Clinical trial results:
A double-blind, randomised, placebo-controlled study to assess the effect of SNF472 on progression of cardiovascular calcification on top of standard of care in end-stage-renal-disease (ESRD) patients on haemodialysis (HD)

Summary

EudraCT number	2016-002834-59
Trial protocol	GB ES
Global end of trial date	14 August 2019

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	SNFCT2015-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02966028
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanifit Therapeutics S.A.
Sponsor organisation address	PARC BIT. Europa Building. 2nd Floor, Palma , Spain, 07121
Public contact	Sanifit Information, Sanifit Therapeutics S.A, info@sanifit.com
Scientific contact	Regulatory Affairs, Sanifit Therapeutics S.A., lydie.yang@sanifit.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 August 2019
Global end of trial reached?	Yes
Global end of trial date	14 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to assess the effect of 2 dose levels of SNF472 (300 mg and 600 mg) compared to placebo on the progression of absolute change in coronary artery calcium volume score over a 12 month (52 weeks) period in ESRD patients on HD.

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Spain: 94
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	274
EEA total number of subjects	108

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)	160
From 65 to 84 years	114
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were required to meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in the study. Subjects with existing coronary artery calcification based on Agatston scores at screening were enrolled because they were more likely to show progressive calcification during the study.

Pre-assignment

Screening details:

Screening was conducted in 2 steps:
- Step 1: After written informed consent was obtained, a CT scan of the coronary arteries was obtained and bone mineral density was measured by DXA.
- Step 2: If eligibility criterion in Step 1 was confirmed, then baseline data were collected at this visit.

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, Carer

Blinding implementation details:

Investigators, all clinical staff, study subjects, and study administrators remained blinded throughout the clinical trial, unless safety concerns or a regulatory requirement made unblinding necessary.

Arms

Are arms mutually exclusive?	Yes
Arm title	SNF472 300 mg

Arm description:

Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline.

Arm type	Experimental
Investigational medicinal product name	SNF472
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SNF472 was provided as 10 mL of sterile liquid in transparent glass vials, containing either 300 mg of SNF472 for a concentration of 30 mg/mL. The full volume of the vial was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.
The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

Investigational medicinal product name	Physiologic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Physiologic saline was provided as 10 mL of sterile liquid in transparent glass vials. The full volume of

the physiologic saline was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.
The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

Arm title	SNF472 600 mg

Arm description:

Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).

Arm type	Experimental
Investigational medicinal product name	SNF472
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SNF472 was provided as 10 mL of sterile liquid in transparent glass vials, containing either 300 mg of SNF472 for a concentration of 30 mg/mL. The full volume of the vial was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.
The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

Arm title	Placebo

Arm description:

Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the
subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.

Arm type	Placebo
Investigational medicinal product name	Physiologic saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Physiologic saline was provided as 10 mL of sterile liquid in transparent glass vials. The full volume of the physiologic saline was injected into a bag of saline (0.9% sodium chloride) and administered as a constant rate intravenous (IV) infusion connected to an infusion pump, which was connected directly to the dialysis machine via an IV giving set and an accessory heparin line. The preferred physiologic saline bag size for dilution of the study drug was 100 mL.
The infusion was initiated approximately 30 minutes after the start of the hemodialysis procedure and was to be completed in 2.5 hours.

Number of subjects in period 1	SNF472 300 mg	SNF472 600 mg	Placebo
Started	92	91	91
Received dose	92	91	90
Completed	68	57	60
Not completed	24	34	31
Adverse event, serious fatal	1	6	3
Physician decision	1	-	-
Consent withdrawn by subject	7	5	5
Transferred to other clinic	2	-	-
Transfer to other clinic	-	2	1
Adverse event, non-fatal	6	7	7
Subject determination	-	-	1
Physician decision Death	-	-	2
Site/visit compliance	1	-	-
Kidney transplant	6	12	8
Site/visit non-compliance	-	2	4

Baseline characteristics

Reporting groups	
Reporting group title	SNF472 300 mg
Reporting group description:	
Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline.	
Reporting group title	SNF472 600 mg
Reporting group description:	
Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).	
Reporting group title	Placebo
Reporting group description:	
Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.	

Reporting group values	SNF472 300 mg	SNF472 600 mg	Placebo
Number of subjects	92	91	91
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	51	40
From 65-84 years	38	40	51
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.0	63.6	64.1
standard deviation	± 9.48	± 8.94	± 8.18
Gender categorical Units: Subjects			
Female	38	36	33
Male	54	55	58
Race			
Race was self reported by the subjects. Subjects could select more than one option.			
Units: Subjects			
Asian	2	4	4
American Indian or Alaska Native	2	0	0
Black or African American	26	15	19
Native Hawaiian or Other Pacific Islander	0	1	0
White	59	67	63

Not Reported	3	4	5

Reporting group values	Total		
Number of subjects	274		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	145		
From 65-84 years	129		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	107		
Male	167		
Race			
Race was self reported by the subjects. Subjects could select more than one option.			
Units: Subjects			
Asian	10		
American Indian or Alaska Native	2		
Black or African American	60		
Native Hawaiian or Other Pacific Islander	1		
White	189		
Not Reported	12		

Subject analysis sets

Subject analysis set title	SNF472 300 mg - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population included subjects who received at least 1 dose of study drug	
Subject analysis set title	SNF472 600 mg - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population included subjects who received at least 1 dose of study drug	
Subject analysis set title	Placebo - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Population included subjects who received at least 1 dose of study drug	

Subject analysis set title	SNF472 Combined - mITT LOCF
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)

Subject analysis set title	SNF472 300 mg - mITT LOCF
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)

Subject analysis set title	SNF472 600 mg - mITT LOCF
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)

Subject analysis set title	Placebo - mITT LOCF
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)

Reporting group values	SNF472 300 mg - Safety Population	SNF472 600 mg - Safety Population	Placebo - Safety Population
Number of subjects	92	91	90
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	51	40
From 65-84 years	38	40	50
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	63.0	63.6	64.1
standard deviation	± 9.48	± 8.94	± 8.18
Gender categorical Units: Subjects			
Female	38	36	33
Male	54	55	57
Race			
Race was self reported by the subjects. Subjects could select more than one option.			
Units: Subjects			
Asian	1		
American Indian or Alaska Native	2		
Black or African American	26		
Native Hawaiian or Other Pacific Islander	0		
White	59		

Not Reported	3		

Reporting group values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF
Number of subjects	142	77	65
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	63.8	63.0	64.5
standard deviation	± 9.07	± 9.63	± 9.39
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Race was self reported by the subjects. Subjects could select more than one option.			
Units: Subjects			
Asian			
American Indian or Alaska Native			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Not Reported			

Reporting group values	Placebo - mITT LOCF		
Number of subjects	77		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			

85 years and over			

Age continuous Units: years			
arithmetic mean	64.1		
standard deviation	± 8.25		
Gender categorical Units: Subjects			
Female			
Male			
Race			
Race was self reported by the subjects. Subjects could select more than one option.			
Units: Subjects			
Asian			
American Indian or Alaska Native			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Not Reported			

End points

End points reporting groups

Reporting group title	SNF472 300 mg
Reporting group description:	
Subjects were assigned to receive 300 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 1 vial of SNF472 (300 mg/vial) and 1 vial of physiologic saline.	
Reporting group title	SNF472 600 mg
Reporting group description:	
Subjects were assigned to receive 600 mg SNF472 administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vials of SNF472 (300 mg/vial).	
Reporting group title	Placebo
Reporting group description:	
Subjects were assigned to receive physiologic saline (0.9% sodium chloride) administered 3 times per week in conjunction with the subject's hemodialysis sessions. All subjects received 2 identical vials of 10 mL each: 2 vial of physiologic saline.	
Subject analysis set title	SNF472 300 mg - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population included subjects who received at least 1 dose of study drug	
Subject analysis set title	SNF472 600 mg - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population included subjects who received at least 1 dose of study drug	
Subject analysis set title	Placebo - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety Population included subjects who received at least 1 dose of study drug	
Subject analysis set title	SNF472 Combined - mITT LOCF
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)	
Subject analysis set title	SNF472 300 mg - mITT LOCF
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)	
Subject analysis set title	SNF472 600 mg - mITT LOCF
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)	
Subject analysis set title	Placebo - mITT LOCF
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The mITT Population included subjects who received at least 1 dose of study drug and had an evaluable baseline and post randomization CT scan with a non missing CAC volume score (Week 52/ET)	

Primary: Change in log coronary artery calcification (CAC) volume score from Baseline to Week 52 for the combined dose groups vs placebo

End point title	Change in log coronary artery calcification (CAC) volume score from Baseline to Week 52 for the combined dose groups vs placebo

End point description:

Change is geometric least squares mean (95% confidence intervals)

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	SNF472 Combined - mITT LOCF	Placebo - mITT LOCF		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	142	77		
Units: volume score				
geometric mean (confidence interval 95%)	1.11 (1.067 to 1.153)	1.20 (1.138 to 1.262)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis

Statistical analysis description:

The primary endpoint was the change in log CAC volume scores between baseline and Week 52 for the combined dose groups vs placebo.
The primary comparison was that of the combined dose groups vs the placebo group. The primary efficacy analysis in the mITT Population imputed missing Week 52 CAC volume score using the last observation carried forward (LOCF) from the early termination visit.

Comparison groups	SNF472 Combined - mITT LOCF v Placebo - mITT LOCF
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0163 [1]
Method	ANCOVA
Parameter estimate	ratio
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.869
upper limit	0.986

Notes:

[1] - P-value for treatment effect ratio between the combined dose groups and placebo

Secondary: Change in log coronary artery calcification (CAC) volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo

End point title	Change in log coronary artery calcification (CAC) volume score between baseline and Week 52 for each dose group (300 mg

	and 600 mg) vs placebo
End point description:	
Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	77	65	77	
Units: volume score				
geometric mean (confidence interval 95%)	1.12 (1.060 to 1.175)	1.10 (1.042 to 1.165)	1.20 (1.138 to 1.262)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log coronary artery calcification (CAC) Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and for the combined dose groups vs the placebo group

End point title	Change in log coronary artery calcification (CAC) Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and for the combined dose groups vs the placebo group
End point description:	
Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	142	77	65	77
Units: Agatson score				
geometric mean (confidence interval 95%)	1.11 (1.060 to 1.170)	1.10 (1.027 to 1.170)	1.13 (1.055 to 1.215)	1.20 (1.122 to 1.278)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with <15% progression in coronary artery calcification (CAC) Agatston score at Week 52 for each dose group and the combined dose groups vs placebo

End point title	Number of subjects with <15% progression in coronary artery calcification (CAC) Agatston score at Week 52 for each dose group and the combined dose groups vs placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	142	77	65	77
Units: subjects	87	46	41	37

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ≥15% progression in coronary artery calcification (CAC) volume score at Week 52 for each dose group and the combined dose groups vs placebo

End point title	Number of subjects with ≥15% progression in coronary artery calcification (CAC) volume score at Week 52 for each dose group and the combined dose groups vs placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	142	77	65	77
Units: subjects	53	31	22	38

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log thoracic aorta calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

End point title	Change in log thoracic aorta calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo
End point description:	
Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	134	74	60	75
Units: volume score				
geometric mean (confidence interval 95%)	1.23 (1.161 to 1.302)	1.25 (1.156 to 1.346)	1.21 (1.113 to 1.318)	1.28 (1.187 to 1.381)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log thoracic aorta calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

End point title	Change in log thoracic aorta calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo
End point description:	
Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	134	74	60	75
Units: Agatston score				
geometric mean (confidence interval 95%)	1.29 (1.201 to 1.384)	1.30 (1.186 to 1.432)	1.28 (1.149 to 1.416)	1.32 (1.205 to 1.452)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log aortic valve calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

End point title	Change in log aortic valve calcification volume score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo
End point description:	
Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe:	
Baseline to Week 52	

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	138	75	63	69
Units: volume score				
geometric mean (confidence interval 95%)	1.14 (1.048 to 1.235)	1.28 (1.143 to 1.426)	1.01 (0.899 to 1.144)	1.98 (1.768 to 2.226)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in log aortic valve calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

End point title	Change in log aortic valve calcification Agatston score between baseline and Week 52 for each dose group (300 mg and 600 mg) vs placebo and the combined dose groups vs placebo

End point description: Change is geometric least squares mean (95% confidence intervals)	
End point type	Secondary
End point timeframe: Baseline to Week 52	

End point values	SNF472 Combined - mITT LOCF	SNF472 300 mg - mITT LOCF	SNF472 600 mg - mITT LOCF	Placebo - mITT LOCF
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	138	75	63	69
Units: Agatston score				
geometric mean (confidence interval 95%)	1.14 (1.022 to 1.277)	1.33 (1.141 to 1.541)	0.98 (0.836 to 1.160)	2.86 (2.449 to 3.349)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of the composite safety endpoint (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) for each dose group and placebo

End point title	Incidence of the composite safety endpoint (death from cardiovascular causes, myocardial infarction, stroke, or heart failure) for each dose group and placebo
End point description:	
End point type	Secondary
End point timeframe: Baseline to Week 52	

End point values	SNF472 300 mg - Safety Population	SNF472 600 mg - Safety Population	Placebo - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	92	91	90	
Units: subjects	7	6	10	

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality rate (all-cause and cardiovascular) for each dose group and placebo

End point title	Mortality rate (all-cause and cardiovascular) for each dose group and placebo

End point description:

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	SNF472 300 mg - Safety Population	SNF472 600 mg - Safety Population	Placebo - Safety Population	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	92	91	90	
Units: subjects	1	6	5	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 52

Adverse event reporting additional description:

Treatment-emergent adverse events (TEAEs), defined as adverse events with an onset date on or after the date of first dose of study drug through the subject's early termination visit or until scheduled completion (Week 52 visit)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SNF472 300 mg - Safety Population
Reporting group description: -	
Reporting group title	SNF472 600 mg - Safety Population
Reporting group description: -	
Reporting group title	Placebo - Safety Population

Reporting group description: -

Serious adverse events	SNF472 300 mg - Safety Population	SNF472 600 mg - Safety Population	Placebo - Safety Population
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 92 (41.30%)	55 / 91 (60.44%)	49 / 90 (54.44%)
number of deaths (all causes)	1	6	5
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine benign neoplasm			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			

subjects affected / exposed	3 / 92 (3.26%)	2 / 91 (2.20%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertension			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			
subjects affected / exposed	0 / 92 (0.00%)	2 / 91 (2.20%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body embolism			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Renal transplant			
subjects affected / exposed	6 / 92 (6.52%)	14 / 91 (15.38%)	11 / 90 (12.22%)
occurrences causally related to treatment / all	0 / 6	0 / 14	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lymphadenectomy			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 92 (0.00%)	3 / 91 (3.30%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Asthenia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Blood lactic acid increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac stress test abnormal			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus test positive			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress echocardiogram abnormal			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			

subjects affected / exposed	1 / 92 (1.09%)	3 / 91 (3.30%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula thrombosis			
subjects affected / exposed	2 / 92 (2.17%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 92 (0.00%)	2 / 91 (2.20%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft complication			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial injury			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site haematoma			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft aneurysm			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft thrombosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Post procedural haemorrhage			

subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural hypotension			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 92 (3.26%)	3 / 91 (3.30%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	4 / 90 (4.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 92 (1.09%)	3 / 91 (3.30%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 92 (0.00%)	3 / 91 (3.30%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiogenic shock			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Metabolic encephalopathy			
subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness postural			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myasthenia gravis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uraemic encephalopathy			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agranulocytosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of chronic disease			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrogenic anaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Retinal detachment			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	4 / 91 (4.40%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal mass			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gastroparesis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcerative gastritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			

subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic ischaemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal mass			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 92 (4.35%)	3 / 91 (3.30%)	7 / 90 (7.78%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 92 (2.17%)	2 / 91 (2.20%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site infection			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 92 (0.00%)	2 / 91 (2.20%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			

subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 92 (0.00%)	2 / 91 (2.20%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft site abscess			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysematous cystitis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis viral			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis bacterial			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			

subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis bacterial			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular access site infection			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	3 / 90 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	2 / 92 (2.17%)	1 / 91 (1.10%)	2 / 90 (2.22%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 92 (1.09%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calciphylaxis			
subjects affected / exposed	0 / 92 (0.00%)	0 / 91 (0.00%)	1 / 90 (1.11%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 92 (1.09%)	0 / 91 (0.00%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 92 (0.00%)	1 / 91 (1.10%)	0 / 90 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	SNF472 300 mg - Safety Population	SNF472 600 mg - Safety Population	Placebo - Safety Population
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 92 (44.57%)	29 / 91 (31.87%)	29 / 90 (32.22%)
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 92 (7.61%)	11 / 91 (12.09%)	10 / 90 (11.11%)
occurrences (all)	7	11	10
Abdominal pain upper			

subjects affected / exposed	11 / 92 (11.96%)	2 / 91 (2.20%)	2 / 90 (2.22%)
occurrences (all)	11	2	2
Vomiting			
subjects affected / exposed	1 / 92 (1.09%)	8 / 91 (8.79%)	4 / 90 (4.44%)
occurrences (all)	1	8	4
Nausea			
subjects affected / exposed	2 / 92 (2.17%)	5 / 91 (5.49%)	4 / 90 (4.44%)
occurrences (all)	2	5	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 92 (10.87%)	9 / 91 (9.89%)	8 / 90 (8.89%)
occurrences (all)	10	9	8
Dyspnoea			
subjects affected / exposed	5 / 92 (5.43%)	7 / 91 (7.69%)	7 / 90 (7.78%)
occurrences (all)	5	7	7
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	7 / 92 (7.61%)	7 / 91 (7.69%)	7 / 90 (7.78%)
occurrences (all)	7	7	7
Musculoskeletal pain			
subjects affected / exposed	3 / 92 (3.26%)	6 / 91 (6.59%)	5 / 90 (5.56%)
occurrences (all)	3	6	5
Back pain			
subjects affected / exposed	6 / 92 (6.52%)	2 / 91 (2.20%)	4 / 90 (4.44%)
occurrences (all)	6	2	4
Arthralgia			
subjects affected / exposed	5 / 92 (5.43%)	2 / 91 (2.20%)	4 / 90 (4.44%)
occurrences (all)	5	2	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	2 / 92 (2.17%)	4 / 91 (4.40%)	6 / 90 (6.67%)
occurrences (all)	2	4	6
Nasopharyngitis			
subjects affected / exposed	3 / 92 (3.26%)	1 / 91 (1.10%)	6 / 90 (6.67%)
occurrences (all)	3	1	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2017	Protocol Amendment 1, dated 31 JUL 2017 (Global) The primary purpose of Amendment 1 was to add the sub-study, an opt-in Investigator addition of echocardiographic assessments at 3 time points (sub-study entry, Week 28 and Week 52/Early Termination), to measure reduction in progression of cardiovascular calcification on arterial stiffness for exploratory analyses on subjects participating in the main study and willing to provide additional informed consent. Additionally, this protocol was amended for administrative updates and to clarify procedural details.
29 March 2018	Protocol Amendment 2, dated 29 MAR 2018 (Global) The main goals of Protocol Amendment 2 were to increase the upper limit of the coronary artery calcification (CAC) Agatston score allowed for enrollment from 2000 to 3500, to clarify the planned sample size re-estimation, to clarify the endpoint descriptions, and to provide additional details on planned statistical analyses, including those in the sub-study.
27 June 2018	Protocol Amendment 3, dated 27 JUN 2018 (Global) Protocol Amendment 3 provided a revised sample size calculation that led to a reduction in planned enrollment from approximately 450 to approximately 270 subjects.
22 October 2018	Protocol Amendment 4, dated 22 OCT 2018 (Global) Protocol Amendment 4 added a non binding interim futility analysis to be conducted when approximately N=120 subjects (63% of N=190) had provided Week 52 data on the primary endpoint. Pharmacokinetic and pharmacodynamic analyses were also added at the time of the interim analysis. Phosphorus (phosphate) was added to the list of analytes in the safety laboratory assessments. The amendment also clarified that study drug must be added to the dialysis circuit before the dialyzer.
01 March 2019	Protocol Amendment 5, dated 01 MAR 2019 (Global) Protocol Amendment 5 described additional analyses of the dataset used for the futility analyses that would be conducted in the event of an equivocal result of the futility analysis indicating borderline conditional power of the study. These analyses could include primary and secondary endpoints, demographic and background characteristics, key subgroups, and pharmacokinetic/pharmacodynamic correlations with efficacy.

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/31707860