Clinical trial results:
PROTOCOL RET-D-001: EFFICACY AND SAFETY OF SPARSENTAN (RE-021), A DUAL ENDOTHELIN RECEPTOR AND ANGIOTENSIN RECEPTOR BLOCKER, IN PATIENTS WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS): A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROL, DOSE-ESCALATION STUDY

Summary

EudraCT number	2014-002358-38
Trial protocol	CZ IT BE
Global end of trial date	25 March 2024

Results information

Result version number	v2 (current)
This version publication date	30 March 2025
First version publication date	25 September 2024
Version creation reason	• Correction of full data set Addition of final Open-Label Extension data

Trial information

Trial identification

Sponsor protocol code	RET-D-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01613118
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Travere Therapeutics, Inc.
Sponsor organisation address	3611 Valley Centre Drive, Suite 300, San Diego, United States, 92130
Public contact	Medical Information, Travere Call Center, 001 877.659.5518, medinfo@travere.com
Scientific contact	Medical Information, Travere Call Center, 001 877.659.5518, medinfo@travere.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001984-PIP02-20
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2016
Global end of trial reached?	Yes
Global end of trial date	25 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the change in urine protein/creatinine (Up/C) after 8 weeks of treatment in FSGS patients receiving Sparsentan, a novel dual endothelin receptor and angiotensin receptor blocker, over a range of dose levels (200 mg, 400 mg, and 800 mg) compared to treatment with Irbesartan as active control.

Protection of trial subjects:

Independent Ethics Committee (IEC) or Institutional Review Board (IRB)
The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) at each investigational site reviewed and approved the protocol and informed consent form (ICF)/assent form for the study prior to site initiation in accordance with ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Ethical Conduct of the Study
The study was conducted and monitored in accordance with the individual vendor/contractor procedures and SOPs. All procedures and SOPs comply with the ethical principles of GCP, as required by regulatory authorities, and are in accordance with the Declaration of Helsinki.

Subject Information and Consent
The Investigator was responsible for documenting the consent process within the source documents, and for obtaining consent using an IRB/IEC approved consent form. Subjects and/or their parent/legal guardian signed informed consent/assent at Visit 1 (beginning of the Screening period) prior to undergoing any protocol-related procedures. A signed and dated copy of the consent/assent form(s) was given to the subject.

Background therapy:

None

Evidence for comparator:

While there are currently no approved medicinal products indicated for the treatment of FSGS, an important part of treatment is rigorous blood pressure control using renin-angiotensin-aldosterone system (RAAS) inhibitor therapy (angiotensin-converting enzyme inhibitors [ACEIs] or angiotensin receptor blockers [ARBs]) to target blood pressure values <130/80 mmHg in order to reduce hemodynamic stress and proteinuria and, thereby, slow the progression of renal disease. Randomized, placebo-controlled trials have shown long-term benefit of RAAS inhibitor treatment, which is universally considered to be first-line standard-of-care, as outlined in the KDIGO Clinical Practice Guideline.

Actual start date of recruitment	07 March 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	109
EEA total number of subjects	20

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)	6
Adolescents (12-17 years)	12
Adults (18-64 years)	85
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

185 patients screened, 76 excluded, 109 enrolled

Pre-assignment

Screening details:

Screening was performed between 2 to 4 weeks before Washout began. Patients who failed screening for any reason were allowed to re-screen up to two times. In addition to confirming inclusion and exclusion criteria and repeating any necessary assessment, the following procedures were required: blood pressure, S-potassium, eGFR, and urine Up/C.

Period 1

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

Blinding implementation details:

Irbesartan 150 mg tablets were over-encapsulated (blinded) with size 00 gray opaque hard gelatin capsules (Capsugel) and backfilled with Avicel. Patients randomized to the irbesartan active control may also have received placebo capsules, to maintain the blind by keeping the number of capsules taken consistent with that of sparsentan-treated patients in the same cohort. The placebo product used was a size 00 gray opaque capsule (Capsugel) containing microcrystalline cellulose.

Arms

Are arms mutually exclusive?	Yes
Arm title	Investigational medicinal product

Arm description:

Investigational medicinal product

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

Dosage and administration details:

The doses to be administered in the double-blind period (200, 400, or 800 mg) were dispensed as 100 mg size 00 sparsentan capsules. In the open-label period, doses were dispensed as either 100 mg (size 00 or 0) sparsentan capsules or as 400 mg scored sparsentan tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

Arm title	Active Control

Arm description:

Active control

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

Dosage and administration details:

The irbesartan doses administered in the study (150 and 300 mg) were supplied as double-blinded

over-encapsulated tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

Number of subjects in period 1	Investigational medicinal product	Active Control
Started	73	36
Completed	68	35
Not completed	5	1
Adverse event, non-fatal	3	1
Discontinued	1	-
Protocol deviation	1	-

Period 2	
Period 2 title	Open-label Extension
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Investigational medicinal product

Arm description:

Investigational medicinal product

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

Dosage and administration details:

In the open-label period, doses may be dispensed as either 100 mg (size 00 or 0) sparsentan capsules or as 400 mg scored sparsentan tablets. Patients were instructed to take the appropriate quantity of capsules or tablets for the assigned cohort, orally once daily prior to the morning meal, with the exception of the day of a study visit as the patient took their study medication in the clinic.

