



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, clintrriage.rdg@boehringer-ingelheim.com |
| Scientific contact | Boehringer Ingelheim , Call Center, Boehringer Ingelheim, 001 18002430127, clintrriage.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, Carer, Data analyst, 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 empagliflozin for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF).

| | |
|--|--------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching 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 film-coated placebo tablet matching to empagliflozin for 12 weeks.

| | |
|-----------|------------------|
| Arm title | Placebo Cohort B |
|-----------|------------------|

Arm description:

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

| | |
|--|--------------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo matching 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 film-coated placebo tablet matching to empagliflozin for 12 weeks.

| | |
|-----------|-----------------------------|
| Arm title | Empagliflozin 10mg Cohort A |
|-----------|-----------------------------|

Arm description:

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

| | |
|------------------|-----------------------------|
| Arm title | Empagliflozin 10mg Cohort B |
|------------------|-----------------------------|

Arm description:

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

| | |
|--|--------------------|
| 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 empagliflozin tablet for 12 weeks.

| Number of subjects in period 1^[1] | Placebo Cohort A | Placebo Cohort B | Empagliflozin 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] | Empagliflozin 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 empagliflozin 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 empagliflozin for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF). | |
| Reporting group title | Empagliflozin 10mg Cohort A |
| Reporting group description: Once a day oral administration of a single 10 milligram (mg) film-coated empagliflozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF). | |
| Reporting group title | Empagliflozin 10mg Cohort B |
| Reporting group description: Once a day oral administration of a single 10 milligram (mg) film-coated empagliflozin tablet for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF). | |

| Reporting group values | Placebo Cohort A | Placebo Cohort B | Empagliflozin 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 ³¹ P 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 | Empagliflozin 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 ³¹ P 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 empagliflozin 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 empagliflozin for 12 weeks. Cohort B: Heart failure (HF) with preserved ejection fraction (HFpEF). | |
| Reporting group title | Empagliflozin 10mg Cohort A |
| Reporting group description: Once a day oral administration of a single 10 milligram (mg) film-coated empagliflozin tablet for 12 weeks. Cohort A: Heart failure (HF) with reduced ejection fraction (HFrEF). | |
| Reporting group title | Empagliflozin 10mg Cohort B |
| Reporting group description: Once a day oral administration of a single 10 milligram (mg) film-coated empagliflozin 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 ³¹ P 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 ³¹ P 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 | Empagliflozin 10mg Cohort A | Empagliflozin 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 Empagliflozin 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 Empagliflozin 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 empagliflozin 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 empagliflozin 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 | |
| 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 | |
| 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 | |

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 | 0 / 36 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 36 (0.00%) | 2 / 35 (5.71%) | |
| occurrences (all) | 0 | 2 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 36 (5.56%) | 1 / 35 (2.86%) | |
| occurrences (all) | 2 | 1 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 36 (2.78%) | 3 / 35 (8.57%) | |
| occurrences (all) | 2 | 3 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 26 March 2018 | <ul style="list-style-type: none">• 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 | <ul style="list-style-type: none">• 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: