Clinical trial results:
Personalised prospective comparison of ARni with ArB in patients with natriuretic peptide eLEvation (PARABLE)

Summary

EudraCT number	2015-002928-53
Trial protocol	IE
Global end of trial date	11 June 2021

Results information

Result version number	v1 (current)
This version publication date	21 December 2022
First version publication date	21 December 2022

Trial information

Trial identification

Sponsor protocol code	HBT-GCP-PTCL-01

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Heartbeat Trust
Sponsor organisation address	3 Crofton Terrace, Dun Laoghaire, Dublin, Ireland, A96 K2R5
Public contact	Fiona Ryan, Director of Clinical Trials, The Heartbeat Trust, fiona@heartbeat-trust.org
Scientific contact	Fiona Ryan, Director of Clinical Trials, The Heartbeat Trust, fiona@heartbeat-trust.org

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	12 March 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2020
Global end of trial reached?	Yes
Global end of trial date	11 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the impact of LCZ696 (ARNI) versus angiotensin receptor blocker (ARB) (valsartan) on left ventricular diastolic function (as measured by cardiac magnetic resonance imaging) over 18 months.

Protection of trial subjects:

The PARABLE study was conducted in compliance with the principles laid down in the Declaration of Helsinki, ICH-GCP, the requirements of the EU Data Protection Regulation, and all applicable EU and national laws. The study investigators and staff were provided with information to ensure that the study was performed to the highest possible standard, with particular attention to the patients' rights and their protection. Study protocols including consent documents were approved in by an approved Ethics Committee (EC) and the national competent authority. Safeguards were in place to minimise any risk of privacy and confidentiality breaches. Participants were adequately informed prior to their inclusion about the voluntary nature of his/her participation, confidentiality and protection of his/her data, potential risks and benefits of participation, insurance coverage and the possibility of withdrawal at any time. Freely given informed consent was obtained from and documented in writing, signed and dated personally by each patient before inclusion in the study. Safety information was collected throughout the study. Serious adverse events (SAEs) were reviewed the Principal Investigator and notified to the local EC each month. Listings of SAEs were presented to the Data Management Board every 6 months for discussion and review.

Background therapy:

Following enrollment, therapy with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) were discontinued. Other background medications remained unchanged.

Evidence for comparator:

LCZ696 (sacubitril/valsartan), is a first-in-class angiotensin receptor neprilysin inhibitor (ARNI). In addition to blockade of the renin-angiotensin-aldosterone system (RAAS) via the valsartan moiety, the sacubitril component inhibits neprilysin, resulting in reduced degradation of biologically active natriuretic peptides. A previous 36-week study showed that LCZ696 in comparison with valsartan can provide greater reduction in left atrial volume index (LAVI), a continuous imaging surrogate of left ventricular diastolic dysfunction, when given to patients with heart failure. In the PARABLE study, valsartan was chosen as the comparator to assess the relative impact of both agents on LAVI in at-risk, asymptomatic patients with elevated natriuretic peptides over 18 months.

200mg of LCZ696 twice daily delivers similar exposure of valsartan (assessed by AUC) as valsartan 160mg twice daily. (Novartis Company Information).

Actual start date of recruitment	05 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 250

Worldwide total number of subjects	250
EEA total number of subjects	250

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)	39
From 65 to 84 years	202
85 years and over	9

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

323 people were screened and 250 were enrolled into the study. Male or females, ≥40 years with cardiovascular risk factors were invited to participate (this information was available from their medical notes). Subjects underwent an echocardiographic assessment of LAVI and a blood sample was obtained for measurement of natriuretic peptide levels.

Period 1

Period 1 title	Baseline
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	LCZ696

Arm description:

Treatment with LCZ696 (sacubitril/valsartan).
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of LCZ696 50mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 100mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 200mg (Phase 3) twice daily for the remaining 18-month study period.

Arm type	Experimental
Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	Sacubitril/valsartan, Entresto
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.
Lower dose regimen: LCZ696 50mg (Phase 1) twice daily, for 2 weeks, titrated to 100mg (Phase 2) twice daily for 2 weeks, then further titrated to 200mg (Phase 3) twice daily for the remaining 18 month study period. The formulation was a coated tablet for oral administration.

Arm title	Valsartan

Arm description:

Treatment with Valsartan.
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: Valsartan 80mg (Phase 2) twice daily for 2 weeks titrated to 160mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of valsartan 40mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 80mg (Phase 2) twice daily for

another 2 weeks then titrated to the target dose of 160mg (Phase 3) twice daily for the remaining 18-month study period.

Arm type	Active comparator
Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	Diovan
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.
Lower dose regimen: LCZ696 50mg (Phase 1) twice daily, for 2 weeks, titrated to 100mg (Phase 2) twice daily for 2 weeks, then further titrated to 200mg (Phase 3) twice daily for the remaining 18 month study period. The formulation was a coated tablet for oral administration.

Number of subjects in period 1	LCZ696	Valsartan
Started	122	128
Completed	122	128

Period 2

Period 2 title	Treatment Phase
Is this the baseline period?	No
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	LCZ696

Arm description:

Treatment with LCZ696 (sacubitril/valsartan).
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of LCZ696 50mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 100mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 200mg (Phase 3) twice daily for the remaining 18-month study period.

Arm type	Experimental

Investigational medicinal product name	LCZ696
Investigational medicinal product code	
Other name	Sacubitril/valsartan, Entresto
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.
Lower dose regimen: LCZ696 50mg (Phase 1) twice daily, for 2 weeks, titrated to 100mg (Phase 2) twice daily for 2 weeks, then further titrated to 200mg (Phase 3) twice daily for the remaining 18 month study period. The formulation was a coated tablet for oral administration.

Arm title	Valsartan

Arm description:

Treatment with Valsartan.
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: Valsartan 80mg (Phase 2) twice daily for 2 weeks titrated to 160mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of valsartan 40mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 80mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 160mg (Phase 3) twice daily for the remaining 18-month study period.

Arm type	Active comparator
Investigational medicinal product name	Valsartan
Investigational medicinal product code	
Other name	Diovan
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.
Lower dose regimen: LCZ696 50mg (Phase 1) twice daily, for 2 weeks, titrated to 100mg (Phase 2) twice daily for 2 weeks, then further titrated to 200mg (Phase 3) twice daily for the remaining 18 month study period. The formulation was a coated tablet for oral administration.

Number of subjects in period 2	LCZ696	Valsartan
Started	122	128
Completed	96	104
Not completed	26	24
Adverse event, serious fatal	2	3
Consent withdrawn by subject	-	3
Adverse event, non-fatal	10	14
Personal Reasons	10	-
Lost to follow-up	4	4

Baseline characteristics

Reporting groups	
Reporting group title	LCZ696

Reporting group description:

Treatment with LCZ696 (sacubitril/valsartan).
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of LCZ696 50mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 100mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 200mg (Phase 3) twice daily for the remaining 18-month study period.

Reporting group title	Valsartan

Reporting group description:

Treatment with Valsartan.
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: Valsartan 80mg (Phase 2) twice daily for 2 weeks titrated to 160mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of valsartan 40mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 80mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 160mg (Phase 3) twice daily for the remaining 18-month study period.

Reporting group values	LCZ696	Valsartan	Total
Number of subjects	122	128	250
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	72.4	71.1	
standard deviation	± 7.73	± 7.52	-
Gender categorical Units: Subjects			
Female	43	53	96
Male	79	75	154
Hypertension Units: Subjects			
Yes	120	125	245
No	2	3	5
Diabetes mellitus Units: Subjects			
Yes	35	25	60
No	87	103	190

Paroxysmal atrial fibrillation Units: Subjects			
Yes	15	10	25
No	107	118	225
Dyslipidemia Units: Subjects			
Yes	109	113	222
No	13	15	28
Other vascular disease Units: Subjects			
Yes	2	4	6
No	120	124	244
Stroke/TIA Units: Subjects			
Yes	8	15	23
No	114	113	227
Angiotensin converting enzyme inhibitor Units: Subjects			
Yes	60	63	123
No	62	65	127
Angiotensin receptor blocker Units: Subjects			
Yes	52	49	101
No	70	79	149
Beta-blocker Units: Subjects			
Yes	70	69	139
No	52	59	111
Chronic kidney disease Units: Subjects			
Yes	23	24	47
No	99	104	203
Alpha-blocker Units: Subjects			
Yes	21	25	46
No	101	103	204
Calcium channel blocker Units: Subjects			
Yes	49	61	110
No	73	67	140
Aldosterone antagonist Units: Subjects			
Yes	12	7	19
No	110	121	231
Statin Units: Subjects			
Yes	98	102	200
No	24	26	50
Other lipid lowering agent (excluding statins) Units: Subjects			

