Clinical trial results:
Controlled trial on the short-term effects of sacubitril/valsartan therapy on cardiac oxygen consumption and efficiency of cardiac work in patients with NYHA II-III heart failure and reduced systolic function using 11C-acetate positron emission tomography and echocardiography

Summary

EudraCT number	2017-002113-64
Trial protocol	FI
Global end of trial date	23 March 2022

Results information

Result version number	v1 (current)
This version publication date	05 April 2023
First version publication date	05 April 2023

Trial information

Trial identification

Sponsor protocol code	CLCZ696BFI03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03300427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NovartisPharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Study Director , Novartis PharmaAG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Study Director , Novartis PharmaAG, 41 613241111, Novartis.email@Novartis.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	23 March 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the effects of 6 weeks of stable sacubitril/valsartan therapy, as compared with valsartan therapy, on the efficiency of cardiac work in patients with New York Heart Association (NYHA) II-III heart failure (HF) and reduced systolic function using 11C-acetate and echocardiography. In order to do this, the difference in cardiac efficiency was evaluated by comparing the results obtained after 6 weeks of stable treatment to the results from the Baseline visit.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 July 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	Finland: 55
Worldwide total number of subjects	55
EEA total number of subjects	55

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)	24

From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The patients who signed the ICF entered the screening/run-in period of the study. After the screening evaluations and confirmation of eligibility, the patients were allocated randomization numbers and randomized to receive the treatment assigned to each number in a blinded manner.

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	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	sacubitril/valsartan

Arm description:

subjects receive sacubitril/valsartan 100 mg orally twice daily (BID). The dose is then up-titrated to 200 mg BID (or maintained at the starting dose level, if up-titration is not possible).

Arm type	Experimental
Investigational medicinal product name	sacubitril/valsartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

100 mg or 200 mgoral tablet

Arm title	valsartan

Arm description:

subjects receive 80 mg orally twice daily (BID). The dose is then up-titrated to 160 mg BID (or maintained at the starting level, if up-titration is not possible)

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

Dosage and administration details:

80 mg or 160 mgoral tablet

Number of subjects in period 1	sacubitril/valsartan	valsartan
Started	27	28
Completed	27	28

Baseline characteristics

Reporting groups	
Reporting group title	sacubitril/valsartan
Reporting group description:	
subjects receive sacubitril/valsartan 100 mg orally twice daily (BID). The dose is then up-titrated to 200 mg BID (or maintained at the starting dose level, if up-titration is not possible).	
Reporting group title	valsartan
Reporting group description:	
subjects receive 80 mg orally twice daily (BID). The dose is then up-titrated to 160 mg BID (or maintained at the starting level, if up-titration is not possible)	

Reporting group values	sacubitril/valsartan	valsartan	Total
Number of subjects	27	28	55
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)	12	12	24
From 65-84 years	15	16	31
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	63.1	64.4	
standard deviation	± 10.1	± 7.5	-
Sex: Female, Male Units: participants			
Female	5	7	12
Male	22	21	43
Race/Ethnicity, Customized Units: Subjects			
White	27	28	55

End points

End points reporting groups

Reporting group title	sacubitril/valsartan
Reporting group description:	
subjects receive sacubitril/valsartan 100 mg orally twice daily (BID). The dose is then up-titrated to 200 mg BID (or maintained at the starting dose level, if up-titration is not possible).	
Reporting group title	valsartan
Reporting group description:	
subjects receive 80 mg orally twice daily (BID). The dose is then up-titrated to 160 mg BID (or maintained at the starting level, if up-titration is not possible)	

Primary: Myocardial energetic efficiency

End point title	Myocardial energetic efficiency[1]
End point description:	
Positron emission tomography (PET) imaging and echocardiography were performed before randomization (after a minimum of 4 weeks on stable dose of 80 mg BID or 160 mg BID of valsartan) and repeated after 6 weeks on a stable dose of either 80 mg BID or 160 mg BID of valsartan or 100 mg BID or 200 mg BID of sacubitril/valsartan. Cardiac efficiency was calculated based on the following formula: Myocardial efficiency = ((SBP x SV x HR)/LV mass)/Kmono Where - SBP : Systolic blood pressure during PET - SV : Stroke volume (Echocardiography) - HR : Heart rate - Kmono: Mono-exponential clearance rate (11C-acetate PET- scan) - LV mass: Left ventricular mass Visit 3 was performed after the study treatment was on a stable dose for a minimum of 6 weeks. It could be performed before or after 8 weeks, based on when the last dose modification was performed. No imputation of missing data was performed.	
End point type	Primary
End point timeframe:	
Baseline, Visit 3 (approximately Week 8)	
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: No statistical analysis was planned for this outcome.	

End point values	sacubitril/valsartan	valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: (((mmhg x ml x bpm) /g)/(1/min))				
arithmetic mean (standard deviation)				
Baseline (Day 1)	48621.3 (± 17001.4)	50035.7 (± 18068.2)		
Visit 3	50301.0 (± 20842.7)	52942.8 (± 19702.5)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in myocardial energetic efficiency

End point title	Change from baseline in myocardial energetic efficiency

End point description:

Positron emission tomography (PET) imaging and echocardiography were performed before randomization (after a minimum of 4 weeks on stable dose of 80 mg BID or 160 mg BID of valsartan) and repeated after 6 weeks on a stable dose of either 80 mg BID or 160 mg BID of valsartan or 100 mg BID or 200 mg BID of sacubitril/valsartan.

Cardiac efficiency was calculated based on the following formula: Myocardial efficiency = ((SBP x SV x HR)/LV mass)/Kmono
Where
- SBP : Systolic blood pressure during PET
- SV : Stroke volume (Echocardiography)
- HR : Heart rate
- Kmono: Mono-exponential clearance rate (11C-acetate PET- scan)
- LV mass: Left ventricular mass

Visit 3 was performed after the study treatment was on a stable dose for a minimum of 6 weeks. It could be performed before or after 8 weeks, based on when the last dose modification was performed.

No imputation of missing data was performed.

End point type	Primary

End point timeframe:

Baseline, Visit 3 (approximately Week 8)

End point values	sacubitril/valsartan	valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: (((mmhg x ml x bpm) /g)/(1/min))				
arithmetic mean (standard deviation)	1679.8 (± 9282.4)	2907.1 (± 11571.5)		

Statistical analyses

Statistical analysis title	Myocardial energetic efficiency

Statistical analysis description:

Analysis of change from baseline in Myocardial energetic efficiency. The study hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in subjects with systolic HF.

Comparison groups	sacubitril/valsartan v valsartan
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7594
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	-900

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6781.7
upper limit	4981.8

Primary: Viable myocardial energetic efficiency (sensitivity analysis)

End point title	Viable myocardial energetic efficiency (sensitivity analysis)[2]

End point description:

In addition to the derivation of the primary endpoint, an alternative formula was used, where the viable myocardial energetic efficiency was derived as:
Viable myocardial energetic efficiency = ((SBP x SV x HR)/LV mass) / vKmono
Where vKmono is the viable myocardium clearance rate. This alternative parameter was included as a sensitivity analysis to exclude possible bias related to scar tissue in patients with ischemic myopathy.

End point type	Primary

End point timeframe:

Baseline, Visit 3 (approximately Week 8)

Notes:

[2] - 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: No statistical analysis was planned for this outcome.

End point values	sacubitril/valsartan	valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: (((mmhg x ml x bpm) /g)/(1/min))				
arithmetic mean (standard deviation)				
Baseline	48163.0 (± 16719.8)	49575.6 (± 18255.8)		
Visit 3	49914.4 (± 20821.2)	52249.9 (± 19585.8)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from baseline in viable myocardial energetic efficiency (sensitivity analysis)

End point title	Change from baseline in viable myocardial energetic efficiency (sensitivity analysis)

End point description:

In addition to the derivation of the primary endpoint, an alternative formula was used, where the viable myocardial energetic efficiency was derived as:
Viable myocardial energetic efficiency = ((SBP x SV x HR)/LV mass) / vKmono
Where vKmono is the viable myocardium clearance rate. This alternative parameter was included as a sensitivity analysis to exclude possible bias related to scar tissue in patients with ischemic myopathy.

End point type	Primary

End point timeframe:

Baseline, Visit 3 (approximately Week 8)

End point values	sacubitril/valsartan	valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	28		
Units: (((mmhg x ml x bpm) /g)/(1/min))				
arithmetic mean (standard deviation)	1751.4 (± 9098.1)	2674.3 (± 11551.2)		

Statistical analyses

Statistical analysis title	Viable myocardium energetic efficiency

Statistical analysis description:

Analysis of change from baseline in Viable myocardium energetic efficiency. The study hypothesis is that short-term therapy with sacubitril/valsartan added on standard HF therapy improves cardiac efficiency in subjects with systolic HF.

Comparison groups	sacubitril/valsartan v valsartan
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8422
Method	ANCOVA
Parameter estimate	difference in least square means
Point estimate	-575.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6365.5
upper limit	5214.5

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 86 days.

Adverse event reporting additional description:

The occurrence of adverse events was sought by non-directive questioning of the patient at each visit during the study. Adverse events were also detected when they were volunteered by the patient during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Valsartan

Reporting group description:

Valsartan

Reporting group title	Sacubitril/Valsartan

Reporting group description:

Sacubitril/Valsartan

Serious adverse events	Valsartan	Sacubitril/Valsartan	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Valsartan	Sacubitril/Valsartan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)	4 / 27 (14.81%)	
Investigations			

Blood potassium increased			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 28 (3.57%)	2 / 27 (7.41%)	
occurrences (all)	1	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	1 / 28 (3.57%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 28 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 January 2019	The possibility to perform Screening visit 2 and Visit 2 as remote visits to reduce the number of site visits and thus the burden caused by the study on the patients.
24 June 2020	Changing the upper age limit of the eligible patients from 75 to 80 years to improve of recruitment rate. Several eligible study candidates had been aged between 75 and 80 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported