



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	v1
This version publication date	25 September 2024
First version publication date	25 September 2024

Trial information

Trial identification

Sponsor protocol code	RET-D-001
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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)	EMA-001984-PIP02-20
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	Interim
Date of interim/final analysis	08 October 2020
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, Monitor, Data analyst, Carer, Assessor

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 receive 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
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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	34
Not completed	69
Consent withdrawn by subject	18
Physician decision	16
Adverse event, non-fatal	19
Other	5
Pregnancy	4
Non-compliance with study intervention	2
Lost to follow-up	4
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
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	-

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomized subjects who received at least 1 dose of investigational product (ie, sparsentan or irbesartan) and have at least 1 postbaseline efficacy evaluation. Subjects were analyzed based on their randomized treatment.

Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

Defined as all subjects in the EES who completed the 8-week double-blind treatment period without major protocol deviations and who were 80% to 120% compliant with investigational product. Specific disallowed medications and other protocol deviations that excluded subjects from the PP analysis set were identified prior to unblinding the database for the primary analysis. Subjects were analyzed based on their randomized treatment.

Subject analysis set title	Efficacy Evaluable Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Defined as all subjects who received at least 1 dose of double-blind investigational product and have both baseline and Week 8 UP/C values. This population does not include subjects that were replaced due to missing a UP/C value. This analysis set was used for the analysis of the primary efficacy endpoint. Subjects were analyzed based on their randomized treatment.

Reporting group values	Full Analysis Set	Per Protocol Set	Efficacy Evaluable Set
Number of subjects	109	87	96
Age categorical			
Age (years) at screening			
Units: Subjects			
Children (2-11 years)	6	6	6
Adolescents (12-17 years)	12	11	11
Adults (18-64 years)	85	64	73
From 65-84 years	6	6	6
Gender categorical			
Male or Female			
Units: Subjects			
Female	60	36	41
Male	49	51	55
Ethnicity			
Units: Subjects			
Hispanic or Latino	20	17	18
Not Hispanic or Latino	89	70	78
Race			
Race			
Units: Subjects			
Asian	6	3	5
Black	15	11	12
White	83	69	74
Other	5	4	5

Weight			
Weight in kilograms			
Units: Kilograms			
arithmetic mean	81.40	80.65	81.05
standard deviation	± 22.288	± 22.045	± 22.070
Height			
Height in centimeters			
Units: centimetre			
arithmetic mean	167.77	167.74	167.80
standard deviation	± 13.201	± 13.550	± 3.501
BMI			
Body Mass Index			
Units: kg/m2			
arithmetic mean	28.49	28.22	28.33
standard deviation	± 6.199	± 6.225	± 6.085

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	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: All randomized subjects who received at least 1 dose of investigational product (ie, sparsentan or irbesartan) and have at least 1 postbaseline efficacy evaluation. Subjects were analyzed based on their randomized treatment.	
Subject analysis set title	Per Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description: Defined as all subjects in the EES who completed the 8-week double-blind treatment period without major protocol deviations and who were 80% to 120% compliant with investigational product. Specific disallowed medications and other protocol deviations that excluded subjects from the PP analysis set were identified prior to unblinding the database for the primary analysis. Subjects were analyzed based on their randomized treatment.	
Subject analysis set title	Efficacy Evaluable Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: Defined as all subjects who received at least 1 dose of double-blind investigational product and have both baseline and Week 8 UP/C values. This population does not include subjects that were replaced due to missing a UP/C value. This analysis set was used for the analysis of the primary efficacy endpoint. Subjects were analyzed based on their randomized treatment.	

Primary: Primary Endpoint 1

End point title	Primary Endpoint 1
End point description: Change from baseline to Week 8 in urine protein to creatinine ratio in the 200, 400 and 800 mg groups combined	
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: g/g				
arithmetic mean (standard deviation)				

Baseline	4.707 (± 3.7810)	4.017 (± 2.6717)		
Week 8	3.300 (± 3.5719)	3.164 (± 2.2713)		

Attachments (see zip file)	primary Endpoint Chart/Primary Endpoint Chart (1).pdf
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Statistical analyses

Statistical analysis title	Primary Endpoint
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Statistical analysis description:

A multiple-comparisons adjustment procedure (gated sequential testing) was used to evaluate sparsentan dose effects while controlling the Type 1 error rate at 5%. Specifically, the sparsentan doses were compared to irbesartan in a pre defined hierarchal order.

Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	ANCOVA

Primary: Primary Endpoint 2

End point title	Primary Endpoint 2
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End point description:

Change from baseline to Week 8 in urine protein to creatinine ratio in the 400 and 800 mg groups combined

End point type	Primary
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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: g/g				
arithmetic mean (standard deviation)				
Baseline	4.824 (± 4.0506)	3.816 (± 2.7160)		
Week 8	3.208 (± 3.4738)	2.990 (± 2.3598)		

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	superiority
P-value	= 0.011
Method	ANCOVA

Primary: Primary Endpoint 3

End point title	Primary Endpoint 3
End point description:	Change from baseline to Week 8 in urine protein to creatinine ratio in the 400 mg 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: g/g				
arithmetic mean (standard deviation)				
Baseline	4.749 (± 4.1696)	3.482 (± 2.6074)		
Week 8	2.452 (± 2.6254)	2.795 (± 2.4581)		

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	superiority
P-value	= 0.056
Method	ANCOVA

Primary: Primary Endpoint 4

End point title	Primary Endpoint 4
End point description:	Change from baseline to Week 8 in urine protein to creatinine ratio in the 800 mg 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	30	8		
Units: g/g				
arithmetic mean (standard deviation)				
Baseline	4.876 (\pm 4.0362)	4.526 (\pm 2.9842)		
Week 8	3.737 (\pm 3.9177)	3.405 (\pm 2.2343)		

Statistical analyses

Statistical analysis title	Primary Endpoint 4
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.127
Method	ANCOVA

Primary: Primary Endpoint 5

End point title	Primary Endpoint 5
End point description:	
Change from baseline to Week 8 in urine protein to creatinine ratio in the 200 mg 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: g/g				
arithmetic mean (standard deviation)				
Baseline	4.248 (\pm 2.5304)	4.734 (\pm 2.5701)		

Week 8	3.663 (\pm 4.0650)	3.786 (\pm 1.9501)		
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Statistical analyses

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

Secondary: Secondary Endpoint 1

End point title	Secondary Endpoint 1
End point description:	Proportion of Subjects Achieving UP/C <1.5 g/g and >40% Reduction from Baseline in UP/C (FPRE) at Week 8 in the 200, 400, and 800 mg groups combined
End point type	Secondary
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: Subjects				
Number of subjects achieving FPRE	18	3		

Statistical analyses

Statistical analysis title	Secondary Endpoints
Statistical analysis description:	Analyses of the secondary endpoints were conducted using a Fisher's exact test to compare sparsentan doses (or combination of doses) with irbesartan
Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Fisher exact

Statistical analysis title	Secondary Endpoint 1
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Fisher exact

Secondary: Secondary Endpoint 2

End point title	Secondary Endpoint 2
End point description: Proportion of Subjects Achieving UP/C <1.5 g/g and >40% Reduction from Baseline in UP/C at Week 8 in the 400 and 800 mg groups combined	
End point type	Secondary
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: Subjects				
Number of subjects achieving FPPE	16	3		

Statistical analyses

Statistical analysis title	Secondary Endpoint 2
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	76
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Fisher exact

Secondary: Secondary Endpoint 3

End point title	Secondary Endpoint 3
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End point description:

Proportion of Subjects Achieving UP/C <1.5 g/g and >40% Reduction from Baseline in UP/C (FPRE) at Week 8 in the 400 mg group

End point type	Secondary
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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: Subjects				
Number of subjects achieving FPRE	8	3		

Statistical analyses

Statistical analysis title	Secondary Endpoint 3
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Comparison groups	Investigational medicinal product v Active Control
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Number of subjects included in analysis	38
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.282
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Method	Fisher exact
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Secondary: Secondary Endpoint 4

End point title	Secondary Endpoint 4
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End point description:

Proportion of Subjects Achieving UP/C <1.5 g/g and >40% Reduction from Baseline in UP/C (FPRE) at Week 8 in the 800 mg group

End point type	Secondary
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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	30	8		
Units: Subjects				
Number of subjects achieving FPRE	8	0		

Statistical analyses

Statistical analysis title	Secondary Endpoint 4
Comparison groups	Investigational medicinal product v Active Control
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164
Method	Fisher exact

Secondary: Secondary Endpoint 5

End point title	Secondary Endpoint 5
End point description:	Proportion of Subjects Achieving UP/C <1.5 g/g and >40% Reduction from Baseline in UP/C (FPRE) at Week 8 in the 200 mg group
End point type	Secondary
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: Subjects				
Number of subjects achieving FPRE	2	0		

Statistical analyses

Statistical analysis title	Secondary Endpoint 5
Comparison groups	Investigational medicinal product v Active Control

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.521
Method	Fisher exact

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	All Sparsentan Analysis Set
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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	44 / 108 (40.74%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
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			
Angiopathy			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
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		
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 crisis			
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			
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		
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		
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		
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		
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		
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			
Corona test positive			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
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 / 1		
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		
Perirenal hematoma			
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			
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		
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		
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 extrasystoles			
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	1 / 108 (0.93%)		
occurrences causally related to treatment / all	1 / 1		
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		
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		
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		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences causally related to treatment / all	0 / 10		
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		
End stage renal 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		
Proteinuria			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
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		
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		
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			
Appendicitis			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Corona virus infection			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences causally related to treatment / all	0 / 7		
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		
Pneumonia			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
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		
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		
Metabolism and nutrition disorders			
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		
Fluid overload			
subjects affected / exposed	3 / 108 (2.78%)		
occurrences causally related to treatment / all	0 / 3		
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		
Hypervolaemia			
subjects affected / exposed	1 / 108 (0.93%)		
occurrences causally related to treatment / all	0 / 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			
Hypertension			
subjects affected / exposed	18 / 108 (16.67%)		
occurrences (all)	29		
Hypotension			
subjects affected / exposed	22 / 108 (20.37%)		
occurrences (all)	37		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	8		
Chest pain			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	14		
Fatigue			
subjects affected / exposed	12 / 108 (11.11%)		
occurrences (all)	15		
Oedema peripheral			
subjects affected / exposed	29 / 108 (26.85%)		
occurrences (all)	44		
Pyrexia			
subjects affected / exposed	16 / 108 (14.81%)		
occurrences (all)	19		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	13 / 108 (12.04%)		
occurrences (all)	18		
Dyspnoea			
subjects affected / exposed	8 / 108 (7.41%)		
occurrences (all)	8		
Nasal congestion			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	15		

Oropharyngeal pain subjects affected / exposed occurrences (all)	11 / 108 (10.19%) 18		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	10 / 108 (9.26%) 10		
Investigations Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) Blood creatine increased subjects affected / exposed occurrences (all) Coronavirus test positive subjects affected / exposed occurrences (all) Glomerular filtration rate decreased subjects affected / exposed occurrences (all) Haemoglobin decreased subjects affected / exposed occurrences (all) N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all)	17 / 108 (15.74%) 21 15 / 108 (13.89%) 22 6 / 108 (5.56%) 7 11 / 108 (10.19%) 14 7 / 108 (6.48%) 7 6 / 108 (5.56%) 8		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 8		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache	18 / 108 (16.67%) 27		

subjects affected / exposed occurrences (all)	32 / 108 (29.63%) 43		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	18 / 108 (16.67%) 20		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	6 / 108 (5.56%) 9 6 / 108 (5.56%) 7 25 / 108 (23.15%) 31 25 / 108 (23.15%) 35 18 / 108 (16.67%) 29		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	7 / 108 (6.48%) 9		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Proteinuria subjects affected / exposed occurrences (all) Renal impairment subjects affected / exposed occurrences (all)	14 / 108 (12.96%) 19 15 / 108 (13.89%) 20 6 / 108 (5.56%) 7		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	14 / 108 (12.96%)		
occurrences (all)	21		
Back pain			
subjects affected / exposed	13 / 108 (12.04%)		
occurrences (all)	14		
Flank pain			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Muscle spasms			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	13		
Musculoskeletal pain			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Osteoarthritis			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	15		
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 108 (6.48%)		
occurrences (all)	10		
Cellulitis			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	6		
Corona virus infection			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	12		
Influenza			

subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	10		
Nasopharyngitis			
subjects affected / exposed	12 / 108 (11.11%)		
occurrences (all)	21		
Sinusitis			
subjects affected / exposed	9 / 108 (8.33%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	15 / 108 (13.89%)		
occurrences (all)	40		
Urinary tract infection			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	21		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	7		
Gout			
subjects affected / exposed	11 / 108 (10.19%)		
occurrences (all)	22		
Hyperkalaemia			
subjects affected / exposed	21 / 108 (19.44%)		
occurrences (all)	40		
Metabolic acidosis			
subjects affected / exposed	10 / 108 (9.26%)		
occurrences (all)	11		
Vitamin D deficiency			
subjects affected / exposed	6 / 108 (5.56%)		
occurrences (all)	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