Clinical trial results:
A two-year, three-arm, randomized, double masked, multicenter, phase III study
assessing the efficacy and safety of brolucizumab versus aflibercept in adult patients with visual
impairment due to diabetic macular edema (KESTREL)

Summary

EudraCT number	2017-004742-23
Trial protocol	NL AT ES PT GB IT
Global end of trial date	18 October 2021

Results information

Result version number	v1
This version publication date	13 August 2022
First version publication date	13 August 2022

Trial information

Trial identification

Sponsor protocol code	CRTH258B2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03481634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	18 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the visual outcome after the first year of treatment.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	Israel: 53
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Japan: 59
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Portugal: 44
Country: Number of subjects enrolled	Spain: 63
Country: Number of subjects enrolled	United States: 183
Worldwide total number of subjects	566
EEA total number of subjects	149

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)	294
From 65 to 84 years	267
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of a total of 873 subjects who were screened,566 subjects were randomized in a 1:1:1 ratio to the brolucizumab 6 mg (n=189) or 3 mg (n=190) arms, or to the aflibercept 2 mg arm (n=187) between 30-Jul-2018 and 14-Nov-2019, and 307 subjects were not randomized due to screen failures.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Brolucizumab 3 mg

Arm description:

Brolucizumab 3 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule

Arm type	Experimental
Investigational medicinal product name	Brolucizumab
Investigational medicinal product code	RTH258
Other name	Beovu
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

3 mg/0.05 mL administered 5xq6w during loading phase then q12w/q8w during maintenance phase.

Arm title	Brolucizumab 6 mg

Arm description:

Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule

Arm type	Experimental
Investigational medicinal product name	Brolucizumab
Investigational medicinal product code	RTH258
Other name	Beovu
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

6 mg/0.05 mL administered 5xq6w during loading phase then q12w/q8w during maintenance phase.

Arm title	Aflibercept 2 mg

Arm description:

Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks

Arm type	Active comparator

Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	EYLEA
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg/0.05 mL administered 5xq4w during loading phase then q8w during maintenance phase.

Number of subjects in period 1	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Started	190	189	187
Completed	157	154	153
Not completed	33	35	34
Adverse event, serious fatal	4	8	7
Physician decision	3	-	1
Subject decision	16	19	14
Adverse event, non-fatal	6	3	7
Lost to follow-up	3	4	4
Progressive disease	-	1	-
Protocol deviation	1	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 3 mg
Reporting group description:	
Brolucizumab 3 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule	
Reporting group title	Brolucizumab 6 mg
Reporting group description:	
Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks	

Reporting group values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg
Number of subjects	190	189	187
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	97	104	93
>=65 years	93	85	94
Age Continuous Units: years			
arithmetic mean	64.4	62.4	63.9
standard deviation	± 9.76	± 10.14	± 10.09
Sex: Female, Male Units: Participants			
Female	71	79	61
Male	119	110	126
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	25	25	26
Native Hawaiian or Other Pacific Islander	0	2	0
Black or African American	13	4	7
White	151	158	152
More than one race	0	0	1
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	566		
Age Categorical Units: Participants			
<=18 years	0		
Between 18 and 65 years	294		
>=65 years	272		

Age Continuous Units: years arithmetic mean standard deviation	- 		
Sex: Female, Male Units: Participants			
Female	211		
Male	355		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	76		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	24		
White	461		
More than one race	1		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Brolucizumab 3 mg
Reporting group description:	
Brolucizumab 3 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule	
Reporting group title	Brolucizumab 6 mg
Reporting group description:	
Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks	

Primary: Change from baseline in best-corrected visual acuity (BCVA) at Week 52

End point title	Change from baseline in best-corrected visual acuity (BCVA) at Week 52
End point description:	
BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. Visual Function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 78 to 23 (approximate Snellen equivalent of 20/32 to 20/320) in the study eye were included. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning. This endpoint was analyzed via the pairwise ANOVA method where the 2 dose groups of Brolucizumab are compared to Aflibercept.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Scores on a scale				
least squares mean (standard error)				
Brolucizumab 3 mg v Aflibercept 2 mg	7.3 (± 0.66)	999 (± 999)	10.6 (± 0.67)	
Brolucizumab 6 mg v Aflibercept 2 mg	999 (± 999)	9.2 (± 0.57)	10.5 (± 0.57)	

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [1]
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.81

Notes:

[1] - 1-sided p-value

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.227 [2]
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	-1.4
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[2] - 1-sided p-value

Secondary: Average change from baseline in BCVA over the period Week 40 through Week 52

End point title	Average change from baseline in BCVA over the period Week 40 through Week 52

End point description:

BCVA will be assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.

Visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 78 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/32 to 20/320) in the study eye were included.

Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

This endpoint was analyzed via the pairwise ANOVA method where the 2 dose groups of Brolucizumab are compared to Aflibercept.

End point type	Secondary

End point timeframe:
Baseline and Week 40 through Week 52 (average)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Scores on a scale				
least squares mean (standard error)				
Brolucizumab 3 mg v Aflibercept 2 mg	7.0 (± 0.63)	999 (± 999)	10.5 (± 0.64)	
Brolucizumab 6 mg v Aflibercept 2 mg	999 (± 999)	9.0 (± 0.53)	10.5 (± 0.53)	

Statistical analyses

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	-1.7
Variability estimate	Standard error of the mean
Dispersion value	0.9

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001 [3]
Method	ANOVA
Parameter estimate	Mean difference (net)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	0

Variability estimate	Standard error of the mean
Dispersion value	0.75

Notes:

[3] - (1-sided)

Secondary: Patients maintained at q12w - Probability of maintaining on q12w

End point title	Patients maintained at q12w - Probability of maintaining on q12w[4]

End point description:

Positive treatment status is defined as intravitreal (IVT) injections per planned dosing regimen [every 12 weeks (q12w)]. This outcome measure is pre-specified for brolucizumab treatment arms only.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 32, 36 and 48

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not applicable for the active comparator arm.

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	189		
Units: Probability				
number (confidence interval 95%)				
Prob. of maintaining on q12w (survival)-Week 0	1 (-999 to 999)	1 (-999 to 999)		
Prob. of maintaining on q12w (survival)-Week 32	0.758 (0.685 to 0.816)	0.801 (0.732 to 0.854)		
Prob. of maintaining on q12w (survival)-Week 36	0.545 (0.463 to 0.619)	0.628 (0.548 to 0.698)		
Prob. of maintaining on q12w (survival)-Week 48	0.474 (0.393 to 0.551)	0.551 (0.469 to 0.625)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients maintained at q12w (for those patients who qualified for q12w at week 36) - probability of maintaining on q12w

End point title	Patients maintained at q12w (for those patients who qualified for q12w at week 36) - probability of maintaining on q12w[5]

End point description:

Positive treatment status is defined as intravitreal (IVT) injections per planned dosing regimen [every 8 weeks (q8w)]. This outcome measure is pre-specified for brolucizumab treatment arms only.

End point type	Secondary

End point timeframe:

Weeks 36 and 48

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Not applicable for the active comparator arm.

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	190	189		
Units: Probability				
number (confidence interval 95%)				
Prob. of maintaining on q12w (survival) - Week 36	1 (-999 to 999)	1 (-999 to 999)		
Prob. of maintaining on q12w (survival) - Week 48	0.870 (0.772 to 0.928)	0.876 (0.788 to 0.930)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BCVA at each visit up to Week 52

End point title	Change from baseline in BCVA at each visit up to Week 52

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.

Visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 78 to 23 (approximate Snellen equivalent of 20/32 to 20/320) in the study eye were included.

Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 4, 6, 8, 12, 16, 18, 20, 24, 28, 32, 36, 40, 44, 48, and 52

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 4 (n=187, 186, 185)	4.0 (± 5.02)	4.5 (± 5.22)	5.1 (± 6.74)	
Week 6 (n=185,186,180)	5.1 (± 5.86)	6.0 (± 6.22)	6.8 (± 6.80)	
Week 8 (n=183,184,181)	5.6 (± 5.90)	6.6 (± 6.54)	7.1 (± 7.57)	
Week 12 (n=183,186,182)	6.7 (± 5.93)	7.3 (± 6.57)	8.1 (± 7.63)	
Week 16 (n=173,179,179)	7.0 (± 7.00)	7.5 (± 6.83)	8.5 (± 7.36)	
Week 18 (n=175,181,172)	7.6 (± 6.35)	8.0 (± 6.84)	8.8 (± 7.27)	
Week 20 (n=176,177,176)	7.8 (± 7.59)	8.3 (± 7.51)	9.8 (± 7.47)	
Week 24 (n=174,178,177)	8.1 (± 6.42)	9.3 (± 7.08)	9.2 (± 7.84)	
Week 28 (n=170,175,170)	8.2 (± 6.58)	9.6 (± 7.40)	10.3 (± 7.26)	
Week 32 (n=155,161,162)	8.2 (± 7.76)	9.2 (± 7.20)	9.9 (± 7.89)	
Week 36 (n=154,166,165)	6.9 (± 8.10)	8.6 (± 8.15)	10.2 (± 7.84)	
Week 40 (n=160,163,163)	7.3 (± 10.47)	9.5 (± 7.99)	10.0 (± 8.28)	
Week 44 (n=156,157,163)	7.5 (± 10.92)	9.6 (± 7.66)	10.7 (± 8.25)	
Week 48 (n=155,154,159)	7.2 (± 11.53)	10.0 (± 7.63)	11.1 (± 8.75)	

