Clinical trial results:
The Effect of Trimetazidine on Mitochondrial Function, Myocardial Performance, and Invasive Hemodynamics in Patients Diagnosed with Wild-Type Transthyretin Cardiac Amyloidosis.

Summary

EudraCT number	2020-001617-21
Trial protocol	DK
Global end of trial date	07 August 2023

Results information

Result version number	v1 (current)
This version publication date	29 October 2024
First version publication date	29 October 2024

Trial information

Trial identification

Sponsor protocol code	72864

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Aarhus University Hospital
Sponsor organisation address	Palle Juul-Jensens Boulevard 99, Aarhus, Denmark,
Public contact	Department of Cardiology, Aarhus University Hospital, berlad@rm.dk
Scientific contact	Department of Cardiology, Aarhus University Hospital, berlad@rm.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	10 July 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is:
1) to characterize the oxidative capacity of myocardial mitochondria as well as to investigate the treatment effect of Trimetazidine (TMZ) in patients with stage 1 cardiac amyloidosis in a double-blind, placebo-controlled cross-over study;
2) to examine the effect of TMZ at rest and during exercise on systolic and diastolic function measured by right heart catheterization (RHC) and advanced echocardiography;
3) to investigate and characterize the morphology of myocardial myocytes and mitochondria by electron microscopy;
4) to compare the oxidative capacity, morphology, and myocardial function of mitochondria in patients with early-stage asymptomatic disease versus patients with more advanced symptomatic disease.

Protection of trial subjects:

Data monitoring was performed by the Good Clinical Practice Unit at Aarhus University.
All subject were enrolled after providing written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2020
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: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	0
From 65 to 84 years	22
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients with early-stage wild-type transthyretin cardiac amyloidosis were recruited at the department of cardiology at Aarhus University Hospital.

Pre-assignment

Screening details:

Inclusion criteria
- Age ≥ 60 years for men. Age ≥ 70 years for women
- TC99-DPD-scintigraphy positive for cardiac involvement
- Negative serum immunofixation
- Normal Kappa/Lambda ratio
- NAC stage I (NT-proBNP ≤ 3000 ng/L, eGFR ≥ 45 mL/min)
- NYHA-class I-IIa
- Written informed consent

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	No
Arm title	Trimetazidine

Arm description:

Trimetazidine 20 mg three times daily

Arm type	Experimental
Investigational medicinal product name	trimetazidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

20 mg three times daily

Arm title	Placebo

Arm description:

Placebo three times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo three times daily

Number of subjects in period 1	Trimetazidine	Placebo
Started	24	24
Completed	22	22
Not completed	2	2
Adverse event, non-fatal	2	2

Period 2	
Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Trimetazidine

Arm description:
Trimetazidine 20 mg times three daily

Arm type	Experimental
Investigational medicinal product name	trimetazidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:
20 mg three times daily

Arm title	Placebo

Arm description:
Placebo capsule three times daily

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:
Placebo three times daily

Number of subjects in period 2	Trimetazidine	Placebo
Started	24	24
Completed	22	22
Not completed	2	2
Adverse event, non-fatal	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	24	24	
Age categorical 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)	0	0	
From 65-84 years	24	24	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	1	1	
Male	23	23	

End points

End points reporting groups	
Reporting group title	Trimetazidine
Reporting group description: Trimetazidine 20 mg three times daily	
Reporting group title	Placebo
Reporting group description: Placebo three times daily	
Reporting group title	Trimetazidine
Reporting group description: Trimetazidine 20 mg times three daily	
Reporting group title	Placebo
Reporting group description: Placebo capsule three times daily	

Primary: Pulmonary artery wedge pressure at peak exercise	
End point title	Pulmonary artery wedge pressure at peak exercise
End point description: The primary end point was a difference in peak pulmonary artery wedge pressure at peak exercise between trimetazidine and placebo.	
End point type	Primary
End point timeframe: ..	

End point values	Trimetazidine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: mmHg				
arithmetic mean (standard deviation)	31 (± 12)	31 (± 13)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Trimetazidine v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.05
Method	Mixed models analysis

Secondary: Cardiac mitochondrial oxidative capacity

End point title	Cardiac mitochondrial oxidative capacity

End point description:

The secondary end point was cardiac mitochondrial oxidative phosphorylation capacity.

End point type	Secondary

End point timeframe:

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End point values	Trimetazidine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	22		
Units: pmol O2/(mg*s)				
arithmetic mean (standard deviation)	73.4 (± 7.7)	75.3 (± 7.7)		

Statistical analyses

Statistical analysis title	Linear mixed model
Comparison groups	Trimetazidine v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	> 0.05
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

01Nov2020 to 01Aug2023

Adverse event reporting additional description:

Collected by the study team and assessed by the investigator and supervisor.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	Treatment arm

Reporting group description: -

Reporting group title	Placebo arm

Reporting group description: -

Serious adverse events	Treatment arm	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Pericardial effusion	Additional description: During biopsy procedure the patient suffered a pericardial effusion which was treated with pericardiocentesis.		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia	Additional description: After the procedures, the patient showed sustained VT on the telemetry.		
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	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	Treatment arm	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 24 (20.83%)	5 / 24 (20.83%)	
Cardiac disorders			
Dizzyness			
subjects affected / exposed	3 / 24 (12.50%)	2 / 24 (8.33%)	
occurrences (all)	3	2	
Chest discomfort			
subjects affected / exposed	1 / 24 (4.17%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Gastrointestinal disorders			
Stomach pain			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Infections and infestations			
Flu-like symptoms			
subjects affected / exposed	0 / 24 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	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