Clinical trial results:
A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Patients with Diabetic Macular Edema

Summary

EudraCT number	2020-000402-29
Trial protocol	PT CZ DE DK HU GB SK AT PL BG IT
Global end of trial date	11 October 2023

Results information

Result version number	v1 (current)
This version publication date	23 October 2024
First version publication date	23 October 2024

Trial information

Trial identification

Sponsor protocol code	GR41987

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04432831
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche, Ltd.
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, 4058
Public contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.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	11 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 October 2023
Global end of trial reached?	Yes
Global end of trial date	11 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long term ocular and systemic safety and tolerability of faricimab administered intravitreally in patients with DME

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice (GCP) and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. An Informed Consent Form (ICF) was required to be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 August 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 76
Country: Number of subjects enrolled	Australia: 23
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czechia: 56
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Hungary: 61
Country: Number of subjects enrolled	Israel: 33
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 48
Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Peru: 12
Country: Number of subjects enrolled	Poland: 166

Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Russian Federation: 27
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Slovakia: 26
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Thailand: 14
Country: Number of subjects enrolled	Türkiye: 15
Country: Number of subjects enrolled	Taiwan: 16
Country: Number of subjects enrolled	United Kingdom: 43
Country: Number of subjects enrolled	United States: 606
Worldwide total number of subjects	1474
EEA total number of subjects	448

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)	750
From 65 to 84 years	714
85 years and over	10

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 1479 patients were enrolled, but 5 participants in total were excluded from the analysis populations because of Good Clinical Practice (GCP) non-compliance at a single site.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Faricimab PTI (prior Faricimab Q8W)

Arm description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Faricimab
Investigational medicinal product code	RO6867461
Other name	VABYSMO®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

Arm title	Faricimab PTI (prior Faricimab PTI)

Arm description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Arm type	Experimental
Investigational medicinal product name	Faricimab
Investigational medicinal product code	RO6867461
Other name	VABYSMO®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

Arm title	Faricimab PTI (prior Aflibercept Q8W)

Arm description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Arm type	Experimental

Investigational medicinal product name	Faricimab
Investigational medicinal product code	RO6867461
Other name	VABYSMO®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

Number of subjects in period 1	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)
Started	493	506	475
Received at Least One Dose of Study Drug	491	500	473
Completed	405	407	392
Not completed	88	99	83
Adverse event, serious fatal	23	23	17
Consent withdrawn by subject	24	28	21
Physician decision	1	3	6
Adverse event, non-fatal	7	7	7
Final End of Study Visit Not Completed	10	11	7
Pregnancy	-	1	-
Lost to follow-up	15	15	12
Reason not specified	7	11	9
Protocol deviation	1	-	2
Lack of efficacy	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Faricimab PTI (prior Faricimab Q8W)
Reporting group description:	
This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.	
Reporting group title	Faricimab PTI (prior Faricimab PTI)
Reporting group description:	
This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.	
Reporting group title	Faricimab PTI (prior Aflibercept Q8W)
Reporting group description:	
This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.	

Reporting group values	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)
Number of subjects	493	506	475
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)	264	243	243
From 65-84 years	223	261	230
85 years and over	6	2	2
Age Continuous Units: Years			
arithmetic mean	63.4	64.0	63.5
standard deviation	± 9.9	± 9.8	± 9.4
Sex: Female, Male Units: Participants			
Female	191	184	205
Male	302	322	270
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	4	4
Asian	54	52	45
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	27	32	25

White	392	406	389
More than one race	1	0	0
Unknown or Not Reported	13	12	11
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	68	87	79
Not Hispanic or Latino	415	408	386
Unknown or Not Reported	10	11	10

Reporting group values	Total		
Number of subjects	1474		
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)	750		
From 65-84 years	714		
85 years and over	10		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	580		
Male	894		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	13		
Asian	151		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	84		
White	1187		
More than one race	1		
Unknown or Not Reported	36		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	234		
Not Hispanic or Latino	1209		
Unknown or Not Reported	31		

End points

End points reporting groups

Reporting group title	Faricimab PTI (prior Faricimab Q8W)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Reporting group title	Faricimab PTI (prior Faricimab PTI)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Reporting group title	Faricimab PTI (prior Aflibercept Q8W)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Primary: Incidence and Severity of Ocular Adverse Events in the Study Eye, with Severity Determined According to Adverse Event Severity Grading Scale

End point title	Incidence and Severity of Ocular Adverse Events in the Study Eye, with Severity Determined According to Adverse Event Severity Grading Scale[1]

End point description:

This is an analysis of participants with at least one ocular adverse event (AE) that occurred in the study eye. Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity (e.g., mild, moderate, or severe intensity), and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score ≥30 letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

End point type	Primary

End point timeframe:

From the day of the first dose of faricimab until the end of the study (up to 108 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

End point values	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	491	500	473	
Units: Participants				
Any Adverse Event (AE), Any Severity	219	188	197	
AE by Severity: Mild	119	109	109	
AE by Severity: Moderate	74	66	74	

AE by Severity: Severe	20	10	12	
AE by Severity: Missing	6	3	2	
Serious Adverse Event (SAE)	31	15	26	
AE Leading to Withdrawal from Study Treatment	3	0	6	
Treatment-related AE	10	10	11	
Treatment-related SAE	0	1	1	
Any AE of Special Interest (AESI)	30	14	24	
AESI: Drop in Visual Acuity Score ≥30 Letters	23	10	20	
AESI: Associated with Severe IOI	1	1	1	
AESI: Intervention Req. to Prev. Perm. Vision Loss	6	3	3	
AESI: Suspect. Transm. of Infectious Agent by Drug	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Incidence of Ocular Adverse Events in the Fellow Eye

End point title	Incidence of Ocular Adverse Events in the Fellow Eye[2]

End point description:

This is an analysis of participants with at least one ocular adverse event (AE) that occurred in the fellow eye (i.e., non-study eye). Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity, and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score ≥30 letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

End point type	Primary

End point timeframe:

From the day of the first dose of faricimab until the end of the study (up to 108 weeks)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

End point values	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	491	500	473	
Units: Participants				
Any Adverse Event (AE)	186	185	179	
Serious Adverse Event (SAE)	16	17	15	
Any AE of Special Interest (AESI)	13	16	14	
AESI: Drop in Visual Acuity Score ≥30 Letters	6	9	10	
AESI: Associated with Severe IOI	0	1	1	

AESI: Intervention Req. to Prev. Perm. Vision Loss	7	6	4	
AESI: Suspect. Transm. of Infectious Agent by Drug	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Incidence and Severity of Non-Ocular Adverse Events, with Severity Determined According to Adverse Event Severity Grading Scale

End point title	Incidence and Severity of Non-Ocular Adverse Events, with Severity Determined According to Adverse Event Severity Grading Scale[3]

End point description:

This is an analysis of participants with at least one non-ocular (systemic) adverse event (AE). Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity (e.g., mild, moderate, or severe intensity), and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score ≥30 letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

End point type	Primary

End point timeframe:

From the day of the first dose of faricimab until the end of the study (up to 108 weeks)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

End point values	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	491	500	473	
Units: Participants				
Any Adverse Event (AE), Any Severity	317	295	297	
AE by Severity: Mild	91	94	97	
AE by Severity: Moderate	124	124	115	
AE by Severity: Severe	102	77	85	
Serious Adverse Event (SAE)	122	100	112	
AE Leading to Withdrawal from Study Treatment	2	7	4	
Any AE of Special Interest (AESI)	0	0	1	
AESI: Drop in Visual Acuity Score ≥30 Letters	0	0	1	
AESI: High ALT/AST & High Bilir. or Clin. Jaundice	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day of the first dose of faricimab until the end of the study (up to 108 weeks)

Adverse event reporting additional description:

Total number of deaths and adverse events (AEs) are reported for the Safety-Evaluable Population, which included all participant who enrolled and received at least one dose of faricimab during the study. For ocular AEs, the number of participants and events reported per term are specified to have occurred in the study eye or the fellow eye.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Faricimab PTI (prior Faricimab Q8W)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Reporting group title	Faricimab PTI (prior Faricimab PTI)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Reporting group title	Faricimab PTI (prior Aflibercept Q8W)

Reporting group description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

Serious adverse events	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)
Total subjects affected by serious adverse events			
subjects affected / exposed	158 / 491 (32.18%)	124 / 500 (24.80%)	134 / 473 (28.33%)
number of deaths (all causes)	22	20	17
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clear cell renal cell carcinoma			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Adenocarcinoma of colon			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Benign anorectal neoplasm			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Colon cancer metastatic			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Breast cancer			
subjects affected / exposed	0 / 491 (0.00%)	4 / 500 (0.80%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast neoplasm			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Cervix carcinoma			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer stage III			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Gastric cancer			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Gastric cancer stage IV			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Leukaemia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Neoplasm malignant			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Neuroendocrine carcinoma of the skin			