Week 52 (n=156,153,160)	7.8 (± 10.72)	10.2 (± 7.66)	10.7 (± 8.87)	

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA (letters read): ANOVA results for average change from baseline over the period Week 88 through Week 100 for the study eye (FAS - LOCF)

End point title	BCVA (letters read): ANOVA results for average change from baseline over the period Week 88 through Week 100 for the study eye (FAS - LOCF)
End point description:	
Assessed with ETDRS visual acuity testing charts	
End point type	Secondary
End point timeframe:	
Baseline, and Week 88 through Week 100 (average)	

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: BCVA letters read				
least squares mean (standard error)				
Brolucizumab 3mg vAflibercept 2mg (n=190, 0, 187)	6.7 (± 0.77)	999 (± 999)	10.6 (± 0.78)	
Brolucizumab 6mg v Aflibercept 2mg) (n=0, 189,187)	999 (± 999)	8.6 (± 0.72)	10.6 (± 0.73)	

Statistical analyses

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	-1.7

Variability estimate	Standard error of the mean
Dispersion value	1.09

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.03

Secondary: Patients maintained at q12w up to Week 64 (after three q12w-treatment intervals) and Week 100 - Probability of maintaining on q12w (survival)

End point title	Patients maintained at q12w up to Week 64 (after three q12w-treatment intervals) and Week 100 - Probability of maintaining on q12w (survival)
End point description:	
This outcome measure is pre-specified for brolucizumab treatment arms only	
End point type	Secondary
End point timeframe:	
Baseline (Week 0), Weeks 32, 36, 48, 60, 72, 84, and 96	

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	0[6]	
Units: Probability				
number (confidence interval 95%)				
Prob. of maintaining on q12w (survival)-Week 0	1 (-999 to 999)	1 (-999 to 999)	(to)	
Prob. of maintaining on q12w (survival)-Week 32	0.758 (0.685 to 0.816)	0.807 (0.739 to 0.860)	(to)	
Prob. of maintaining on q12w (survival)-Week 36	0.545 (0.463 to 0.619)	0.628 (0.548 to 0.698)	(to)	
Prob. of maintaining on q12w (survival)-Week 48	0.474 (0.393 to 0.551)	0.550 (0.468 to 0.625)	(to)	
Prob. of maintaining on q12w (survival)-Week 60	0.403 (0.323 to 0.482)	0.520 (0.437 to 0.596)	(to)	

Prob. of maintaining on q12w (survival)-Week 72	0.394 (0.314 to 0.473)	0.487 (0.404 to 0.565)	(to)	
Prob. of maintaining on q12w (survival)-Week 84	0.365 (0.285 to 0.445)	0.460 (0.376 to 0.539)	(to)	
Prob. of maintaining on q12w (survival)-Week 96	0.334 (0.254 to 0.415)	0.441 (0.357 to 0.521)	(to)	

Notes:

[6] - Does not apply to the Aflibercept 2 mg arm

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary: Patients maintained at q12w up to Week 64 (after three q12w- treatment intervals) and Week 100, within those patients that qualified for q12w at Week 36 - Probability of maintaining on q12w (survival)

End point title	Secondary: Patients maintained at q12w up to Week 64 (after three q12w- treatment intervals) and Week 100, within those patients that qualified for q12w at Week 36 - Probability of maintaining on q12w (survival)

End point description:

This outcome measure is pre-specified for brolucizumab treatment arms only

End point type	Secondary

End point timeframe:

Baseline (Week 0), Weeks 32, 36, 48, 60, 72, 84, and 96

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	0[7]	
Units: Probability				
number (confidence interval 95%)				
Prob. of maintaining on q12w (survival)-Week 0	1 (-999 to 999)	1 (-999 to 999)	(to)	
Prob. of maintaining on q12w (survival)-Week 32	1 (-999 to 999)	1 (-999 to 999)	(to)	
Prob. of maintaining on q12w (survival)-Week 36	1 (-999 to 999)	1 (-999 to 999)	(to)	
Prob. of maintaining on q12w (survival)-Week 48	0.870 (0.772 to 0.928)	0.876 (0.788 to 0.930)	(to)	
Prob. of maintaining on q12w (survival)-Week 60	0.740 (0.622 to 0.826)	0.828 (0.730 to 0.892)	(to)	
Prob. of maintaining on q12w (survival)-Week 72	0.723 (0.603 to 0.812)	0.775 (0.670 to 0.851)	(to)	
Prob. of maintaining on q12w (survival)-Week 84	0.670 (0.544 to 0.769)	0.732 (0.621 to 0.816)	(to)	
Prob. of maintaining on q12w (survival)-Week 96	0.613 (0.482 to 0.720)	0.702 (0.587 to 0.791)	(to)	

Notes:

[7] - Does not apply to the Aflibercept 2 mg arm

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in central subfield thickness (CSFT) at each visit up to week 52 - Pairwise ANOVA results

End point title	Change from baseline in central subfield thickness (CSFT) at each visit up to week 52 - Pairwise ANOVA results

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.
Afliber = Aflibercept; Wk = Week

End point type	Secondary

End point timeframe:

Baseline up to week 52

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: µm				
least squares mean (standard error)				
Brolucizumab 3mg v Afliber 2mg-Wk4 (n=190, 0, 187)	-104.7 (± 6.11)	999 (± 999)	-104.1 (± 6.15)	
Brolucizumab 6mg v Afliber 2mg-Wk4 (n=0, 189, 187)	999 (± 999)	-105.6 (± 5.92)	-103.4 (± 5.95)	
Brolucizumab 3mg v Afliber 2mg-Wk6 (n=190, 0, 187)	-107.1 (± 6.24)	999 (± 999)	-119.3 (± 6.29)	
Brolucizumab 6mg v Afliber 2mg-Wk6 (n=0, 189, 187)	999 (± 999)	-116.1 (± 5.89)	-118.6 (± 5.92)	
Brolucizumab 3mg vAfliber 2mg-Wk8 (n=190, 0, 187)	-125.1 (± 6.06)	999 (± 999)	-126.1 (± 6.11)	
Brolucizumab 6mg v Afliber 2mg-Wk8 (n=0, 189, 187)	999 (± 999)	-128.9 (± 5.82)	-125.6 (± 5.86)	
Brolucizumab 3mg v Afliber2mg-Wk12 (n=190, 0, 187)	-131.0 (± 6.14)	999 (± 999)	-137.4 (± 6.19)	
Brolucizumab6mg v Afliber2mg-Wk12 (n=0, 189, 187)	999 (± 999)	-134.5 (± 6.22)	-137.3 (± 6.26)	
Brolucizumab3mg v Afliber2mg-Wk16 (n=190, 0, 187)	-142.3 (± 5.98)	999 (± 999)	-143.3 (± 6.02)	
Brolucizumab6mg v Afliber2mg-Wk16 (n=0, 189, 187)	999 (± 999)	-146.5 (± 5.83)	-143.1 (± 5.86)	
Brolucizumab3mg v Afliber2mg-Wk18 (n=190, 0, 187)	-138.1 (± 6.27)	999 (± 999)	-147.0 (± 6.32)	
Brolucizumab6mg v Afliber2mg-Wk18 (n=0, 189, 187)	999 (± 999)	-144.2 (± 5.96)	-146.8 (± 5.99)	
Brolucizumab3mg v Afliber2mg-Wk20 (n=190, 0, 187)	-151.8 (± 6.01)	999 (± 999)	-148.3 (± 6.06)	
Brolucizumab6mg v Afliber2mg-Wk20 (n=0, 189, 187)	999 (± 999)	-153.8 (± 5.71)	-148.0 (± 5.74)	
Brolucizumab3mg v Afliber2mg-Wk24 (n=190, 0, 187)	-152.6 (± 6.37)	999 (± 999)	-138.7 (± 6.42)	
Brolucizumab6mg v Afliber2mg-Wk24 (n=0, 189, 187)	999 (± 999)	-156.2 (± 6.30)	-138.4 (± 6.33)	
Brolucizumab3mg v Afliber2mg-Wk28 (n=190, 0, 187)	-163.4 (± 5.81)	999 (± 999)	-154.6 (± 5.85)	
Brolucizumab6mg v Afliber2mg-Wk28 (n=0, 189, 187)	999 (± 999)	-163.3 (± 5.97)	-154.6 (± 6.00)	

Brolucizumab3mg v Afliber2mg-Wk32 (n=190, 0, 187)	-147.4 (± 6.68)	999 (± 999)	-144.3 (± 6.73)	
Brolucizumab6mg v Afliber2mg-Wk32 (n=0, 189, 187)	999 (± 999)	-156.0 (± 6.35)	-144.2 (± 6.38)	
Brolucizumab3mg v Afliber2mg-Wk36 (n=190, 0, 187)	-119.8 (± 7.74)	999 (± 999)	-156.0 (± 7.81)	
Brolucizumab6mg v Afliber2mg-Wk36 (n=0, 189, 187)	999 (± 999)	-135.1 (± 7.01)	-155.5 (± 7.05)	
Brolucizumab3mg v Afliber2mg-Wk40 (n=190, 0, 187)	-155.8 (± 6.46)	999 (± 999)	-149.7 (± 6.51)	
Brolucizumab6mg v Afliber2mg-Wk40 (n=0, 189, 187)	999 (± 999)	-156.9 (± 6.68)	-150.4 (± 6.72)	
Brolucizumab3mg v Afliber2mg-Wk44 (n=190, 0, 187)	-155.4 (± 6.56)	999 (± 999)	-163.4 (± 6.62)	
Brolucizumab6mg v Afliber2mg-Wk44 (n=0, 189, 187)	999 (± 999)	-162.2 (± 6.17)	-163.3 (± 6.21)	
Brolucizumab3mg v Afliber2mg-Wk48 (n=190, 0, 187)	-144.2 (± 6.92)	999 (± 999)	-157.8 (± 6.98)	
Brolucizumab6mg v Afliber2mg-Wk48 (n=0, 189, 187)	999 (± 999)	-153.5 (± 6.52)	-158.2 (± 6.55)	
Brolucizumab3mg v Afliber2mg-Wk52 (n=190, 0, 187)	-156.4 (± 6.70)	999 (± 999)	-160.7 (± 6.75)	
Brolucizumab6mg v Afliber2mg-Wk52 (n=0, 189, 187)	999 (± 999)	-165.5 (± 6.17)	-160.4 (± 6.21)	

Statistical analyses

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 4	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	16.4
Variability estimate	Standard error of the mean
Dispersion value	8.68

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 4	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.7
upper limit	14.4
Variability estimate	Standard error of the mean
Dispersion value	8.41

Statistical analysis title	Brolucizumab 3 mg Aflibercept 2 mg
Statistical analysis description:	
Week 6 v	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	29.7
Variability estimate	Standard error of the mean
Dispersion value	8.87

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 8	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	17.9
Variability estimate	Standard error of the mean
Dispersion value	8.61

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 6	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	18.9
Variability estimate	Standard error of the mean
Dispersion value	8.38

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 8	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.6
upper limit	12.9
Variability estimate	Standard error of the mean
Dispersion value	8.28

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 12	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	6.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	23.6
Variability estimate	Standard error of the mean
Dispersion value	8.73

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 12	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.6
upper limit	20.2
Variability estimate	Standard error of the mean
Dispersion value	8.85

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 16	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg

Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.7
upper limit	17.8
Variability estimate	Standard error of the mean
Dispersion value	8.5

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 16	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.7
upper limit	12.9
Variability estimate	Standard error of the mean
Dispersion value	8.29

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 18	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	8.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.6
upper limit	26.5
Variability estimate	Standard error of the mean
Dispersion value	8.92

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 18	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.1
upper limit	19.2
Variability estimate	Standard error of the mean
Dispersion value	8.47

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 20	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	13.4
Variability estimate	Standard error of the mean
Dispersion value	8.55

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 20	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.7
upper limit	10.2
Variability estimate	Standard error of the mean
Dispersion value	8.12

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 24	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-13.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.7
upper limit	3.9
Variability estimate	Standard error of the mean
Dispersion value	9.06

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 24	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.4
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	8.95

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 28	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-8.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25
upper limit	7.5
Variability estimate	Standard error of the mean
Dispersion value	8.26

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 28	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-8.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.4
upper limit	8
Variability estimate	Standard error of the mean
Dispersion value	8.49

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 32	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.8
upper limit	15.5
Variability estimate	Standard error of the mean
Dispersion value	9.49

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 32	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-11.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.5
upper limit	6
Variability estimate	Standard error of the mean
Dispersion value	9.02

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 36	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	36.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	14.6
upper limit	57.9
Variability estimate	Standard error of the mean
Dispersion value	11.01

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 36	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	20.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	40
Variability estimate	Standard error of the mean
Dispersion value	9.97

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 40	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg

Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	11.9
Variability estimate	Standard error of the mean
Dispersion value	9.19

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 40	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.2
upper limit	12.2
Variability estimate	Standard error of the mean
Dispersion value	9.5

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 44	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	7.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.4
upper limit	26.3
Variability estimate	Standard error of the mean
Dispersion value	9.33

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 44	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.2
upper limit	18.3
Variability estimate	Standard error of the mean
Dispersion value	8.78

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 48	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	23
Variability estimate	Standard error of the mean
Dispersion value	9.26

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 48	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	13.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	32.9
Variability estimate	Standard error of the mean
Dispersion value	9.84

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 52	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	23
Variability estimate	Standard error of the mean
Dispersion value	9.52

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 52	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.3
upper limit	12.2
Variability estimate	Standard error of the mean
Dispersion value	8.78

Secondary: Central subfield thickness (CSFT) (micrometers): ANOVA results for average change from baseline over the period Week 88 through Week 100 for the study eye (Full Analysis Set – LOCF)

End point title	Central subfield thickness (CSFT) (micrometers): ANOVA results for average change from baseline over the period Week 88 through Week 100 for the study eye (Full Analysis Set – LOCF)

End point description:

Central subfield thickness (average thickness of circular 1mm area centered around fovea measured from RPE to ILM, inclusively). Assessed with Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts

End point type	Secondary

End point timeframe:

Baseline, and Week 88 through Week 100 (average)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: micrometers				
least squares mean (standard error)				
Brolucizumab 3mg v Aflibercept 2mg (n=190, 0, 187)	-167.1 (± 6.54)	999 (± 999)	-168.8 (± 6.59)	
Brolucizumab 6mg vAflibercept 2mg (n=0, 189,187)	999 (± 999)	-171.9 (± 6.18)	-168.5 (± 6.22)	

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	376
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.7
upper limit	13.8
Variability estimate	Standard error of the mean
Dispersion value	8.79

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	377
Analysis specification	Pre-specified
Analysis type	
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.6
upper limit	20
Variability estimate	Standard error of the mean
Dispersion value	9.3

Secondary: Number and percentage of patients with presence of subretinal fluid (SRF) at each assessment visit

End point title	Number and percentage of patients with presence of subretinal fluid (SRF) at each assessment visit

End point description:

Subretinal Fluid (SRF) status in the central subfield: proportion of subjects with presence of SRF in the study eye by visit

End point type	Secondary

End point timeframe:

Baseline up to Week 52 (primary analysis) and Week 100 (final analysis)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Participants				
Week 4	26	23	27	
Week 6	20	17	17	
Week 8	10	9	12	
Week 12	11	8	8	
Week16	6	6	7	
Week18	7	4	6	
Week 20	5	4	6	
Week 24	7	3	6	
Week 28	5	2	3	
Week 32	11	1	6	
Week 36	16	14	4	
Week 40	8	5	6	
Week 44	4	4	4	
Week 48	7	8	3	
Week 52	4	4	4	
Week 56	9	3	5	
Week 60	9	5	5	
Week 64	6	4	5	
Week 68	6	4	3	
Week 72	5	4	4	
Week 76	4	4	4	
Week 80	5	4	5	
Week 84	6	3	3	
Week 88	7	2	4	
Week 92	4	2	4	
Week 96	5	3	5	
Week 100	3	2	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with presence of intraretinal fluid (IRF) at each assessment visit

End point title	Number and percentage of patients with presence of intraretinal fluid (IRF) at each assessment visit

End point description:

Intraretinal Fluid (IRF) status in the central subfield: proportion of subjects with presence of IRF in the study eye by visit

End point type	Secondary

End point timeframe:

Baseline, up to Week 52 (primary analysis) and Week 100 (final analysis)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Participants				
Week 4	176	169	169	
Week 6	177	169	169	
Week 8	166	161	164	
Week 12	167	162	165	
Week 16	155	150	156	
Week 18	152	149	154	
Week 20	142	147	145	
Week 24	142	140	153	
Week 28	139	130	144	
Week 32	143	131	156	
Week 36	153	141	144	
Week 40	129	114	150	
Week 44	127	118	135	
Week 48	132	123	147	
Week 52	113	114	137	
Week 56	111	103	138	
Week 60	119	115	126	
Week 64	102	105	131	
Week 68	109	98	118	
Week 72	107	103	126	
Week 76	98	96	118	
Week 80	96	85	120	
Week 84	102	92	108	
Week 88	89	85	114	
Week 92	91	86	105	
Week 96	92	90	107	
Week 100	87	79	101	

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with presence of SRF and/or IRF in the study eye by visit

End point title	Number and percentage of patients with presence of SRF and/or IRF in the study eye by visit

End point description:

Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) status in the central subfield: proportion of subjects with presence of SRF and/or IRF in the study eye by visit

End point type	Secondary

End point timeframe:

Baseline, up to Week 52 (primary analysis) and Week 100 (final analysis)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Participants				
Week 4	177	172	171	
Week 6	177	173	169	
Week 8	166	162	164	
Week 12	168	162	165	
Week 16	156	150	156	
Week 18	153	149	154	
Week 20	142	147	145	
Week 24	142	140	153	
Week 28	139	130	144	
Week 32	143	131	156	
Week 36	153	141	144	
Week 40	129	114	150	
Week 44	127	118	135	
Week 48	132	123	147	
Week 52	113	114	137	
Week 56	111	103	138	
Week 60	120	115	126	
Week 64	102	105	131	
Week 68	109	98	118	
Week 72	107	103	126	
Week 76	98	96	118	
Week 80	96	85	120	
Week 84	102	92	108	
Week 88	89	85	114	
Week 92	91	86	105	
Week 96	92	90	107	
Week 100	87	79	101	

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with presence of leakage on fluorescein angiography (FA) at Week 52 (Primary Analysis)

End point title	Number and percentage of patients with presence of leakage on fluorescein angiography (FA) at Week 52 (Primary Analysis)

End point description:

Assessed by angiography.

End point type	Secondary

End point timeframe:
Week 52 (Primary Analysis)

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	189	188	186	
Units: Participants	114	108	140	

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with presence of leakage on fluorescein angiography (FA) at Week 100 (Final Analysis)

End point title	Number and percentage of patients with presence of leakage on fluorescein angiography (FA) at Week 100 (Final Analysis)
End point description: Assessed by angiography.	
End point type	Secondary
End point timeframe: Week 100 (Final Analysis)	

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	188	186	
Units: Participants	94	80	104	

Statistical analyses

No statistical analyses for this end point

Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) : proportion of subjects with >=2-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Number of subjects

End point title	Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) : proportion of subjects with >=2-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Number of subjects

End point description:
Severity of Diabetic Retinopathy (DR) was evaluated using the ETDRS DRSS score assessed by the

Central Reading Center (CRC) based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the ≥2-step and ≥3-step change from baseline for each post-baseline assessment".

A lower score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28, 52, 76, 100

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	186	184	
Units: Participants				
Week 28 Proportion of subjects	44	49	39	
Week 52 Proportion of subjects	53	55	40	
Week 76 Proportion of subjects	59	55	51	
Week 100 Proportion of subjects	60	61	54	

Statistical analyses

No statistical analyses for this end point

Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) : proportion of subjects with >=2-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Proportion estimates (%)

End point title	Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS) : proportion of subjects with >=2-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Proportion estimates (%)

End point description:

Severity of Diabetic Retinopathy (DR) was evaluated using the ETDRS DRSS score assessed by the Central Reading Center (CRC) based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the ≥2-step and ≥3-step change from baseline for each post-baseline assessment".

A lower score represents better visual functioning.

Abbreviation: Afliber = Aflibercept; Wk = Week

End point type	Secondary

End point timeframe:

Baseline, Weeks 28, 52, 76, 100

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	186	184	
Units: Proportion estimates (%)				
number (not applicable)				
Brolucizumab3mg v Afliber2mg Wk28 (n=185,0, 184)	23.3	999	21.7	
Brolucizumab6mg v Afliber2mg Wk28 (n=0, 186, 184)	999	25.8	21.7	
Brolucizumab3mg v Afliber2mg Wk52 (n=185,0, 184)	28.0	999	22.3	
Brolucizumab6mg v Afliber2mg Wk52 (n=0, 186, 184)	999	29.0	22.2	
Brolucizumab3mg v Afliber2mg Wk76 (n=185,0, 184)	31.2	999	28.4	
Brolucizumab6mg v Afliber2mg Wk76 (n=0, 186, 184)	999	29.0	28.3	
Brolucizumab3mg v Afliber2mg Wk100 (n=185,0,184)	31.7	999	30.1	
Brolucizumab6mg v Afliber2mg Wk 100 (n=0,186,184)	999	32.1	30.0	

Statistical analyses

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	8.4

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	4.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	10.3

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	12.4

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	12.9

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	9.4

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	7

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	8.1

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	2.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	8.4

Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS): proportion of subjects with >=3-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Number of subjects

End point title	Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS): proportion of subjects with >=3-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Number of subjects

End point description:

Severity of Diabetic Retinopathy (DR) was evaluated using the ETDRS DRSS score assessed by the Central Reading Center (CRC) based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the ≥2-step and ≥3-step change from baseline for each post-baseline assessment".

A lower score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Weeks 28, 52, 76, 100

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	186	184	
Units: Participants				
Week 28 Proportion of subjects	23	32	22	
Week 52 Proportion of subjects	24	39	30	
Week 76 Proportion of subjects	27	40	42	
Week 100 Proportion of subjects	29	44	41	

Statistical analyses

No statistical analyses for this end point

Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS): proportion of subjects with >=3-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Proportion estimates (%)

End point title	Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic Retinopathy Severity Scale (DRSS): proportion of subjects with >=3-step improvement from baseline in the DRSS score at each assessment visit for the study eye - Proportion estimates

	(%)

End point description:

Severity of Diabetic Retinopathy (DR) was evaluated using the ETDRS DRSS score assessed by the Central Reading Center (CRC) based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the ≥2-step and ≥3-step change from baseline for each post-baseline assessment".

A lower score represents better visual functioning.

Abbreviation: Afliber = Aflibercept; Wk = Week

End point type	Secondary

End point timeframe:

Baseline, Weeks 28, 52, 76, 100

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	185	186	184	
Units: Proportion estimates (%)				
number (not applicable)				
Brolucizumab3mg v Afliber2mg Wk28 (n=185, 0,184)	12.1	999	12.3	
Brolucizumab6mg v Afliber2mg Wk28 (n=0, 186, 184)	999	16.8	12.2	
Brolucizumab3mg v Afliber2mg Wk52(n=185, 0,184)	12.6	999	16.8	
Brolucizumab6mg v. Afliber2mg Wk52(n=0, 186,184)	999	20.5	16.7	
Brolucizumab3mg v Afliber2mg Wk76 (n=185, 0,184)	14.2	999	23.4	
Brolucizumab6mg v Afliber2mg Wk76 (n=0, 186, 184)	999	21.1	23.3	
Brolucizumab3mg v Afliber2mg Wk100 (n=185, 0, 84)	15.2	999	22.9	
Brolucizumab6mg v Afliber2mg Wk100 (n=0,186,184)	999	23.2	22.8	

Statistical analyses

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	-0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.4
upper limit	5.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	11

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	-4.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	2.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	3.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	10.5

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	-9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.5
upper limit	-2.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	4.4

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	369
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	-7.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14
upper limit	-1.6

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	370
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.7
upper limit	6.8

Secondary: Change from baseline in patient reported outcomes Visual Functioning Questionnaire-25 (VFQ-25) total and subscale scores up to Week 52 (Primary Analysis) and Week 100 (Final Analysis)

End point title	Change from baseline in patient reported outcomes Visual Functioning Questionnaire-25 (VFQ-25) total and subscale scores up to Week 52 (Primary Analysis) and Week 100 (Final Analysis)

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. A composite score is derived based on the average of the 11 subscales. Change from baseline in the composite and subscale scores are summarized.

Abbreviation: Afliber = Aflibercept; Wk = Week

End point type	Secondary

End point timeframe:

Baseline, Weeks 28, 52, 76, 100

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	165	173	168	
Units: overall scores				
least squares mean (confidence interval 95%)				
Wk 28 Brolucizumab3mg v Afliber2mg (n=165,0,168)	6.2 (-999 to 999)	999 (-999 to 999)	7.1 (-999 to 999)	
Wk28 Brolucizumab6mg v Afliber2mg (n=0,173,168)	999 (999 to 999)	5.9 (-999 to 999)	7.9 (-999 to 999)	
Wk52 Brolucizumab3mg v Afliber2mg(n=151,0,157)	5.4 (-999 to 999)	999 (-999 to 999)	7.7 (-999 to 999)	
Wk52 Brolucizumab6mg v Afliber2mg (n=0,148,157)	999 (999 to 999)	7.1 (-999 to 999)	8.1 (-999 to 999)	
Wk76 Brolucizumab3mg v Afliber2mg (n=133, 0,143)	7.2 (-999 to 999)	999 (999 to 999)	6.6 (-999 to 999)	
Wk76 Brolucizumab6mg v Afliber2mg (n=0,138,143)	999 (999 to 999)	5.6 (-999 to 999)	7.3 (-999 to 999)	
Wk100 Brolucizumab3mg v Afliber2mg (n=140, 0,142)	7.0 (-999 to 999)	999 (999 to 999)	5.8 (-999 to 999)	
Wk100 Brolucizumab6mg v Afliber2mg(n=0,141,142)	999 (999 to 999)	6.2 (-999 to 999)	6.4 (-999 to 999)	

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 28	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	0.3

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 28	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	1.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 52	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	1.4

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 52	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	0.1

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 76	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	3.1

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description: Week 76	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	1.1

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Statistical analysis description: Week 100	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.1

Statistical analysis title	Brolucizumab 3 mg v Aflibercept 2 mg
Statistical analysis description:	
Week 100	
Comparison groups	Brolucizumab 3 mg v Aflibercept 2 mg
Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	2.6

Secondary: Ocular Adverse Events (AEs) (>=2% in any treatment arm) by preferred term for the study eye

End point title	Ocular Adverse Events (AEs) (>=2% in any treatment arm) by preferred term for the study eye
End point description:	
End point type	Secondary
End point timeframe:	
Adverse events were reported from first dose of study treatment until Week 96, plus 30 days post treatment, up to a maximum duration of 100 weeks.	

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Participants				
Number of subjects with at least one AE	103	92	94	
Cataract	17	16	13	
Conjunctival haemorrhage	19	16	19	
Intraocular pressure increased	14	11	3	
Vitreous detachment	9	10	3	
Vitreous floaters	7	10	6	
Diabetic retinal oedema	12	9	4	

Conjunctivitis	4	6	1	
Dry eye	10	6	5	
Eye pain	3	6	5	
Posterior capsule opacification	3	6	3	
Eye irritation	3	5	4	
Blepharitis	3	4	4	
Keratitis	0	4	3	
Vitreous haemorrhage	2	4	3	
Punctate keratitis	8	3	1	
Vision blurred	6	3	1	
Visual acuity reduced	7	3	9	
Iridocyclitis	4	2	0	
Ocular hypertension	4	2	2	
Uveitis	4	2	0	
Corneal abrasion	3	1	4	
Retinal exudates	7	1	3	
Cataract subcapsular	1	0	4	
Conjunctival hyperaemia	4	0	1	
Vitreoretinal traction syndrome	1	0	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with non-ocular Adverse Events (AEs) (>=2% in any treatment arm)

End point title	Number of subjects with non-ocular Adverse Events (AEs) (>=2% in any treatment arm)

End point description:

End point type	Secondary

End point timeframe:

Adverse events were reported from first dose of study treatment until Week 96, plus 30 days post treatment, up to a maximum duration of 100 weeks.

End point values	Brolucizumab 3 mg	Brolucizumab 6 mg	Aflibercept 2 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	190	189	187	
Units: Participants	146	146	143	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until Week 96, plus 30 days post treatment, up to a maximum duration of 100 weeks.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Brolucizumab 3mg

Reporting group description:

Brolucizumab 3mg

Reporting group title	Brolucizumab 6mg

Reporting group description:

Brolucizumab 6mg

Reporting group title	Aflibercept 2mg

Reporting group description:

Aflibercept 2mg

Reporting group title	Overall

Reporting group description:

Overall

Serious adverse events	Brolucizumab 3mg	Brolucizumab 6mg	Aflibercept 2mg
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 190 (30.53%)	59 / 189 (31.22%)	63 / 187 (33.69%)
number of deaths (all causes)	4	8	7
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Breast cancer metastatic			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colon cancer			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Endometrial cancer			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Lung neoplasm malignant			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Ovarian cancer metastatic			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	0 / 187 (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
Prostate cancer			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			

subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry gangrene			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Embolism venous			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Extremity necrosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Haematoma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	2 / 190 (1.05%)	0 / 189 (0.00%)	0 / 187 (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
Hypertensive crisis			

subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Hypertensive urgency			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Pregnancy, puerperium and perinatal conditions			
Pre-eclampsia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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

Generalised oedema			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Pyrexia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Prostatic disorder			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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	1 / 190 (0.53%)	2 / 189 (1.06%)	0 / 187 (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
Asthma			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	0 / 187 (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
Haemothorax			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Pleural effusion			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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 embolism			
subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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			
Hepatitis C antibody positive			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Intraocular pressure increased - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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 operation complication - Fellow eye			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			

subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Laryngeal injury			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
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 artery restenosis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Skin flap necrosis			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Subdural haematoma			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 myocardial infarction			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 190 (1.05%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Atrial fibrillation			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Bradycardia			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 arrest			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure chronic			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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	5 / 190 (2.63%)	2 / 189 (1.06%)	5 / 187 (2.67%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiorenal syndrome			

subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular disorder			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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 disease			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	3 / 187 (1.60%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve disease mixed			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 infarction			
subjects affected / exposed	2 / 190 (1.05%)	3 / 189 (1.59%)	3 / 187 (1.60%)
occurrences causally related to treatment / all	1 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 2
Myocardial ischaemia			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral atrophy			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	3 / 190 (1.58%)	4 / 189 (2.12%)	4 / 187 (2.14%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar stroke			

subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic neuritis - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Syncope			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Microcytic anaemia			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Amaurosis fugax - Fellow eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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 - Fellow eye			
subjects affected / exposed	0 / 190 (0.00%)	3 / 189 (1.59%)	4 / 187 (2.14%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	5 / 189 (2.65%)	3 / 187 (1.60%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctival cyst - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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 retinal oedema - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy - Fellow eye			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiretinal membrane - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Glaucoma - Fellow eye			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 - Study eye			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Macular oedema - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Posterior capsule opacification - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Pterygium - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Retinal artery occlusion - Fellow eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Retinal artery occlusion - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	0 / 187 (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
Retinal detachment - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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 occlusive vasculitis - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Retinal vasculitis - Study eye			

subjects affected / exposed	2 / 190 (1.05%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein thrombosis - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Uveitis - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Visual acuity reduced - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous floaters - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	2 / 190 (1.05%)	1 / 189 (0.53%)	0 / 187 (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
Vitritis - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Duodenal ulcer			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Dysphagia			

subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Gastric polyps			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Haematemesis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Hiatus hernia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Inguinal hernia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Mechanical ileus			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Obstructive pancreatitis			

subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Proctitis ulcerative			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal polyp			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Ulcerative gastritis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	0 / 187 (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
Cholecystitis acute			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder disorder			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Hepatitis acute			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
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	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder pain			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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 kidney disease			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	0 / 187 (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
Diabetic nephropathy			

subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
End stage renal disease			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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 failure			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	4 / 187 (2.14%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder rupture			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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

Exostosis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periarthritis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Rhabdomyolysis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 190 (0.53%)	1 / 189 (0.53%)	0 / 187 (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
Bacteraemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
COVID-19			

subjects affected / exposed	2 / 190 (1.05%)	3 / 189 (1.59%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cellulitis			
subjects affected / exposed	2 / 190 (1.05%)	1 / 189 (0.53%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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 foot infection			
subjects affected / exposed	2 / 190 (1.05%)	1 / 189 (0.53%)	0 / 187 (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
Encephalitis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Endophthalmitis - Study eye			
subjects affected / exposed	2 / 190 (1.05%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal sepsis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Gas gangrene			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Localised infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Osteomyelitis			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	3 / 187 (1.60%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Periodontitis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			

subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Postoperative abscess			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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 sepsis			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 190 (1.05%)	2 / 189 (1.06%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Staphylococcal infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Urinary tract infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			

subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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			
subjects affected / exposed	0 / 190 (0.00%)	3 / 189 (1.59%)	0 / 187 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Hyperglycaemia			

subjects affected / exposed	2 / 190 (1.05%)	1 / 189 (0.53%)	0 / 187 (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
Hyperkalaemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	0 / 187 (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
Hypoglycaemia			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 190 (0.00%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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
Ketoacidosis			
subjects affected / exposed	0 / 190 (0.00%)	1 / 189 (0.53%)	0 / 187 (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

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	180 / 566 (31.80%)		
number of deaths (all causes)	19		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Brain neoplasm			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Breast cancer metastatic				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial cancer				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatocellular carcinoma				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intraductal proliferative breast lesion				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer metastatic				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Prostate cancer				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroid cancer				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Accelerated hypertension				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dry gangrene				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolism venous				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extremity necrosis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertension				

subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypertensive crisis				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hypertensive emergency				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive urgency				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Pre-eclampsia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				

Death				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Generalised oedema				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Reproductive system and breast disorders				
Benign prostatic hyperplasia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostatic disorder				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Asthma				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	4 / 566 (0.71%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatitis C antibody positive				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
International normalised ratio increased				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intraocular pressure increased - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Ankle fracture				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cataract operation complication - Fellow eye				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hand fracture				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Head injury				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngeal injury				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Peripheral artery restenosis				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin flap necrosis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subdural haematoma				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute left ventricular failure				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				

subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	4 / 566 (0.71%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 1			
Cardiac failure chronic				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	12 / 566 (2.12%)			
occurrences causally related to treatment / all	0 / 12			
deaths causally related to treatment / all	0 / 0			
Cardiorenal syndrome				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiovascular disorder				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	6 / 566 (1.06%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic cardiomyopathy				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve disease mixed				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mitral valve incompetence				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				

subjects affected / exposed	8 / 566 (1.41%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 3			
Myocardial ischaemia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery occlusion				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral atrophy				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cerebrovascular accident				
subjects affected / exposed	11 / 566 (1.94%)			
occurrences causally related to treatment / all	2 / 11			
deaths causally related to treatment / all	0 / 0			
Encephalopathy				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lacunar stroke				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Optic neuritis - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Microcytic anaemia				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Amaurosis fugax - Fellow eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cataract - Fellow eye				
subjects affected / exposed	7 / 566 (1.24%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Cataract - Study eye				
subjects affected / exposed	9 / 566 (1.59%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Conjunctival cyst - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic retinal oedema - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic retinopathy - Fellow eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epiretinal membrane - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glaucoma - Fellow eye				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glaucoma - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Macular oedema - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Posterior capsule opacification - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pterygium - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal artery occlusion - Fellow eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal artery occlusion - Study eye				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal detachment - Study eye				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal occlusive vasculitis - Study eye				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal vasculitis - Study eye				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal vein thrombosis - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Uveitis - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous floaters - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage - Fellow eye				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vitritis - Study eye				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Duodenal ulcer				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric polyps				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mesenteric vein thrombosis				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Obstructive pancreatitis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis ulcerative				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Rectal polyp				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcerative gastritis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholecystitis acute				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gallbladder disorder				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatitis acute				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Decubitus ulcer				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic foot				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	5 / 566 (0.88%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Bladder pain				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic kidney disease				

subjects affected / exposed	2 / 566 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetic nephropathy			
subjects affected / exposed	3 / 566 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
End stage renal disease			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephropathy			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	6 / 566 (1.06%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Urinary bladder rupture			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Exostosis			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periarthritis			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	2 / 566 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rotator cuff syndrome			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	2 / 566 (0.35%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bacteraemia			

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	7 / 566 (1.24%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 2			
COVID-19 pneumonia				
subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Cellulitis				
subjects affected / exposed	5 / 566 (0.88%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic foot infection				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Encephalitis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endophthalmitis - Study eye				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Fungal sepsis				

subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gas gangrene				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Localised infection				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	6 / 566 (1.06%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis acute				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Periodontitis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	4 / 566 (0.71%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Postoperative abscess				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary sepsis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	4 / 566 (0.71%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Septic shock				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Staphylococcal infection				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				

subjects affected / exposed	2 / 566 (0.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection bacterial				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetes mellitus				
subjects affected / exposed	3 / 566 (0.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Diabetic ketoacidosis				
subjects affected / exposed	1 / 566 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic metabolic decompensation				

subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	3 / 566 (0.53%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 566 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	2 / 566 (0.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ketoacidosis			
subjects affected / exposed	1 / 566 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Brolucizumab 3mg	Brolucizumab 6mg	Aflibercept 2mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 190 (76.84%)	148 / 189 (78.31%)	137 / 187 (73.26%)
Vascular disorders			
Hypertension			
subjects affected / exposed	22 / 190 (11.58%)	21 / 189 (11.11%)	24 / 187 (12.83%)
occurrences (all)	25	21	30
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	4 / 190 (2.11%)	5 / 189 (2.65%)	5 / 187 (2.67%)
occurrences (all)	5	5	5
Pyrexia			
subjects affected / exposed	1 / 190 (0.53%)	8 / 189 (4.23%)	3 / 187 (1.60%)
occurrences (all)	1	8	3
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	4 / 187 (2.14%)
occurrences (all)	2	4	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 190 (3.68%)	11 / 189 (5.82%)	10 / 187 (5.35%)
occurrences (all)	7	12	11
Dyspnoea			
subjects affected / exposed	0 / 190 (0.00%)	6 / 189 (3.17%)	2 / 187 (1.07%)
occurrences (all)	0	6	3
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 190 (0.00%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	0	4	3
Investigations			
Blood glucose increased			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	1 / 187 (0.53%)
occurrences (all)	2	5	1
Blood pressure increased			
subjects affected / exposed	6 / 190 (3.16%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	6	4	4
Glucose urine present			

subjects affected / exposed	1 / 190 (0.53%)	4 / 189 (2.12%)	2 / 187 (1.07%)
occurrences (all)	1	4	2
Glycosylated haemoglobin increased			
subjects affected / exposed	4 / 190 (2.11%)	1 / 189 (0.53%)	4 / 187 (2.14%)
occurrences (all)	4	1	5
Intraocular pressure increased - Fellow eye			
subjects affected / exposed	5 / 190 (2.63%)	0 / 189 (0.00%)	3 / 187 (1.60%)
occurrences (all)	5	0	4
Intraocular pressure increased - Study eye			
subjects affected / exposed	14 / 190 (7.37%)	11 / 189 (5.82%)	3 / 187 (1.60%)
occurrences (all)	14	17	5
Injury, poisoning and procedural complications			
Corneal abrasion - Study eye			
subjects affected / exposed	3 / 190 (1.58%)	1 / 189 (0.53%)	4 / 187 (2.14%)
occurrences (all)	3	1	4
Fall			
subjects affected / exposed	5 / 190 (2.63%)	5 / 189 (2.65%)	2 / 187 (1.07%)
occurrences (all)	9	11	3
Limb injury			
subjects affected / exposed	4 / 190 (2.11%)	1 / 189 (0.53%)	1 / 187 (0.53%)
occurrences (all)	4	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 190 (4.21%)	1 / 189 (0.53%)	1 / 187 (0.53%)
occurrences (all)	9	1	1
Cardiac failure congestive			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	2	4	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 190 (2.63%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	5	4	3
Headache			
subjects affected / exposed	3 / 190 (1.58%)	10 / 189 (5.29%)	3 / 187 (1.60%)
occurrences (all)	3	11	4

Migraine			
subjects affected / exposed	1 / 190 (0.53%)	2 / 189 (1.06%)	5 / 187 (2.67%)
occurrences (all)	1	4	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 190 (3.16%)	9 / 189 (4.76%)	9 / 187 (4.81%)
occurrences (all)	6	10	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 190 (1.05%)	3 / 189 (1.59%)	5 / 187 (2.67%)
occurrences (all)	2	4	5
Eye disorders			
Blepharitis - Fellow eye			
subjects affected / exposed	4 / 190 (2.11%)	5 / 189 (2.65%)	4 / 187 (2.14%)
occurrences (all)	4	5	5
Blepharitis - Study eye			
subjects affected / exposed	3 / 190 (1.58%)	4 / 189 (2.12%)	4 / 187 (2.14%)
occurrences (all)	3	4	5
Cataract - Fellow eye			
subjects affected / exposed	11 / 190 (5.79%)	12 / 189 (6.35%)	5 / 187 (2.67%)
occurrences (all)	11	12	5
Cataract - Study eye			
subjects affected / exposed	17 / 190 (8.95%)	12 / 189 (6.35%)	10 / 187 (5.35%)
occurrences (all)	17	12	10
Cataract subcapsular - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	4 / 187 (2.14%)
occurrences (all)	1	0	4
Conjunctival haemorrhage - Fellow eye			
subjects affected / exposed	2 / 190 (1.05%)	5 / 189 (2.65%)	7 / 187 (3.74%)
occurrences (all)	2	6	7
Conjunctival haemorrhage - Study eye			
subjects affected / exposed	19 / 190 (10.00%)	16 / 189 (8.47%)	19 / 187 (10.16%)
occurrences (all)	22	18	25
Conjunctival hyperaemia - Study eye			
subjects affected / exposed	4 / 190 (2.11%)	0 / 189 (0.00%)	1 / 187 (0.53%)
occurrences (all)	4	0	2

Conjunctivitis allergic - Fellow eye			
subjects affected / exposed	3 / 190 (1.58%)	2 / 189 (1.06%)	4 / 187 (2.14%)
occurrences (all)	3	2	5
Diabetic retinal oedema - Fellow eye			
subjects affected / exposed	17 / 190 (8.95%)	12 / 189 (6.35%)	12 / 187 (6.42%)
occurrences (all)	19	14	15
Diabetic retinal oedema - Study eye			
subjects affected / exposed	12 / 190 (6.32%)	9 / 189 (4.76%)	4 / 187 (2.14%)
occurrences (all)	17	12	6
Diabetic retinopathy - Fellow eye			
subjects affected / exposed	6 / 190 (3.16%)	6 / 189 (3.17%)	8 / 187 (4.28%)
occurrences (all)	6	6	9
Dry eye - Fellow eye			
subjects affected / exposed	9 / 190 (4.74%)	5 / 189 (2.65%)	5 / 187 (2.67%)
occurrences (all)	9	5	6
Dry eye - Study eye			
subjects affected / exposed	11 / 190 (5.79%)	6 / 189 (3.17%)	5 / 187 (2.67%)
occurrences (all)	11	6	6
Eye irritation - Fellow eye			
subjects affected / exposed	0 / 190 (0.00%)	6 / 189 (3.17%)	2 / 187 (1.07%)
occurrences (all)	0	6	2
Eye irritation - Study eye			
subjects affected / exposed	3 / 190 (1.58%)	5 / 189 (2.65%)	4 / 187 (2.14%)
occurrences (all)	3	5	4
Eye pain - Fellow eye			
subjects affected / exposed	2 / 190 (1.05%)	2 / 189 (1.06%)	4 / 187 (2.14%)
occurrences (all)	2	2	4
Eye pain - Study eye			
subjects affected / exposed	3 / 190 (1.58%)	6 / 189 (3.17%)	5 / 187 (2.67%)
occurrences (all)	3	8	7
Iridocyclitis - Study eye			
subjects affected / exposed	4 / 190 (2.11%)	2 / 189 (1.06%)	0 / 187 (0.00%)
occurrences (all)	8	2	0
Keratitis - Study eye			
subjects affected / exposed	0 / 190 (0.00%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	0	4	3

Macular oedema - Fellow eye			
subjects affected / exposed	5 / 190 (2.63%)	6 / 189 (3.17%)	2 / 187 (1.07%)
occurrences (all)	5	7	2
Ocular hypertension - Fellow eye			
subjects affected / exposed	2 / 190 (1.05%)	5 / 189 (2.65%)	2 / 187 (1.07%)
occurrences (all)	2	5	2
Ocular hypertension - Study eye			
subjects affected / exposed	4 / 190 (2.11%)	2 / 189 (1.06%)	2 / 187 (1.07%)
occurrences (all)	7	2	2
Posterior capsule opacification - Study eye			
subjects affected / exposed	3 / 190 (1.58%)	5 / 189 (2.65%)	3 / 187 (1.60%)
occurrences (all)	3	5	3
Punctate keratitis - Study eye			
subjects affected / exposed	8 / 190 (4.21%)	3 / 189 (1.59%)	1 / 187 (0.53%)
occurrences (all)	8	4	1
Retinal exudates - Fellow eye			
subjects affected / exposed	5 / 190 (2.63%)	3 / 189 (1.59%)	3 / 187 (1.60%)
occurrences (all)	5	3	3
Retinal exudates - Study eye			
subjects affected / exposed	7 / 190 (3.68%)	1 / 189 (0.53%)	3 / 187 (1.60%)
occurrences (all)	7	1	3
Retinal haemorrhage - Fellow eye			
subjects affected / exposed	5 / 190 (2.63%)	2 / 189 (1.06%)	1 / 187 (0.53%)
occurrences (all)	5	2	1
Retinal haemorrhage - Study eye			
subjects affected / exposed	4 / 190 (2.11%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences (all)	4	0	2
Vision blurred - Study eye			
subjects affected / exposed	6 / 190 (3.16%)	3 / 189 (1.59%)	1 / 187 (0.53%)
occurrences (all)	6	3	1
Visual acuity reduced - Fellow eye			
subjects affected / exposed	4 / 190 (2.11%)	3 / 189 (1.59%)	3 / 187 (1.60%)
occurrences (all)	4	3	3
Visual acuity reduced - Study eye			

subjects affected / exposed	7 / 190 (3.68%)	3 / 189 (1.59%)	8 / 187 (4.28%)
occurrences (all)	7	3	11
Vitreoretinal traction syndrome - Study eye			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	5 / 187 (2.67%)
occurrences (all)	1	0	5
Vitreous detachment - Fellow eye			
subjects affected / exposed	5 / 190 (2.63%)	5 / 189 (2.65%)	4 / 187 (2.14%)
occurrences (all)	5	5	4
Vitreous detachment - Study eye			
subjects affected / exposed	9 / 190 (4.74%)	10 / 189 (5.29%)	3 / 187 (1.60%)
occurrences (all)	9	10	3
Vitreous floaters - Fellow eye			
subjects affected / exposed	7 / 190 (3.68%)	5 / 189 (2.65%)	5 / 187 (2.67%)
occurrences (all)	8	5	5
Vitreous floaters - Study eye			
subjects affected / exposed	7 / 190 (3.68%)	10 / 189 (5.29%)	6 / 187 (3.21%)
occurrences (all)	10	11	6
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	4 / 190 (2.11%)	4 / 189 (2.12%)	5 / 187 (2.67%)
occurrences (all)	5	5	6
Vitreous haemorrhage - Study eye			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	2	4	3
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 190 (2.11%)	4 / 189 (2.12%)	5 / 187 (2.67%)
occurrences (all)	4	4	5
Diarrhoea			
subjects affected / exposed	5 / 190 (2.63%)	10 / 189 (5.29%)	6 / 187 (3.21%)
occurrences (all)	5	12	6
Nausea			
subjects affected / exposed	2 / 190 (1.05%)	5 / 189 (2.65%)	3 / 187 (1.60%)
occurrences (all)	2	5	3
Vomiting			

subjects affected / exposed	5 / 190 (2.63%)	7 / 189 (3.70%)	2 / 187 (1.07%)
occurrences (all)	6	7	2
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	4 / 190 (2.11%)	4 / 189 (2.12%)	2 / 187 (1.07%)
occurrences (all)	4	4	2
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 190 (0.53%)	4 / 189 (2.12%)	3 / 187 (1.60%)
occurrences (all)	1	4	3
Chronic kidney disease			
subjects affected / exposed	1 / 190 (0.53%)	7 / 189 (3.70%)	7 / 187 (3.74%)
occurrences (all)	1	8	7
Renal failure			
subjects affected / exposed	5 / 190 (2.63%)	2 / 189 (1.06%)	3 / 187 (1.60%)
occurrences (all)	5	2	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 190 (6.32%)	6 / 189 (3.17%)	5 / 187 (2.67%)
occurrences (all)	16	6	6
Back pain			
subjects affected / exposed	4 / 190 (2.11%)	5 / 189 (2.65%)	6 / 187 (3.21%)
occurrences (all)	4	5	6
Muscle spasms			
subjects affected / exposed	4 / 190 (2.11%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences (all)	5	0	2
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 190 (2.63%)	5 / 189 (2.65%)	4 / 187 (2.14%)
occurrences (all)	6	5	4
COVID-19			
subjects affected / exposed	8 / 190 (4.21%)	7 / 189 (3.70%)	7 / 187 (3.74%)
occurrences (all)	8	7	7
Cellulitis			
subjects affected / exposed	0 / 190 (0.00%)	2 / 189 (1.06%)	4 / 187 (2.14%)
occurrences (all)	0	2	4

Conjunctivitis - Fellow eye			
subjects affected / exposed	3 / 190 (1.58%)	6 / 189 (3.17%)	4 / 187 (2.14%)
occurrences (all)	3	8	5
Conjunctivitis - Study eye			
subjects affected / exposed	4 / 190 (2.11%)	6 / 189 (3.17%)	1 / 187 (0.53%)
occurrences (all)	4	9	1
Ear infection			
subjects affected / exposed	4 / 190 (2.11%)	0 / 189 (0.00%)	2 / 187 (1.07%)
occurrences (all)	6	0	2
Herpes zoster			
subjects affected / exposed	5 / 190 (2.63%)	0 / 189 (0.00%)	0 / 187 (0.00%)
occurrences (all)	5	0	0
Influenza			
subjects affected / exposed	6 / 190 (3.16%)	8 / 189 (4.23%)	7 / 187 (3.74%)
occurrences (all)	6	8	9
Lower respiratory tract infection			
subjects affected / exposed	4 / 190 (2.11%)	1 / 189 (0.53%)	0 / 187 (0.00%)
occurrences (all)	4	1	0
Nasopharyngitis			
subjects affected / exposed	20 / 190 (10.53%)	18 / 189 (9.52%)	16 / 187 (8.56%)
occurrences (all)	29	24	18
Pneumonia			
subjects affected / exposed	3 / 190 (1.58%)	4 / 189 (2.12%)	4 / 187 (2.14%)
occurrences (all)	3	4	4
Sinusitis			
subjects affected / exposed	4 / 190 (2.11%)	5 / 189 (2.65%)	4 / 187 (2.14%)
occurrences (all)	5	5	5
Tooth infection			
subjects affected / exposed	1 / 190 (0.53%)	0 / 189 (0.00%)	4 / 187 (2.14%)
occurrences (all)	1	0	4
Upper respiratory tract infection			
subjects affected / exposed	6 / 190 (3.16%)	5 / 189 (2.65%)	5 / 187 (2.67%)
occurrences (all)	7	6	6
Urinary tract infection			
subjects affected / exposed	17 / 190 (8.95%)	20 / 189 (10.58%)	8 / 187 (4.28%)
occurrences (all)	30	28	12

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 190 (1.05%)	6 / 189 (3.17%)	0 / 187 (0.00%)
occurrences (all)	2	6	0
Diabetes mellitus			
subjects affected / exposed	7 / 190 (3.68%)	4 / 189 (2.12%)	7 / 187 (3.74%)
occurrences (all)	7	4	7
Diabetes mellitus inadequate control			
subjects affected / exposed	4 / 190 (2.11%)	3 / 189 (1.59%)	3 / 187 (1.60%)
occurrences (all)	4	3	3
Dyslipidaemia			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	2 / 187 (1.07%)
occurrences (all)	2	4	2
Hyperglycaemia			
subjects affected / exposed	2 / 190 (1.05%)	4 / 189 (2.12%)	1 / 187 (0.53%)
occurrences (all)	2	4	1
Type 2 diabetes mellitus			
subjects affected / exposed	3 / 190 (1.58%)	6 / 189 (3.17%)	3 / 187 (1.60%)
occurrences (all)	4	8	3

Non-serious adverse events	Overall		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	431 / 566 (76.15%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	67 / 566 (11.84%)		
occurrences (all)	76		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	14 / 566 (2.47%)		
occurrences (all)	15		
Pyrexia			
subjects affected / exposed	12 / 566 (2.12%)		
occurrences (all)	12		
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	10 / 566 (1.77%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 566 (4.95%)		
occurrences (all)	30		
Dyspnoea			
subjects affected / exposed	8 / 566 (1.41%)		
occurrences (all)	9		
Psychiatric disorders			
Depression			
subjects affected / exposed	7 / 566 (1.24%)		
occurrences (all)	7		
Investigations			
Blood glucose increased			
subjects affected / exposed	7 / 566 (1.24%)		
occurrences (all)	8		
Blood pressure increased			
subjects affected / exposed	13 / 566 (2.30%)		
occurrences (all)	14		
Glucose urine present			
subjects affected / exposed	7 / 566 (1.24%)		
occurrences (all)	7		
Glycosylated haemoglobin increased			
subjects affected / exposed	9 / 566 (1.59%)		
occurrences (all)	10		
Intraocular pressure increased - Fellow eye			
subjects affected / exposed	8 / 566 (1.41%)		
occurrences (all)	9		
Intraocular pressure increased - Study eye			
subjects affected / exposed	28 / 566 (4.95%)		
occurrences (all)	36		
Injury, poisoning and procedural complications			

Corneal abrasion - Study eye subjects affected / exposed occurrences (all)	8 / 566 (1.41%) 8		
Fall subjects affected / exposed occurrences (all)	12 / 566 (2.12%) 23		
Limb injury subjects affected / exposed occurrences (all)	6 / 566 (1.06%) 6		
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	10 / 566 (1.77%) 11		
Cardiac failure congestive subjects affected / exposed occurrences (all)	9 / 566 (1.59%) 9		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	12 / 566 (2.12%) 12		
Headache subjects affected / exposed occurrences (all)	16 / 566 (2.83%) 18		
Migraine subjects affected / exposed occurrences (all)	8 / 566 (1.41%) 10		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	24 / 566 (4.24%) 26		
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	10 / 566 (1.77%) 11		
Eye disorders			
Blepharitis - Fellow eye			

subjects affected / exposed	13 / 566 (2.30%)			
occurrences (all)	14			
Blepharitis - Study eye				
subjects affected / exposed	11 / 566 (1.94%)			
occurrences (all)	12			
Cataract - Fellow eye				
subjects affected / exposed	28 / 566 (4.95%)			
occurrences (all)	28			
Cataract - Study eye				
subjects affected / exposed	39 / 566 (6.89%)			
occurrences (all)	39			
Cataract subcapsular - Study eye				
subjects affected / exposed	5 / 566 (0.88%)			
occurrences (all)	5			
Conjunctival haemorrhage - Fellow eye				
subjects affected / exposed	14 / 566 (2.47%)			
occurrences (all)	15			
Conjunctival haemorrhage - Study eye				
subjects affected / exposed	54 / 566 (9.54%)			
occurrences (all)	65			
Conjunctival hyperaemia - Study eye				
subjects affected / exposed	5 / 566 (0.88%)			
occurrences (all)	6			
Conjunctivitis allergic - Fellow eye				
subjects affected / exposed	9 / 566 (1.59%)			
occurrences (all)	10			
Diabetic retinal oedema - Fellow eye				
subjects affected / exposed	41 / 566 (7.24%)			
occurrences (all)	48			
Diabetic retinal oedema - Study eye				
subjects affected / exposed	25 / 566 (4.42%)			
occurrences (all)	35			
Diabetic retinopathy - Fellow eye				

subjects affected / exposed	20 / 566 (3.53%)			
occurrences (all)	21			
Dry eye - Fellow eye				
subjects affected / exposed	19 / 566 (3.36%)			
occurrences (all)	20			
Dry eye - Study eye				
subjects affected / exposed	22 / 566 (3.89%)			
occurrences (all)	23			
Eye irritation - Fellow eye				
subjects affected / exposed	8 / 566 (1.41%)			
occurrences (all)	8			
Eye irritation - Study eye				
subjects affected / exposed	12 / 566 (2.12%)			
occurrences (all)	12			
Eye pain - Fellow eye				
subjects affected / exposed	8 / 566 (1.41%)			
occurrences (all)	8			
Eye pain - Study eye				
subjects affected / exposed	14 / 566 (2.47%)			
occurrences (all)	18			
Iridocyclitis - Study eye				
subjects affected / exposed	6 / 566 (1.06%)			
occurrences (all)	10			
Keratitis - Study eye				
subjects affected / exposed	7 / 566 (1.24%)			
occurrences (all)	7			
Macular oedema - Fellow eye				
subjects affected / exposed	13 / 566 (2.30%)			
occurrences (all)	14			
Ocular hypertension - Fellow eye				
subjects affected / exposed	9 / 566 (1.59%)			
occurrences (all)	9			
Ocular hypertension - Study eye				
subjects affected / exposed	8 / 566 (1.41%)			
occurrences (all)	11			
Posterior capsule opacification -				

Study eye				
subjects affected / exposed	11 / 566 (1.94%)			
occurrences (all)	11			
Punctate keratitis - Study eye				
subjects affected / exposed	12 / 566 (2.12%)			
occurrences (all)	13			
Retinal exudates - Fellow eye				
subjects affected / exposed	11 / 566 (1.94%)			
occurrences (all)	11			
Retinal exudates - Study eye				
subjects affected / exposed	11 / 566 (1.94%)			
occurrences (all)	11			
Retinal haemorrhage - Fellow eye				
subjects affected / exposed	8 / 566 (1.41%)			
occurrences (all)	8			
Retinal haemorrhage - Study eye				
subjects affected / exposed	6 / 566 (1.06%)			
occurrences (all)	6			
Vision blurred - Study eye				
subjects affected / exposed	10 / 566 (1.77%)			
occurrences (all)	10			
Visual acuity reduced - Fellow eye				
subjects affected / exposed	10 / 566 (1.77%)			
occurrences (all)	10			
Visual acuity reduced - Study eye				
subjects affected / exposed	18 / 566 (3.18%)			
occurrences (all)	21			
Vitreoretinal traction syndrome - Study eye				
subjects affected / exposed	6 / 566 (1.06%)			
occurrences (all)	6			
Vitreous detachment - Fellow eye				
subjects affected / exposed	14 / 566 (2.47%)			
occurrences (all)	14			
Vitreous detachment - Study eye				

subjects affected / exposed	22 / 566 (3.89%)		
occurrences (all)	22		
Vitreous floaters - Fellow eye			
subjects affected / exposed	17 / 566 (3.00%)		
occurrences (all)	18		
Vitreous floaters - Study eye			
subjects affected / exposed	23 / 566 (4.06%)		
occurrences (all)	27		
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	13 / 566 (2.30%)		
occurrences (all)	16		
Vitreous haemorrhage - Study eye			
subjects affected / exposed	9 / 566 (1.59%)		
occurrences (all)	9		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 566 (2.30%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	21 / 566 (3.71%)		
occurrences (all)	23		
Nausea			
subjects affected / exposed	10 / 566 (1.77%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	14 / 566 (2.47%)		
occurrences (all)	15		
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	10 / 566 (1.77%)		
occurrences (all)	10		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 566 (1.41%)		
occurrences (all)	8		
Chronic kidney disease			

subjects affected / exposed	15 / 566 (2.65%)		
occurrences (all)	16		
Renal failure			
subjects affected / exposed	10 / 566 (1.77%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	23 / 566 (4.06%)		
occurrences (all)	28		
Back pain			
subjects affected / exposed	15 / 566 (2.65%)		
occurrences (all)	15		
Muscle spasms			
subjects affected / exposed	6 / 566 (1.06%)		
occurrences (all)	7		
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 566 (2.47%)		
occurrences (all)	15		
COVID-19			
subjects affected / exposed	22 / 566 (3.89%)		
occurrences (all)	22		
Cellulitis			
subjects affected / exposed	6 / 566 (1.06%)		
occurrences (all)	6		
Conjunctivitis - Fellow eye			
subjects affected / exposed	13 / 566 (2.30%)		
occurrences (all)	16		
Conjunctivitis - Study eye			
subjects affected / exposed	11 / 566 (1.94%)		
occurrences (all)	14		
Ear infection			
subjects affected / exposed	6 / 566 (1.06%)		
occurrences (all)	8		
Herpes zoster			

subjects affected / exposed	5 / 566 (0.88%)		
occurrences (all)	5		
Influenza			
subjects affected / exposed	21 / 566 (3.71%)		
occurrences (all)	23		
Lower respiratory tract infection			
subjects affected / exposed	5 / 566 (0.88%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	54 / 566 (9.54%)		
occurrences (all)	71		
Pneumonia			
subjects affected / exposed	11 / 566 (1.94%)		
occurrences (all)	11		
Sinusitis			
subjects affected / exposed	13 / 566 (2.30%)		
occurrences (all)	15		
Tooth infection			
subjects affected / exposed	5 / 566 (0.88%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	16 / 566 (2.83%)		
occurrences (all)	19		
Urinary tract infection			
subjects affected / exposed	45 / 566 (7.95%)		
occurrences (all)	70		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	8 / 566 (1.41%)		
occurrences (all)	8		
Diabetes mellitus			
subjects affected / exposed	18 / 566 (3.18%)		
occurrences (all)	18		
Diabetes mellitus inadequate control			
subjects affected / exposed	10 / 566 (1.77%)		
occurrences (all)	10		

Dyslipidaemia			
subjects affected / exposed	8 / 566 (1.41%)		
occurrences (all)	8		
Hyperglycaemia			
subjects affected / exposed	7 / 566 (1.24%)		
occurrences (all)	7		
Type 2 diabetes mellitus			
subjects affected / exposed	12 / 566 (2.12%)		
occurrences (all)	15		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2018	Definition of "personal data" was added and WOC was updated. Added clarification on the framework of analysis on study information collected from withdrawn subjects.
11 February 2020	Purpose and timing of interim analyses/design adaptations were updated for the primary analysis to be conducted when the first 534 randomized subjects have completed their Week 52 visit or terminated the study prior to Week 52. Clarification that data for the additional subjects randomized in Japan beyond the study target of 534 subjects was to be analyzed once these subjects had completed their Week 52 visit or terminated the study prior to Week 52. Details were added regarding the primary Week 52 analysis and additional analyses to allow for consistency assessment of data between Japanese and non-Japanese subjects. Clarification was added regarding treatment masking. Aflibercept was removed from ADA and systemic exposure.
12 June 2020	Changes in relation to emerging safety issue are: Information was added to describe a new safety signal from post-marketing case reports. Additional guidance was added emphasizing that if any sign of intraocular inflammation is present, an IVT injection must not be performed and subjects should be treated for intraocular inflammation according to clinical practice. Additional examination and assessments included to fully characterize cases of intraocular inflammation were made. Modifications were made to include importance of estimands per ICH E9(R1) guidance. Changes were incorporated to address the COVID-19 pandemic. Other changes incorporated in this amendment: Three endpoints were moved from Secondary to Exploratory. Clarifications were added regarding unmasked investigator/site personnel, injection procedure, IOP measurement procedure, and SAE reporting period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: