Clinical trial results:
Effects of the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin on left ventricular myocardial DYsfunction in patients with type 2 DiAbetes mellitus and concentric left ventricular geometry.

Summary

EudraCT number	2014-004683-38
Trial protocol	IT
Global end of trial date	01 April 2019

Results information

Result version number	v1 (current)
This version publication date	29 November 2021
First version publication date	29 November 2021

Trial information

Trial identification

Sponsor protocol code	G113

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02851745
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione per il Tuo cuore onlus
Sponsor organisation address	Via La Marmora, 36, Florence, Italy, 50121
Public contact	Centro Studi ANMCO, Fondazione per il Tuo cuore onlus, 0039 0555101359, centrostudi@anmco.it
Scientific contact	Centro Studi ANMCO, Fondazione per il Tuo cuore onlus, 0039 0555101359, centrostudi@anmco.it

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	19 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2019
Global end of trial reached?	Yes
Global end of trial date	01 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the effect of linagliptin 5 mg daily versus the corresponding placebo on the LV systolic function (measured by midwall shortening analysis) in patients with T2DM and a documented baseline concentric LV geometry and LV systolic dysfunction.

Protection of trial subjects:

The trial was conducted in accordance with the Helsinki Declaration and the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).
During the study were monitored pre-defined safety and tolerability end-points, all serious adverse events, the regular measurements of vital signs and laboratory parameters.
A specific surveillance was adopted on:
- symptomatic or severe hypoglycemia;
- severe pain in upper stomach spreading to back, nausea and vomiting, loss of appetite, fast heart rate (symptoms possibly related to pancreatitis);
- fever, sore throat, "runny nose", and headache with a severe blistering, peeling, and red skin rash
Specific attention was paid to patients at high risk, such as those are receiving insulin secretagogue and those with a history of pancreatitis.

Background therapy:

None

Evidence for comparator:

None

Actual start date of recruitment	23 July 2015
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	Italy: 188
Worldwide total number of subjects	188
EEA total number of subjects	188

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)	57
From 65 to 84 years	124
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

DYDA 2 enrollment was initiated on 23 July 2015 and terminated on 26 April 2018. A total of 14 Italian centres participated in the project.
The patients were followed-up for 48 weeks from random assignment. The follow-up was completed in April 2019

Pre-assignment

Screening details:

Patients with LV hypertrophy diagnosed by an ECG and/or a history of concentric LV geometry diagnosed by standard ECHO was asked to give their consent to participate to the study and to perform a complete transthoracic ColorDoppler echocardiographic examination and an ECG in order to verify if they fulfill all the inclusion criteria.

Period 1

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

Blinding implementation details:

The randomization scheme was accessible only to data analyst in a semi-blinded fashion, until the time of the unblinding for the analysis of results. Within the randomization system, the randomization numbers will be used to link the patient identification number to the correct drug medication number on the treatment packs. Only when the study was completed, the data file verified, and the protocol violations determined the drug codes was broken and made available for data analyses.

Arms

Are arms mutually exclusive?	Yes
Arm title	Linagliptin 5 mg

Arm description:

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide.

Arm type	Experimental
Investigational medicinal product name	Trajenta
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Linagliptin 5 mg was taken orally once daily.

Arm title	Placebo

Arm description:

Matching placebo tablets

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo was taken orally once daily. Placebo tablets was of identical appearance to those of the active drug.

Number of subjects in period 1	Linagliptin 5 mg	Placebo
Started	93	95
Completed	93	95

Baseline characteristics

Reporting groups	
Reporting group title	Linagliptin 5 mg
Reporting group description:	
Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets	

Reporting group values	Linagliptin 5 mg	Placebo	Total
Number of subjects	93	95	188
Age categorical			
Units: Subjects			
Adults (18-64 years)	31	26	57
From 65-84 years	59	65	124
85 years and over	3	4	7
Age continuous			
Units: years			
arithmetic mean	68	70	
standard deviation	± 9	± 8	-
Gender categorical			
Units: Subjects			
Female	39	44	83
Male	54	51	105
Obesity			
Obesity defined as BMI ≥30 kg/m2			
Units: Subjects			
Obesity	38	42	80
No obesity	55	53	108
Dyslipidemia			
Units: Subjects			
Dyslipidemia	67	72	139
No dislipidemia	26	23	49
History of hypertension			
Units: Subjects			
History of hypertension	71	83	154
No history of hypertension	22	12	34
LV hypertrophy			
LV hypertrophy is defined as LV mass index >=51 g/m^2.7 at baseline echocardiogram			
Units: Subjects			
LV hypertrophy	55	50	105
No LV hypertrophy	37	45	82
Unknown	1	0	1
MFS			
Midwall fractional shortening			
Units: percent			
arithmetic mean	13.2	13.5	

standard deviation	± 2.6	± 2.4	-
Ejection fraction			
Units: percent			
arithmetic mean	66.0	65.0	
standard deviation	± 7.6	± 8.5	-
Duration of diabetes			
Units: year			
median	8	7	
inter-quartile range (Q1-Q3)	4 to 12	3 to 12	-
HbA1c			
Units: percent			
arithmetic mean	6.4	6.5	
standard deviation	± 0.8	± 0.9	-
E/A ratio			
Units: ratio			
arithmetic mean	0.8	0.9	
standard deviation	± 0.2	± 0.4	-

End points

End points reporting groups

Reporting group title	Linagliptin 5 mg
Reporting group description:	
Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones GLP-1 and glucose-dependent insulinotropic polypeptide.	
Reporting group title	Placebo
Reporting group description:	
Matching placebo tablets	

Primary: Change in MFS from baseline to 48-weeks

End point title	Change in MFS from baseline to 48-weeks
End point description:	
The primary hypothesis to be investigated is whether linagliptin is superior to placebo in terms of improvement in LV systolic function using the midwall shortening as the primary efficacy variable. The treatment effect on the echocardiographic measurements was tested by one-way ANOVA on the intra-subjects difference between basal and end of treatment response (48 weeks) using treatment group as factor and basal response as covariate.	
End point type	Primary
End point timeframe:	
Changes from baseline to 48-weeks of LV systolic function measured by midwall shortening analysis (MFS).	

End point values	Linagliptin 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	86		
Units: percent				
arithmetic mean (standard error)	0.55 (± 3.37)	0.26 (± 3.57)		

Attachments (see zip file)	Change in MFS /DYDA2_MFS.pdf

Statistical analyses

Statistical analysis title	Change in MFS from baseline to 48-weeks
Statistical analysis description:	
The primary efficacy variable is the modification of midwall shortening (MFS). This was calculated for each surviving patient as the difference between the final echocardiographic measures and those done at randomization. The treatment effect on the echocardiographic measurements was tested by one-way ANOVA on the intra-subjects difference between basal and end of treatment response using treatment group as factor and basal response as covariate.	
Comparison groups	Placebo v Linagliptin 5 mg

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86 [1]
Method	ANCOVA

Notes:

[1] - Criteria for efficacy: Linagliptin considered superior to placebo if the difference between the treatment arms is statistically significant in favor of linagliptin using a two-sided p level ≤0.05

Secondary: Change in mitral annular systolic velocity from baseline to 48-weeks

End point title	Change in mitral annular systolic velocity from baseline to 48-weeks

End point description:

The treatment effect on the echocardiographic measurements was tested by one-way ANOVA on the intra-subjects difference between basal and end of treatment response (48 weeks) using treatment group as factor and basal response as covariate.

End point type	Secondary

End point timeframe:

Changes from baseline to 48 weeks in the longitudinal component of LVSF measured by tissue Doppler technique (peak systolic velocity of S’ wave of mitral annulus).

End point values	Linagliptin 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: cm/sec				
arithmetic mean (standard error)	-0.09 (± 0.21)	-0.40 (± 0.24)		

Statistical analyses

Statistical analysis title	Change in mitral annular systolic velocity

Statistical analysis description:

The change was calculated for each surviving patient as the difference between the final echocardiographic measures and those done at randomization. The treatment effect on the echocardiographic measurements was tested by one-way ANOVA on the intra-subjects difference between basal and end of treatment response using treatment group as factor and basal response as covariate.

Comparison groups	Linagliptin 5 mg v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12 [2]
Method	ANCOVA

Notes:

[2] - Criteria for efficacy: Linagliptin considered superior to placebo if the difference between the treatment arms is statistically significant in favor of linagliptin using a two-sided p level ≤0.05

Secondary: Improvement in S' from baseline to 48-weeks

End point title	Improvement in S' from baseline to 48-weeks

End point description:

patients who significantly improved the LV longitudinal component of systolic function (improvement in S' >25% from baseline)

End point type	Secondary

End point timeframe:

From baseline to 48-weeks

End point values	Linagliptin 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	80	78		
Units: Subjects				
Improvement>25%	9	7		

Statistical analyses

Statistical analysis title	S' improvement >25%

Statistical analysis description:

Incidence of patients who had an improvement in S’ > 25% from baseline

Comparison groups	Linagliptin 5 mg v Placebo
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.65
Method	Chi-squared

Secondary: Diastolic LV function

End point title	Diastolic LV function

End point description:

Patients with normalization of diastolic LV function at end follow-up (48 weeks).
Diastolic disfunction (DD) was defined as follows:
E/A ratio of transmitral flow <0.75 or E/A>1.50

End point type	Secondary

End point timeframe:

From enrollment to 48-weeks

End point values	Linagliptin 5 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	86		
Units: Subjects				
Normalization of DD	15	14		

Statistical analyses

Statistical analysis title	Normalization of diastolic function

Statistical analysis description:

Incidence of patients with normalization of diastolic LV function (patients with diastolic disfunction at baseline and without diastolic disfunction at end of study, 48-weeks).
Diastolic disfunction (DD) was defined as: E/A ratio of transmitral flow <0.75 or E/A>1.50

Comparison groups	Placebo v Linagliptin 5 mg
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89
Method	Chi-squared

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the randomization to 4 weeks after the study treatment (lingliptin/placebo) discontinuation at the final visit (48 weeks).

Adverse event reporting additional description:

All SAEs was monitored through the data collected in the CRFs based on information provided by the patient at each visit. Other AEs not considered serious was only recorded if they are suspected to be related to study treatment (ADRs) or leading to drug discontinuation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Linagliptin 5mg

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Linagliptin 5mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 93 (4.30%)	5 / 95 (5.26%)	
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)			
Mixed hepatocellular cholangiocarcinoma			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary revascularisation			

subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	
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: 5 %

Non-serious adverse events	Linagliptin 5mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 93 (1.08%)	1 / 95 (1.05%)	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 95 (1.05%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 93 (1.08%)	0 / 95 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2015	The amendment has been prepared following a note from AIFA requiring to detail in the protocol the contexts in which the researcher should have evaluated the discontinuation of the treatment
03 March 2017	This is a substantial amendment made necessary by a modification of the originally submitted CTA form. The clinical trial medicinal product undergoes a change in primary packaging (from blister to vial).

Notes:

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/33755143