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Oesophageal cancer metastatic			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ovarian fibroma			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Pancreatic carcinoma			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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
Prostate cancer			
subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer stage IV			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Spinal cord neoplasm			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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			
Angiopathy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Hypertensive urgency			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 artery occlusion			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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
Aortic stenosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Arteriosclerosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Deep vein thrombosis			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 emergency			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 artery thrombosis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 vascular disorder			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			

subjects affected / exposed	1 / 491 (0.20%)	3 / 500 (0.60%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Organ failure			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Death			
subjects affected / exposed	3 / 491 (0.61%)	5 / 500 (1.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 5	0 / 2
Hernia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Oedema peripheral			

subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	0 / 473 (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
Chest pain			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Immune system disorders			
Food allergy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Drug hypersensitivity			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Contrast media allergy			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Allergy to arthropod sting			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Reproductive system and breast disorders			
Orchitis noninfective			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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

Pelvic cyst			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine polyp			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Dyspnoea			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic respiratory failure			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	0 / 473 (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
Asthma			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 respiratory failure			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Atelectasis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Pneumothorax			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 fibrosis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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 failure			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Substance-induced psychotic disorder			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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

Mental status changes			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device leakage			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Ammonia increased			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glycosylated haemoglobin abnormal			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate increased			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Precancerous cells present			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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

Liver function test abnormal			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Intraocular pressure increased	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Red blood cell count decreased			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Corneal abrasion	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Cataract traumatic	Additional description: SAEs occurred the study eye		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Comminuted fracture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 injury	Additional description: SAEs occurred the study eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Fall			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	0 / 473 (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
Foot fracture			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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
Foreign body			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Fracture displacement			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Ocular procedural complication	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Lumbar vertebral fracture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Hip fracture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 dialysis complication			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Post procedural constipation			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Post procedural inflammation	Additional description: SAEs occurred in the fellow eye		

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Pelvic fracture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Spinal compression fracture			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Skull fracture			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Shoulder fracture			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Tendon rupture			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Wound necrosis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 procedure complication			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Tibia fracture			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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			
Atrioventricular block complete			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Atrial fibrillation			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	4 / 473 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 pectoris			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 491 (0.20%)	4 / 500 (0.80%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	2 / 491 (0.41%)	2 / 500 (0.40%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Cardiac discomfort			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Cardiac arrest			
subjects affected / exposed	2 / 491 (0.41%)	2 / 500 (0.40%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Bradycardia			

subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 second degree			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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	7 / 491 (1.43%)	3 / 500 (0.60%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 9	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 valve disease			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Cardiogenic shock			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Cardiac failure			

subjects affected / exposed	0 / 491 (0.00%)	3 / 500 (0.60%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	6 / 491 (1.22%)	5 / 500 (1.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular hypokinesia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Tachycardia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	9 / 491 (1.83%)	3 / 500 (0.60%)	8 / 473 (1.69%)
occurrences causally related to treatment / all	0 / 9	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 3	0 / 1	0 / 3
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Coronary artery occlusion			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	0 / 473 (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
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Encephalomalacia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Cerebrovascular accident			
subjects affected / exposed	4 / 491 (0.81%)	3 / 500 (0.60%)	10 / 473 (2.11%)
occurrences causally related to treatment / all	0 / 4	0 / 3	1 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Cerebral infarction			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Lethargy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 encephalopathy			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Migraine			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukoencephalopathy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Paraparesis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Toxic encephalopathy			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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	1 / 491 (0.20%)	2 / 500 (0.40%)	0 / 473 (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
Status epilepticus			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Seizure			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Transient ischaemic attack			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral artery stenosis			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord paralysis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 491 (0.41%)	2 / 500 (0.40%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Leukocytosis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrogenic anaemia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Neutropenia			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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			
Cataract	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 11[491]11, 8[500]8, 15[473]15) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 6[500]6, 0[473]0)		
subjects affected / exposed	12 / 491 (2.44%)	14 / 500 (2.80%)	15 / 473 (3.17%)
occurrences causally related to treatment / all	0 / 12	0 / 14	0 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinal oedema	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 7[491]8, 0[500]0, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 1[500]1, 2[473]2)		
subjects affected / exposed	8 / 491 (1.63%)	1 / 500 (0.20%)	4 / 473 (0.85%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Cataract cortical	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Angle closure glaucoma	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Neovascular age-related macular degeneration	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Posterior capsule opacification	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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

Iridocyclitis	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Iridocele	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Glaucoma	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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

Rhegmatogenous retinal detachment	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Retinal tear	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 0[473]0) and the fellow eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 0[473]0)		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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

Retinal neovascularisation	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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

Tractional retinal detachment	Additional description: SAEs occurred in the fellow eye		
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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

Diabetic retinopathy	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 2[491]2, 3[500]3, 2[473]2)		
subjects affected / exposed	2 / 491 (0.41%)	3 / 500 (0.60%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epiretinal membrane	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 2[473]2)		
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 0[500]0, 1[473]1)		
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 0[473]0) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 0[500]0, 1[473]1)		
subjects affected / exposed	3 / 491 (0.61%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	0 / 473 (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
Vitreous haemorrhage	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 1[491]1, 1[500]1, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 4[491]4, 3[500]3, 6[473]6)		
subjects affected / exposed	5 / 491 (1.02%)	4 / 500 (0.80%)	8 / 473 (1.69%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis	Additional description: SAEs occurred in the study eye		
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Haematochezia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Colitis ulcerative			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Constipation			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Diarrhoea			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Oral mucosal hypertrophy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Umbilical hernia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Portal vein thrombosis			

subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 cirrhosis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gallbladder rupture			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract disorder			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cellulite			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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			
subjects affected / exposed	2 / 491 (0.41%)	3 / 500 (0.60%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			

subjects affected / exposed	3 / 491 (0.61%)	1 / 500 (0.20%)	0 / 473 (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
Renal and urinary disorders			
Diabetic nephropathy			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	2 / 491 (0.41%)	3 / 500 (0.60%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	8 / 491 (1.63%)	5 / 500 (1.00%)	5 / 473 (1.06%)
occurrences causally related to treatment / all	0 / 9	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	1 / 491 (0.20%)	2 / 500 (0.40%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcapsular renal haematoma			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 impairment			

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 haemorrhage			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 failure			
subjects affected / exposed	3 / 491 (0.61%)	1 / 500 (0.20%)	0 / 473 (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
Nephropathy			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 491 (0.20%)	3 / 500 (0.60%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Back pain			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Spondylolisthesis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Spinal stenosis			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Neuropathic arthropathy			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Neck pain			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 chest pain			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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			
Abdominal abscess			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Appendicitis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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	1 / 491 (0.20%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Bacteraemia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	10 / 491 (2.04%)	9 / 500 (1.80%)	5 / 473 (1.06%)
occurrences causally related to treatment / all	0 / 10	0 / 9	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 0
Arthritis infective			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Arthritis bacterial			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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
Bronchitis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Diabetic gangrene			

subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 intestinal haemorrhagic			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 foot infection			
subjects affected / exposed	2 / 491 (0.41%)	1 / 500 (0.20%)	0 / 473 (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
Device related sepsis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 colitis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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 infective			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	0 / 473 (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
Cellulitis			
subjects affected / exposed	3 / 491 (0.61%)	4 / 500 (0.80%)	6 / 473 (1.27%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			

subjects affected / exposed	4 / 491 (0.81%)	2 / 500 (0.40%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis	Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 1[473]1)		
subjects affected / exposed	4 / 491 (0.81%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	1 / 4	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	0 / 473 (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
Gangrene			
subjects affected / exposed	1 / 491 (0.20%)	2 / 500 (0.40%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Infected dermal cyst			

subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	0 / 473 (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
Febrile infection			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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	7 / 491 (1.43%)	0 / 500 (0.00%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Influenza			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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	7 / 491 (1.43%)	4 / 500 (0.80%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paronychia			

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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 chronic			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Systemic bacterial infection			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic endocarditis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Sepsis			
subjects affected / exposed	4 / 491 (0.81%)	2 / 500 (0.40%)	4 / 473 (0.85%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Staphylococcal infection			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Pneumonia aspiration			

subjects affected / exposed	0 / 491 (0.00%)	2 / 500 (0.40%)	0 / 473 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Pyelonephritis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Pneumonia			
subjects affected / exposed	5 / 491 (1.02%)	8 / 500 (1.60%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 5	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 tract infection			
subjects affected / exposed	2 / 491 (0.41%)	0 / 500 (0.00%)	3 / 473 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	0 / 473 (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
Malnutrition			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 491 (0.20%)	1 / 500 (0.20%)	2 / 473 (0.42%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypervolaemia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 / 491 (0.20%)	2 / 500 (0.40%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 491 (0.00%)	0 / 500 (0.00%)	1 / 473 (0.21%)
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 ketoacidosis			
subjects affected / exposed	1 / 491 (0.20%)	0 / 500 (0.00%)	0 / 473 (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
Diabetes mellitus inadequate control			

subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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
Diabetes mellitus			
subjects affected / exposed	0 / 491 (0.00%)	1 / 500 (0.20%)	0 / 473 (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

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Faricimab PTI (prior Faricimab Q8W)	Faricimab PTI (prior Faricimab PTI)	Faricimab PTI (prior Aflibercept Q8W)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 491 (47.45%)	213 / 500 (42.60%)	219 / 473 (46.30%)
Investigations			
Intraocular pressure increased	Additional description: AEs occurred in the study eye		
subjects affected / exposed	16 / 491 (3.26%)	12 / 500 (2.40%)	12 / 473 (2.54%)
occurrences (all)	20	15	13
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 491 (3.67%)	20 / 500 (4.00%)	23 / 473 (4.86%)
occurrences (all)	18	20	24
Eye disorders			
Cataract	Additional description: AEs occurred in both the study eye (subjects affected [exposed] occurrences = 65[491]65, 60[500]60, 63[473]63) and the fellow eye (subjects affected [exposed] occurrences = 56[491]56, 41[500]41, 51[473]52)		
subjects affected / exposed	90 / 491 (18.33%)	72 / 500 (14.40%)	84 / 473 (17.76%)
occurrences (all)	115	91	110
Posterior capsule opacification	Additional description: AEs occurred in both the study eye (subjects affected [exposed] occurrences = 16[491]17, 17[500]17, 14[473]14) and the fellow eye (subjects affected [exposed] occurrences = 13[491]14, 20[500]20, 13[473]13)		
subjects affected / exposed	19 / 491 (3.87%)	29 / 500 (5.80%)	20 / 473 (4.23%)
occurrences (all)	27	34	27
Diabetic retinal oedema	Additional description: AEs occurred in the fellow eye		
subjects affected / exposed	22 / 491 (4.48%)	27 / 500 (5.40%)	24 / 473 (5.07%)
occurrences (all)	22	31	27
Conjunctival haemorrhage	Additional description: AEs occurred in the study eye		
subjects affected / exposed	16 / 491 (3.26%)	9 / 500 (1.80%)	5 / 473 (1.06%)
occurrences (all)	17	9	5

Diabetic retinopathy	Additional description: AEs occurred in the fellow eye		
subjects affected / exposed	17 / 491 (3.46%)	8 / 500 (1.60%)	12 / 473 (2.54%)
occurrences (all)	17	8	12
Vitreous detachment	Additional description: AEs occurred in the study eye		
subjects affected / exposed	16 / 491 (3.26%)	12 / 500 (2.40%)	6 / 473 (1.27%)
occurrences (all)	16	12	6
Vitreous floaters	Additional description: AEs occurred in the study eye		
subjects affected / exposed	16 / 491 (3.26%)	7 / 500 (1.40%)	8 / 473 (1.69%)
occurrences (all)	18	7	8
Infections and infestations			
COVID-19			
subjects affected / exposed	63 / 491 (12.83%)	49 / 500 (9.80%)	46 / 473 (9.73%)
occurrences (all)	70	50	49
Nasopharyngitis			
subjects affected / exposed	18 / 491 (3.67%)	12 / 500 (2.40%)	23 / 473 (4.86%)
occurrences (all)	21	12	27
Urinary tract infection			
subjects affected / exposed	16 / 491 (3.26%)	15 / 500 (3.00%)	16 / 473 (3.38%)
occurrences (all)	19	17	18

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2020	Protocol Version 2: An exclusion criterion was added relating to a history of reaction or hypersensitivity to biologic agents including any component of the faricimab injection or study treatment procedures.
13 December 2021	Protocol Version 3: -A Final End-of-Study (FEOS) visit, to be completed 28-35 days after the last PTI dosing visit, was included for all patients. Therefore, the study was extended to a maximum of 108 weeks for patients who received their final dose of faricimab at Week 104; -The list of prohibited therapies was amended to clarify that continuous usage of topical ophthalmic corticosteroids for 100 days or more is considered prohibited therapy, and to add the use of kallidinogenase and other medications claiming to have an effect on macular pathology to the list of prohibited therapies.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported