Clinical trial results:
TrimetaziDine as a Performance-enhancING drug in Heart Failure with Preserved Ejection Fraction (DoPING-HFpEF)

Summary

EudraCT number	2018-002170-52
Trial protocol	NL
Global end of trial date	22 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	Summary (Final Report CCMO METC Doping-HFpEF Manuscript version 2.7 16nov2022.pdf)

Trial information

Trial identification

Sponsor protocol code	66242

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VU University Medical Center (VUmc)
Sponsor organisation address	De Boelelaan 1117, Amsterdam, Netherlands, 1081HV
Public contact	dr. M.L. Handoko, cardiologist, VU University Medical Center (VUmc), 31 204440123, ml.handoko@vumc.nl
Scientific contact	dr. M.L. Handoko, cardiologist, VU University Medical Center (VUmc), 31 204440123, ml.handoko@vumc.nl

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	17 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2021
Global end of trial reached?	Yes
Global end of trial date	22 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the effect of a 3-month trimetazidine treatment in patients with HFpEF on LV diastology (change in exercise PCWP measured by exercise right heart catheterization or RHC)

Protection of trial subjects:

Regular medical check ups, including assesment of (serious) adverse events and kidney function. Also, strict exclusion criteria were used to exclude patients with higher risks of adverse events due to the drug.

Background therapy:

cardiofitness traject before study, weight reduction if possible, spironolacton and loop diuretics (in case of congestions).

Evidence for comparator:

Placebo.

Actual start date of recruitment	29 April 2019
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	Netherlands: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	10
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the Amsterdam University Medical Centers outpatient dyspnea/HFpEF clinic and by referral from satellite hospitals. Between May 2019 and February 2021, 231 patients were screened, 30 patients were included and randomized, of whom 25 patients completed the trial. The last patient's last follow-up visit was November 2021.

Pre-assignment

Screening details:

The key inclusion criteria were the diagnosis of clinically stable HFpEF with New York Heart Association (NYHA) functional class II or higher, despite optimal medical treatment. HFpEF was diagnosed based on symptoms of heart failure, LV ejection fraction ≥50% and evidence of LV diastolic dysfunction.

Period 1

Period 1 title	First period: Trimetazidine or placebo
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Trimetazidine

Arm description:

trimetazidine 20mg trice dialy, or twice daily in case of moderate kidney dysfunction, for three months.

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

Dosage and administration details:

Trimetazidine tablet was packed in a red capsule, indistinguishable from placebo

Arm title	Placebo

Arm description:

Placebo trice daily (or twice daily in case of moderate kidney dysfunction) for three months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Powder for concentrate
Routes of administration	Oral use

Dosage and administration details:

visually indistinguishable from trimetazidine. Powder consisted of microcrystalline cellulose powder.

Number of subjects in period 1	Trimetazidine	Placebo
Started	10	20
Completed	10	19
Not completed	0	1
Adverse event, non-fatal	-	1

Period 2

Period 2 title	Second period: trimetazidine or placebo
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Trice or twice based on kidney function, for three months

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Powder for concentrate
Routes of administration	Oral use

Dosage and administration details:

visually indistinguishable from trimetazidine. Powder consisted of microcrystalline cellulose powder.

Arm title	Trimetazidine

Arm description:

Trimetazidine 20mg trice (or twice daily in case of moderate kidney dysfunction) for three months.

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

Dosage and administration details:

Trimetazidine tablet was packed in a red capsule, indistinguishable from placebo

Number of subjects in period 2	Placebo	Trimetazidine
Started	10	19
Completed	8	17
Not completed	2	2
Adverse event, serious fatal	1	-
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	First period: Trimetazidine or placebo

Reporting group description: -

Reporting group values	First period: Trimetazidine or placebo	Total	
Number of subjects	30	30	
Age categorical Units: Subjects			
Adults	10	10	
Elderly	20	20	
Gender categorical Units: Subjects			
Female	20	20	
Male	10	10	

End points

End points reporting groups

Reporting group title	Trimetazidine
Reporting group description: trimetazidine 20mg trice dialy, or twice daily in case of moderate kidney dysfunction, for three months.	
Reporting group title	Placebo
Reporting group description: Placebo trice daily (or twice daily in case of moderate kidney dysfunction) for three months.	
Reporting group title	Placebo
Reporting group description: Trice or twice based on kidney function, for three months	
Reporting group title	Trimetazidine
Reporting group description: Trimetazidine 20mg trice (or twice daily in case of moderate kidney dysfunction) for three months.	

Primary: Change in Pulmonary Capillary Wedge Pressure at multiple levels of exercise

End point title	Change in Pulmonary Capillary Wedge Pressure at multiple levels of exercise
End point description:	
End point type	Primary
End point timeframe: at the end of the study periods	

End point values	Trimetazidine	Placebo	Trimetazidine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8[1]	8[2]	17[3]	17[4]
Units: mmHg				
geometric mean (confidence interval 95%)	0 (-2 to 2)	0 (0 to 0)	0 (-2 to 2)	0 (0 to 0)

Notes:

[1] - together with group 3. actual statistics is with mixed model but cannot be imputed here

[2] - together with group 2. =baseline

[3] - - average change (endpoint is measured with mixed model, but this cannot be imputed here). +group1

[4] - baseline (compared to trim)

Statistical analyses

Statistical analysis title	mixed-model of repeated measures analyses
Comparison groups	Trimetazidine v Trimetazidine v Placebo v Placebo

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.05
Method	Mixed models analysis

Notes:

[5] - period 1 and period 2 trimetazidine were considered one group. Compared to period 1 and 2 placebo. In total 25 patients with complete follow up were included in this analyses

Secondary: phosphocreatine (PCr) / adenosine triphosphate (ATP)

End point title	phosphocreatine (PCr) / adenosine triphosphate (ATP)

End point description:

measured with phosphorus-31 magnetic resonance spectroscopy.

End point type	Secondary

End point timeframe:

Measured at the end of both study periods

End point values	Trimetazidine	Placebo	Trimetazidine	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10[6]	10[7]	15[8]	15[9]
Units: ratio				
median (inter-quartile range (Q1-Q3))	1.08 (0.76 to 1.76)	1.30 (0.95 to 1.86)	1.08 (0.76 to 1.76)	1.30 (0.95 to 1.86)

Notes:

[6] - Trimetazidine

[7] - Placebo

[8] - Trimetazidine (together with group 1)

[9] - together with group 2 placebo

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Start screening until 4 weeks after latest drug administration	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	1
Reporting groups	
Reporting group title	Trimetazidine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: subjects affected by non-serious adverse events =23 , but cannot submit this number	

Serious adverse events	Trimetazidine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 29 (10.34%)	5 / 30 (16.67%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	1	
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Bradyarrhythmia	Additional description: Tachycardia-bradycardia requiring pacemaker		
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Appendicitis			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19	Additional description: hospitalization		
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Trimetazidine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 29 (79.31%)	20 / 30 (66.67%)	
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
worsening of heart failure	Additional description: requiring (extra) diuretics		
subjects affected / exposed	3 / 29 (10.34%)	2 / 30 (6.67%)	
occurrences (all)	3	2	
Angina pectoris			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Worsening of fatigue			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	0 / 29 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	5 / 29 (17.24%)	6 / 30 (20.00%)	
occurrences (all)	5	6	
Musculoskeletal and connective tissue disorders			
Spasm/cramp			
alternative dictionary used: SNOMED CT 1			
subjects affected / exposed	6 / 29 (20.69%)	1 / 30 (3.33%)	
occurrences (all)	6	1	
muscle pain			
subjects affected / exposed	3 / 29 (10.34%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
common cold			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2019	Adjustment of exclusion criterium 2 (to increase inclusion rate); initially all patients with a history of myocardial infarction were excluded, this was changed to patients with suspected septal scar (for the inability to perform PCr/ATP assesment in these patients). Endpoint: assesment of white blood cell mitochondrial function was removed, as we were unable to perform this at our hospital.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 May 2020	Inclusions were temporarily halted during the first COVID-19 outbreak.	15 June 2020

Notes:

Limitations and caveats

None reported