Clinical trial results:
A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KINGFISHER)

Summary

EudraCT number	2019-001004-37
Trial protocol	SK HU
Global end of trial date	24 March 2021

Results information

Result version number	v2 (current)
This version publication date	22 May 2022
First version publication date	08 April 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRTH258B2305

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03917472
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	16 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective for this study was to demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in visual acuity (VA) from baseline compared to Week 52 summarized below along with their respective endpoints.

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	17 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 51
Country: Number of subjects enrolled	Israel: 27
Country: Number of subjects enrolled	Slovakia: 47
Country: Number of subjects enrolled	United States: 392
Worldwide total number of subjects	517
EEA total number of subjects	98

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	323
From 65 to 84 years	191
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Study centers (no. of sites): Hungary (5), Israel (5), Slovakia (7), United States (78).

Approximately, 495 subjects were planned to be randomized. Overall, 517 subjects were randomized either to brolucizumab 6 mg q4w arm (n=346) or aflibercept 2 mg q4w arm (n=171).

Pre-assignment

Screening details:

The study included a screening period of up to 2 wks to assess eligibility, followed by a double-masked treatment period (Day 1 to Wk 48). For all subjects, the last study assessment was performed at the Wk 52/end of study (EOS) visit. All subjects had study visits q4w through Wk 52. The primary analysis was performed at the EOS visit (Wk 52).

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	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Brolucizumab 6mg q4w

Arm description:

Brolucizumab 6 mg/0.05 mL every 4 weeks.

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

Arm title	Aflibercept 2mg q4w

Arm description:

Aflibercept 2mg/0.05 mL every 4 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

Number of subjects in period 1	Brolucizumab 6mg q4w	Aflibercept 2mg q4w
Started	346	171
Completed	311	156
Not completed	35	15
Adverse event, serious fatal	7	5
Physician decision	4	-
Consent withdrawn by subject	11	4
Adverse event, non-fatal	3	1
Lost to follow-up	10	5

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 6mg q4w
Reporting group description: Brolucizumab 6 mg/0.05 mL every 4 weeks.	
Reporting group title	Aflibercept 2mg q4w
Reporting group description: Aflibercept 2mg/0.05 mL every 4 weeks	

Reporting group values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w	Total
Number of subjects	346	171	517
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	208	115	323
>=65 years	138	56	194
Age Continuous Units: years			
arithmetic mean	60.9	60.2	
standard deviation	± 10.59	± 9.31	-
Sex: Female, Male Units: participants			
Female	152	66	218
Male	194	105	299
Race/Ethnicity, Customized Units: Subjects			
White	288	145	433
Black or African American	40	15	55
Asian	14	7	21
Native Hawaiian or Other Pacific Islander	1	0	1
American Indian or Alaska Native	0	1	1
Unknown	1	3	4
More than one race	2	0	2

End points

End points reporting groups

Reporting group title	Brolucizumab 6mg q4w
Reporting group description: Brolucizumab 6 mg/0.05 mL every 4 weeks.	
Reporting group title	Aflibercept 2mg q4w
Reporting group description: Aflibercept 2mg/0.05 mL every 4 weeks	
Subject analysis set title	Brolucizumab 6mg q4w
Subject analysis set type	Full analysis
Subject analysis set description: Brolucizumab 6mg q4w	
Subject analysis set title	Aflibercept 2mg q4w
Subject analysis set type	Full analysis
Subject analysis set description: Aflibercept 2mg q4w	

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 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 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.

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

Last observation carried forward (LOCF) was used for the imputation of missing values.

