Clinical trial results:
Effects of metformin treatment on myocardial efficiency in patients with heart failure:
A randomized, double-blind, placebo-controlled study

Summary

EudraCT number	2015-002767-42
Trial protocol	DK
Global end of trial date	14 February 2018

Results information

Result version number	v1 (current)
This version publication date	17 January 2021
First version publication date	17 January 2021
Summary attachment (see zip file)	Manuscript (Larsen 2019 Efficiency in metformin-treated HF patients EJHF.pdf)

Trial information

Trial identification

Sponsor protocol code	2015-588

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02810132
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark,
Public contact	Henrik Wiggers, Aarhus University Hospital, henrikwiggers@dadlnet.dk
Scientific contact	Henrik Wiggers, Aarhus University Hospital, henrikwiggers@dadlnet.dk

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	01 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2018
Global end of trial reached?	Yes
Global end of trial date	14 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate in a randomized, double-blinded placebo-controlled design if metformin treatment in patients with heart failure has beneficial effects on left ventricular myocardial oxidative metabolism, efficiency, contractile function and physical performance.

Protection of trial subjects:

The study was conducted in compliance with the standards of Good Clinical Practice and the Helsinki Declaration. Data collection, storage, processing and disclosure of personal information were in accordance with the principles the Danish Data Protection Agency.
from the Danish Medicines Agency. Access to collated participant data were restricted to the invetigators treating the participants. Computers used to collate the data have limited access measures via user names and passwords. Published results do not contain any personal data that could allow identification of individual participants. All the participants were clinically periodically monitored while in the study. Any AE's and SAE's were reported to the sponsor who ensured all was resolved.

Background therapy:

Standard of care heart failure treatment.

Evidence for comparator:

-

Actual start date of recruitment	23 January 2017
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	Denmark: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	15
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients attending the outpatient clinic at the Aarhus University Hospital, Department of Cardiology were recruited. 149 patients were assessed for eligibilty of which 54 were screened between january 2017 and february 2018. 36 patients fulfilled the criteria and were included in the study.

Pre-assignment

Screening details:

Patients attending the outpatient clinic at the Aarhus University Hospital, Department of Cardiology were recruited. 149 patients were assessed for eligibilty of which 54 were screened between january 2017 and february 2018. using research databases, hospital records, and local general practices.

Period 1

Period 1 title	Jan 2017 to Feb 2018 (Overall period) (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

Arms

Are arms mutually exclusive?	Yes
Arm title	Metformin arm

Arm description:

Metformin 500 mg tablets.
GLUCOPHAGE XR 500 mg tablet; clinical product (Product No. 207150-V500-038)

Arm type	Active comparator
Investigational medicinal product name	EMD 89502
Investigational medicinal product code	
Other name	GLUCOPHAGE XR 500 mg tablet; clinical product (Product No. 207150-V500-038)
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Starting dose was 500 mg q.d. with uptitration after 2 weeks to 500 mg b.i.d. and after 4 weeks from randomization to a target dose of 1000 mg b.i.d. (if eGFR 30–60 mL/min/1.73 m2, target dose was 500 mg b.i.d.).

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Starting dose was 500 mg q.d. with uptitration after 2 weeks to 500 mg b.i.d. and after 4 weeks from randomization to a target dose of 1000 mg b.i.d. (if eGFR 30–60 mL/min/1.73 m2, target dose was 500 mg b.i.d.).

Number of subjects in period 1	Metformin arm	Placebo
Started	19	17
Completed	19	17

Baseline characteristics

Reporting groups	
Reporting group title	Metformin arm
Reporting group description:	
Metformin 500 mg tablets. GLUCOPHAGE XR 500 mg tablet; clinical product (Product No. 207150-V500-038)	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Metformin arm	Placebo	Total
Number of subjects	19	17	36
Age categorical Units: Subjects			
Adults (18-64 years)	6	9	15
From 65-84 years	13	8	21
Gender categorical Units: Subjects			
Female	2	5	7
Male	17	12	29

End points

End points reporting groups

Reporting group title	Metformin arm
Reporting group description:	
Metformin 500 mg tablets. GLUCOPHAGE XR 500 mg tablet; clinical product (Product No. 207150-V500-038)	
Reporting group title	Placebo
Reporting group description: -	

Primary: Change in Myocardial efficiency (expressed as Work Metabolic Index)

End point title	Change in Myocardial efficiency (expressed as Work Metabolic Index)
End point description:	
End point type	Primary
End point timeframe:	
3 months	

End point values	Metformin arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	17		
Units: 36				
number (not applicable)	0.6	-0.4		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Metformin arm v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	1.8

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Entire study duration	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Metformin arm
Reporting group description: Metformin 500 mg tablets. GLUCOPHAGE XR 500 mg tablet; clinical product (Product No. 207150-V500-038)	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Metformin arm	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)	1 / 17 (5.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Ventricular tachycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulitis			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (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	Metformin arm	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 19 (47.37%)	7 / 17 (41.18%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache / dizziness			
subjects affected / exposed	0 / 19 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	9 / 19 (47.37%)	5 / 17 (29.41%)	
occurrences (all)	9	5	
Nausea / abdominal pain			
subjects affected / exposed	3 / 19 (15.79%)	4 / 17 (23.53%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Dry cough / dyspnea			
subjects affected / exposed	3 / 19 (15.79%)	0 / 17 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Reduced kidney function			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	1 / 17 (5.88%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	 0 / 19 (0.00%) 0	 1 / 17 (5.88%) 1	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3186355