Number of subjects in period 2	Investigational medicinal product
Started	103
Completed	1
Not completed	102
Consent withdrawn by subject	18
Physician decision	16
Adverse event, non-fatal	21
Other	5
Termination by sponsor	30
Pregnancy	4
Non-compliance with study intervention	2
Lost to follow-up	5
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Investigational medicinal product
Reporting group description: Investigational medicinal product	
Reporting group title	Active Control
Reporting group description: Active control	

Reporting group values	Investigational medicinal product	Active Control	Total
Number of subjects	73	36	109
Age categorical			
Age (years) at screening			
Units: Subjects			
Children (2-11 years)	4	2	6
Adolescents (12-17 years)	7	5	12
Adults (18-64 years)	57	28	85
From 65-84 years	5	1	6
Age continuous Units: years			
arithmetic mean	38	34.1	
standard deviation	± 16.78	± 15.96	-
Gender categorical			
Male or Female			
Units: Subjects			
Female	32	17	49
Male	41	19	60
Ethnicity Units: Subjects			
Hispanic or Latino	14	6	20
Not Hispanic or Latino	59	30	89
Race			
Race			
Units: Subjects			
Asian	5	1	6
Black	8	7	15
White	57	26	83
Other	3	2	5
Weight			
Weight in kilograms			
Units: Kilograms			
arithmetic mean	81	82	
standard deviation	± 22.48	± 22.19	-
Height			
Height in centimeters			
Units: centimetre			
arithmetic mean	168	168	

standard deviation	± 12.77	± 14.22	-
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	28	29	
standard deviation	± 6.139	± 6.404	-

End points

End points reporting groups	
Reporting group title	Investigational medicinal product
Reporting group description: Investigational medicinal product	
Reporting group title	Active Control
Reporting group description: Active control	
Reporting group title	Investigational medicinal product
Reporting group description: Investigational medicinal product	

Primary: Primary endpoint 1	
End point title	Primary endpoint 1
End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 200, 400 and 800 mg sparsentan groups combined and the 300 mg irbesartan group	
End point type	Primary
End point timeframe: baseline to week 8	

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	32		
Units: percent change				
number (confidence interval 95%)				
week 8	-44.8 (-52.7 to -35.7)	-18.5 (-34.6 to 1.7)		

Attachments (see zip file)	Primary Endpoint Chart/Primary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Primary endpoint 1
Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.006
Method	ANCOVA

Notes:

[1] - percent change

Primary: Primary endpoint 2

End point title	Primary endpoint 2

End point description:

Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 400 and 800 mg sparsentan groups combined and 300 mg irbesartan group

End point type	Primary

End point timeframe:

baseline to week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: Percent change				
number (confidence interval 95%)				
Week 8	-47.4 (-56.3 to -36.9)	-19.0 (-38.0 to 5.9)		

Attachments (see zip file)	Primary Endpoint Chart/Primary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Primary endpoint 2
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.011
Method	ANCOVA

Notes:

[2] - percent change

Primary: Primary endpoint 3

End point title	Primary endpoint 3

End point description:

Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 400 mg sparsentan group and the 300 mg irbesartan group

End point type	Primary

End point timeframe:

baseline to week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	17		
Units: percent change				
number (confidence interval 95%)				
Week 8	-52.7 (-64.3 to -37.2)	-28.1 (-47.5 to -1.6)		

Attachments (see zip file)	Primary Endpoint Chart/Primary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Primary endpoint 3
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.056
Method	ANCOVA

Notes:

[3] - percent change

Primary: Primary endpoint 4

End point title	Primary endpoint 4

End point description:

Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 800 mg group and the 300 mg irbesartan group

End point type	Primary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	8		
Units: percent change				
number (confidence interval 95%)				

Week 8	-41.3 (-54.4 to -24.4)	-9.3 (-45.3 to 50.3)		

Attachments (see zip file)	Primary Endpoint Chart/Primary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Primary endpoint 4
Statistical analysis description: percent change from baseline to week 8	
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.127
Method	ANCOVA
Parameter estimate	least squares
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[4] - percent change

Primary: Primary endpoint 5	
End point title	Primary endpoint 5
End point description: Percent change from baseline to Week 8 in urine protein to creatinine ratio in the 200 mg group and the 300 mg irbesartan group	
End point type	Primary
End point timeframe: baseline to week 8	

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: percent change				
number (confidence interval 95%)				
Week 8	-33.1 (-49.3 to -11.6)	-15.0 (-41.8 to 24.2)		

Attachments (see zip file)	Primary Endpoint Chart/Primary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Primary endpoint 5
Comparison groups	Active Control v Investigational medicinal product
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.298
Method	ANCOVA

Notes:

[5] - percent change from baseline

Secondary: Secondary endpoint 1

End point title	Secondary endpoint 1

End point description:

Percent difference in subjects achieving FSGS Partial Remission Endpoint (FPRE – patients experiencing a UP/C ratio ≤ 1.5 g/g and >40% reduction from baseline in UP/C) at Week 8 in the 200, 400, and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

End point type	Secondary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	32		
Units: percent				
number (not applicable)				
Week 8	28.13	9.38		

Attachments (see zip file)	Secondary Endpoint Chart/Secondary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Secondary endpoint 1

Statistical analysis description:

Percent difference in subjects achieving FPRE at Week 8 in the 200, 400, and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.04
Method	Fisher exact
Parameter estimate	% Difference (Sparsentan-Irbesartan)
Point estimate	18.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	36.04

Notes:

[6] - Percent difference (Sparsentan - Irbesartan)

Secondary: Secondary endpoint 2

End point title	Secondary endpoint 2

End point description:

Percent difference in subjects achieving FPRE at Week 8 in the 400 and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

End point type	Secondary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: percent				
number (not applicable)				
Week 8	31.37	12		

Attachments (see zip file)	Secondary Endpoint Chart/Secondary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Secondary endpoint 2

Statistical analysis description:

Percent difference in subjects achieving FPRE at Week 8 in the 400 and 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage Difference (Sparsentan-Irbesartan)

Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.092
Method	Fisher exact
Parameter estimate	% Difference (Sparsentan-Irbesartan)
Point estimate	19.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	40.37

Notes:

[7] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 3

End point title	Secondary endpoint 3

End point description:

Percent difference in subjects achieving FPRE at Week 8 in the 400 mg sparsentan group vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

End point type	Secondary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	17		
Units: percent				
number (not applicable)				
Week 8	38.10	17.65		

Attachments (see zip file)	Secondary Endpoint Chart/Secondary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Secondary endpoint 3

Statistical analysis description:

Percent difference in subjects achieving FPRE at Week 8 in the 400 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage Difference (Sparsentan-Irbesartan)

Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.282
Method	Fisher exact
Parameter estimate	% Difference (Sparsentan-Irbesartan)
Point estimate	20.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.44
upper limit	53.33

Notes:

[8] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 4

End point title	Secondary endpoint 4

End point description:

Percent difference in subjects achieving FPRE at Week 8 in the 800 mg sparsentan group vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

End point type	Secondary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	8		
Units: percent				
number (not applicable)				
Week 8	26.67	0		

Attachments (see zip file)	Secondary Endpoint Chart/Secondary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Secondary endpoint 4

Statistical analysis description:

Percent difference in subjects achieving FPRE at Week 8 in the 800 mg sparsentan groups combined vs. the 300 mg irbesartan group

Percentage Difference (Sparsentan-Irbesartan)

Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.164
Method	Fisher exact
Parameter estimate	% Difference (Sparsentan-Irbesartan)
Point estimate	26.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.93
upper limit	50.41

Notes:

[9] - Percentage Difference (Sparsentan-Irbesartan)

Secondary: Secondary endpoint 5

End point title	Secondary endpoint 5

End point description:

Percent difference in subjects achieving FPRE at Week 8 in the 200 mg sparsentan group vs. the 300 mg irbesartan group

Percentage of subjects achieving FPRE

End point type	Secondary

End point timeframe:

Week 8

End point values	Investigational medicinal product	Active Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	7		
Units: percent				
number (not applicable)				
Week 8	15.38	0		

Attachments (see zip file)	Secondary Endpoint Chart/Secondary Endpoint Chart.pdf

Statistical analyses

Statistical analysis title	Secondary endpoint 5

Statistical analysis description:

Percent difference in subjects achieving FPRE at Week 8 in the 200 mg sparsentan group vs. the 300 mg irbesartan group

Percentage Difference (Sparsentan-Irbesartan)

Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.521
Method	Fisher exact
Parameter estimate	% Difference (Sparsentan-Irbesartan)
Point estimate	15.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.22
upper limit	45.99

Notes:

[10] - Percentage Difference (Sparsentan-Irbesartan)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Period 1 + Period 2

Adverse event reporting additional description:

Included all subjects who were randomized and took at least 1 dose of sparsentan during either the Double Blind Period (those randomized to sparsentan in Period 1) or OLE Period (all subjects who entered the OLE [Period 2]) were included in the All Sparsentan Analysis Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	All Sparsentan Analysis Set

Reporting group description:

The All Sparsentan Analysis Set was included all subjects who were randomized and took at least 1 dose of sparsentan during either the Double Blind Period (those randomized to sparsentan in Period 1) or OLE Period (all subjects who entered the OLE [Period 2]) were included in the All Sparsentan Analysis Set.

Serious adverse events	All Sparsentan Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 108 (44.44%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Angioimmunoblastic T-cell lymphoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cell carcinoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			

Deep vein thrombosis				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angiopathy				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive urgency				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	4 / 108 (3.70%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Chest discomfort				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Drug withdrawal syndrome				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Generalised oedema				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Endometrial hyperplasia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Apnoea				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulse absent			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Jaw fracture				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular pseudoaneurysm				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Conduction disorder				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinus bradycardia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular extrasystolesn				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 108 (1.85%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Iron deficiency anaemia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Anal fistula			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Erosive oesophagitis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Liver injury				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Septic shock				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	10 / 108 (9.26%)			
occurrences causally related to treatment / all	5 / 11			
deaths causally related to treatment / all	0 / 0			
Proteinuria				

subjects affected / exposed	3 / 108 (2.78%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
End stage renal disease				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrotic syndrome				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcapsular renal haematoma				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hyperaldosteronism				

subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone infarction			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Flank pain			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	4 / 108 (3.70%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Abscess limb			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Appendicitis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hypervolaemia				
subjects affected / exposed	3 / 108 (2.78%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	2 / 108 (1.85%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 108 (0.93%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	All Sparsentan Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 108 (96.30%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	23 / 108 (21.30%)		
occurrences (all)	38		
Hypertension			
subjects affected / exposed	19 / 108 (17.59%)		
occurrences (all)	30		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	30 / 108 (27.78%)		
occurrences (all)	45		
Pyrexia			
subjects affected / exposed	16 / 108 (14.81%)		
occurrences (all)	19		
Fatigue			
subjects affected / exposed	12 / 108 (11.11%)		
occurrences (all)	15		
Chest pain			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	14		
Asthenia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 108 (12.04%)		
occurrences (all)	18		
Nasal congestion			
subjects affected / exposed	12 / 108 (11.11%)		
occurrences (all)	17		

Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 108 (10.19%) 18		
Dyspnoea subjects affected / exposed occurrences (all)	8 / 108 (7.41%) 8		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	11 / 108 (10.19%) 11		
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	17 / 108 (15.74%) 21		
Blood creatine increased subjects affected / exposed occurrences (all)	16 / 108 (14.81%) 23		
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	11 / 108 (10.19%) 15		
Haemoglobin decreased subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 7		
N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 8		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 8		
Skin laceration subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 9		
Nervous system disorders			

Headache			
subjects affected / exposed	32 / 108 (29.63%)		
occurrences (all)	43		
Dizziness			
subjects affected / exposed	19 / 108 (17.59%)		
occurrences (all)	28		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 108 (17.59%)		
occurrences (all)	20		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	27 / 108 (25.00%)		
occurrences (all)	36		
Nausea			
subjects affected / exposed	26 / 108 (24.07%)		
occurrences (all)	37		
Vomiting			
subjects affected / exposed	19 / 108 (17.59%)		
occurrences (all)	30		
Abdominal pain			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	10		
Abdominal pain upper			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	22		
Proteinuria			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	21		
Renal impairment			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 108 (17.59%)		
occurrences (all)	28		
Back pain			
subjects affected / exposed	14 / 108 (12.96%)		
occurrences (all)	15		
Muscle spasms			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	13		
Pain in extremity			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	15		
Osteoarthritis			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	8		
Flank pain			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Infections and infestations			
COVID-19			
subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	19		
Upper respiratory tract infection			

subjects affected / exposed	17 / 108 (15.74%)		
occurrences (all)	43		
Nasopharyngitis			
subjects affected / exposed	13 / 108 (12.04%)		
occurrences (all)	23		
Urinary tract infection			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	22		
Influenza			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	10		
Sinusitis			
subjects affected / exposed	8 / 108 (7.41%)		
occurrences (all)	11		
Bronchitis			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	10		
Cellulitis			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Pneumonia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	22 / 108 (20.37%)		
occurrences (all)	41		
Gout			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	29		
Metabolic acidosis			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	12		
Dehydration			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		

Vitamin D deficiency subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2012	Amendment 1
11 July 2013	Amendment 2
20 September 2013	Amendment 3
25 November 2013	Amendment 4
21 May 2014	Amendment 5
22 December 2014	Amendment 6
05 December 2016	Amendment 7
20 December 2017	Amendment 8
24 October 2018	Amendment 9
25 July 2019	Amendment 10
27 February 2020	Amendment 11
01 November 2021	Amendment 12

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported