Clinical trial results:
Impact of empagliflozin on left ventricular functions: a single center, phase III, randomized, open-label, active treatment-controlled, parallel study in patients with type 2 diabetes and normal left ventricular function

Summary

EudraCT number	2016-002225-10
Trial protocol	IT
Global end of trial date	27 September 2021

Results information

Result version number	v1 (current)
This version publication date	19 June 2022
First version publication date	19 June 2022
Summary attachment (see zip file)	table 1 (3) Table 1.pdf) table 2 (4) Table 2 (clinical par).pdf) table 3 (5) Table 3 (Diff echo+cpt).pdf) figure 1 (6) Figure 1&2 EMPA HEART.pdf) supplemental figure 1 (7) Suppl Figure 1.pdf) supplemental table 1 (7) Suppl Table 1 (Echo all).pdf) supplemental table 2 (8) Suppl table 2 (Echo mean).pdf) supplemental table 3 (9) Suppl table 3 (CPT).pdf) supplemental table 4 (10) Suppl Table 4 (biomarkers).pdf) complete report (Final report EMPA-HEART.pdf)

Trial information

Trial identification

Sponsor protocol code	EMPA-HEART

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Azienda Ospedaliero Universitaria Pisana
Sponsor organisation address	Via Savi, 10, Pisa, Italy, 56100
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric	No

investigation plan (PIP)	
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	12 December 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To verify whether, in type 2 diabetic patients with normal 2-D ejection fraction (>50%) and without inducible myocardial ischemia at the cardiopulmonary test, the treatment with empagliflozin is associated with an improvement in left ventricular systolic function, as measured by global lungitudinal strain (GLS) through speckle tracking echography, in comparison to sitagliptin, an equally effective plasma glucose lowering agent, presumably neutral on cardiac function

Protection of trial subjects:

The study will be carried out in accordance with the most recent international GCP guidelines (CPMP/ICH/135/1995), EU Directive and guidance and the local legislation on the conduct of clinical trials.
Before enrolment in the study, every participant will receive detailed information about study procedures, risks, and benefits, from the staff of the study and he/she will be given all the necessary time to ask any question about the study. The informed consent form, as well as the form for the general practitioner will be given to the participant (see attached files). The informed consent form will be signed during the screening visit, after having checked the eligibility criteria, and a 6-digit PatientID code will be assigned to each patient by the study staff, as the first two letters of the name + the first two letters of surname + a two-digit progressive number from 01 to 75. The enrolment list, including name and surname of the patients, together with the PatientID code, will be stored in the Clinical trial office of Laboratory of nutrition, diabetes and atherosclerosis of the Department of Clinical and Experimental Medicine (Building 43 - Santa chiara Hospital) under the responsibility of Prof. Andrea Natali.

Background therapy:

Allowed background therapy is stable hypoglycemic therapy since three months with:
1. Metformin
2. Metformin + basal insulin
and assuming stable cardio-active therapies since three months (anti-hypertensive drugs, diuretics, drugs for asthma, drugs for migraine).

Patients assuming any other hypoglycemic therapy and those who received any investigational new drug within the last 12 weeks will be excluded from the study.

With the exception of those drugs listed among non-permitted medications, participants will be allowed to use any concomitant medication necessary for the treatment of pre-existing concomitant pathologies or intercurrent diseases. However, it is recommended that concomitant chronic medication for underlying diseases are given at constant dose for at least 4 weeks prior to entry in the study and for the entire study duration. All medications taken for any reason (including those taken for intercurrent diseases) must be recorded in the appropriate section of the case report form (CRF).

The initiation of treatment or changes in dosage of the following medications is not permitted during the

total study period. If this occurs at any time during the study it constitutes a protocol violation and it necessitates the discontinuation of the patient from the study.
Any glucose lowering drugs in addition to those included in the present protocol;
Any change in metformin or insulin dose greater than 20% with respect to the entry dosage;
Any drug able to interfere with cardiac function (i.e. beta blockers, ACE inhibitors, calcium antagonists, alpha blockers, diuretics, theophylline, thyroid hormones)
Any drug with potential interference with treatment (cyclosporine, digoxine).
The treatment with the following drugs in the 7 days preceding the primary or secondary outcome assessments:
Any drug able to interfere with inflammation when assumed systemically (NSAID, steroids, any other immune suppressors-modulator)

Evidence for comparator:

Sitagliptin 100 mg/die was chosen as an active comparator because of its similar potency to empagliflozin in terms of glucose control and, on the bases of large clinical trials, does not influence the risk of developing HF (ref 1).
The recent evidence of the PROLOGUE trial (Yamada), showing that sitagliptin is able to prevent the time-related deterioration of diastolic function, raises the possibility that our comparator is not completely neutral on cardiac function. However, this effect was evident after 12, but not after 6 months of treatment and sitagliptin has been shown to be neutral on systolic function in patients with post-ischemic heart failure with mildly reduced ejection fraction [ref 2]. Therefore, there will be, if any, a small risk of type 2 error, which we consider acceptable and eventually would, in case, reinforce any observed positive outcome of empagliflozin.

References
1. Green JB, Bethel MA, Armstrong PW, et al. (2015) Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 373: 232-242
2. Yamada H, Tanaka A, Kusunose K, et al. (2017) Effect of sitagliptin on the echocardiographic parameters of left ventricular diastolic function in patients with type 2 diabetes: a subgroup analysis of the PROLOGUE study. Cardiovasc Diabetol 16: 63

Actual start date of recruitment	01 September 2016
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: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	28
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Volunteers will be recruited among patients attending visits at the Diabetes Outpatient Unit of UO Medicina Interna 1 (AOUP), according to the following inclusion /exclusion criteria:
5.1. Inclusion criteria:
Male of female patients affected by type 2 diabetes mellitus (T2DM)
Subjects aged >40 and <80 years
HbA1c levels ≥53 and ≤ 69 mmol/mo

Pre-assignment

Screening details:

Male of female patients affected by type 2 diabetes mellitus (T2DM)

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

In order to prevent any influence of the researcher expectations (type 1 error) we will take care that the cardiologist performing the primary and several of the secondary outcome variables measurements are blind with respect to the treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	empagliflozin

Arm description:

experimental arm

Arm type	Experimental
Investigational medicinal product name	Jardiance
Investigational medicinal product code	A10BK03
Other name	Jardiance
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Empagliflozin 10 mg/die

Arm title	sitagliptin

Arm description:

active comparator

Arm type	Active comparator
Investigational medicinal product name	Januvia
Investigational medicinal product code	A10BH01
Other name	Januvia, Sitagliptin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin 100 mg/die

Number of subjects in period 1	empagliflozin	sitagliptin
Started	27	29
Completed	22	22
Not completed	5	7
Consent withdrawn by subject	1	3
Physician decision	3	4
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	empagliflozin
Reporting group description: experimental arm	
Reporting group title	sitagliptin
Reporting group description: active comparator	

Reporting group values	empagliflozin	sitagliptin	Total
Number of subjects	27	29	56
Age categorical			
age			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	14	27
From 65-84 years	14	15	29
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	4	4	8
Male	23	25	48

End points

End points reporting groups	
Reporting group title	empagliflozin
Reporting group description: experimental arm	
Reporting group title	sitagliptin
Reporting group description: active comparator	

Primary: Primary objective	
End point title	Primary objective
End point description: The primary aim is to verify whether, in type 2 diabetic patients with normal 2-D ejection fraction (≥50%) and without inducible myocardial ischemia at the cardiopulmonary test, the treatment with empagliflozin is associated with an improvement in left ventricular systolic function, as measured by global lungitudinal strain (GLS) through speckle tracking echography, in comparison to sitagliptin, an equally effective plasma glucose lowering agent, presumably neutral on cardiac function.	
End point type	Primary
End point timeframe: 2	

End point values	empagliflozin	sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[1]	22[2]		
Units: %				
number (not applicable)	22	22		

Notes:

[1] - 22

[2] - 22

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: In an MANOVA design for three repeated measures (baseline, 1 month, 6 months) the power of the study to detect a difference between the treatments of 2.5% or 1.7% is 0.98 and 0.80, respectively. In an ANCOVA design with 4 covariates a sample size of 60 subjects will have the power of 0.71 to detect an effect of 0.10 (expressed as of proportion of variance explained by the effect under consideration), which is commonly considered small in biostatistics and a power of 0.99 to detect a medium effec	
Comparison groups	empagliflozin v sitagliptin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05 [4]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	90

Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	100
Variability estimate	Standard deviation
Dispersion value	2

Notes:

[3] - In an MANOVA design for three repeated measures (baseline, 1 month, 6 months) the power of the study to detect a difference between the treatments of 2.5% or 1.7% is 0.98 and 0.80, respectively. In an ANCOVA design with 4 covariates a sample size of 60 subjects will have the power of 0.71 to detect an effect of 0.10 (expressed as of proportion of variance explained by the effect under consideration), which is commonly considered small in biostatistics and a power of 0.99 to detect a medium effec
[4] - significant

Secondary: Secondary objectives

End point title	Secondary objectives

End point description:

To assess the effects of the two treatments on the following parameters:
Changes from baseline at 6 months after treatment initiation in HbA1c;
Changes from baseline at 1 and 6 months after treatment initiation in other well established parameters of cardiac function, such as 3-D ejection fraction, left atrial volume, and E/E'.
Changes from baseline at 6 months after treatment initiation in VO2 max (Cardiopulmonary exercise test), an extremely clinically relevant parameter that will help in appreciating the relevance of the imaging data.

End point type	Secondary

End point timeframe:

2

End point values	empagliflozin	sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[5]	22[6]		
Units: %				
number (not applicable)	22	22		

Notes:

[5] - 22

[6] - 22

Statistical analyses

No statistical analyses for this end point

Other pre-specified: exploratory objectives

End point title	exploratory objectives

End point description:

Given the exploratory nature of the study, we will verify the following hypothesis:
Whether changes from baseline at 6 months after treatment initiation in plasma markers of myocyte strain (BNP, NT-proBNP, proadrenomedullin), inflammation/oxidative stress (hsCRP, TNF-a, myeloperoxydase, uric acid), matrix remodeling (procollagen type III) and myocyte injury (Troponin T) help understanding the mechanisms of action through which the treatments exert their effect/s on the heart.
Whether changes from baseline at 6 months after treatment initiation in cardiac autonomic function score (based on RR changes with Valsalva, deep breathing, standing-to-laying) contribute to the

mechanisms of action of the treatments.
Whether the effects of the treatments differ in the subgroup of patients whom at baseline have mild abnormalities in cardiac systolic function or abnormal values of plasma biomarkers or abnormal cardiac autonomic function tests.
Whether the changes in cardiac function a

End point type	Other pre-specified

End point timeframe:

2

End point values	empagliflozin	sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[7]	22[8]		
Units: %				
number (not applicable)	22	22		

Notes:

[7] - 22

[8] - 22

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

2-sided, per protocol population (PPP), no interim analysis

Comparison groups	empagliflozin v sitagliptin
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.05 [10]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	90
upper limit	100
Variability estimate	Standard deviation
Dispersion value	2

Notes:

[9] - 2-sided, per protocol population (PPP), no interim analysis

[10] - significant

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months

Adverse event reporting additional description:

No patient developed serious adverse events (SAEs) and/or serious adverse drug reactions (SARs) with either sitagliptin or empagliflozin.
• No patient experienced Unexpected Adverse Reactions (UARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)
• No death was recorded during the study period and during the 30 days following the end

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Empagliflozin

Reporting group description:

Infective balanopostitis

Serious adverse events	Empagliflozin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Empagliflozin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 2 (100.00%)		
Reproductive system and breast disorders			
Balanoposthitis infective	Additional description: 2 subjects		
subjects affected / exposed	2 / 2 (100.00%)		
occurrences (all)	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