Clinical trial results:
A randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly subcutaneous administrations of a low and high dose cohort of osocimab to ESRD patients on regular hemodialysis

Summary

EudraCT number	2019-003957-27
Trial protocol	CZ AT GR BE PT NL LT PL HU BG IT
Global end of trial date	30 May 2022

Results information

Result version number	v1 (current)
This version publication date	21 May 2023
First version publication date	21 May 2023

Trial information

Trial identification

Sponsor protocol code	BAY1213790/20115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04523220
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	27 June 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to clinically assess the safety and tolerability of different doses of osocimab administered subcutaneously once a month during main treatment period as compared to placebo.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2020
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	Japan: 60
Country: Number of subjects enrolled	Bulgaria: 40
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Hungary: 50
Country: Number of subjects enrolled	Lithuania: 5
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Russian Federation: 110
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	Ukraine: 91
Country: Number of subjects enrolled	United States: 114
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	Belgium: 23
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Israel: 28
Country: Number of subjects enrolled	Italy: 20

Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Portugal: 30
Worldwide total number of subjects	704
EEA total number of subjects	275

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)	418
From 65 to 84 years	271
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 19 countries/regions, between 28-Aug-2020 (first subject first visit) and 30-May-2022 (last subject last visit).

Pre-assignment

Screening details:

A total of 859 subjects were screened; 155 subjects were not randomized. Most common reasons for not being randomized was screen failure (144 subjects). 704 subjects were randomized to treatment; 18 subjects did not receive treatment. The remaining 686 subjects were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Higher-dose osocimab

Arm description:

Subjects were randomized to receive Osocimab (BAY1213790) 210 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 105 mg for 6 months in main treatment phase.

Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous abdominal injection; starting with 1 loading dose of 210 mg, followed by monthly maintenance doses of 105 mg until the end of the main treatment period for 6 months.

Arm title	Lower-dose osocimab

Arm description:

Subjects were randomized to receive Osocimab (BAY1213790) 105 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 52.5 mg for 6 months in main treatment phase.

Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous abdominal injection; starting with 1 loading dose of 105 mg, followed by monthly maintenance doses of 52.5 mg until the end of the main treatment period for 6 months.

Arm title	Placebo

Arm description:

Subjects were randomized to receive matching placebo subcutaneously in the same manner as Osocimab until the end of the main treatment period for 6 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo, subcutaneous abdominal injection; starting with 1 loading dose, followed by monthly maintenance doses in the same manner as Osocimab until the end of the main treatment period for 6 months.

Number of subjects in period 1	Higher-dose osocimab	Lower-dose osocimab	Placebo
Started	234	235	235
Treated	224	232	230
Completed	194	199	206
Not completed	40	36	29
Consent withdrawn by subject	3	3	4
Physician decision	1	1	-
Subject Decision	5	7	3
Study drug never adminstered	10	3	5
Adverse event, non-fatal	11	9	9
Other	5	2	4
Death	5	11	4

Period 2

Period 2 title	Extension treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Higher-dose osocimab

Arm description:

Subjects received Osocimab (BAY1213790) at monthly maintenance doses of 105 mg up to a maximum of 12 months or until the last subject randomized to the study has performed the end of main treatment (EOMT) visit (whichever comes first) in extension treatment period.

Arm type	Experimental

Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous abdominal injection; monthly maintenance doses of 105 mg until the end of the extension treatment period.

Arm title	Lower-dose osocimab

Arm description:

Subjects received Osocimab (BAY1213790) at monthly maintenance doses of 52.5 mg up to a maximum of 12 months or until the last subject randomized to the study has performed the end of main treatment (EOMT) visit (whichever comes first) in extension treatment period.

Arm type	Experimental
Investigational medicinal product name	Osocimab
Investigational medicinal product code	BAY1213790
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous abdominal injection; monthly maintenance doses of 52.5 mg until the end of the extension treatment period.

Arm title	Placebo

Arm description:

Subjects received matching placebo subcutaneously in the same manner as Osocimab in extension treatment period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo, subcutaneous abdominal injection; monthly maintenance doses in the same manner as Osocimab until the end of the extension treatment period.

Number of subjects in period 2	Higher-dose osocimab	Lower-dose osocimab	Placebo
Started	194	199	206
Completed	174	178	176
Not completed	20	21	30
Physician decision	1	-	3
Consent withdrawn by subject	-	1	1
Subject Decision	5	2	4
Adverse event, non-fatal	6	7	9
Other	2	6	6
Death	6	4	7
Study drug never administered	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Higher-dose osocimab
Reporting group description:	
Subjects were randomized to receive Osocimab (BAY1213790) 210 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 105 mg for 6 months in main treatment phase.	
Reporting group title	Lower-dose osocimab
Reporting group description:	
Subjects were randomized to receive Osocimab (BAY1213790) 105 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 52.5 mg for 6 months in main treatment phase.	
Reporting group title	Placebo
Reporting group description:	
Subjects were randomized to receive matching placebo subcutaneously in the same manner as Osocimab until the end of the main treatment period for 6 months.	

Reporting group values	Higher-dose osocimab	Lower-dose osocimab	Placebo
Number of subjects	234	235	235
Age Categorical Units: Subjects			
Age Continuous Units: years			
median	61.0	61.1	59.5
standard deviation	± 13.4	± 12.9	± 13.3
Gender Categorical Units: Subjects			
Female	85	90	81
Male	149	145	154
Race Units: Subjects			
WHITE	193	194	190
BLACK OR AFRICAN AMERICAN	19	18	22
ASIAN	21	21	21
AMERICAN INDIAN OR ALASKA NATIVE	1	0	1
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	1	1
MULTIPLE	0	1	0
Activated partial thromboplastin time (aPTT) value at baseline			
aPTT was measured via the kaolin-trigger method (clotting assay). Furthermore, the aPTT assay was conducted after in vitro- neutralization of heparin in order to separate potential heparin effects from the PD effect of osocimab.The actual number of subjects entering the analysis was 628 (Higher-dose osocimab 209 subjects; Lower-dose osocimab 213 subjects; Placebo 206 subjects).			
Units: seconds			
geometric mean	31.49	31.32	31.65
standard deviation	± 1.10	± 1.10	± 1.09
Factor XI (FXI) activity at baseline			
Factor XI activity was assessed with an aPTT-based coagulation test using FXI deficient plasma.			

Furthermore, the assay was conducted after in vitro-neutralization of heparin in order to separate potential heparin effects from the PD effect of osocimab. The actual number of subjects entering the analysis was 622 (Higher-dose osocimab 208 subjects; Lower-dose osocimab 212 subjects; Placebo 202 subjects).			
Units: percent			
geometric mean	100.54	102.27	103.09
standard deviation	± 1.29	± 1.28	± 1.25

Reporting group values	Total		
Number of subjects	704		
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
median			
standard deviation	-		
Gender Categorical			
Units: Subjects			
Female	256		
Male	448		
Race			
Units: Subjects			
WHITE	577		
BLACK OR AFRICAN AMERICAN	59		
ASIAN	63		
AMERICAN INDIAN OR ALASKA NATIVE	2		
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2		
MULTIPLE	1		
Activated partial thromboplastin time (aPTT) value at baseline			
aPTT was measured via the kaolin-trigger method (clotting assay). Furthermore, the aPTT assay was conducted after in vitro- neutralization of heparin in order to separate potential heparin effects from the PD effect of osocimab.The actual number of subjects entering the analysis was 628 (Higher-dose osocimab 209 subjects; Lower-dose osocimab 213 subjects; Placebo 206 subjects).			
Units: seconds			
geometric mean			
standard deviation	-		
Factor XI (FXI) activity at baseline			
Factor XI activity was assessed with an aPTT-based coagulation test using FXI deficient plasma. Furthermore, the assay was conducted after in vitro-neutralization of heparin in order to separate potential heparin effects from the PD effect of osocimab. The actual number of subjects entering the analysis was 622 (Higher-dose osocimab 208 subjects; Lower-dose osocimab 212 subjects; Placebo 202 subjects).			
Units: percent			
geometric mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Higher-dose osocimab

Reporting group description:

Subjects were randomized to receive Osocimab (BAY1213790) 210 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 105 mg for 6 months in main treatment phase.

Reporting group title	Lower-dose osocimab

Reporting group description:

Subjects were randomized to receive Osocimab (BAY1213790) 105 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 52.5 mg for 6 months in main treatment phase.

Reporting group title	Placebo

Reporting group description:

Subjects were randomized to receive matching placebo subcutaneously in the same manner as Osocimab until the end of the main treatment period for 6 months.

Reporting group title	Higher-dose osocimab

Reporting group description:

Subjects received Osocimab (BAY1213790) at monthly maintenance doses of 105 mg up to a maximum of 12 months or until the last subject randomized to the study has performed the end of main treatment (EOMT) visit (whichever comes first) in extension treatment period.

Reporting group title	Lower-dose osocimab

Reporting group description:

Subjects received Osocimab (BAY1213790) at monthly maintenance doses of 52.5 mg up to a maximum of 12 months or until the last subject randomized to the study has performed the end of main treatment (EOMT) visit (whichever comes first) in extension treatment period.

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo subcutaneously in the same manner as Osocimab in extension treatment period.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects randomly assigned to study intervention.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects randomly assigned to study intervention who took at least 1 dose of study intervention. Subjects were analyzed according to the intervention they actually received.

Subject analysis set title	Pharmacodynamic analysis set (PDS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All subjects with at least 1 PD sample in accordance with the PD sampling schedule and without deviation from the protocol that would have interfered with the evaluation of the PD data were included in the PD analysis.

Primary: Composite of major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) events as assessed by blinded Central Independent Adjudication Committee (CIAC)

End point title	Composite of major bleeding (MB) and clinically-relevant non-major bleeding (CRNMB) events as assessed by blinded Central Independent Adjudication Committee (CIAC)

End point description:

Descriptive time to composite of treatment emergent major and CRNMB events [in alignment with International Society on Thrombosis and Haemostatsis (ISTH) guidelines] analyses were performed. The

cumulative incidence function for the event-of-interest together with the corresponding confidence interval were estimated for each treatment arm using Aalen-Johansen estimators. Cumulative incidence of events up to the day, inclusive.

End point type	Primary

End point timeframe:

From the first dose of study intervention up till 30 days after last study intervention in the main treatment period, up to 6 months

End point values	Higher-dose osocimab	Lower-dose osocimab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224[1]	232[2]	230[3]	
Units: Percentage				
number (confidence interval 90%)	3.57 (1.91 to 6.04)	4.32 (2.48 to 6.91)	6.09 (3.84 to 9.04)	

Notes:

[1] - SAF

[2] - SAF

[3] - SAF

Statistical analyses

Statistical analysis title	Cause-specific Hazard Ratios

Statistical analysis description:

Two-sided log-rank tests and Cox proportional hazards model were used in the analyses.

Comparison groups	Placebo v Higher-dose osocimab
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.222
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.59
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.28
upper limit	1.21

Statistical analysis title	Cause-specific Hazard Ratios

Statistical analysis description:

Two-sided log-rank tests and Cox proportional hazards model were used in the analyses.

Comparison groups	Lower-dose osocimab v Placebo

Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.427
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.36
upper limit	1.42

Primary: Composite of moderate and severe adverse events (AEs) and serious adverse events (SAEs)

End point title	Composite of moderate and severe adverse events (AEs) and serious adverse events (SAEs)

End point description:

An AE was any untoward medical occurrence in a patient or clinical study subject, whether or not considered related to the study intervention.

End point type	Primary

End point timeframe:

From the first dose of study intervention up until 30 days after last study intervention in the main treatment period, up to 6 months

End point values	Higher-dose osocimab	Lower-dose osocimab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	224[4]	232[5]	230[6]	
Units: Percentages				
number (confidence interval 90%)	38.84 (33.46 to 44.17)	38.37 (33.10 to 43.60)	32.17 (27.16 to 37.28)	

Notes:

[4] - SAF

[5] - SAF

[6] - SAF

Statistical analyses

Statistical analysis title	Cause-specific Hazard Ratios

Statistical analysis description:

Two-sided log-rank tests and Cox proportional hazards model were used in the analyses.

Comparison groups	Lower-dose osocimab v Placebo

Number of subjects included in analysis	462
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.166
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.61

Statistical analysis title	Cause-specific Hazard Ratios
Statistical analysis description:	
Two-sided log-rank tests and Cox proportional hazards model were used in the analyses.	
Comparison groups	Higher-dose osocimab v Placebo
Number of subjects included in analysis	454
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.128
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.64

Secondary: Activated partial thromboplastin time (aPTT) at trough levels	
End point title	Activated partial thromboplastin time (aPTT) at trough levels
End point description:	
aPTT was measured via the kaolin-trigger method (clotting assay).	
End point type	Secondary
End point timeframe:	
At baseline and after 6 months (V19 / Day 30)	

End point values	Higher-dose osocimab	Lower-dose osocimab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	167[7]	174[8]	174[9]	
Units: Ratio				
geometric mean (standard deviation)				
Ratio to Baseline at V19 / Day 30	1.26 (± 1.11)	1.19 (± 1.11)	1.02 (± 1.08)	

Notes:

[7] - PDS

[8] - PDS

[9] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Factor XI (FXI) activity at trough levels

End point title	Factor XI (FXI) activity at trough levels

End point description:

Factor XI activity was assessed with an aPTT-based coagulation test using FXI deficient plasma.

End point type	Secondary

End point timeframe:

At baseline and after 6 months (V19 / Day 30)

End point values	Higher-dose osocimab	Lower-dose osocimab	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	164[10]	175[11]	171[12]	
Units: Ratio				
geometric mean (standard deviation)				
Ratio to Baseline at V19 / Day 30	0.87 (± 1.27)	0.94 (± 1.23)	0.96 (± 1.20)	

Notes:

[10] - PDS

[11] - PDS

[12] - PDS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first study dose up until 30 days after last study dose, with up to approx. 19 months. AE reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, with up to approx. 23 months

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Higher-dose osocimab

Reporting group description:

Subjects received Osocimab (BAY1213790) 210 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 105 mg

Reporting group title	Placebo

Reporting group description:

Subjects received matching placebo subcutaneously in the same manner as Osocimab

Reporting group title	Lower-dose osocimab

Reporting group description:

Subjects received Osocimab (BAY1213790) 105 mg single loading dose as subcutaneous abdominal injection, followed by monthly maintenance doses of 52.5 mg

Serious adverse events	Higher-dose osocimab	Placebo	Lower-dose osocimab
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 224 (27.23%)	63 / 230 (27.39%)	67 / 232 (28.88%)
number of deaths (all causes)	19	15	24
number of deaths resulting from adverse events	9	13	16
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Lung adenocarcinoma			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Lung neoplasm malignant			

subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Aortic stenosis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Hypertension			
subjects affected / exposed	3 / 224 (1.34%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Vena cava thrombosis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Iliac artery dissection			

subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Hypertensive emergency			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vein occlusion			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Arteriovenous fistula operation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Hip arthroplasty			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parathyroidectomy			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Renal transplant			

subjects affected / exposed	5 / 224 (2.23%)	5 / 230 (2.17%)	3 / 232 (1.29%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toe amputation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Central venous catheterisation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Intervertebral disc operation			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Dialysis device insertion			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous graft			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm surgery			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Peritoneal catheter insertion			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Chest pain			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac death			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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

Acute respiratory failure			
subjects affected / exposed	2 / 224 (0.89%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Pulmonary oedema			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	0 / 232 (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
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Investigations			
Angiocardiogram			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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 thrombosis			
subjects affected / exposed	1 / 224 (0.45%)	3 / 230 (1.30%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Foot fracture			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Joint dislocation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Rib fracture			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt occlusion			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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

Spinal compression fracture			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Ulna fracture			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
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 pseudoaneurysm			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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 haemorrhage			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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 complication			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula occlusion			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Shunt stenosis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Shunt aneurysm			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft thrombosis			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	0 / 232 (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
Unintentional medical device removal			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Vascular access site inflammation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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			
Acute myocardial infarction			
subjects affected / exposed	2 / 224 (0.89%)	2 / 230 (0.87%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Angina pectoris			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atrial fibrillation			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Bradycardia			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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 arrest			
subjects affected / exposed	2 / 224 (0.89%)	1 / 230 (0.43%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Cardiac failure chronic			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Dressler's syndrome			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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 infarction			
subjects affected / exposed	0 / 224 (0.00%)	3 / 230 (1.30%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus bradycardia			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Acute coronary syndrome			
subjects affected / exposed	2 / 224 (0.89%)	1 / 230 (0.43%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery insufficiency			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Mitral valve disease			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Syncope			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Ischaemic stroke			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	0 / 232 (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
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 224 (0.00%)	2 / 230 (0.87%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Thrombocytopenia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 224 (0.00%)	2 / 230 (0.87%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Diabetic retinopathy			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
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			
Abdominal pain			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Anal fissure			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Intestinal dilatation			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Pancreatitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Tongue haematoma			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
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 wall thickening			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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			
Bile duct stone			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Cholecystitis			

subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Cholecystitis chronic			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrosclerosis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal haematoma			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Renal cyst ruptured			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

Bacteraemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Cellulitis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Localised infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Osteomyelitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Peritonitis			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	4 / 224 (1.79%)	4 / 230 (1.74%)	0 / 232 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Sepsis			
subjects affected / exposed	1 / 224 (0.45%)	2 / 230 (0.87%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Tuberculous pleurisy			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	0 / 232 (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
Urinary tract infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Urosepsis			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Abscess limb			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronavirus infection			
subjects affected / exposed	0 / 224 (0.00%)	2 / 230 (0.87%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Febrile infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Perirectal abscess			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula site infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Renal cyst infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Pneumonia bacterial			

subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical mycobacterial infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Device related infection			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Vascular access site infection			
subjects affected / exposed	2 / 224 (0.89%)	0 / 230 (0.00%)	0 / 232 (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
COVID-19			
subjects affected / exposed	7 / 224 (3.13%)	5 / 230 (2.17%)	8 / 232 (3.45%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	3 / 224 (1.34%)	8 / 230 (3.48%)	9 / 232 (3.88%)
occurrences causally related to treatment / all	0 / 3	0 / 8	0 / 9
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 4
Device related bacteraemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Asymptomatic COVID-19			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 224 (0.45%)	1 / 230 (0.43%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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
Hypocalcaemia			
subjects affected / exposed	0 / 224 (0.00%)	1 / 230 (0.43%)	0 / 232 (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
Hypoglycaemia			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	2 / 232 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic complication			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ketoacidosis			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 224 (0.00%)	0 / 230 (0.00%)	1 / 232 (0.43%)
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 metabolic decompensation			

subjects affected / exposed	1 / 224 (0.45%)	0 / 230 (0.00%)	0 / 232 (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

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

Non-serious adverse events	Higher-dose osocimab	Placebo	Lower-dose osocimab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	90 / 224 (40.18%)	88 / 230 (38.26%)	85 / 232 (36.64%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 224 (8.04%)	16 / 230 (6.96%)	18 / 232 (7.76%)
occurrences (all)	20	17	24
Hypotension			
subjects affected / exposed	15 / 224 (6.70%)	18 / 230 (7.83%)	13 / 232 (5.60%)
occurrences (all)	22	28	27
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 224 (8.48%)	14 / 230 (6.09%)	23 / 232 (9.91%)
occurrences (all)	21	15	26
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 224 (4.46%)	12 / 230 (5.22%)	12 / 232 (5.17%)
occurrences (all)	10	13	12
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 224 (6.25%)	14 / 230 (6.09%)	9 / 232 (3.88%)
occurrences (all)	15	17	12
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 224 (5.80%)	16 / 230 (6.96%)	6 / 232 (2.59%)
occurrences (all)	16	18	6
Vomiting			
subjects affected / exposed	7 / 224 (3.13%)	12 / 230 (5.22%)	8 / 232 (3.45%)
occurrences (all)	7	16	10
Musculoskeletal and connective tissue disorders			

Muscle spasms subjects affected / exposed occurrences (all)	12 / 224 (5.36%) 20	15 / 230 (6.52%) 23	9 / 232 (3.88%) 17
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	11 / 224 (4.91%) 11	12 / 230 (5.22%) 12	14 / 232 (6.03%) 14

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported