study was the randomised, placebo-controlled, double-blind design, which, combined with the long duration of intervention (24 weeks), gave us the opportunity to examine long-term efficacy outcomes. In this study we used a liquid mixed meal test to evaluate on postprandial glucose, GLP-1, glucagon and gastric emptying rate. To investigate postprandial glucose it would probably have been more correct to use a solid meal to imitate a real life situation. However, the liquid meal gave us the opportunity to test for gastric emptying rate in a setting where the scintigraphic method was not available.

Within both groups, there were more men than women, so we did an exploratory post-hoc adjustment of the primary and secondary outcomes for sex. For HbA_{1c} we noted that the women assigned to placebo had a higher HbA_{1c} at baseline and responded less to the treatment compared with the rest of the participants. As a consequence, when we compared the subgroups of women assigned to either liraglutide or placebo, the difference in HbA_{1c} between groups at end of treatment was larger than in the unadjusted analysis ($p=0.0680$). When we compared the subgroups of only men assigned to either liraglutide or placebo, we did not find any significant difference between groups at any timepoint. We searched the scientific literature and did not find any evidence that sex should have an effect on the efficacy of liraglutide. Accordingly, we deemed this finding to be a statistical coincidence in a small group of patients.

In total, 742 patients with type 1 diabetes were invited, by letter, from outpatient clinics in the Capital Region of Copenhagen, to participate in a clinical trial with five visits that lasted for 6 months. Almost one in seven

patients agreed to participate, and were included in the study. This participation rate was as expected and as such, we do not consider it a limitation of the study.

In conclusion, treatment with liraglutide 1.8 mg once per day as an add-on to insulin in overweight patients with insufficiently controlled type 1 diabetes did not improve glycaemic control compared with insulin alone after 24 weeks of treatment. However, we identified a reduced risk of hypoglycaemia, reduction in insulin dose, and clinically significant weight loss in patients who received liraglutide. Thus, this study adds important information for both clinicians and treatment regulatory bodies. Because the improvement in HbA_{1c} seen with the addition of liraglutide to insulin is similar to that seen with insulin alone, and because treatment with liraglutide is associated with additional expense, we cannot currently recommend combined treatment for the general population with type 1 diabetes. We believe that larger well-designed trials to investigate the effects of short-acting GLP-1 receptor agonists are needed to improve knowledge about the therapeutic potentials of different GLP-1 receptor agonists. The potential effect of GLP-1 receptor agonist therapy in newly-diagnosed type 1 diabetes is also an area of major interest, and active research is ongoing on this subject.

Contributors

TFD, TSH, LT, TA, JJH, FKK, and HUA initiated and designed the trial. TFD, CSF, TSH, UP-B, SU, TJ, LT, SM, and HUA participated in the data collection. AKJ, TFD, and CSF did the statistical analysis. TFD wrote the first draft of the manuscript. All authors revised the manuscript for crucial intellectual content.

Declaration of interests

TFD and CSF have received research support and received lecture fees from Novo Nordisk. TSH, TA, and TJ own stock in Novo Nordisk. SU owns stock in Novo Nordisk and has received lecture fees from Novo Nordisk, AstraZeneca, Boehringer Ingelheim, and Amgen. UP-B has served on advisory boards for AstraZeneca, Bristol-Myers Squibb, and Novo Nordisk, and has received lecture fees from AstraZeneca, Bristol-Myers Squibb, Sanofi-Aventis and Novo Nordisk. JJH has consulted for Merck Sharp and Dome, Novo Nordisk and Roche. LT owns stock in Novo Nordisk, has received lecture fees, and consulted for Novo Nordisk. FKK has received lecture fees from AstraZeneca, Boehringer Ingelheim Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Company, Gilead Sciences, Merck Sharp & Dohme, Novo Nordisk, Ono Pharmaceuticals, Sanofi, and Zealand Pharma, has served on advisory boards of Eli Lilly, Bristol-Myers Squibb and AstraZeneca, Novo Nordisk and Zealand Pharma, has consulted for AstraZeneca, Gilead Sciences, Ono Pharmaceuticals, Novo Nordisk and Zealand Pharma, and has received research support from Sanofi. SM has served on advisory boards for Novartis Pharma, Novo Nordisk, Merck Sharp & Dome, Sanofi-Aventis, AstraZeneca, Johnson & Johnson, Roche, Mankind, Boehringer Ingelheim, Zealand, Eli Lilly, and Intarcia Therapeutics, and has received lecture fees from Novo Nordisk, Merck Sharp & Dome, AstraZeneca, Johnson and Johnson, Roche, Shering-Plough, Sanofi-Aventis, Novartis Pharma, Eli Lilly and Bristol-Myers Squibb. HUA owns stock in Novo Nordisk and has served on an advisory board for Abbott. AKJ declares no competing interests.

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