

Effect of liraglutide on physical performance in type 2 diabetes (LIPER2): A randomised, double-blind, controlled trial



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ABSTRACT

Preclinical studies and small clinical trials suggest that glucagon-like peptide 1 (GLP1) may have a positive effect on ventricular function. Liraglutide is a GLP1-analogue used in the treatment of type 2 diabetes.

LIPER2 is a phase IV, randomised, double-blind, placebo-controlled, parallel-design trial, assessing the effect of 6 months' liraglutide 1.8 mg/d on measures of cardiac function and physical performance in patients with type 2 diabetes.

A total of 30 patients with type 2 diabetes will be included, if their HbA1c is between 7 and 10% while on oral agents (including metformin if tolerated and not contraindicated), a maximum of 2 intermediate or long-acting insulin injections per day or a combination of both.

After their baseline examinations, patients are randomised to receive a daily subcutaneous liraglutide or placebo injection (titrated to 1.8 mg/d if tolerated) for 6 months.

The primary end-point is the maximal oxygen consumption during cycle ergometry at the end of the study period. Other end-points include distance covered during a 6-min walk test, left ventricular ejection fraction and other measures of ventricular systolic and diastolic functions assessed by echocardiography, heart rate, blood pressure, pro-brain natriuretic peptide, C-reactive protein, HbA1c, lipids, apolipoprotein B, body weight and waist girth. Safety end-points include adverse event reporting, blood count, kidney and liver function, amylase, lipase, electrolytes, calcitonin, CA19.9 and pregnancy test for fertile women.

At the time of this report, recruitment is still ongoing. Results are expected to be reported in December 2016.

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Abbreviations: LIPER2, Liraglutide and physical PERFORMANCE in type 2 diabetes; T2D, Type 2 diabetes mellitus; GLP1, glucagon-like peptide 1; DPP4, dipeptidyl peptidase 4; VO2 máx, maximal oxygen consumption.

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1. Introduction

Glucagon-like peptide 1 (GLP1) analogues have been incorporated as a treatment possibility for type 2 diabetes (T2D), based on their insulin-secreting effects and associated moderate weight-loss

[1]. However, other effects of GLP1-based therapies have also been described. In fact, cardiovascular actions are of major potential interest, since they may have a big impact on patient prognosis.

GLP1 receptors are present both in the heart and in the autonomous nervous system. GLP1 receptor knock-out mice show reduced resting heart rate and increased ventricular thickness [2]. Indeed, in some animal models of dilated cardiomyopathy and myocardial ischaemia, GLP1 improves left ventricular function [3,4]. Studies in humans are scarce so far and their results are controversial. Two small, randomised, controlled trials showed that acute GLP1 infusion prevented post-angioplasty stunning [5] and improved left ventricular ejection fraction after dobutamide injection in patients with ischaemic heart disease [6]. However, these results were not replicated in non-diabetic subjects with chronic heart failure [7]. A larger trial, analysing 105 patients undergoing primary percutaneous coronary intervention for an ST-segment elevation acute myocardial infarction, showed no effects of intravenous exenatide, a GLP1 analogue, on left ventricular ejection fraction at 3 months or on final infarct size [8]. Furthermore, a trial assessing the dipeptidyl peptidase 4 (DPP4) inhibitor saxagliptin, which delays the degradation of GLP1, showed an increase in hospital admissions due to heart failure [9]. This was not the case, however, with the DPP4 inhibitor sitagliptin [10] or the GLP1 analogue lixisenatide [11], which were not associated with any changes in the risk of cardiovascular events.

Thus, some, but not all, short-term studies assessing the effect of GLP-1 show improved ventricular function in non-diabetic patients with established heart disease. Although there are currently trials in progress, studies in patients with T2D receiving chronic treatment with GLP1 analogues are still scarce [4,12,13].

Liraglutide is a GLP1 receptor agonist approved for the treatment of T2D. Its use is associated with an improvement in some cardiovascular risk markers, such as brain natriuretic peptide, plasminogen activator inhibitor 1 [14] and fasting [15] and post-prandial triglyceridaemia [16] and a trial assessing cardiovascular events is ongoing [13].

2. Objectives and purpose

The aim of this trial is to assess the effect of liraglutide, a GLP1 agonist, on clinically relevant measures of myocardial function in patients with T2D.

3. Trial design

Randomised, placebo-controlled, double blind, parallel group, phase IV trial (see Fig. 1 and Table 1).

4. Study population: selection of subjects

A total of 30 subjects will be included for randomisation. They are identified and invited to participate in the outpatient clinics at the Endocrinology Department and at the primary care centres to which the hospital is the referral centre.

4.1. Inclusion criteria

To be included, the patients should have T2D, treated with oral agents (including metformin if tolerated and not contraindicated), a maximum of 2 intermediate or long acting insulin injections per day or a combination of both. With this treatment, their HbA1c should be between 7% and 10%, both included.

4.2. Exclusion criteria

The following criteria would preclude patients from participating: severe renal failure (estimated glomerular filtration rate <30 ml/min), liver failure (Child-Pugh score > 6 points), present or planned pregnancy or breastfeeding or inadequate contraception, intolerance or allergy to liraglutide, familial or personal history of medullary thyroid cancer or type 2 multiple endocrine neoplasia, personal history of pancreatitis, triglyceride concentrations above 500 mg/dl or alcohol intake >40 g/day, known active malignancy, treatment with GLP1 agonists or DPP4 inhibitors in the previous 3 months, known coronary artery disease with exercise-induced ischaemia, planned revascularisations in the following 6 months, severe symptoms of heart failure (NYHA class IV), impossibility to perform a cycle ergometry (osteoarthritis or other reasons) or factors potentially interfering with adherence to treatment or follow-up (according to the investigator's criteria).

4.3. Withdrawal of subjects

Participants will be withdrawn from the study at the 3-month visit, or as soon as the investigator receives notice, in case of fulfillment of any of the discontinuation criteria (see above). If the patient decides not to participate at any time after randomisation or is withdrawn from the study, follow-up visits will be attempted in order to obtain as complete information as possible, for intention-to-treat analysis and for safety assessment. Although a lower dropout is expected, power calculation takes into account a withdrawal rate of up to 25%. Thus, no replacement of withdrawn subjects is planned.

4.4. Study setting

Regardless of where patients are identified, study visits take place at the hospital. Participants are followed at the Endocrinology Department, whereas study procedures are also performed at the Cardiology (echocardiography) and Physical Medicine and Rehabilitation departments. Lab measurements are performed in the hospital's central laboratories.

5. Intervention

5.1. Dose titration and administration

Liraglutide (Victoza[®], Novo Nordisk) 1.2–1.8 mg/day will be given, as a daily, self-administered subcutaneous injection using a pre-filled injection pen containing 3 ml (18 mg). The aimed dose will be 1.8 mg/d, but 1.2 mg/d will be accepted if the higher dose is not tolerated. Participants will administer 0.6 mg/d during the first week, increase to 1.2 mg/d during the second week and to 1.8 mg/d during the third week. If gastrointestinal side-effects occur, the highest tolerated dose will be continued throughout the trial. The same will be applied for the presence of repeated hypoglycaemia in the absence of concomitant secretagogue/insulin treatment.

Patients will be assessed at a screening visit, after having received oral information and having signed a written informed consent. If they fulfill all of the inclusion criteria and none of the exclusion criteria, a baseline visit will be performed within one month of the screening visit and randomisation will proceed. Patients will initiate the assigned treatment and, after safety assessment at 3 months (12–16 weeks), will complete the 6 month treatment period (26 ± 2 weeks) before final assessment. Additional telephone contact will evaluate the need for treatment adjustment within the two weeks following treatment initiation.

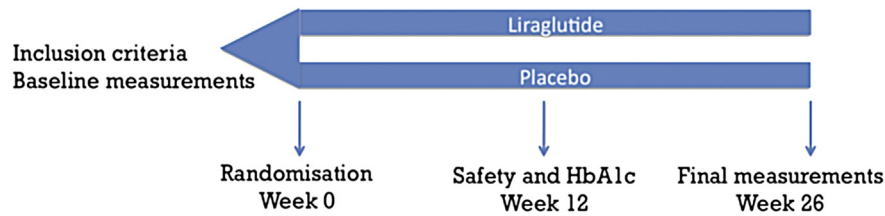


Fig. 1. Visit outline.

5.2. Concomitant treatment

Patients will be allowed to use any oral agents prescribed from the beginning of the trial, one being metformin (if well tolerated and not contraindicated). Patients should not receive DPP4 inhibitors or GLP1 agonists (liraglutide, exenatide) in the 3 months prior to randomisation or throughout the duration of the trial.

All patients will be instructed regarding lifestyle measures to optimise glycaemic control and, if already treated with insulin, on how to modify their insulin dose during the trial. Participants are warned about the possibility of hypoglycaemia at the start of the new treatment, especially if HbA1c is already close to 7%. In case of hypoglycaemia (or risk of hypoglycaemia, according to the investigator's criteria), the insulin or sulphonylurea dose may be reduced.

5.3. Rescue medication

In patients with an HbA1c above 8% at the 3-month visit despite adequate lifestyle measures, one dose of insulin may be started (at 0.1–0.2 ui/Kg, and adjusted to achieve morning/pre-dinner glycaemic concentrations between 70 and 130 mg/dl) in those not receiving insulin already. In those participants receiving insulin treatment already, its dose will be adjusted to achieve the mentioned glycaemic target. An additional intermediate or long-acting insulin injection may be prescribed if deemed necessary in those patients treated with one injection only. Concomitant oral agents will not be modified during the duration of the trial unless hypoglycaemia occurs.

5.4. Drug accountability

At each follow-up visit, participants will be asked about compliance with study drug and concomitant treatments. In addition, unused, half-full and empty injection pens will be

collected, counted and kept at the Hospital for monitoring and thereafter destroyed following standard procedures.

6. Outcomes

6.1. Primary end-point

The primary end-point will be fitness, or physical performance, defined as the maximal oxygen consumption (VO₂max; Breeze Suite 6.4, Medgraphics, Medical Graphics Corporation, Saint Paul, MN, USA) during a cycle ergometer test (Ergoselect, Ergoline, Bitz, Germany) performed at the end of the study. An incremental protocol is used, where the first 3 min are performed without resistance and the latter is then increased by 10–20 W/minute (adjusted according to weight, height, age and ethnicity). The total duration of the test rarely exceeds 10–12 min. Before the test is started, the procedure is described in detail and participants sign written informed consent. Cardiorespiratory fitness is determined during cycle ergometry using respiratory gas exchange analysis, which involves the direct, non-invasive measurement of ventilation and expired oxygen and carbon dioxide. It provides the most accurate and reproducible quantification of cardiorespiratory fitness, a grading of the etiology and severity of impairment, and an objective assessment of the response to intervention. Ergometry and VO₂ máx measurement are performed according to international guidelines [17]. Calibration is performed with a 3 L air-syringe, adjusting for ambient temperature and atmospheric pressure. Maximal exertion ergometry (HR > 85% theoretical maximum and RER > 1.10) is attempted and participants are encouraged to perform as well as they can.

All patients perform the test at the Rehabilitation and Physical Medicine Department, in the morning, on the same ergometre and supervised by the same staff (GM, CM) at baseline and at the end of the study. A neoprene mask is used as interface, tightly adjusted to the participant's face, to avoid air leakage. If the patient is feeling

Table 1
Visit description.

Visit	V0	V1	V2	V2a+b	V3	V4	V5
Time (weeks, range)	-2 (-5–(-1))	-1 (-3–0)	0	+1, +2	+14 (12–16)	+25 (24–26)	+26 (25–28)
Clinical history	X						
Physical examination	X						X
EuroQoL			X				X
Glycaemic control	X		X		X		X
Lab tests		X			X	X	
Pregnancy test		X			X	X	
Echocardiography		X				X	
6-min walking test		X				X	
Cycle ergometry		X				X	
Physical activity Holter		X				X	
Randomisation			X				
Drug dispensation			X		X		
Recovery of unused/used drug					X		X
Assessment of adverse events					X		X
Telephone follow-up					X		

unwell or not fit for the test, the latter is rescheduled. Unlike for treadmill ergometry, on cycle ergometry, power (watt) and VO₂ max measurements are direct, rather than estimated. Both tests are performed with the same resistance scheme and results are referred to theoretical standards (based on weight, height, age and ethnicity). Thus, the theoretical standards may change during the study if the participant's weight changes.

6.2. Secondary end-points

Secondary endpoints include additional fitness-related variables, to be recorded during the cycle ergometer test (blood pressure, pulse oxymetry, heart rate response, perceived exertion during exercise (Borg's scale) as well as time to exhaustion, anaerobic threshold (absolute and relative to VO₂max), maximal work load (watt), breakpoint of ventilatory equivalent of oxygen (VE/VO₂), breakpoint of ventilatory equivalent of carbon dioxide (VE/VCO₂), respiratory exchange ratio (RER), 1 and 3 min heart rate recovery and clinical and electrocardiographic ischaemia (CardioPerfect, Welch Allyn, Skaneateles Falls, NY, USA). We also determine absolute values of peak oxygen pulse (VO₂/HR) and the pattern of change of the values (early plateau, followed by decline or continuously ascending).

A 6 min walking test is performed following international guidelines [18] and the following variables are registered: distance covered, blood pressure, pulse oxymetry, heart rate response and perceived exertion.

Transthoracic echocardiography is carried out according to international guidelines [19] and the following parameters are assessed: left ventricular ejection fraction, systolic angular speed with tissular doppler image, myocardial performance index and diastolic function, classified according to international echocardiography recommendations [20].

Glycaemic control is assessed using HbA1c, measured by HPLC, using a NGSP/DCCT-based standard, and examining the patients' glucose registers, as well as questioning them about hypoglycaemic episodes (see below), daily insulin dose and other concomitant medication. Endogenous insulin production is assessed by fasting C-Peptide (chemoluminescence). Anthropometric parameters (height, weight, waist girth) are also recorded. Other laboratory measurements are performed using routine, automatic methods. They include: lipids, apolipoprotein B, C-reactive protein (turbidimetry) and pro-brain natriuretic peptide (NT-pro-BNP). The hospital's laboratory has been certified by the Spanish Society of Clinical Biochemistry and Molecular Pathology (SEQC, Barcelona, Spain).

Quality of life is assessed using a validated questionnaire, available in Spanish, and its Visual Analogue Scale (*Spain (Spanish) v.2  2009. EQ-5D-5L, EuroQoL Foundation, Rotterdam, The Netherlands*).

Spontaneous physical activity is recorded using a physical activity Holter (SenseWear Pro, BodyMedia, Pittsburgh, PA, USA) for three days: number of steps, time spent on exercise >3 METs and energy consumption (Calories) per 24 h are registered.

The primary and secondary endpoints will be assessed at baseline and at the end of the study (6 months), except those related to glucose control, which will be evaluated at the 3 months visit, too.

6.3. Safety end-points

The safety end-points include adverse event (AE) reporting, blood count, liver and kidney function, electrolytes, lipase, amylase, CA19.9 and calcitonin. A general physical examination is performed at baseline and at the end of the study. A pregnancy test is

performed on all women with childbearing potential before randomisation and during follow-up (visits 3 and 5). Pregnancy will not be considered an adverse event but study drug will be interrupted and the patient closely monitored until 6 months after delivery. Pregnancies will be reported to the local EC, the Spanish National Drug Agency and the manufacturer.

Patients are specifically asked at each visit about AEs and each one is registered in a standardised manner, where severity (mild, moderate, severe), outcome, potential causality relationship (unlikely, possible, probable) and action taken are recorded. In addition, at baseline and at each follow-up visit, hypoglycaemic events are assessed and recorded as referred by the patients or recorded in their diary. Hypoglycaemia is defined as capillary blood glucose concentrations below 60 mg/dl, with or without symptoms or symptoms suggestive of hypoglycaemia, which resolve after treatment, even if no blood glucose measurement is performed. Severe hypoglycaemia is identified separately and defined as an episode of hypoglycaemia, which needs external assistance to be solved.

In addition, at the end of the study, an endoscopic ultrasound is offered to the patients, in order to assess pancreatic architecture. A separate, standard consent form is provided and signed before the examination.

7. Statistical considerations

7.1. Sample size

Based on a previous study in patients with T2D performing an exercise test on a treadmill [21], we assumed a mean between 29.5 and 37.7 ml/kg*min and a standard deviation of 3.5 ml/kg*min in VO₂max, similar in both intervention groups. Training programmes in older men increase VO₂ max by 16–45% [22], which would correspond to an absolute change of 5–14 ml/kg*min, approximately. Including 15 patients per group would allow the detection of a difference between groups of 5 ml/kg*min in VO₂max with 98% power and bilateral alpha of 5%. Even in the event of an unexpectedly high drop-out rate of 25%, the power to detect this difference between groups would be of 90%. Given the high correlation between cycle and treadmill ergometry [23] and the lack of sufficient data on cycle ergometry in T2D, we assumed that these calculations are applicable to the described trial.

7.2. Statistical analyses

Analysis will be performed on an intention-to-treat and per-protocol basis. The intention-to-treat population will be defined as those patients who have been randomised, regardless of treatment adherence or follow-up. In the absence of complete follow-up data, the "last observation carry-forward method" will be used. This should be conservative enough, since, for most of the measurements, only baseline and 6-month results will be available. In case of missing follow-up, baseline measurements would be carried over. For "per protocol" analysis, only those subjects who have completed treatment and follow-up will be included. Variables will be expressed as percentages (qualitative), as mean (SD) (quantitative, Gaussian distribution) or as median (range) (quantitative, non-Gaussian distribution). Comparison between the intervention and placebo groups will be performed using chi-squared (qualitative data), Student's T test (quantitative, Gaussian distribution) and Mann-Whitney's U (quantitative, non-Gaussian). ANCOVA analysis will be performed to adjust for age, gender, smoking and baseline VO₂max.

8. Blinding and randomisation

Both the active drug and the identically-looking placebo are provided by the manufacturer in pre-filled injection pens. Neither the patient nor the investigators are aware of the content of the injections. The manufacturer provided the computer-generated randomisation code and sent it to the unblinded pharmacist, who arranges study drug dispensation according to randomisation. A sealed, opaque envelope with the allocation sequence is kept in the investigator file, for use in case of emergency. Patients are enrolled and assigned consecutive numbers by the investigators and thereafter sent to the hospital pharmacy for treatment allocation, which is performed by sequentially revealing the assigned treatment kit number. The randomisation number is unique for each patient and constant for the duration of the trial.

9. Ethics considerations and compliance with guidelines and regulations

The study has been approved by the Ethics Committee of the Complejo Hospitalario Universitario Insular Materno Infantil and by the Spanish Medical Agency. Before inclusion, patients receive oral and written information about the study and a written, informed consent document is signed by each participant. The trial will be performed in compliance with the protocol and in accordance with the Declaration of Helsinki and the International Conference on Harmonisation of Good Clinical Practice.

Data accuracy and compliance with the protocol, with Good Clinical Practice International Guidelines and with national regulations is assessed by external, qualified staff from CRAnarias SL, Las Palmas de Gran Canaria, Spain. Monitoring includes personal visits and telephone communication. The monitoring staff have access to the case report forms and to the source data.

10. Funding

The LIPER2 trial was approved and funded by Novo Nordisk, Bagsvaerd, Denmark. The investigators designed and are conducting the study, will perform all study analyses and have written and are responsible for the contents of this manuscript.

The manufacturer will not interfere with collection, analysis, interpretation, writing, or publication of data. The principal investigator will have full access to all the data and the final responsibility for the decision to submit for publication. The results of the trial will be published regardless of whether they are positive or negative.

11. Study status

The first patient was recruited in June 2013. At the time of this report, 35 participants have been screened, 11 have been excluded after screening and 24 have been randomised. A total of 22 have finished the study. The last visit of the last patient is planned for August 2016 and the report of the results is expected by December 2016.

12. Discussion

Patients with T2D have an increased risk of cardiovascular disease, which is the main cause of death in this population. The identification of agents that not only lower blood glucose, but also improve cardiovascular prognosis, would be of great interest.

13. Conclusions

The LIPER2 trial assesses the effect of 6 months' treatment with liraglutide, as compared with placebo, on measures of physical performance and ventricular function in patients with T2D who have a baseline HbA1c between 7 and 10%.

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Clinical trials

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Sponsor and PI

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