Clinical trial results:
Influence of liraglutide on diastolic cardiac function and myocardial perfusion as determined by magnetic resonance imaging in patients with type 2 diabetes: a double-blind randomized parallel-group trial

Summary

EudraCT number	2015-000410-22
Trial protocol	DK
Global end of trial date	31 December 2019

Results information

Result version number	v1 (current)
This version publication date	23 April 2021
First version publication date	23 April 2021

Trial information

Trial identification

Sponsor protocol code	U1111-1140-6242

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02655770
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Cardiovascular MR Group, Dept. 2011, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen Ø, Denmark, 2100
Public contact	Att: Niels Vejlstrup, The Cardiovascular MR Group, Dept. 2011, Rigshospitalet, +45 26114145, niels.vejlstrup@regionh.dk
Scientific contact	Att: Niels Vejlstrup, The Cardiovascular MR Group, Dept. 2011, Rigshospitalet, +45 26114145, niels.vejlstrup@regionh.dk

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	05 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to test if 18 weeks of treatment with liraglutide (up to 1.8 mg s.c. once daily) improves (or worsens) diastolic performance in T2DM patients with diastolic dysfunction, compared to placebo.

Protection of trial subjects:

Overall we aimed at minimizing the trial subjects pain and distress as much as possible

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	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)	23
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the Department of Endocrinology and Cardiology at NSR Hospital in Denmark between May 2016 and August 2019. Patients with type 2 diabetes were identified in the endocrinology or cardiology outpatient clinic by a nurse or a physician responsible for their treatment.

Pre-assignment

Screening details:

372 patients were invited to participate either by letter or in person. After written patient information about the study and information about patient’s rights, and if they expressed interest in participating in the study, pre-screening interviews by telephone were conducted. Forty-two eligible patients were invited to the first in-person screenin

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Liraglutide

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Victoza
Investigational medicinal product code	EU/1/09/529/001-005
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injection of 1.8 mg/per day

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1.8mg/day

Number of subjects in period 1	Liraglutide	Placebo
Started	20	20
Completed	20	19
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Liraglutide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Liraglutide	Placebo	Total
Number of subjects	20	20	40
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			
median	64	63	
inter-quartile range (Q1-Q3)	55 to 68	58 to 67	-
Gender categorical Units: Subjects			
Female	2	6	8
Male	18	14	32
Weight Units: kilogram(s)			
median	96	91	
inter-quartile range (Q1-Q3)	88 to 102	80 to 96	-
Body mass index Units: kilogram(s)/square meterm			
arithmetic mean	30.8	30.8	
standard deviation	± 4.5	± 5.1	-
Heart rate Units: beats per minut			
arithmetic mean	71	70	
standard deviation	± 11	± 11	-
Systolic blood pressure Units: mmHg			
median	133	134	
inter-quartile range (Q1-Q3)	129 to 138	126 to 140	-
Diastolic blood pressure Units: mmHg			

arithmetic mean	82	79	
standard deviation	± 7	± 11	-
Diabetes duration			
Units: Years			
median	9.5	5.5	
inter-quartile range (Q1-Q3)	4.8 to 13.5	2.0 to 14.5	-

End points

End points reporting groups

Reporting group title	Liraglutide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Early peak filling rate at rest

End point title	Early peak filling rate at rest
End point description:	
End point type	Primary
End point timeframe:	
18 weeks	

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mL/sec				
arithmetic mean (standard deviation)	-24 (± 60)	-6 (± 46)		

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53
upper limit	16

Primary: Early peak filling rate during stress

End point title	Early peak filling rate during stress

End point description:

End point type	Primary

End point timeframe:

18 weeks

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: mL/sec				
arithmetic mean (standard deviation)	2 (± 58)	-2 (± 38)		

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30
upper limit	37

Primary: LA passive emptying fraction at rest

End point title	LA passive emptying fraction at rest

End point description:

End point type	Primary

End point timeframe:

18 weeks change

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Precentage				
median (inter-quartile range (Q1-Q3))	-4.3 (-7.9 to 1.9)	-0.6 (-3.1 to 2.2)		

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.2
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	1.5

Primary: LA passive emptying fraction during stress

End point title	LA passive emptying fraction during stress

End point description:

End point type	Primary

End point timeframe:

18 weeks

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Precentage				
median (inter-quartile range (Q1-Q3))	-3.1 (-9.0 to 1.1)	1.0 (-2.9 to 6.1)		

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.049
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-4.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.98
upper limit	-0.07

Secondary: Average E/e'	
End point title	Average E/e'
End point description:	
End point type	Secondary
End point timeframe:	
18 weeks	

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Ratio				
median (inter-quartile range (Q1-Q3))	0.7 (-0.1 to 1.5)	0.1 (-1.3 to 2.4)		

Statistical analyses

Statistical analysis title	Treatment effect
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.6
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.9

Secondary: Myocardial perfusion index

End point title	Myocardial perfusion index

End point description:

End point type	Secondary

End point timeframe:

18 weeks

End point values	Liraglutide	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: noon unit				
median (inter-quartile range (Q1-Q3))	-0.41 (-0.71 to -0.15)	-0.15 (-0.22 to 0.28)		

Statistical analyses

Statistical analysis title	Mann-Whitney U test
Comparison groups	Liraglutide v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.74
upper limit	0.28

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
20 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	March 2021

Reporting groups	
Reporting group title	Liraglutide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Liraglutide	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Liraglutide	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 20 (80.00%)	14 / 20 (70.00%)	
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Angina pectoris			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	6 / 20 (30.00%)	3 / 20 (15.00%)	
occurrences (all)	6	3	
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
poor appetite			
subjects affected / exposed	6 / 20 (30.00%)	3 / 20 (15.00%)	
occurrences (all)	6	3	
Dry mouth			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	3 / 20 (15.00%)	1 / 20 (5.00%)	
occurrences (all)	3	1	
Blood glucose abnormal			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
emotionally labile			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
leucocytosis			

subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
meteorism			
subjects affected / exposed	2 / 20 (10.00%)	2 / 20 (10.00%)	
occurrences (all)	2	2	
Abdominal discomfort			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
pain of joint of knee			
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences (all)	0	1	
Dizzinesss			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Administration site discomfort			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
thoracic facet joint pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 20 (15.00%)	2 / 20 (10.00%)	
occurrences (all)	3	2	
Constipation			
subjects affected / exposed	1 / 20 (5.00%)	1 / 20 (5.00%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	2 / 20 (10.00%)	0 / 20 (0.00%)	
occurrences (all)	2	0	

heartburn subjects affected / exposed occurrences (all)	3 / 20 (15.00%) 3	0 / 20 (0.00%) 0	
Skin and subcutaneous tissue disorders Hot sweats subjects affected / exposed occurrences (all) Rash erythematous subjects affected / exposed occurrences (all)	 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1	 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0	
Endocrine disorders Hypoglycaemia subjects affected / exposed occurrences (all)	 2 / 20 (10.00%) 2	 3 / 20 (15.00%) 3	
Musculoskeletal and connective tissue disorders muscle cramp subjects affected / exposed occurrences (all)	 0 / 20 (0.00%) 0	 1 / 20 (5.00%) 1	
Infections and infestations acute nasopharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	 5 / 20 (25.00%) 5 0 / 20 (0.00%) 0	 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

MPRI was only analysable in 16 patients

Notes: