Clinical trial results:
Effect of liraglutide on physical performance: a randomised, double-blind, controlled study in patiens with type 2 diabetes.

Summary

EudraCT number	2012-005197-63
Trial protocol	ES
Global end of trial date	31 August 2016

Results information

Result version number	v1 (current)
This version publication date	27 June 2022
First version publication date	27 June 2022

Trial information

Trial identification

Sponsor protocol code	U1111-1128-8762

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1128-8762

Notes:

Sponsors

Sponsor organisation name	Complejo Hospitalario Universitario Insular Materno-Infantil
Sponsor organisation address	Av Marítima s/n, Las Palmas, Spain, 35016
Public contact	David Valido, CRAnarias Investigación y Desarrollo, S.L., david.valido@cranarias.com
Scientific contact	Ana M Wägner, Complejo Hospitalario Universitario Insular Materno-Infantil, awagfah@gobiernodecanarias.org

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2016
Global end of trial reached?	Yes
Global end of trial date	31 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this trial is to assess the effect of a GLP1 agonist on clinically relevant measures of myocardial function.

Protection of trial subjects:

In patients with an HbA1c above 8% at the 3-month visit, one dose of insulin may be started (at 0.1-0.2 ui/Kg, and adjusted to achieve morning/pre-dinner glycaemic concentrations between 70-130mg/dl) in those not receiving insulin already, if lifestyle measures cannot be improved. 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.

Background therapy:

Metformin if tolerated and not contraindicated, a maximum of 2 intermediate-long acting insulin injections per day or a combination of both

Evidence for comparator:

Patients with type 2 diabetes with insufficient glycaemic control despite treatment with lifestyle measures, oral treatments including metformin and/or 1-2 intermediate or long-acting insulin injections.

Previous studies assessing the effects of GLP1 on heart function have been performed in patients with clinically significant ischaemia (Nikolaidis et al 2004, Read et al 2011). To our knowledge, no equivalent reports are available which have been performed in the average patient receiving GLP1 agonists.

Actual start date of recruitment	20 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	21
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited at one single centre, a university hospital, mostly from the Endocrinology outpatient clinic, if they fulfilled the inclusion criteria
Type 2 diabetes on oral agents (including metformin if tolerated and not contraindicated), a maximum of 2 intermediate-long acting insulin injections per day or a combination HbA1c 7-10%

Pre-assignment

Screening details:

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.

Period 1

Period 1 title	Study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Both the active drug and the identically-looking placebo were provided by Novo Nordisk in pre-filled injection pens. Neither the patient nor the investigators were aware of the content of the injections. Novo Nordisk sent the computer-generated randomisation code to the unblinded pharmacist and she arranged study drug dispensation according to randomisation. Sealed, sequentially numbered, opaque containers with information about the assigned treatment were provided by Novo Nordisk

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

Liraglutide 1.8 mg vs placebo administered once daily injection for 26 weeks.

Liraglutide 1.8 mg, will be administered subcutaneously, from a pre-filled, multidose, injection pen, containing 3 ml (18mg) of liraglutide at a concentration of 6mg/ml. The same volume of placebo, from an identical pre-filled, injection pen, will be administered to the control group.

Arm type	Experimental
Investigational medicinal product name	Liraglutide
Investigational medicinal product code	
Other name	Victoza
Pharmaceutical forms	Suspension for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Liraglutide 1.8 mg, administered subcutaneously, from a pre-filled, multidose, injection pen, containing 3 ml (18mg) of liraglutide at a concentration of 6mg/ml.

Arm title	Placebo

Arm description:

COntrol arm

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Identical to experimental group

Number of subjects in period 1	Intervention	Placebo
Started	12	12
Completed	11	10
Not completed	1	2
Adverse event, non-fatal	1	-
Fear of adverse events	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
Liraglutide 1.8 mg vs placebo administered once daily injection for 26 weeks. Liraglutide 1.8 mg, will be administered subcutaneously, from a pre-filled, multidose, injection pen, containing 3 ml (18mg) of liraglutide at a concentration of 6mg/ml. The same volume of placebo, from an identical pre-filled, injection pen, will be administered to the control group.	

Reporting group title	Placebo
Reporting group description:	
COntrol arm	

Reporting group values	Intervention	Placebo	Total
Number of subjects	12	12	24
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	53.2	52.6	
standard deviation	± 9.7	± 13.8	-
Gender categorical Units: Subjects			
Female	7	8	15
Male	5	4	9
VO2 max			
Primary outcome: maximal oxygen consumption.			
Units: ml/Kg/min			
arithmetic mean	16.96	15.88	
standard deviation	± 4.32	± 4.91	-

End points

End points reporting groups

Reporting group title	Intervention

Reporting group description:

Liraglutide 1.8 mg vs placebo administered once daily injection for 26 weeks.

Liraglutide 1.8 mg, will be administered subcutaneously, from a pre-filled, multidose, injection pen, containing 3 ml (18mg) of liraglutide at a concentration of 6mg/ml. The same volume of placebo, from an identical pre-filled, injection pen, will be administered to the control group.

Reporting group title	Placebo

Reporting group description:

COntrol arm

Primary: VO2 max

End point title	VO2 max

End point description:

The primary endpoint was physical fitness or performance as defined by maximum oxygen consumption (VO2max), using BreezeSuite 6.4 software (MGC Diagnostics Corporation, St Paul, MN, USA), during a cycle ergometer test (ergoselect, ergoline GmbH, Bitz, Germany) performed at the end of the study. An incremental protocol was used: the first 3 min were without resistance, but thereafter increased by 10–20 W/min. Total duration of the test rarely exceeded 10–12 min. Ergometry and VO2max measurements were performed according to international guidelines at our Rehabilitation and Physical Medicine Department at baseline and at the end of the study

End point type	Primary

End point timeframe:

6 months

End point values	Intervention	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: ml/min/Kg				
arithmetic mean (standard deviation)				
VO2max	17.98 (± 4.80)	15.90 (± 4.96)		

Statistical analyses

Statistical analysis title	Student's t

Statistical analysis description:

At the final external monitoring on completing the study, the treatment assignment list was opened by an individual external to the study, thereby allowing the two treatment groups to be separated for blinded analyses by study investigators. These were

performed on an intention-to-treat (ITT) and per-protocol (PP) basis, as described in the statistical plan (see publications for complete information)

Comparison groups	Intervention v Placebo
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months

Adverse event reporting additional description:

The occurrence of AEs sought and recorded at every visit during the study, though they may be detected when they are spontaneously referred by the patient, a laboratory test, or other assessments.
Adverse event reporting using Novo Nordisk standard forms.

Assessment type	Systematic

Dictionary used

Dictionary name	Non-specified
Dictionary version	1

Reporting groups

Reporting group title	Intervention

Reporting group description:

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Liraglutide 1.8 mg, will be administered subcutaneously, from a pre-filled, multidose, injection pen, containing 3 ml (18mg) of liraglutide at a concentration of 6mg/ml. The same volume of placebo, from an identical pre-filled, injection pen, will be administered to the control group.

Reporting group title	Placebo

Reporting group description:

COntrol arm

Serious adverse events	Intervention	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Intervention	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	7 / 12 (58.33%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 12 (8.33%)	2 / 12 (16.67%)	
occurrences (all)	1	2	
Gastrointestinal disorders			

Nausea, vomitting or diarrhoea			
subjects affected / exposed	12 / 12 (100.00%)	3 / 12 (25.00%)	
occurrences (all)	12	3	
Infections and infestations			
Upper respiratory tract infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 12 (25.00%)	2 / 12 (16.67%)	
occurrences (all)	3	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30223083

http://www.ncbi.nlm.nih.gov/pubmed/29736469