End point type	Primary
End point timeframe: Baseline, Week 52	

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	12.2 (11.2 to 13.2)	11.0 (9.6 to 12.4)		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Aflibercept 2mg q4w v Brolucizumab 6mg q4w

Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.099
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	0.89

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANOVA

Secondary: Change from baseline in central subfield thickness (CSFT) at each post-baseline visit

End point title	Change from baseline in central subfield thickness (CSFT) at each post-baseline visit

End point description:

Central Subfield Thickness assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: µm				
least squares mean (confidence interval 95%)				
Week 4	-146.9 (-157.9 to -136.0)	-119.5 (-135.1 to -103.9)		
Week 8	-174.4 (-185.3 to -163.4)	-144.1 (-159.7 to -128.5)		

Week 12	-191.3 (-201.8 to -180.8)	-156.7 (-171.7 to -141.8)		
Week 16	-200.5 (-211.0 to -189.9)	-162.4 (-177.4 to -147.4)		
Week 20	-209.5 (-219.6 to -199.4)	-168.7 (-183.1 to -154.2)		
Week 24	-217.5 (-227.3 to -207.6)	-178.8 (-192.8 to -164.7)		
Week 28	-222.4 (-232.5 to -212.4)	-183.6 (-197.8 to -169.3)		
Week 32	-227.2 (-237.2 to -217.1)	-185.9 (-200.2 to -171.6)		
Week 36	-229.7 (-240.1 to -219.3)	-186.7 (-201.5 to -172.0)		
Week 40	-233.6 (-243.7 to -223.6)	-188.4 (-202.6 to -174.1)		
Week 44	-237.5 (-247.4 to -227.5)	-188.1 (-202.3 to -173.9)		
Week 48	-237.7 (-247.7 to -227.6)	-192.0 (-206.4 to -177.7)		
Week 52	-237.8 (-247.9 to -227.7)	-196.5 (-210.8 to -182.1)		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-41.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.9
upper limit	-23.8
Variability estimate	Standard error of the mean
Dispersion value	8.94

Secondary: Number of participants with fluid-free macula in the study eye at each post-baseline visit

End point title	Number of participants with fluid-free macula in the study eye at each post-baseline visit

End point description:

Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) status in the central subfield: proportion of subjects with simultaneous absence of SRF and IRF in the study eye by visit. Events and censoring after 52 weeks are included in week 52 row.

End point type	Secondary

End point timeframe:
Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
Week 4	23	4		
Week 8	31	4		
Week 12	38	10		
Week 16	48	11		
Week 20	54	9		
Week 24	84	19		
Week 28	65	13		
Week 32	76	17		
Week 36	91	21		
Week 40	96	23		
Week 44	96	20		
week 48	92	23		
Week 52	144	38		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Clopper-Pearson exact method.
Parameter estimate	Difference - %
Point estimate	20
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.5
upper limit	28.6

Secondary: Number of participants with absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) at each post-baseline visit for the study eye

End point title	Number of participants with absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) at each post-baseline visit for the study eye

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
Week 4	61	9		
Week 8	93	24		
Week 12	124	33		
Week 16	147	42		
Week 20	167	47		
Week 24	177	52		
Week 28	186	57		
Week 32	195	62		
Week 36	206	63		
Week 40	211	65		
Week 44	216	69		
Week 48	222	68		
Week 52	229	71		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Number of subjects with absence of SRF / IRF and Number of subjects censored by visit

End point title	Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Number of subjects with absence of SRF / IRF and Number of subjects censored by visit

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. Fluid status assessments after start of alternative DME treatment in the study eye are censored. Time to first fluid-free macula analysis is based on the subset of subjects with fluid present at baseline and at least one post-baseline assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	170		
Units: Participants				
N w/ absence of SRF/IRF at Wk 0 (n=344,170)	0	0		
N w/ absence of SRF/IRF at Wk 4 (n=344,170)	6	1		
N w/ absence of SRF/IRF at Wk 8 (n=335,168)	18	3		
N w/ absence of SRF/IRF at Wk 12 (n=314, 165)	13	2		
N w/ absence of SRF/IRF at Wk 16 (n=297, 161)	17	4		
N w/ absence of SRF/IRF at Wk 20 (n=277, 156)	8	6		
N w/ absence of SRF/IRF at Wk 24 (n=265,150)	16	2		
N w/ absence of SRF/IRF at Wk 28 (n=246,146)	18	7		
N w/ absence of SRF/IRF at Wk 32 (n=224,139)	3	1		
N w/ absence of SRF/IRF at Wk 36 (n=220,138)	8	2		
N w/ absence of SRF/IRF at Wk 40 (n=211, 134)	16	4		
N w/ absence of SRF/IRF at Wk 44 (194, 129)	11	2		
N w/ absence of SRF/IRF at Wk 48 (n=181, 125)	3	0		
N w/ absence of SRF/IRF at Wk 52 (n=177, 122)	30	12		
N censored at Week 0 (n=344, 170)	0	0		
N censored at Week 4 (n-344, 170)	3	1		
N censored at Week 8 (n=335,168)	3	0		
N censored at Week 12 (n=314, 165)	4	2		
N censored at Week 16 (n=297, 161)	3	1		
N censored at Week 20 (n=277, 156)	4	0		
N censored at Week 24 (n=265, 150)	3	2		
N censored at Week 28 (n=246, 146)	4	0		
N censored at Week 32 (n=224,139)	1	0		
N censored at Week 36 (220, 138)	1	2		
N censored at Week 40 (n=211,134)	1	1		
N censored at Week 44 (n=194,129)	2	2		
N censored at Week 48 (n=181, 125)	1	3		
N censored at Week 52 (n=177, 122)	147	110		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Kaplan-Meier analysis - Probability of absence of SRF/IRF by visit

End point title	Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Kaplan-Meier analysis - Probability of absence of SRF/IRF by visit

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. Fluid status assessments after start of alternative DME treatment in the study eye are censored. Time to first fluid-free macula analysis is based on the subset of subjects with fluid present at baseline and at least one post-baseline assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	344	170		
Units: Probability of absence of SRF/IRF				
number (confidence interval 95%)				
Prob. of absence of SRF/IRF at Wk 4 (n=344,170)	0.018 (0.007 to 0.036)	0.006 (0.001 to 0.030)		
Prob. of absence of SRF/IRF at Wk 8 (n=335,168)	0.071 (0.047 to 0.101)	0.024 (0.008 to 0.056)		
Prob. of absence of SRF/IRF at Wk 12 (n=314, 165)	0.109 (0.079 to 0.145)	0.036 (0.015 to 0.072)		
Prob. of absence of SRF/IRF at Wk 16 (n=297, 161)	0.161 (0.124 to 0.202)	0.060 (0.030 to 0.103)		
Prob.of absence of SRF/IRF at Wk 20 (n=277, 156)	0.185 (0.145 to 0.228)	0.096 (0.057 to 0.146)		
Prob. of absence of SRF/IRF at Wk 24 (n=265,150)	0.234 (0.190 to 0.281)	0.108 (0.067 to 0.161)		
Prob. of absence of SRF/IRF at Wk 28 (n=246,146)	0.291 (0.243 to 0.341)	0.151 (0.101 to 0.210)		
Prob. of absence of SRF/IRF at Wk 32 (n=224,139)	0.300 (0.252 to 0.351)	0.157 (0.106 to 0.217)		
Prob. of absence of SRF/IRF at Wk 36 (n=220,138)	0.326 (0.275 to 0.377)	0.169 (0.116 to 0.230)		
Prob. of absence of SRF/IRF at Wk 40 (n=211, 134)	0.377 (0.324 to 0.430)	0.194 (0.137 to 0.258)		
Prob. of absence of SRF/IRF at Wk 44 (194, 129)	0.412 (0.358 to 0.466)	0.206 (0.148 to 0.271)		
Prob. of absence of SRF/IRF at Wk 48 (n=181, 125)	0.422 (0.368 to 0.476)	0.206 (0.148 to 0.271)		
Prob. of absence of SRF/IRF at Wk 52 (n=177, 122)	0.653 (0.540 to 0.745)	0.328 (0.234 to 0.426)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Number of subjects with Probability of absence of DME and Number censored by visit

End point title	Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Number of subjects with Probability of absence of DME and Number censored by visit

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. CSFT assessments after start of alternative DME treatment in the study eye are censored. Time to first absence of DME based on subjects with valid baseline and at least one post-baseline CSFT assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
N w/ Prob. of absence of DME at Wk 0 (n=346,171)	0	0		
N w/ Prob. of absence of DME at Wk 4 (n=346,171)	14	1		
N w/ Prob. of absence of DME at Wk 8 (n=329,169)	54	12		
N w/ Prob. of absence of DME at Wk 12 (n=272, 157)	32	13		
N w/ Prob. of absence of DME at Wk 16 (n=239, 142)	33	11		
N w/ Prob. of absence of DME at Wk 20 (n=204, 130)	26	10		
N w/ Prob. of absence of DME at Wk 24 (n=174,120)	12	4		
N w/ Prob. of absence of DME at Wk 28 (n=161,115)	13	7		
N w/ Prob. of absence of DME at Wk 32 (n=146,107)	9	5		
N w/ Prob. of absence of DME at Wk 36 (n=135,102)	10	2		
N w/ Prob. of absence of DME at Wk 40 (n=125, 98)	7	1		
N w/ Prob. of absence of DME at Wk 44 (117, 96)	11	2		
N w/ Prob. of absence of DME at Wk 48 (n=106, 92)	6	3		
N w/ Prob. of absence of DME at Wk 52 (n=99, 88)	13	4		
Number censored at Week 0 (n=346,171)	0	0		

Number censored at Week 4 (n=346,171)	3	1		
Number censored at Week 8 (n=329,169)	3	0		
Number censored at Week 12 (n=272, 157)	1	2		
Number censored at Week 16 (n=239, 142)	2	1		
Number censored at Week 20 (n=204, 130)	4	0		
Number censored at Week 24 (n=174,120)	1	1		
Number censored at Week 28 (n=161,115)	2	1		
Number censored at Week 32 (n=146,107)	2	0		
Number censored at Week 36 (n=135,102)	0	2		
Number censored at Week 40 (n=125, 98)	1	1		
Number censored at Week 44 (117, 96)	0	2		
Number censored at Week 48 (n=106, 92)	1	1		
Number censored at Week 52 (n=99, 88)	86	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Kaplan-Meier analysis - Probability of absence of DME by visit

End point title	Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Kaplan-Meier analysis - Probability of absence of DME by visit

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. CSFT assessments after start of alternative DME treatment in the study eye are censored. Time to first absence of DME based on subjects with valid baseline and at least one post-baseline CSFT assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Probability of absence of DME				
number (confidence interval 95%)				

Prob. of absence of DME at Week 4 (n=346,171)	0.041 (0.023 to 0.066)	0.006 (0.001 to 0.030)		
Prob. of absence of DME at Week 8 (n=329,169)	0.199 (0.158 to 0.243)	0.076 (0.043 to 0.123)		
Prob. of absence of DME at Week 12 (n=272, 157)	0.293 (0.246 to 0.342)	0.153 (0.104 to 0.212)		
Prob. of absence of DME at Week 16 (n=239, 142)	0.391 (0.339 to 0.443)	0.219 (0.160 to 0.284)		
Prob. of absence of DME at Week 20 (n=204, 130)	0.470 (0.416 to 0.522)	0.279 (0.213 to 0.348)		
Prob. of absence of DME at Week 24 (n=174,120)	0.506 (0.452 to 0.559)	0.303 (0.235 to 0.374)		
Prob. of absence of DME at Week 28 (n=161,115)	0.547 (0.491 to 0.598)	0.346 (0.274 to 0.418)		
Prob. of absence of DME at Week 32 (n=146,107)	0.575 (0.520 to 0.626)	0.376 (0.303 to 0.450)		
Prob. of absence of DMEE at Week 36 (n=135,102)	0.606 (0.551 to 0.657)	0.389 (0.314 to 0.462)		
Prob. of absence of DME at Week 40 (n=125, 98)	0.628 (0.574 to 0.678)	0.395 (0.320 to 0.468)		
Prob. of absence of DME at Week 44 (117, 96)	0.663 (0.609 to 0.712)	0.408 (0.332 to 0.482)		
Prob. of absence of DME at Week 48 (n=106, 92)	0.682 (0.629 to 0.730)	0.427 (0.351 to 0.501)		
Prob. of absence of DME at Week 52 (n=99, 88)	0.866 (0.302 to 0.983)	0.516 (0.357 to 0.654)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Corrected Visual Acuity (letters read): Change from baseline in best-corrected visual acuity (BCVA) at each post-baseline visit for the study eye

End point title	Best Corrected Visual Acuity (letters read): Change from baseline in best-corrected visual acuity (BCVA) at each post-baseline visit for the study eye

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 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.

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

End point type	Secondary

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: scores on a scale				
least squares mean (confidence interval 95%)				
Week 4	5.7 (5.1 to 6.4)	5.4 (4.5 to 6.4)		
Week 8	7.7 (6.9 to 8.5)	7.4 (6.4 to 8.5)		
Week 12	9.1 (8.3 to 9.9)	8.0 (6.9 to 9.1)		
Week 16	9.6 (8.8 to 10.4)	8.5 (7.3 to 9.7)		
Week 20	10.2 (9.3 to 11.1)	9.2 (7.9 to 10.5)		
Week 24	10.7 (9.8 to 11.6)	9.6 (8.3 to 10.9)		
Week 28	10.9 (10.0 to 11.8)	10.7 (9.3 to 12.0)		
Week 32	11.5 (10.6 to 12.5)	10.5 (9.2 to 11.9)		
Week 36	11.6 (10.6 to 12.6)	10.8 (9.4 to 12.2)		
Week 40	11.7 (10.7 to 12.6)	10.7 (9.4 to 12.1)		
Week 44	12.0 (11.0 to 13.0)	10.6 (9.2 to 12.0)		
Week 48	12.2 (11.2 to 13.2)	10.7 (9.3 to 12.1)		
Week 52	12.2 (11.2 to 13.2)	11.0 (9.6 to 12.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Gain in best-corrected visual acuity (BCVA) (letters read): number (%) of subjects who gained ≥ 5, 10, or 15 letters in BCVA from baseline or reached BCVA ≥ 84 letters in the study eye at Week 52

End point title	Gain in best-corrected visual acuity (BCVA) (letters read): number (%) of subjects who gained ≥ 5, 10, or 15 letters in BCVA from baseline or reached BCVA ≥ 84 letters in the study eye at 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 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.

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

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
≥5 letters gain from b/l or BCVA≥84letters at Wk52	286	127		
≥10 letters gain from b/l or BCVA≥84letters at W52	211	95		
≥15 letters gain from b/l or BCVA≥84letters at W52	151	69		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Statistical analysis description: ≥ 5 letters gain from baseline or BCVA ≥ 84 letters at Week 52	
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	9.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	17

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Statistical analysis description: ≥ 15 letters gain from baseline or BCVA ≥ 84 letters at Week 52	
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	5.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	14.3

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Statistical analysis description: ≥ 10 letters gain from baseline or BCVA ≥ 84 letters at Week 52	
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	517
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	-1.5
upper limit	17

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

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

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative.

Severity of Diabetic retinopathy was evaluated using the ETDRS DRSS score assessed by the Central Reading Center 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 functioning.

Subjects who had full/partial panretinal photocoagulation or local photocoagulation for new vessel (DRSS score 60) at any visit were excluded.

DRSS scores after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	118		
Units: Participants				
Week 12	56	21		
Week 24	82	38		
Week 52	95	45		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	16.5

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002 [1]
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	16.1

Notes:

[1] - (10% margin) (1-sided)

	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w

Statistical analysis title	
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	14.9

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

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

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative.

Severity of Diabetic retinopathy was evaluated using the ETDRS DRSS score assessed by the Central Reading Center 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 functioning.

Subjects who had full/partial panretinal photocoagulation or local photocoagulation for new vessel (DRSS score 60) at any visit were excluded.

DRSS scores after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Weeks 12, 24 and 52

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	118		
Units: Participants				
Week 12	18	8		
Week 24	33	16		
Week 52	40	18		

Statistical analyses

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	7.7

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	
Method	Clopper-Pearson exact method
Parameter estimate	Difference - %
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	6.6

Statistical analysis title	Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w
Comparison groups	Brolucizumab 6mg q4w v Aflibercept 2mg q4w
Number of subjects included in analysis	339
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
upper limit	9.8

Secondary: Anti-Drug Antibody (ADA): frequency distribution of pre-existing ADA status in the Brolucizumab arm

End point title	Anti-Drug Antibody (ADA): frequency distribution of pre-existing ADA status in the Brolucizumab arm

End point description:

End point type	Secondary

End point timeframe:

Baseline

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	342	0[2]		
Units: Participants				
Negative	112			
Positive	230			

Notes:

[2] - Endpoint only defined for the Brolucizumab 6mg q4w arm

Statistical analyses

No statistical analyses for this end point

Post-hoc: Ocular AEs (greater than or equal to 2% in any treatment arm) by preferred term in the study eye

End point title	Ocular AEs (greater than or equal to 2% in any treatment arm) by preferred term in the study eye

End point description:

End point type	Post-hoc

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 weeks.

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
Number of subjects with at least one AE	105	59		
Vitreous detachment	10	7		
Cataract	9	6		
Conjunctival haemorrhage	9	7		
Punctate keratitis	9	2		
Uveitis	8	1		
Vitreous floaters	8	5		
Dry eye	7	4		
Eye pain	6	5		
Corneal abrasion	0	5		
Diabetic retinal oedema	0	4		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Number of subjects with non-ocular AEs (greater than or equal to 2% in any treatment arm)

End point title	Number of subjects with non-ocular AEs (greater than or equal to 2% in any treatment arm)

End point description:

End point type	Post-hoc

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 weeks.

End point values	Brolucizumab 6mg q4w	Aflibercept 2mg q4w		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	346	171		
Units: Participants				
Number of subjects with at least one AE	209	96		

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 end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 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	24.0

Reporting groups	
Reporting group title	Brolucizumab 6mg
Reporting group description:	
Brolucizumab 6mg	
Reporting group title	Overall
Reporting group description:	
Overall	
Reporting group title	Aflibercept 2mg
Reporting group description:	
Aflibercept 2mg	

Serious adverse events	Brolucizumab 6mg	Overall	Aflibercept 2mg
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 346 (21.39%)	110 / 517 (21.28%)	36 / 171 (21.05%)
number of deaths (all causes)	7	12	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adrenal adenoma			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Bladder cancer			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Leukaemia			

subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Gastric neoplasm			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Hypertensive emergency			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Hypertension			
subjects affected / exposed	1 / 346 (0.29%)	3 / 517 (0.58%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive urgency			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Peripheral vascular disorder			

subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Chest pain			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Generalised oedema			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Oedema peripheral			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Sudden death			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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

Dyspnoea			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Interstitial lung disease			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Pulmonary embolism			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pulmonary oedema			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Investigations			
Blood potassium increased			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Blood glucose increased			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Injury, poisoning and procedural			

complications			
Ankle fracture			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Anastomotic ulcer haemorrhage			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Forearm fracture			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Contusion			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation complication - Fellow eye			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Rib fracture			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Postoperative ileus			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Post-traumatic neck syndrome			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Arrhythmia			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			

subjects affected / exposed	4 / 346 (1.16%)	4 / 517 (0.77%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	3 / 346 (0.87%)	4 / 517 (0.77%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Atrioventricular block second degree			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Cardiopulmonary failure			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	3 / 346 (0.87%)	4 / 517 (0.77%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 346 (0.87%)	4 / 517 (0.77%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			

subjects affected / exposed	2 / 346 (0.58%)	3 / 517 (0.58%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	6 / 346 (1.73%)	12 / 517 (2.32%)	6 / 171 (3.51%)
occurrences causally related to treatment / all	0 / 6	0 / 12	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Epilepsy			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Lacunar stroke			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Ischaemic stroke			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Thrombotic stroke			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Hypochromic anaemia			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy - Fellow eye			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Cataract subcapsular - Study eye			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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

Retinal vasculitis - Study eye			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage - Study eye			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gastroparesis			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Vomiting			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal perforation			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Hepatobiliary disorders			

Liver disorder			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic wound			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 346 (1.16%)	5 / 517 (0.97%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 346 (0.58%)	2 / 517 (0.39%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Renal colic			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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

Hydronephrosis			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Renal impairment			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	3 / 346 (0.87%)	3 / 517 (0.58%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Infections and infestations			
Abscess bacterial			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abscess limb			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
COVID-19			
subjects affected / exposed	8 / 346 (2.31%)	9 / 517 (1.74%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 8	0 / 9	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 3	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	4 / 346 (1.16%)	4 / 517 (0.77%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	3 / 346 (0.87%)	3 / 517 (0.58%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest wall abscess			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Diabetic foot infection			
subjects affected / exposed	1 / 346 (0.29%)	3 / 517 (0.58%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			

subjects affected / exposed	2 / 346 (0.58%)	3 / 517 (0.58%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic gangrene			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Kidney infection			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Lymphangitis			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Osteomyelitis			
subjects affected / exposed	3 / 346 (0.87%)	5 / 517 (0.97%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 346 (0.87%)	5 / 517 (0.97%)	2 / 171 (1.17%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sepsis			
subjects affected / exposed	2 / 346 (0.58%)	3 / 517 (0.58%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Staphylococcal sepsis			

subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Subcutaneous abscess			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Wound infection staphylococcal			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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
Hyperkalaemia			
subjects affected / exposed	1 / 346 (0.29%)	2 / 517 (0.39%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 346 (0.00%)	1 / 517 (0.19%)	1 / 171 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 346 (0.29%)	1 / 517 (0.19%)	0 / 171 (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

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

Non-serious adverse events	Brolucizumab 6mg	Overall	Aflibercept 2mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	144 / 346 (41.62%)	236 / 517 (45.65%)	92 / 171 (53.80%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 346 (5.20%)	31 / 517 (6.00%)	13 / 171 (7.60%)
occurrences (all)	19	32	13
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 346 (0.87%)	7 / 517 (1.35%)	4 / 171 (2.34%)
occurrences (all)	3	7	4
Pyrexia			
subjects affected / exposed	4 / 346 (1.16%)	8 / 517 (1.55%)	4 / 171 (2.34%)
occurrences (all)	6	10	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 346 (0.87%)	12 / 517 (2.32%)	9 / 171 (5.26%)
occurrences (all)	4	13	9
Investigations			
Blood pressure increased			
subjects affected / exposed	7 / 346 (2.02%)	12 / 517 (2.32%)	5 / 171 (2.92%)
occurrences (all)	7	12	5
Blood creatinine increased			
subjects affected / exposed	4 / 346 (1.16%)	11 / 517 (2.13%)	7 / 171 (4.09%)
occurrences (all)	4	11	7
Injury, poisoning and procedural complications			
Corneal abrasion - Study eye			
subjects affected / exposed	0 / 346 (0.00%)	5 / 517 (0.97%)	5 / 171 (2.92%)
occurrences (all)	0	5	5
Fall			
subjects affected / exposed	9 / 346 (2.60%)	13 / 517 (2.51%)	4 / 171 (2.34%)
occurrences (all)	10	14	4
Nervous system disorders			

Headache			
subjects affected / exposed	3 / 346 (0.87%)	10 / 517 (1.93%)	7 / 171 (4.09%)
occurrences (all)	3	11	8
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 346 (2.31%)	12 / 517 (2.32%)	4 / 171 (2.34%)
occurrences (all)	8	12	4
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	6 / 346 (1.73%)	10 / 517 (1.93%)	4 / 171 (2.34%)
occurrences (all)	6	10	4
Cataract - Study eye			
subjects affected / exposed	9 / 346 (2.60%)	15 / 517 (2.90%)	6 / 171 (3.51%)
occurrences (all)	9	15	6
Conjunctival haemorrhage - Fellow eye			
subjects affected / exposed	4 / 346 (1.16%)	9 / 517 (1.74%)	5 / 171 (2.92%)
occurrences (all)	4	10	6
Conjunctival haemorrhage - Study eye			
subjects affected / exposed	9 / 346 (2.60%)	16 / 517 (3.09%)	7 / 171 (4.09%)
occurrences (all)	10	20	10
Diabetic retinal oedema - Fellow eye			
subjects affected / exposed	10 / 346 (2.89%)	17 / 517 (3.29%)	7 / 171 (4.09%)
occurrences (all)	10	17	7
Diabetic retinal oedema - Study eye			
subjects affected / exposed	0 / 346 (0.00%)	4 / 517 (0.77%)	4 / 171 (2.34%)
occurrences (all)	0	4	4
Dry eye - Fellow eye			
subjects affected / exposed	6 / 346 (1.73%)	12 / 517 (2.32%)	6 / 171 (3.51%)
occurrences (all)	6	12	6
Dry eye - Study eye			
subjects affected / exposed	7 / 346 (2.02%)	11 / 517 (2.13%)	4 / 171 (2.34%)
occurrences (all)	7	11	4
Eye pain - Fellow eye			
subjects affected / exposed	3 / 346 (0.87%)	7 / 517 (1.35%)	4 / 171 (2.34%)
occurrences (all)	3	7	4
Vitreous detachment - Study eye			

subjects affected / exposed	10 / 346 (2.89%)	17 / 517 (3.29%)	7 / 171 (4.09%)
occurrences (all)	10	17	7
Uveitis - Study eye			
subjects affected / exposed	8 / 346 (2.31%)	9 / 517 (1.74%)	1 / 171 (0.58%)
occurrences (all)	9	10	1
Punctate keratitis - Study eye			
subjects affected / exposed	9 / 346 (2.60%)	11 / 517 (2.13%)	2 / 171 (1.17%)
occurrences (all)	12	15	3
Eye pain - Study eye			
subjects affected / exposed	6 / 346 (1.73%)	11 / 517 (2.13%)	5 / 171 (2.92%)
occurrences (all)	6	11	5
Vitreous floaters - Study eye			
subjects affected / exposed	8 / 346 (2.31%)	13 / 517 (2.51%)	5 / 171 (2.92%)
occurrences (all)	8	13	5
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	10 / 346 (2.89%)	14 / 517 (2.71%)	4 / 171 (2.34%)
occurrences (all)	11	15	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 346 (0.87%)	7 / 517 (1.35%)	4 / 171 (2.34%)
occurrences (all)	3	8	5
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 346 (2.31%)	12 / 517 (2.32%)	4 / 171 (2.34%)
occurrences (all)	9	13	4
Chronic kidney disease			
subjects affected / exposed	8 / 346 (2.31%)	12 / 517 (2.32%)	4 / 171 (2.34%)
occurrences (all)	9	13	4
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 346 (0.87%)	7 / 517 (1.35%)	4 / 171 (2.34%)
occurrences (all)	3	7	4
Infections and infestations			
COVID-19			
subjects affected / exposed	11 / 346 (3.18%)	22 / 517 (4.26%)	11 / 171 (6.43%)
occurrences (all)	12	23	11

Cellulitis			
subjects affected / exposed	7 / 346 (2.02%)	11 / 517 (2.13%)	4 / 171 (2.34%)
occurrences (all)	8	12	4
Influenza			
subjects affected / exposed	2 / 346 (0.58%)	6 / 517 (1.16%)	4 / 171 (2.34%)
occurrences (all)	2	6	4
Urinary tract infection			
subjects affected / exposed	11 / 346 (3.18%)	13 / 517 (2.51%)	2 / 171 (1.17%)
occurrences (all)	12	14	2
Nasopharyngitis			
subjects affected / exposed	8 / 346 (2.31%)	14 / 517 (2.71%)	6 / 171 (3.51%)
occurrences (all)	8	14	6
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	7 / 346 (2.02%)	7 / 517 (1.35%)	0 / 171 (0.00%)
occurrences (all)	7	7	0
Type 2 diabetes mellitus			
subjects affected / exposed	5 / 346 (1.45%)	9 / 517 (1.74%)	4 / 171 (2.34%)
occurrences (all)	5	9	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2020	The main purpose of this amendment was to provide clarification and guidance on safety assessments in accordance with the urgent safety measure regarding the post-marketing reports with brolucizumab (Beovu®) in the treatment of nAMD, which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI, that could result in severe vision loss. In addition, the amendment included the modifications due to COVID-19 pandemic.

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: