Clinical trial results:
EMPA-VISION: A randomised, double-blind, placebo-controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac physiology and metabolism in patients with heart failure

Summary

EudraCT number	2017-000376-28
Trial protocol	GB
Global end of trial date	28 May 2020

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	1245-0148

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03332212
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany,
Public contact	Boehringer Ingelheim , Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim , Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com

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	14 July 2020

Is this the analysis of the primary completion data?	Yes
Primary completion date	21 May 2020
Global end of trial reached?	Yes
Global end of trial date	28 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial was to assess the effect of empagliflozin on cardiac physiology and metabolism aiming to provide a scientific explanation of the underlying mechanism by which empagliflozin improves heart failure (HF) related outcomes in patients with chronic HF.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 March 2018
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	United Kingdom: 101
Worldwide total number of subjects	101
EEA total number of subjects	0

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)	34
From 65 to 84 years	64
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

A randomised, double-blind, placebo controlled, mechanistic cardiac magnetic resonance study to investigate the effects of empagliflozin treatment on cardiac
physiology and metabolism in patients with heart failure

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in trial. Subjects attended specialist site to ensure that they (the subjects) met all implemented inclusion/exclusion criteria.

Period 1

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

Blinding implementation details:

Patients, investigators, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial remained blinded with regard to the randomised treatment assignments within a cohort until after all patients in the cohort had completed the study and database lock had taken place.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo Cohort A

Arm description:

Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).

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

Dosage and administration details:

Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks.

Arm title	Placebo Cohort B

Arm description:

Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).

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

Dosage and administration details:

Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks.

Arm title	Empaglifozin 10mg Cohort A

Arm description:

Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).

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

Dosage and administration details:

Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks.

Arm title	Empaglifozin 10mg Cohort B

Arm description:

Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).

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

Dosage and administration details:

Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks.

Number of subjects in period 1[1]	Placebo Cohort A	Placebo Cohort B	Empaglifozin 10mg Cohort A
Started	19	18	17
Treated	19	17	17
Completed	18	16	17
Not completed	1	2	0
worsening of disease under study	1	1	-
Adverse event, non-fatal	-	-	-
Not treated	-	1	-

Number of subjects in period 1[1]	Empaglifozin 10mg Cohort B
Started	18
Treated	18
Completed	17
Not completed	1
worsening of disease under study	-
Adverse event, non-fatal	1
Not treated	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of the 101 screened and enrolled subjects, 72 were randomized and treated in the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo Cohort A
Reporting group description:	
Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).	
Reporting group title	Placebo Cohort B
Reporting group description:	
Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).	
Reporting group title	Empaglifozin 10mg Cohort A
Reporting group description:	
Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).	
Reporting group title	Empaglifozin 10mg Cohort B
Reporting group description:	
Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).	

Reporting group values	Placebo Cohort A	Placebo Cohort B	Empaglifozin 10mg Cohort A
Number of subjects	19	18	17
Age categorical			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
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)	8	2	4
From 65-84 years	10	15	13
85 years and over	1	1	0
Age Continuous			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: years			
arithmetic mean	64.7	72.1	67.5
standard deviation	± 12.7	± 7.0	± 14.1
Sex: Female, Male			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
Female	6	9	7
Male	13	9	10

Race (NIH/OMB)			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	19	18	17
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	19	18	17
Unknown or Not Reported	0	0	0
Ratio of phosphocreatine to adenosine triphosphate concentration			
The ratio of phosphocreatine to adenosine triphosphate concentration (PCr/ATP) reflects the energetic state of the heart and was assessed by 31P cardiac magnetic resonance spectroscopy (MRS). Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle. In the Placebo arm (Cohort B) there was one patient without baseline Cardiac magnetic resonance (CMR) measures.			
Units: Ratio			
arithmetic mean	1.924	1.719	1.889
standard deviation	± 0.354	± 0.431	± 0.407

Reporting group values	Empaglifozin 10mg Cohort B	Total	
Number of subjects	18	72	
Age categorical			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	7	21	
From 65-84 years	11	49	
85 years and over	0	2	
Age Continuous			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: years			
arithmetic mean	69.1		
standard deviation	± 10.9	-	

Sex: Female, Male			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
Female	8	30	
Male	10	42	
Race (NIH/OMB)			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	16	70	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB)			
Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.			
Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	18	72	
Unknown or Not Reported	0	0	
Ratio of phosphocreatine to adenosine triphosphate concentration			
The ratio of phosphocreatine to adenosine triphosphate concentration (PCr/ATP) reflects the energetic state of the heart and was assessed by 31P cardiac magnetic resonance spectroscopy (MRS). Randomised set (RS): This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle. In the Placebo arm (Cohort B) there was one patient without baseline Cardiac magnetic resonance (CMR) measures.			
Units: Ratio			
arithmetic mean	1.896		
standard deviation	± 0.462	-	

End points

End points reporting groups

Reporting group title	Placebo Cohort A
Reporting group description:	
Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).	
Reporting group title	Placebo Cohort B
Reporting group description:	
Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).	
Reporting group title	Empaglifozin 10mg Cohort A
Reporting group description:	
Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).	
Reporting group title	Empaglifozin 10mg Cohort B
Reporting group description:	
Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).	
Subject analysis set title	Randomised set (RS)
Subject analysis set type	Per protocol
Subject analysis set description:	
This set included all patients who were randomised to study treatment, in line with the intention-to-treat principle.	

Primary: Change from baseline to Week 12 in PCr/ATP ratio in the resting state measured by 31P cardiac magnetic resonance spectroscopy (MRS).

End point title	Change from baseline to Week 12 in PCr/ATP ratio in the resting state measured by 31P cardiac magnetic resonance spectroscopy (MRS).
End point description:	
The primary endpoint of efficacy was the change from baseline to Week 12 in phosphocreatine/adenosine triphosphate (PCr/ATP) ratio in the resting state measured by 31P cardiac magnetic resonance spectroscopy (MRS). Adjusted mean values were calculated using an analysis of variance (ANOVA) model, with treatment, history of diabetes, and history of atrial fibrillation (AF) as fixed effects. Per protocol set (PPS): The primary endpoint analysis was performed using the per protocol (PP) set of patients with valid PCr/ATP ratio measurements available at baseline and Week 12, and no important protocol violation relevant to the primary endpoint.	
End point type	Primary
End point timeframe:	
At baseline and at week 12.	

End point values	Placebo Cohort A	Placebo Cohort B	Empaglifozin 10mg Cohort A	Empaglifozin 10mg Cohort B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[1]	11[2]	17[3]	13[4]
Units: PCr / ATP Ratio				
least squares mean (standard error)	0.068 (± 0.114)	0.259 (± 0.156)	-0.179 (± 0.117)	0.100 (± 0.143)

Notes:
[1] - PPS
[2] - PPS
[3] - PPS
[4] - PPS

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
ANOVA on the PCr/ATP ratio absolute change using treatment (empagliflozin vs. placebo), history of diabetes (yes vs, no) and history of atrial fibrillation (yes vs no) as between subjects factor.	
Comparison groups	Placebo Cohort A v Empaglifozin 10mg Cohort A
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1418
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.247
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.582
upper limit	0.087
Variability estimate	Standard error of the mean
Dispersion value	0.164

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
ANOVA on the PCr/ATP ratio absolute change using treatment (empagliflozin vs. placebo), history of diabetes (yes vs, no) and history of atrial fibrillation (yes vs no) as between subjects factor.	
Comparison groups	Placebo Cohort B v Empaglifozin 10mg Cohort B
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.465
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.159
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.604
upper limit	0.286
Variability estimate	Standard error of the mean
Dispersion value	0.213

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring between the start of treatment and end of the residual effect period, 7 days after the last dose of medication. Up to 95 days.

Adverse event reporting additional description:

Treated set (TS): All randomised and treated patients were included in the safety analysis and safety summaries were presented by actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Once a day oral administration of a single film-coated placebo tablet matching to empaglifozin for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF) and Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).

Reporting group title	Empa 10mg

Reporting group description:

Once a day oral administration of a single 10 milligram (mg) film-coated empaglifozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF) and Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF).

Serious adverse events	Placebo	Empa 10mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 36 (19.44%)	1 / 35 (2.86%)	
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)			
Pituitary tumour benign			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (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	1 / 36 (2.78%)	0 / 35 (0.00%)	

occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 36 (5.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Glaucoma			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 36 (5.56%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Euglycaemic diabetic ketoacidosis			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 36 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 36 (2.78%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Empa 10mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 36 (8.33%)	8 / 35 (22.86%)	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 35 (5.71%) 2	
Musculoskeletal and connective tissue disorders Osteoarthritis subjects affected / exposed occurrences (all)	0 / 36 (0.00%) 0	2 / 35 (5.71%) 2	
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all)	2 / 36 (5.56%) 2	1 / 35 (2.86%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 36 (2.78%) 2	3 / 35 (8.57%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2018	• Exclusion criterion 2 revised since patients who had a previous non-ST elevated myocardial infarction (MI) or less extensive MI would still have viable myocardium to produce Adenosine triphosphate (ATP) so those patients were technically eligible for Magnetic resonance spectroscopy (MRS) and there was no reason to exclude them • Dosing information was revised so that a requirement to take trial medication in the morning was changed to a recommendation • A local creatinine test at Visit 1 was added to check patient safety prior to administration of contrast agent • Reticulocyte count and Gamma-glutamyl transferase (GGT) added as standard safety laboratory tests (rather than reactive tests) • Glycated haemoglobin (HbA1c) was added to the list of specified biomarkers • Addition of new section to add blood sampling for metabolomic analysis.
14 August 2018	• Flowchart was amended so ECHO (Echocardiogram) did not need to be repeated at Visit 2 if performed within previous 21 days • Flowchart and relevant section were amended so that a Computed tomography (CT) scan was not required at screening if ischaemic clinical testing had been performed within 6 months and written results were available and adequate (in the opinion of the investigator) to assess eligibility • Body mass index (BMI) was removed from list of inclusion criteria since there was no medical reason to exclude patients with a high BMI who were otherwise eligible and able to undergo MRI scanning. Patients with a high BMI who were unable to undergo Magnetic resonance imaging (MRI) scanning were excluded from the study by exclusion criterion 3, which covered contraindications for MRI scanning. • Exclusion criterion 2 was revised because it excluded patients with flow limitation of the non-septal region. Coronary flow limitation resulting in scars or non-viable myocardium elsewhere (non-septal regions) would not affect measurement of phosphocreatine/adenosine triphosphate (PCr/ATP) so the exclusion criteria was modified to allow inclusion of these patients. • Exclusion criterion 22 was revised so that patients who received chemotherapy or radiotherapy should be considered individually by investigators as the status of malignancy after treatment varies according to individual, type of malignancy, and the effect of treatment. Taking these into account it was considered acceptable to include patients in the trial as soon as 6 months if the investigator believed it is appropriate to do so.

Notes:

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.

Due to COVID-19, the number of patients included in the analysis of efficacy for the HFpEF cohort was substantially reduced, which meant that this cohort was under powered (reduced from 80% to 70%) for the planned analysis of the primary endpoint.

Notes: