Clinical trial results:
Effect of Metformin and Empagliflozin in insulin resistant patients with heart failure with reduced ejection fraction

Summary

EudraCT number	2017-004149-26
Trial protocol	DE
Global end of trial date	28 February 2025

Results information

Result version number	v1
This version publication date	17 April 2025
First version publication date	17 April 2025

Trial information

Trial identification

Sponsor protocol code	METRIS-HF(EMPA)

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Prof. Dr. Wolfram Döhner, Deutsches Herzzentrum der Charité (DHZC) Klinik für Kardiologie, Angiologie & Intensivmedizin, 49 30450553507, wolfram.doehner@charite.de
Scientific contact	Prof. Dr. Wolfram Döhner, Deutsches Herzzentrum der Charité (DHZC) Klinik für Kardiologie, Angiologie & Intensivmedizin , 49 30450553507, wolfram.doehner@charite.de

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	25 March 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2025
Global end of trial reached?	Yes
Global end of trial date	28 February 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Improvement of myocardial contractility and functional capacity in patients with reduced EF (HFrEF and HFmrEF) and insulin resistance in comparison with two control groups (empaglifozin and placebo).

Protection of trial subjects:

Following the principles of Good Clinical Practice and according to international (European) and German law the sponsor established a system to detect any safety signal and to take appropriate measures to protect patient’s safety. An immediate reaction to any risk given by the drug or the conduct of the trial is guaranteed.

Background therapy:

Heart failure (HF) is a major clinical burden in modern society and further growing in prevalence, incidence and in health care costs. Diabetes mellitus (DM) is a common comorbidity of HF with mutual aggravation of both diseases and is a risk factor for advanced symptomatic status and further impaired prognosis of HF.
Based on the newly emerging clinical evidence on SGLT2- inhibitor treatment in patients with heart failure, there is an urgent need for a better understanding of the underlying mechanisms.
The trial design of the METRIS-HF (EMPA) trial offered a unique opportunity to investigate on a mechanistic level the effects of Empagliflozin not only in comparison to placebo but in direct comparison to Metformin which was until now considered first line therapy in patients with HF and diabetes mellitus but may likely be replaced by SGLT2-inhibitors.

Evidence for comparator: -

Actual start date of recruitment	01 October 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	Germany: 88
Worldwide total number of subjects	88
EEA total number of subjects	88

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)	29
From 65 to 84 years	53
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

153 patients were screened in 2 Charité sites and a further site in Berlin (Unfallkrankenhaus Berlin Marzahn) in Germany according the including criteria of whom 95 were randomized. Furthermore 7 patients were discontinued after treatment arm assignment. 88 patients fulfilled the criteria of being randomized and received the IMP.

Pre-assignment

Screening details:

All baseline study-related examinations will be performed within two weeks of randomization.

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, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin 500 mg

Arm description:

Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between 30 and 44 ml/min, received a dose of 500 mg metformin b.i.d

Arm type	Experimental
Investigational medicinal product name	Metformine
Investigational medicinal product code	SUB172801
Other name	METFORMIN HYDROCHLORIDE PH. EUR., Sifor 1000
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2x 500mg/d for the first 2 weeks, afterwards up-titrated to 2x1000mg/d (if applicable) plus 1 placebo tablet of Empagliflozin

Arm title	Empagliflozin 10 mg

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	EMPAGLIFLOZIN
Investigational medicinal product code	SUB35915
Other name	Jardiance Filmtabletten (10 mg)
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1x10mg/d plus 2x ½ placebo tablet of Metformin for the first 2 weeks, afterwards 2x 1 placebo tablet of Metformin

Arm title	Placebo

Arm description:

Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between

30 and 44 ml/min, received a dose of 500 mg metformin b.i.d

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:

1 placebo tablet of Empagliflozin plus 2x ½ placebo tablet of Metformin for the first 2 weeks, afterwards 2x 1 placebo tablet of Metformin

Number of subjects in period 1	Metformin 500 mg	Empagliflozin 10 mg	Placebo
Started	33	18	37
Completed	33	18	37

Baseline characteristics

Reporting groups	
Reporting group title	Metformin 500 mg
Reporting group description:	
Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between 30 and 44 ml/min, received a dose of 500 mg metformin b.i.d	
Reporting group title	Empagliflozin 10 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description:	
Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between 30 and 44 ml/min, received a dose of 500 mg metformin b.i.d	

Reporting group values	Metformin 500 mg	Empagliflozin 10 mg	Placebo
Number of subjects	33	18	37
Age categorical 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)	23	11	19
From 65-84 years	9	6	14
85 years and over	1	1	4
Age continuous Units: years			
arithmetic mean	72.18	67.27	68.27
standard deviation	± 9.28	± 10.33	± 11.92
Gender categorical Units: Subjects			
Female	7	5	6
Male	26	13	31

Reporting group values	Total		
Number of subjects	88		
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)	53		
From 65-84 years	29		
85 years and over	6		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	18		
Male	70		

End points

End points reporting groups

Reporting group title	Metformin 500 mg

Reporting group description:

Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between 30 and 44 ml/min, received a dose of 500 mg metformin b.i.d

Reporting group title	Empagliflozin 10 mg

Reporting group description: -

Reporting group title	Placebo

Reporting group description:

Before authorization of the amendment version 3.1 submitted on 02.12.2020 eligible patients were randomized (1:1) to receive active treatment or matching placebo on top of usual care. A titration step (14 days: 500mg bd) was followed by full dose (1000mg bd) for a total treatment period of 24 weeks. Titration was performed for patients with a GFR > 44 ml/min/1.73m2 only. Patients with a GFR between 30 and 44 ml/min, received a dose of 500 mg metformin b.i.d

Primary: change LV global longitudinal strain (GLS

End point title	change LV global longitudinal strain (GLS[1]

End point description:

LV global longitudinal strain (GLS) will be analysed by means of Gaussian linear model for repeated measures (so-called MMRM) with treatment group (Group A vs. Group B vs. Group C), time (week 12, week24). The error terms are assumed to follow a multivariate normal distribution with unstructured covariance.
Since the primary endpoint will be assessed by echocardiography for patients not eligible for cardiac MRI, the analyses will be carried out stratified by assessement method (echocardiography and cardiac MRI) and combined in a fixed effect meta-analysis of standardized treatment effects. A one-sided p-value smaller than 2.5% will be considered statistically significant.

End point type	Primary

End point timeframe:

week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis has not yet been finalised. The results will be uploaded as soon as they are available.

End point values	Metformin 500 mg	Empagliflozin 10 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	18	37	
Units: Prozent (%)				
median (confidence interval 95%)	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: overall trial, 24 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.3

Reporting groups	
Reporting group title	Metformin
Reporting group description: -	
Reporting group title	Empagliflozin
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Metformin	Empagliflozin	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	3 / 18 (16.67%)	10 / 37 (27.03%)
number of deaths (all causes)	2	0	3
number of deaths resulting from adverse events	0	0	2
Injury, poisoning and procedural complications			
Macrohaematuria			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
heart failure (cardiac decompensation)			
subjects affected / exposed	2 / 33 (6.06%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction/ NSTEMI			

subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	3 / 37 (8.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Atrial flutter			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cardiac chest pain (Angina pectoris)			
subjects affected / exposed	0 / 33 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Surgical and medical procedures - Other - Elective cardiac catheterisation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures - Other - Primary prophylactic implantation of a defilibrator			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
change implanted device to Phrenic nerve stimulation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ischemia/stroke			

subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Synkope			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Death NOS			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Immune system disorders			
Anaphylaxis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis rheumatoide			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
sepsis, pneumogene			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Covid-19-Infektion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Metformin	Empagliflozin	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 33 (51.52%)	12 / 18 (66.67%)	15 / 37 (40.54%)
Injury, poisoning and procedural complications			
Fracture	Additional description: ribs fracture/tibia head fracture/fibula fracture		
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	2 / 37 (5.41%)
occurrences (all)	0	0	3
Cardiac disorders			
cardiac chest pain	Additional description: Angina pectoris		
subjects affected / exposed	1 / 33 (3.03%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	1	1	1
Exercise-induced dyspnea			
subjects affected / exposed	0 / 33 (0.00%)	2 / 18 (11.11%)	1 / 37 (2.70%)
occurrences (all)	0	2	1
Ventricular tachycardia			

subjects affected / exposed	0 / 33 (0.00%)	1 / 18 (5.56%)	2 / 37 (5.41%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Flu like symtoms			
subjects affected / exposed	1 / 33 (3.03%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	1	0	1
Injection site reaction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	10 / 33 (30.30%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	22	0	0
Nausea, Vomiting			
subjects affected / exposed	2 / 33 (6.06%)	0 / 18 (0.00%)	0 / 37 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Renal and urinary disorders			
acute kidney injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 18 (5.56%)	1 / 37 (2.70%)
occurrences (all)	0	1	1
Cystitis noninfective			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			

subjects affected / exposed	1 / 33 (3.03%)	1 / 18 (5.56%)	0 / 37 (0.00%)
occurrences (all)	1	1	0
back pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1
Infections and infestations			
Covid- 19- Infektion			
subjects affected / exposed	2 / 33 (6.06%)	5 / 18 (27.78%)	1 / 37 (2.70%)
occurrences (all)	2	5	1
upper respiratory infections			
subjects affected / exposed	0 / 33 (0.00%)	2 / 18 (11.11%)	0 / 37 (0.00%)
occurrences (all)	0	3	0
Herpes simplex reactivation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 18 (0.00%)	1 / 37 (2.70%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2020	- add a new arm as active comparator "Empagliflozin" - change the sponsor code from Metris-HF to Metris-HF (EMPA) - update protocol Version 3.1 (02/12/2020)
09 February 2021	- Label for study IMP have been modified
06 February 2023	- Extension of the study period until March 2024 -update protocol Version 3.2 (20/01/2023)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported