

**Clinical trial results:****Randomized multicentre pilot study of sacubitril/valsartan (formerly known as LCZ696) versus irbesartan in patients with chronic kidney disease: UK Heart and Renal Protection (HARP)-III****Summary**

EudraCT number	2013-004205-89
Trial protocol	GB
Global end of trial date	02 March 2017

**Results information**

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

**Trial information****Trial identification**

Sponsor protocol code	CTSUHARP3
-----------------------	-----------

**Additional study identifiers**

ISRCTN number	ISRCTN11958993
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Old Road, Oxford, United Kingdom, OX3 7LE
Public contact	Richard Haynes, Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, 01865 743743, richard.haynes@ndph.ox.ac.uk
Scientific contact	Richard Haynes, Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, 01865 743743, richard.haynes@ndph.ox.ac.uk

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	06 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 March 2017
Global end of trial reached?	Yes
Global end of trial date	02 March 2017
Was the trial ended prematurely?	No

Notes:

---

## General information about the trial

Main objective of the trial:

The primary objective of UK HARP-III is to compare the short-term (i.e. over 12 months) effect on kidney function of sacubitril/valsartan (formerly known as LCZ696) with that of irbesartan (a current standard treatment for chronic kidney disease).

Protection of trial subjects:

At every study visit, participants were asked about any serious adverse events, or non-serious adverse events that they believed to be related to study treatment. If a SAE was believed to be related to study treatment it was discussed immediately with a clinician working at the coordinating centre to ensure appropriate action was taken.

At every visit blood and urine samples were taken for analysis in the local laboratory to check kidney function, electrolytes and liver function. Any abnormalities were followed-up and investigated as required.

Participants were also given a 24 hour freefone telephone number so they (or any doctor looking after them) could contact a clinician working at the coordinating centre.

Background therapy:

None

Evidence for comparator:

Sacubitril/valsartan (the experimental drug) has properties that could reduce both renal progression and cardiovascular disease.

Neprilysin (also known as neutral endopeptidase) degrades natriuretic and other vasodilatory peptides and therefore neprilysin inhibition increases concentrations of these peptides and can lower blood pressure (in combination with ACEi or ARB). Omapatrilat inhibited neprilysin but caused unacceptable angioedema when combined with ACEi. However, some data suggested it was renoprotective.

Sacubitril/valsartan is a first-in-class ARNI (angiotensin receptor-neprilysin inhibitor) which has been shown to safely reduce cardiovascular mortality in patients with heart failure. The anti-fibrotic and anti-inflammatory effects of sacubitril/valsartan may be beneficial both in terms of reducing renal progression and reducing CVD events.

Treatment with renin-angiotensin blockade (either ACE inhibitor or angiotensin receptor blocker) is standard of care for patients with proteinuric nephropathy (with or without diabetes) and irbesartan was selected as the comparator for this reason.

---

Actual start date of recruitment	15 September 2014
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	United Kingdom: 414
Worldwide total number of subjects	414
EEA total number of subjects	414

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)	205
From 65 to 84 years	203
85 years and over	6

## Subject disposition

### Recruitment

Recruitment details:

620 participants attended a screening visit after which 566 entered the run-in period and subsequently 414 were randomized between November 2014 and March 2016.

### Pre-assignment

Screening details:

Prior to randomization eligible participants entered a pre-randomization run-in period. They were instructed to stop any previous ACEi or ARB therapy to allow "wash out" and were provided with placebo sacubitril/valsartan (1 tablet daily) and placebo irbesartan (1 tablet daily) to take during the run-in period.

### Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Sacubitril/valsartan

Arm description:

Experimental drug

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

Dosage and administration details:

Sacubitril/valsartan (initially 200 mg once daily titrated to 200 mg twice daily after 2 weeks) and placebo irbesartan (one tablet once daily, titrated to two tablets once daily after 2 weeks)

<b>Arm title</b>	Irbesartan
------------------	------------

Arm description:

Active comparator

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

Dosage and administration details:

Irbesartan (initially one 150 mg tablet once daily, titrated to two 150 mg tablets once daily after 2 weeks) and placebo sacubitril/valsartan (one tablet once daily, titrated to one tablet twice daily after 2 weeks)

<b>Number of subjects in period 1</b>	Sacubitril/valsartan	Irbesartan
Started	207	207
Completed	197	199
Not completed	10	8
Consent withdrawn by subject	8	8
Lost to follow-up	2	-

## Baseline characteristics

### Reporting groups

Reporting group title	Sacubitril/valsartan
Reporting group description:	
Experimental drug	
Reporting group title	Irbesartan
Reporting group description:	
Active comparator	

Reporting group values	Sacubitril/valsartan	Irbesartan	Total
Number of subjects	207	207	414
Age categorical			
Age at randomisation (years)			
Units: Subjects			
<50	37	36	73
≥50 to <70	97	99	196
≥70	73	72	145
Age continuous			
Age at randomisation (years)			
Units: years			
arithmetic mean	62.0	63.6	
standard deviation	± 14.1	± 13.4	-
Gender categorical			
Units: Subjects			
Female	59	57	116
Male	148	150	298
Ethnicity			
Units: Subjects			
White	186	191	377
Black	3	4	7
South Asian	11	7	18
Other	7	5	12
Systolic blood pressure (mmHg)			
Units: Subjects			
<140	76	85	161
≥140 to <160	93	84	177
≥160	38	38	76
Diastolic blood pressure (mmHg)			
Units: Subjects			
<80	96	105	201
≥80 to <90	68	58	126
≥90	43	44	87
Body-mass index (kg/m <sup>2</sup> )			
Units: Subjects			
<25	35	33	68
≥25 to <30	74	73	147
≥30	95	100	195
Not available	3	1	4

CKD-EPI eGFR (mL/min/1.73m <sup>2</sup> )			
CKD-EPI estimated glomerular filtration rate at randomisation			
Units: Subjects			
<30	79	77	156
≥30 to <45	86	91	177
≥45	41	39	80
Not available	1	0	1
Urine albumin:creatinine ratio (mg/mmol)			
Units: Subjects			
<3	30	28	58
≥3 to <30	43	45	88
≥30	134	134	268
Use of RAS blockade at screening visit			
Units: Subjects			
Yes	173	166	339
No	34	41	75
Cause of kidney disease			
*Other known causes and Unknown are all considered 'Miscellaneous renal disorders' by the ERA-EDTA registry			
Units: Subjects			
Glomerular disease	60	51	111
Tubulointerstitial disease	18	32	50
Diabetic kidney disease	36	47	83
Hypertensive/renovascular disease	18	24	42
Other systemic diseases affecting the kidneys	1	2	3
Familial/hereditary nephropathies	30	13	43
Other known causes*	5	4	9
Unknown*	39	34	73
Systolic blood pressure (mmHg)			
Units: mmHg			
arithmetic mean	146	146	
standard deviation	± 16	± 16	-
Diastolic blood pressure (mmHg)			
Units: mmHg			
arithmetic mean	81	80	
standard deviation	± 11	± 11	-
Body mass index (kg/m <sup>2</sup> )			
Units: kg/m <sup>2</sup>			
arithmetic mean	30	31	
standard deviation	± 6	± 6	-
CKD-EPI eGFR (mL/min/1.73m <sup>2</sup> )			
CKD-EPI estimated glomerular filtration rate at randomisation			
Units: mL/min/1.73m <sup>2</sup>			
arithmetic mean	35.4	35.5	
standard deviation	± 11.0	± 11.0	-
24 hour urinary sodium excretion during run-in (mg/24 hours)			
Units: mg/24 hours			
median	2484	2875	
inter-quartile range (Q1-Q3)	1794 to 3795	1932 to 4232	-

Urine albumin:creatinine ratio (mg/mmol)			
Units: mg/mmol			
median	52	56	
inter-quartile range (Q1-Q3)	11 to 162	11 to 146	-

## End points

### End points reporting groups

Reporting group title	Sacubitril/valsartan
Reporting group description:	
Experimental drug	
Reporting group title	Irbesartan
Reporting group description:	
Active comparator	

### Primary: Mean mGFR at 12-months

End point title	Mean mGFR at 12-months
End point description:	The primary outcome is mean measured glomerular filtration rate (mGFR; adjusted for body-surface area) at 12 months. Glomerular filtration rate (GFR) was measured using a standard Cr-EDTA technique, although if this was not available at the site, other methods (99mTc-DTPA or iohexol) could be used with the agreement of the coordinating centre.
End point type	Primary
End point timeframe:	12 months

End point values	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)	29.8 (± 0.5)	29.9 (± 0.5)		

### Statistical analyses

Statistical analysis title	Mean mGFR at 12-months
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.86
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by age

End point title	Mean mGFR at 12-months by age
End point description:	

End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤60 years	29.9 (± 0.8)	29.5 (± 0.8)		
>60 years	29.7 (± 0.6)	30.2 (± 0.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by age
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12 months by gender

End point title	Mean mGFR at 12 months by gender
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
Female	30.3 (± 0.9)	29.5 (± 0.9)		
Male	29.6 (± 0.5)	30.1 (± 0.5)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12 months by gender
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by history of diabetes

End point title	Mean mGFR at 12-months by history of diabetes
End point description:	
End point type	Secondary
End point timeframe:	12 months

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
Prior diabetes - Yes	29.2 (± 0.8)	29.1 (± 0.7)		
Prior diabetes - No	30.2 (± 0.6)	30.5 (± 0.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by history of diabetes
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.76
Method	Test for heterogeneity

---

**Secondary: Mean mGFR at 12-months by history of vascular disease**

---

End point title	Mean mGFR at 12-months by history of vascular disease
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

12 months

---

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
Prior vascular disease - Yes	29.0 (± 1.0)	29.6 (± 0.8)		
Prior vascular disease - No	30.1 (± 0.5)	30.1 (± 0.5)		

**Statistical analyses**

<b>Statistical analysis title</b>	Mean mGFR at 12-months by prior vascular disease
-----------------------------------	--

Comparison groups	Sacubitril/valsartan v Irbesartan
-------------------	-----------------------------------

Number of subjects included in analysis	414
---	-----

Analysis specification	Pre-specified
------------------------	---------------

Analysis type	other
---------------	-------

P-value	= 0.69
---------	--------

Method	Test for heterogeneity
--------	------------------------

---

---

**Secondary: Mean mGFR at 12-months by systolic blood pressure**

---

End point title	Mean mGFR at 12-months by systolic blood pressure
-----------------	---

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

12 months

---

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤140 mmHg	30.5 (± 0.8)	30.9 (± 0.7)		
>140mmHg	29.4 (± 0.6)	29.3 (± 0.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by systolic blood pressure
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.69
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by diastolic blood pressure

End point title	Mean mGFR at 12-months by diastolic blood pressure
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤80 mmHg	29.1 (± 0.7)	30.0 (± 0.6)		
>80 mmHg	30.5 (± 0.6)	29.8 (± 0.7)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by diastolic blood pressure
Comparison groups	Sacubitril/valsartan v Irbesartan

Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.26
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by body mass index

End point title	Mean mGFR at 12-months by body mass index
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤30 kg/m <sup>2</sup>	30.1 (± 0.6)	30.2 (± 0.6)		
>30 kg/m <sup>2</sup>	29.8 (± 0.7)	29.9 (± 0.7)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by body mass index
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.99
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by baseline mGFR

End point title	Mean mGFR at 12-months by baseline mGFR
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤30 mL/min/1.73m <sup>2</sup>	22.4 (± 0.7)	22.0 (± 0.7)		
>30 mL/min/1.73m <sup>2</sup>	35.1 (± 0.6)	35.5 (± 0.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by baseline mGFR
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.52
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by baseline uACR

End point title	Mean mGFR at 12-months by baseline uACR
End point description:	
End point type	Secondary
End point timeframe:	
12 months	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤30 mg/mmol	29.1 (± 0.8)	30.0 (± 0.8)		
>30 mg/mmol	30.3 (± 0.6)	29.9 (± 0.6)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by baseline uACR
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by baseline 24 hour urinary sodium excretion

End point title	Mean mGFR at 12-months by baseline 24 hour urinary sodium excretion
End point description:	
End point type	Secondary
End point timeframe:	12 months

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
≤2680 mg/24 hours	29.9 (± 0.8)	31.0 (± 1.0)		
>2680 mg/24 hours	31.8 (± 0.6)	31.5 (± 0.9)		

### Statistical analyses

<b>Statistical analysis title</b>	Baseline 24 hour urinary sodium excretion
Statistical analysis description:	Mean mGFR at 12-months by baseline 24 hour urinary sodium excretion
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.38
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by use of RAS blockade at screening

End point title	Mean mGFR at 12-months by use of RAS blockade at screening
-----------------	--

End point description:

End point type	Secondary
End point timeframe:	12 month

End point values	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
RAS blockade - Yes	30.0 (± 0.5)	29.7 (± 0.5)		
RAS blockade - No	28.8 (± 1.2)	30.9 (± 1.0)		

### Statistical analyses

Statistical analysis title	Use of RAS blockade at screening
Statistical analysis description:	Mean mGFR at 12-months by use of RAS blockade at screening
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.15
Method	Test for heterogeneity

### Secondary: Mean mGFR at 12-months by cause of kidney disease

End point title	Mean mGFR at 12-months by cause of kidney disease
End point description:	*Includes obstructive renal diseases **All considered 'Systemic diseases affecting the kidney' by the ERA-EDTA registry ***All considered 'Miscellaneous renal disorders' by the ERA-EDTA registry § Includes other systemic kidney diseases
End point type	Secondary
End point timeframe:	12 months

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
Glomerular disease	30.3 (± 0.9)	30.8 (± 0.9)		
Tubulointerstitial disease*	28.6 (± 1.6)	29.7 (± 1.2)		
Diabetic kidney disease**	28.1 (± 1.1)	27.6 (± 0.9)		
Hypertensive/renovascular disease**	31.0 (± 1.6)	31.5 (± 1.4)		
Familial/hereditary nephropathies	28.5 (± 1.2)	31.0 (± 1.9)		
Other known causes§***	32.6 (± 2.8)	29.8 (± 2.6)		
Unknown***	31.2 (± 1.1)	30.7 (± 1.1)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean mGFR at 12-months by cause of kidney disease
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9
Method	Test for heterogeneity

### Secondary: Mean uACR study average

End point title	Mean uACR study average
End point description:	Mean urine albumin:creatinine ratio [uACR]
End point type	Secondary
End point timeframe:	
Study average	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mg/mmol				
arithmetic mean (standard error)				
Study average	16.3 (± 0.6)	17.9 (± 0.7)		

### Statistical analyses

<b>Statistical analysis title</b>	Urinary albumin:creatinine ratio
Comparison groups	Sacubitril/valsartan v Irbesartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.08
Method	Test for heterogeneity

### Secondary: Estimated GFR [eGFR] study average

End point title	Estimated GFR [eGFR] study average
End point description:	Estimated GFR [eGFR] study average from centrally analysed plasma samples using CKD-EPI formula.
End point type	Secondary
End point timeframe:	
Study average	

<b>End point values</b>	Sacubitril/valsartan	Irbesartan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	207		
Units: mL/min/1.73m <sup>2</sup>				
arithmetic mean (standard error)				
Study average	32.3 (± 0.2)	32.2 (± 0.2)		

### Statistical analyses

<b>Statistical analysis title</b>	Estimated GFR [eGFR] study average
Comparison groups	Irbesartan v Sacubitril/valsartan
Number of subjects included in analysis	414
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.66
Method	Test for heterogeneity

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

All serious adverse events were reported via the electronic case report form together with non-serious adverse events that were thought to be related to the randomized study treatment (nSARs).

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.0
--------------------	------

### Reporting groups

Reporting group title	Sacubitril/valsartan
-----------------------	----------------------

Reporting group description:

Experimental drug

Reporting group title	Irbesartan
-----------------------	------------

Reporting group description:

Active comparator

<b>Serious adverse events</b>	Sacubitril/valsartan	Irbesartan	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 207 (29.47%)	59 / 207 (28.50%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	5 / 207 (2.42%)	6 / 207 (2.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 207 (0.48%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			

subjects affected / exposed	19 / 207 (9.18%)	16 / 207 (7.73%)	
occurrences causally related to treatment / all	0 / 28	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy, puerperium and perinatal conditions			
subjects affected / exposed	0 / 207 (0.00%)	1 / 207 (0.48%)	
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			
General disorders and administration site conditions			
subjects affected / exposed	5 / 207 (2.42%)	4 / 207 (1.93%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	6 / 207 (2.90%)	6 / 207 (2.90%)	
occurrences causally related to treatment / all	0 / 7	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	8 / 207 (3.86%)	13 / 207 (6.28%)	
occurrences causally related to treatment / all	0 / 10	0 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	7 / 207 (3.38%)	5 / 207 (2.42%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			

subjects affected / exposed	6 / 207 (2.90%)	5 / 207 (2.42%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Nervous system disorders</b>			
Nervous system disorders			
subjects affected / exposed	3 / 207 (1.45%)	3 / 207 (1.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Blood and lymphatic system disorders</b>			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 207 (0.97%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Eye disorders</b>			
Eye disorders			
subjects affected / exposed	2 / 207 (0.97%)	1 / 207 (0.48%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
Gastrointestinal disorders			
subjects affected / exposed	5 / 207 (2.42%)	6 / 207 (2.90%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Hepatobiliary disorders			
subjects affected / exposed	1 / 207 (0.48%)	2 / 207 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Skin and subcutaneous tissue disorders</b>			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	2 / 207 (0.97%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			

Renal and urinary disorders subjects affected / exposed	11 / 207 (5.31%)	5 / 207 (2.42%)	
occurrences causally related to treatment / all	0 / 14	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders Endocrine disorders subjects affected / exposed	2 / 207 (0.97%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed	3 / 207 (1.45%)	0 / 207 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations Infections and infestations subjects affected / exposed	16 / 207 (7.73%)	15 / 207 (7.25%)	
occurrences causally related to treatment / all	0 / 28	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed	10 / 207 (4.83%)	7 / 207 (3.38%)	
occurrences causally related to treatment / all	1 / 11	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

<b>Non-serious adverse events</b>	Sacubitril/valsartan	Irbesartan	
Total subjects affected by non-serious adverse events subjects affected / exposed	76 / 207 (36.71%)	58 / 207 (28.02%)	
Vascular disorders Vascular disorders subjects affected / exposed	17 / 207 (8.21%)	7 / 207 (3.38%)	
occurrences (all)	19	8	
General disorders and administration site conditions			

General disorders and administration site conditions subjects affected / exposed occurrences (all)	3 / 207 (1.45%) 3	6 / 207 (2.90%) 6	
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	2 / 207 (0.97%) 2	3 / 207 (1.45%) 3	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	4 / 207 (1.93%) 5	4 / 207 (1.93%) 5	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	0 / 207 (0.00%) 0	1 / 207 (0.48%) 1	
Investigations Investigations subjects affected / exposed occurrences (all)	3 / 207 (1.45%) 3	1 / 207 (0.48%) 1	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	0 / 207 (0.00%) 0	2 / 207 (0.97%) 2	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	20 / 207 (9.66%) 23	18 / 207 (8.70%) 21	
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	1 / 207 (0.48%) 1	0 / 207 (0.00%) 0	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	1 / 207 (0.48%) 1	2 / 207 (0.97%) 2	
Eye disorders			

Eye disorders subjects affected / exposed occurrences (all)	0 / 207 (0.00%) 0	1 / 207 (0.48%) 1	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	18 / 207 (8.70%) 21	10 / 207 (4.83%) 13	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	18 / 207 (8.70%) 23	6 / 207 (2.90%) 7	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	5 / 207 (2.42%) 7	7 / 207 (3.38%) 8	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	6 / 207 (2.90%) 6	5 / 207 (2.42%) 7	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	2 / 207 (0.97%) 2	1 / 207 (0.48%) 1	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	9 / 207 (4.35%) 9	2 / 207 (0.97%) 2	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2014	<p>Version 5.1 Amendment: First morning void urine samples will be collected at each study visit for local and central analysis.</p> <p>Rationale: First morning urine samples reduce intra-individual variability compared with random urine samples</p>
09 March 2015	<p>Version 6.0 Original text: Inclusion criteria: eGFR <math>\geq 20 &lt; 60</math> mL/min/1.73m<sup>2</sup> and urine albumin:creatinine ratio <math>&gt; 20</math> mg/mmol</p> <p>Exclusion criteria: Serum potassium <math>&gt; 5.2</math> mmol/L Systolic BP <math>&lt; 130</math> mmHg at Randomization</p> <p>Amended text: Inclusion criteria: eGFR <math>\geq 20 &lt; 45</math> mL/min/1.73m<sup>2</sup>; or eGFR <math>\geq 45 &lt; 60</math> mL/min/1.73m<sup>2</sup> and urine albumin:creatinine ratio <math>&gt; 20</math> mg/mmol</p> <p>Exclusion criteria: Serum potassium <math>&gt; 5.5</math> mmol/L Systolic BP <math>&lt; 110</math> mmHg (or <math>&lt; 130</math> mmHg with symptoms of orthostatic hypotension) at Randomization</p> <p>Rationale: To facilitate recruitment and avoid unnecessary exclusion of participants</p>
11 May 2015	<p>Version 7.0</p> <p>Original text: Follow-up duration 6 months</p> <p>Amended text: Follow-up duration 12 months</p> <p>Rationale: New data from heart failure population suggested that the full effects on renal function may take at least 9 months to emerge with sacubitril/valsartan</p>
25 January 2016	<p>Version 8.0</p> <p>Original text: Original sample size 360 participants (based on assumption that 10% might discontinue study treatment)</p> <p>Amended text: Sample size increased to at least 400 participants</p> <p>Rationale: To allow for up to 15% of participants to discontinue study treatment</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

---

## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/27646835>