Yes	5	9	14
No	117	119	236
Diuretic Units: Subjects			
Yes	122	128	250
No	0	0	0
Angina Units: Subjects			
Yes	10	11	21
No	112	117	229
Aliskiren Units: Subjects			
Yes	122	128	250
No	0	0	0
Digoxin Units: Subjects			
Yes	0	1	1
No	122	127	249
Ivabradine Units: Subjects			
Yes	1	3	4
No	121	125	246
Anti-arrhythmic Units: Subjects			
Yes	6	5	11
No	116	123	239
Myocardial Infarction Units: Subjects			
Yes	18	20	38
No	104	108	212
Aspirin Units: Subjects			
Yes	74	86	160
No	48	42	90
Non-aspirin antiplatelet Units: Subjects			
Yes	8	11	19
No	114	117	231
DOAC Units: Subjects			
Yes	11	8	19
No	111	120	231
Warfarin Units: Subjects			
Yes	3	0	3
No	119	128	247
Oral antidiabetic Units: Subjects			
Yes	28	23	51
No	94	105	199
Insulin			

Units: Subjects			
Yes	6	5	11
No	116	123	239
Sulphonylurea Units: Subjects			
Yes	7	7	14
No	115	121	236
DPP4 inhibitor Units: Subjects			
Yes	4	5	9
No	118	123	241
Gliptin Units: Subjects			
Yes	0	1	1
No	122	127	249
SGLT2 Inhibitor Units: Subjects			
Yes	2	1	3
No	120	127	247
Pioglitizone Units: Subjects			
Yes	1	1	2
No	121	127	248
Systolic blood pressure Units: mmHg			
median	135	137	
inter-quartile range (Q1-Q3)	125 to 147	123 to 149	-
Diastolic blood pressure Units: mmHg			
median	74	75	
inter-quartile range (Q1-Q3)	68 to 82	68 to 83	-
Heart rate Units: beats per minute			
median	61	64	
inter-quartile range (Q1-Q3)	56 to 70	57 to 70	-
Body mass index Units: kg per m2			
arithmetic mean	29.4	29.6	
standard deviation	± 4.93	± 5.21	-
BNP Units: picogram(s) per mL			
median	59	52.4	
inter-quartile range (Q1-Q3)	33.5 to 109	32.7 to 91.2	-
NT-proBNP Units: picogram(s) per mL			
median	136	138	
inter-quartile range (Q1-Q3)	88.2 to 278	84 to 247	-
Total cholesterol Units: millimole(s)/litre			
median	4.15	4.4	
inter-quartile range (Q1-Q3)	3.5 to 5.03	3.8 to 5.1	-

Low density lipoprotein cholesterol			
Units: millimole(s)/litre			
median	2.2	2.2	
inter-quartile range (Q1-Q3)	1.6 to 2.6	1.78 to 2.9	-
Triglycerides			
Units: millimole(s)/litre			
median	1.4	1.35	
inter-quartile range (Q1-Q3)	0.9 to 1.9	0.9 to 1.9	-
Sodium			
Units: millimole(s)/litre			
median	138	138	
inter-quartile range (Q1-Q3)	137 to 140	136 to 140	-
Potassium			
Units: millimole(s)/litre			
median	4.2	4.2	
inter-quartile range (Q1-Q3)	4 to 4.4	3.9 to 4.4	-
Creatinine			
Units: millimole(s)/litre			
median	76	79.5	
inter-quartile range (Q1-Q3)	65 to 94.2	65 to 93.2	-
Estimated glomerular filtration rate (eGFR)			
Units: millilitre(s)/minute/1.73m2			
median	78	77	
inter-quartile range (Q1-Q3)	64 to 90	65 to 90	-
Bilirubin			
Units: micromole(s)/litre			
median	13	13	
inter-quartile range (Q1-Q3)	11 to 16	11 to 17	-
Alkaline phosphatase (Alk phos)			
Units: unit(s)/litre			
median	63	66	
inter-quartile range (Q1-Q3)	52 to 75.2	54 to 76	-
Alanine aminotransferase (ALT)			
Units: unit(s)/litre			
median	22	21	
inter-quartile range (Q1-Q3)	18 to 28	18 to 29	-
Aspartate aminotransferase (AST)			
Units: unit(s)/litre			
median	24	24	
inter-quartile range (Q1-Q3)	21 to 28	22 to 29.2	-
Gamma glutamyl transferase (GGT)			
Units: unit(s)/litre			
median	22	21	
inter-quartile range (Q1-Q3)	16 to 30.5	16 to 33	-
Ferritin			
Units: gram(s)/litre			
median	104	91	
inter-quartile range (Q1-Q3)	58.5 to 142	45.5 to 144	-
Left ventricular ejection fraction (LVEF)			
As measured by echocardiography			
Units: percent			

median	67	67.6	
inter-quartile range (Q1-Q3)	62 to 72.5	62.2 to 72	-
Left ventricular mass index (LVMI)			
As measured by echocardiography			
Units: gram(s)/square meter			
median	106	106	
inter-quartile range (Q1-Q3)	95.9 to 124	90.7 to 121	-
Left atrial volume index (LAVI)			
As measured by echocardiography			
Units: millilitre(s)/square metre			
median	33.5	33.2	
inter-quartile range (Q1-Q3)	30.6 to 37.4	30.8 to 38.5	-
E/E'			
As measured by echocardiography			
Units: ratio			
median	11.1	9.87	
inter-quartile range (Q1-Q3)	9.1 to 13	8.05 to 12.3	-
Hb1Ac			
Units: mmol/mol			
median	39	38	
inter-quartile range (Q1-Q3)	36 to 43.5	36 to 43	-
Chloride			
Units: mmol/L			
median	103	103	
inter-quartile range (Q1-Q3)	100 to 105	101 to 105	-
Urea			
Units: mmol/L			
median	6.70	7.05	
inter-quartile range (Q1-Q3)	5.90 to 8.00	6.00 to 8.50	-
Albumin			
Units: g/L			
median	42.0	42.0	
inter-quartile range (Q1-Q3)	40.0 to 44.0	40.0 to 44.0	-
Bilirubin			
Units: mg/L			
median	13.0	13.0	
inter-quartile range (Q1-Q3)	11.0 to 16.0	11.0 to 17.0	-
Alkaline Phosphatase			
Units: u/L			
median	66.0	63.0	
inter-quartile range (Q1-Q3)	54.0 to 76.0	52.0 to 75.2	-
GGT			
Units: u/L			
median	22.0	21.0	
inter-quartile range (Q1-Q3)	16.0 to 30.5	16.0 to 33.0	-
ALT			
Units: u/L			
median	22.0	21.0	
inter-quartile range (Q1-Q3)	18.0 to 28.0	18.0 to 29.0	-
AST			
Units: u/L			
median	24.0	24.0	

inter-quartile range (Q1-Q3)	21.0 to 28.0	22.0 to 29.2	-
Haemoglobin			
Units: g/dl			
median	13.4	13.5	
inter-quartile range (Q1-Q3)	12.5 to 14.4	12.5 to 14.4	-
Ferritin			
Units: microgram(s)/litre			
median	104	91.0	
inter-quartile range (Q1-Q3)	58.5 to 142	45.5 to 144	-

End points

End points reporting groups

Reporting group title	LCZ696

Reporting group description:

Treatment with LCZ696 (sacubitril/valsartan).
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of LCZ696 50mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 100mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 200mg (Phase 3) twice daily for the remaining 18-month study period.

Reporting group title	Valsartan

Reporting group description:

Treatment with Valsartan.
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: Valsartan 80mg (Phase 2) twice daily for 2 weeks titrated to 160mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of valsartan 40mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 80mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 160mg (Phase 3) twice daily for the remaining 18-month study period.

Reporting group title	LCZ696

Reporting group description:

Treatment with LCZ696 (sacubitril/valsartan).
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: LCZ696 100mg (Phase 2) twice daily for 2 weeks titrated to 200mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of LCZ696 50mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 100mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 200mg (Phase 3) twice daily for the remaining 18-month study period.

Reporting group title	Valsartan

Reporting group description:

Treatment with Valsartan.
Following randomisation, treatment with existing ACEI or ARB therapy was discontinued. A 36-hour wash-out period was required for anyone previously taking an ACEI.
Standard dose regimen: Valsartan 80mg (Phase 2) twice daily for 2 weeks titrated to 160mg (Phase 3) twice daily for the remaining 18-month study period.

Lower dose regimen: A starting dose of valsartan 40mg (Phase 1) twice daily was used for anyone not currently taking an ACEI or ARB and for subjects previously taking low doses of these agents (as per Investigator judgement). A lower dosing regimen was also used for subjects with a systolic BP of ≥100mm to 110mmHg at screening or baseline. This was then titrated to 80mg (Phase 2) twice daily for another 2 weeks then titrated to the target dose of 160mg (Phase 3) twice daily for the remaining 18-month study period.

Primary: Left atrial volume index (LAVI) (cardiac MRI) between baseline and 18 months

End point title	Left atrial volume index (LAVI) (cardiac MRI) between baseline and 18 months

End point description:

Change in left atrial volume index (LAVI) as measured by cardiac MRI between baseline and 18 months

End point type	Primary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: millilitre(s)/meter squared				
arithmetic mean (confidence interval 95%)	6.9 (0.0 to 13.7)	0.7 (-6.3 to 7.7)		

Statistical analyses

Statistical analysis title	Primary Endpoint
Comparison groups	LCZ696 v Valsartan
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	The primary endpoint was presented as po

Secondary: Left ventricular function (Doppler Echocardiography) (average E/e') between baseline and 18 months

End point title	Left ventricular function (Doppler Echocardiography) (average E/e') between baseline and 18 months

End point description:

Change in left ventricular function using Doppler Echocardiography (average E/e') between baseline and 18 months

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: ratio				
number (confidence interval 95%)	-0.55 (-1.63 to 0.53)	-0.26 (-1.31 to 0.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left atrial volume index (Doppler Echocardiography) between baseline and 18 months

End point title	Left atrial volume index (Doppler Echocardiography) between baseline and 18 months

End point description:

Left atrial volume index (Doppler Echocardiography LAV)/BSA* between baseline and 18 months
*BSA calculated using the DuBois formula

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: millilitre(s)/square meter				
arithmetic mean (confidence interval 95%)	0.78 (-0.48 to 2.04)	1.63 (0.49 to 2.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left atrial function (cardiac MRI) measured as left atrial ejection fraction between baseline and 18 months

End point title	Left atrial function (cardiac MRI) measured as left atrial ejection fraction between baseline and 18 months

End point description:

Left atrial function measured as total cardiac MRI LAEF ((LAVimax-LAVimin)/LAVimax) over 18 months

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: percent				
arithmetic mean (confidence interval 95%)	0.9 (-3.5 to 5.4)	1 (-3.5 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left atrial function (cardiac MRI) measured as left atrial stroke volume index between baseline and 18 months

End point title	Left atrial function (cardiac MRI) measured as left atrial stroke volume index between baseline and 18 months

End point description:

Left atrial function measured as cMRI left atrial stroke volume index (LAVmax-LAVmin)/BSA*, or LAVimax-LAVimin over 18 months
*BSA calculated using the DuBois formula

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: millilitre(s)/square meter				
arithmetic mean (confidence interval 95%)	3.1 (-0.2 to 6.4)	0.9 (-2.4 to 4.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular structure (cardiac MRI) measured as left ventricular mass index between baseline and 18 months

End point title	Left ventricular structure (cardiac MRI) measured as left ventricular mass index between baseline and 18 months

End point description:

Left ventricular structure (cMRI LVMi indexed to BSA*) over 18 months
*BSA calculated using the DuBois formula

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: gram(s)/square meter				
arithmetic mean (confidence interval 95%)	-6.2 (-13.4 to 1.1)	-6.2 (-13.7 to 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Left ventricular function (cardiac MRI) as measured by left ventricular ejection fraction between baseline and 18 months

End point title	Left ventricular function (cardiac MRI) as measured by left ventricular ejection fraction between baseline and 18 months

End point description:

Left ventricular function (cardiac MRI) LVEF over 18 months

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	104		
Units: percent				
arithmetic mean (confidence interval 95%)	-1.4 (-4.5 to 1.7)	-1.2 (-4.2 to 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vascular compliance, as measured by pulse pressure (ambulatory blood pressure monitoring) between baseline and 18 months

End point title	Vascular compliance, as measured by pulse pressure (ambulatory blood pressure monitoring) between baseline and 18 months

End point description:

Measures of vascular compliance (ABPM pulse pressure) between baseline and 18 months

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: millimeter(s) of mercury				
arithmetic mean (confidence interval 95%)	-4.2 (-7.2 to -1.2)	-1.2 (-4.1 to 1.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Log transformed NT-proBNP between baseline and 18 months

End point title	Log transformed NT-proBNP between baseline and 18 months

End point description:

Change in log transformed NT-proBNP between baseline and 18 months

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: percent				
arithmetic mean (confidence interval 95%)	-17.7 (-36.9 to 7.4)	4.9 (-15.6 to 9.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first all cardiovascular death and major adverse cardiac events (MACE) requiring hospitalisation over 18 months

End point title	Time to first all cardiovascular death and major adverse cardiac events (MACE) requiring hospitalisation over 18 months

End point description:

Time to first all cardiovascular death and major adverse cardiac events (MACE) requiring hospitalisation over 18 months. MACE includes arrthymia (including atrial fibrillation/flutter), transient ischaemic attack, stroke, valvular heart disease, myocardial infarction, peripheral or pulmonary thrombosis/embolus or heart failure

End point type	Secondary

End point timeframe:

18 months

End point values	LCZ696	Valsartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	128		
Units: Hazard Ratio				
number (confidence interval 95%)	0.38 (0.17 to 0.89)	2.63 (1.12 to 5.88)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
18 months	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	LCZ696 (Intervention)
Reporting group description: -	
Reporting group title	Valsartan (control)
Reporting group description: -	

Serious adverse events	LCZ696 (Intervention)	Valsartan (control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 122 (22.13%)	46 / 128 (35.94%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid tumour of the caecum			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant urinary tract neoplasm			

subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid carcinoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer stage IV			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
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	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 122 (0.82%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 122 (0.82%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Spinal decompression			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 122 (0.82%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimers type			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			

subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral injury			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 122 (4.10%)	8 / 128 (6.25%)	
occurrences causally related to treatment / all	1 / 5	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 122 (0.82%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter			

subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 122 (1.64%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 122 (1.64%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Palpitations			

subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifasicular block			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Muscular weakness			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular hole			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular disease			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Angioedema			

subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 122 (0.00%)	4 / 128 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 122 (0.00%)	3 / 128 (2.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal osteoarthritis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Vestibular neuronitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	3 / 122 (2.46%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 122 (0.82%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 122 (0.82%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 122 (0.00%)	2 / 128 (1.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Community acquired pneumonia			
subjects affected / exposed	0 / 122 (0.00%)	1 / 128 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 122 (1.64%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 122 (0.82%)	0 / 128 (0.00%)	
occurrences causally related to treatment / all	1 / 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	LCZ696 (Intervention)	Valsartan (control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	122 / 122 (100.00%)	124 / 128 (96.88%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	7 / 122 (5.74%)	12 / 128 (9.38%)	
occurrences (all)	7	12	
Injury, poisoning and procedural complications			
Back pain			
subjects affected / exposed	18 / 122 (14.75%)	14 / 128 (10.94%)	
occurrences (all)	18	16	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 122 (4.10%)	8 / 128 (6.25%)	
occurrences (all)	6	9	
Blood pressure inadequately controlled			

subjects affected / exposed	8 / 122 (6.56%)	14 / 128 (10.94%)	
occurrences (all)	9	19	
Hypertension			
subjects affected / exposed	18 / 122 (14.75%)	43 / 128 (33.59%)	
occurrences (all)	20	52	
Hypotension			
subjects affected / exposed	9 / 122 (7.38%)	14 / 128 (10.94%)	
occurrences (all)	9	14	
Palpitations			
subjects affected / exposed	20 / 122 (16.39%)	16 / 128 (12.50%)	
occurrences (all)	23	20	
Nervous system disorders			
Dizziness			
subjects affected / exposed	51 / 122 (41.80%)	45 / 128 (35.16%)	
occurrences (all)	59	59	
Dizziness postural			
subjects affected / exposed	9 / 122 (7.38%)	7 / 128 (5.47%)	
occurrences (all)	9	8	
Headache			
subjects affected / exposed	7 / 122 (5.74%)	22 / 128 (17.19%)	
occurrences (all)	8	29	
Hypoaesthesia			
subjects affected / exposed	5 / 122 (4.10%)	9 / 128 (7.03%)	
occurrences (all)	6	9	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	27 / 122 (22.13%)	31 / 128 (24.22%)	
occurrences (all)	32	35	
Fatigue			
subjects affected / exposed	34 / 122 (27.87%)	47 / 128 (36.72%)	
occurrences (all)	39	55	
Oedema			
subjects affected / exposed	15 / 122 (12.30%)	17 / 128 (13.28%)	
occurrences (all)	16	19	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	2 / 122 (1.64%)	7 / 128 (5.47%)	
occurrences (all)	4	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	18 / 122 (14.75%)	14 / 128 (10.94%)	
occurrences (all)	19	15	
Diarrhoea			
subjects affected / exposed	22 / 122 (18.03%)	18 / 128 (14.06%)	
occurrences (all)	26	22	
Nausea			
subjects affected / exposed	4 / 122 (3.28%)	11 / 128 (8.59%)	
occurrences (all)	4	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	27 / 122 (22.13%)	13 / 128 (10.16%)	
occurrences (all)	31	15	
Dyspnoea			
subjects affected / exposed	19 / 122 (15.57%)	24 / 128 (18.75%)	
occurrences (all)	23	29	
Dyspnoea exertional			
subjects affected / exposed	8 / 122 (6.56%)	11 / 128 (8.59%)	
occurrences (all)	8	11	
Rhinorrhoea			
subjects affected / exposed	8 / 122 (6.56%)	8 / 128 (6.25%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 122 (9.84%)	7 / 128 (5.47%)	
occurrences (all)	14	7	
Rash			
subjects affected / exposed	11 / 122 (9.02%)	8 / 128 (6.25%)	
occurrences (all)	13	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	17 / 122 (13.93%)	21 / 128 (16.41%)	
occurrences (all)	20	31	
Arthritis			
subjects affected / exposed	4 / 122 (3.28%)	11 / 128 (8.59%)	
occurrences (all)	4	13	
Joint swelling			
subjects affected / exposed	6 / 122 (4.92%)	15 / 128 (11.72%)	
occurrences (all)	8	16	
Pain in extremity			
subjects affected / exposed	13 / 122 (10.66%)	20 / 128 (15.63%)	
occurrences (all)	14	23	
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	25 / 122 (20.49%)	23 / 128 (17.97%)	
occurrences (all)	31	30	
Nasopharyngitis			
subjects affected / exposed	28 / 122 (22.95%)	26 / 128 (20.31%)	
occurrences (all)	32	31	
Respiratory tract infection			
subjects affected / exposed	14 / 122 (11.48%)	11 / 128 (8.59%)	
occurrences (all)	14	12	
Sinusitis			
subjects affected / exposed	4 / 122 (3.28%)	8 / 128 (6.25%)	
occurrences (all)	5	10	
Urinary tract infection			
subjects affected / exposed	9 / 122 (7.38%)	5 / 128 (3.91%)	
occurrences (all)	12	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 122 (11.48%)	13 / 128 (10.16%)	
occurrences (all)	16	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 February 2016	Removal of glucose testing as a safety assessment at each timepoint. Glucose assessment was unnecessary and was included in error in the previous version of the protocol. Inclusion of two additional timepoints for cGMP assessment (at 4 weeks and 3 months in addition to baseline, 9 and 12 month timepoints). On reviewing the results of the PARADIGM study (LCZ696 vs enalapril), the maximum change in cGMP was detected at approximately 4 weeks with the levels plateauing out at subsequent timepoints Replacement of the Mini-Mental State Examination (brief version) with the Standardised MMSE as the cognitive assessment tool. This is a more reliable cognitive assessment tool with less variability and variance than the brief version The 'history of malignancy' exclusion criteria was amended to exclude only those with active malignancy or other diseases that would compromise life expectancy. The larger PARADIGM study which randomised 8,442 patients to LCZ696 or enalapril did not exclude patients with a history of malignancy unless their life expectancy was compromised. Further clarification was given on how to measure waist and hip ratio to avoid any variability in this measurement
24 June 2016	The inclusion criteria was amended to allow subjects with lower natriuretic peptide levels to be included in the study. People with BNP between 35 - 280pg/ml were now eligible for inclusion into the study (the previous cut-off was >50pg/ml) People with NT-proBNP between >125 - 1,000 pg/ml were now eligible for inclusion into the study (the previous cut-off was >250pg/ml)
03 August 2016	Updates to the Reference Safety Information for LCZ696 (Investigators Brochure) were submitted to the HPRA. Changes to the RSI are always considered substantial.
19 December 2016	Inclusion criteria amended to include subjects with lower natriuretic peptide levels. People with BNP 20-280pg/ml are now eligible (previous cut-off >35pg/ml). People with NT-proBNP 100-1,000 pg/ml are now eligible (previous cut-off >125pg/ml). Rationale: The aim of the study is to evaluate the effectiveness of LCZ696 in an asymptomatic population at risk of developing heart failure. Elevated levels of NP indicate a heightened risk of heart failure and other cardiovascular events. The results of a prospective study of 3,346 patients without heart failure, with a mean follow-up time of 5.2 years showed an excess risk at BNP levels of 20 pg/ml for men and 23.3 pg/ml for women (Wang, Larson et al. 2004) which is well below current thresholds used to diagnose heart failure. A sub-analysis of the STOP-HF data which included 429 patients with uncomplicated hypertension, showed the optimal threshold for BNP to predict major adverse cardiovascular events and death was 20pg/ml. (Heartbeat Trust, Data on File). Therefore, consistent with an increased risk of developing HF at BNP levels as low as 20pg/ml we would like to propose a lower NP threshold level. The risk thresholds for NT-proBNP are less well-defined. However, based on a correlation between 100 consecutive patients with simultaneous BNP and NT-proBNP measurements, a NT-proBNP level of 100pg/ml is comparable to a BNP level of 20pg/ml (Heartbeat Trust, Data on File). Exclusion criteria amendment. Previously, people with a "history of asymptomatic left ventricular systolic dysfunction defined as LVEF <50%, at any time" were excluded. This criteria was amended to only exclude patients with an LVEF <50% on the most recent measurement. Rationale: The target population is one at increased risk of heart failure which will include subjects with a history of coronary events. A transient drop in LVEF is not unexpected during and shortly after such cardiac events which would exclude patients under the previous criteria.

26 October 2017	The study objectives were amended as follows: "To provide further information in the target population on the safety and tolerability of LCZ696 versus valsartan" was changed from an exploratory objective to a secondary objective. Rationale: The Investigators wished to emphasise the importance of safety by making it a secondary objective. The manner in which safety was assessed during the study was not changed in any way. The timelines for performing cardiac MRI were amended and the 9 month timepoint removed such that this procedure was performed at baseline and end-of-study only. An additional site was added for carrying out MRIs. Rationale: The Investigators had access to a limited number of MRI slots for PARABLE subjects. A second site was opened to increase availability of MRI slots. It is unlikely that any structural changes in the heart would be evident after 9 months of study drug. The need for gadolinium containing contrast during the MRI was removed from the protocol. Rationale: The use of gadolinium was included in the initial protocol in error. Gadolinium is not required for the measurement of left atrial volume index (LAVI). There are risks associated with the use of gadolinium including minor side-effects (nausea, headaches, paraesthesia, hypotension) and rarely anaphylaxis and nephrogenic systemic fibrosis.
19 December 2018	Two secondary objectives added: 1) To assess response based on genetic variants of the NPPB, NPRA and NPRC genes; 2) Change in the incidence of progression of left ventricular dysfunction. Rationale: Genetic variant rs198389 of Nppb increases BNP and this is cardioprotective in at-risk patients. It is important to know if any benefits of LCZ696 are independent of genetic variants of key genes involved in the expression and metabolism of BNP. PARABLE is examining progression of left ventricular diastolic dysfunction. Endpoints include echo and cardiac MRI measures of diastolic dysfunction. An additional composite describing numbers of patients with progression of diastolic dysfunction is added. Two exploratory objectives added: 1) To assess the difference between groups in terms of atrial fibrillation (AF); 2) To assess response of immune cells to LCZ696 Rationale: As AF is influenced by atrial fibrosis, inflammation and hypertrophy, it is important to investigate relationships between AF, LAVI, natriuretic peptide and LCZ696. A non-invasive cardiac rhythm monitor will be placed on a sub-set of up to 60 patients per group for up to 6 days. Monocytosis is present in patients with left ventricular diastolic dysfunction, and monocyte derived macrophages are present in dysfunctional and fibrosed cardiac tissue. BNP can attenuate monocyte chemotaxis. We will examine the relative impact of LCZ696 on monocyte gene expression using next generation sequencing. Exclusion criterion amended. Hepatic dysfunction was defined as any LFT exceeding 3x the upper limit of normal (ULN). This was amended to exclude only with raised AST or ALT. Rationale: GGT is not an exclusion criterion; it is not specific in the diagnosis of liver disease. The statistical methods section was described in more detail. Additional information on sample size included following a blinded review of 9-month echo data/effect size of 125 subjects. However, the sample size remains at 250.
07 March 2019	Changes to the site for QP release of the study drug. At study set-up, the study drug was released by Novartis in their London manufacturing facilities. In preparation for Brexit, an additional site for QP release was identified in the Republic of Ireland. Almac Clinical Services Limited continued to be the distributor but the IMP was transferred from the Craigavon site (Northern Ireland) to the Co Louth facility before 29 March 2019. Future batches of IMP from Novartis, UK, were shipped directly to this Almac site and the QP release was be performed there.

11 June 2019	A nine month follow-up sub-study was added to the protocol. The objective was to evaluate if any of the treatment effects observed during the 18-month study persisted nine-months after study drug discontinuation or whether there was disease regression. This sub-study involved a single visit to the Investigator Site at month 27 (9 months after study drug discontinuation). The assessments and procedures carried out during this follow-up visit were identical to those carried out at baseline, 9 and 18 months (physical exam, measurement of BP, heart rate, height, weight, waist and hip, blood and urine for biomarkers, 24-hour ABPM, echocardiography, ECG and administration of questionnaires; 5-7 day holter monitoring was optional and cardiac MRI was not done).
06 October 2020	Based on research conducted and published by the investigator team, and evidence that intervention can modulate the risk for progression of atrial cardiomyopathy and LAVI, further blood biomarkers of inflammation, fibrosis, inflammation, metabolism, platelet function, thrombosis and coagulation were added to the protocol. The primary endpoint of the study is LAVI, which is an important component of atrial cardiomyopathy. Furthermore, research by the Investigator team suggests that the intervention may favourably modulate the progression of other aspects of atrial cardiomyopathy such as electrophysiological measures and fibrosis, as well ALVDD. Therefore, additional secondary endpoints were added to the protocol to assess the impact of LCZ696 dependent on atrial cardiomyopathy at baseline as well as progression of atrial cardiomyopathy. Final changes, clarifications and additions were made to the secondary and exploratory endpoints. This acknowledges that the study is looking at a range of measures of atrial structure and function, as well as ventricular structure and function. In particular, this reflects new cMRI assessment techniques available. These prespecified endpoints maximise the value of the data in the context of the overall research aims and objectives.
16 April 2021	Amendments relate to the secondary and exploratory objectives and endpoints of the study outlined in Section 10.1 and 10.2 of the study protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported