Clinical trial results:
A Two-Year, Two-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

Summary

EudraCT number	2017-003960-11
Trial protocol	DE LV LT SK SE BE DK HU CZ BG PL
Global end of trial date	08 June 2021

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022

Trial information

Trial identification

Sponsor protocol code	CRTH258B2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03481660
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	08 June 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that brolucizumab was non-inferior to aflibercept with respect to the visual outcome after the first year of treatment

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	27 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	Belgium: 3
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Estonia: 3
Country: Number of subjects enrolled	France: 56
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Hungary: 47
Country: Number of subjects enrolled	India: 24
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Latvia: 4
Country: Number of subjects enrolled	Lebanon: 4
Country: Number of subjects enrolled	Lithuania: 7
Country: Number of subjects enrolled	Malaysia: 15
Country: Number of subjects enrolled	Norway: 4
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Slovakia: 32

Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Taiwan: 24
Country: Number of subjects enrolled	Turkey: 23
Worldwide total number of subjects	360
EEA total number of subjects	220

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)	202
From 65 to 84 years	156
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 79 centers in 23 countries worldwide.

Pre-assignment

Screening details:

360 subjects were randomized in a 1:1 ratio to brolucizumab 6 mg arm (n=179) or aflibercept 2 mg arm (n=181).

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

Arms

Are arms mutually exclusive?	Yes
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	
Other name	RTH258, ESBA1008
Pharmaceutical forms	Injection, Solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

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

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	Injection, Solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

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

Number of subjects in period 1	Brolucizumab 6 mg	Aflibercept 2 mg
Started	179	181
Completed	143	156
Not completed	36	25
Adverse event, serious fatal	13	9
Physician decision	2	3
Consent withdrawn by subject	14	7
Adverse event, non-fatal	5	4
Lost to follow-up	2	2

Baseline characteristics

Reporting groups	
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 6 mg	Aflibercept 2 mg	Total
Number of subjects	179	181	360
Age Categorical Units: Participants			
< 65 years	100	102	202
>= 65 years	79	79	158
Age Continuous Units: Years			
arithmetic mean	62.3	62.2	
standard deviation	± 10.55	± 9.48	-
Sex: Female, Male Units: Participants			
Female	59	66	125
Male	120	115	235
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	43	48	91
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	1	4
White	133	132	265
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	4	7
Not Hispanic or Latino	163	170	333
Unknown or Not Reported	13	7	20

End points

End points reporting groups

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: Mean change from Baseline in best-corrected visual acuity (BCVA) at Week 52 for the study eye

End point title	Mean change from Baseline in best-corrected visual acuity (BCVA) at Week 52 for the study eye
End point description:	
Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	10.6 (9.3 to 11.9)	9.4 (8.1 to 10.7)		

Statistical analyses

Statistical analysis title	BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[1] - (4-letter margin) (1-sided)

Secondary: Average mean change from Baseline in BCVA over the period Week 40 through Week 52 for the study eye

End point title	Average mean change from Baseline in BCVA over the period Week 40 through Week 52 for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the period Week 40 through Week 52. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, period Week 40 through Week 52

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	10.3 (9.1 to 11.5)	9.4 (8.2 to 10.6)		

Statistical analyses

Statistical analysis title	BCVA over period Week 40 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.164
Method	ANOVA

	BCVA over period Week 40 through Week 52

Statistical analysis title	
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.001
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.88

Notes:

[2] - (4-letter margin) (1-sided)

Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 and up to q12w/q16w up to Week 100.

End point title	(Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 and up to q12w/q16w up to Week 100.

End point description:

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

End point type	Secondary

End point timeframe:

Week 52, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[3]		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 48	50.3 (42.5 to 57.7)	(to)		
Week 96	36.8 (29.1 to 45.5)	(to)		

Notes:

[3] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36

End point title	(Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36

End point description:

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

End point type	Secondary

End point timeframe:

Week 36, Week 52

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	0[4]		
Units: Percentage of participants				
number (confidence interval 95%)	95.1 (87.4 to 98.1)	(to)		

Notes:

[4] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36

End point title	(Brolucizumab treatment arm only): Percentage of participants maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36

End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.
The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

End point type	Secondary

End point timeframe:

Week 36, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	0[5]		
Units: Percentage of participants				
number (confidence interval 95%)	69.6 (57.4 to 78.9)	(to)		

Notes:

[5] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76

End point title	(Brolucizumab treatment arm only): Percentage of participants maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76

End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.
The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

End point type	Secondary

End point timeframe:

Week 68, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	0[6]		
Units: Percentage of participants				
number (confidence interval 95%)	87.9 (73.3 to 94.8)	(to)		

Notes:

[6] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: (Brolucizumab treatment arm only): Percentage of participants re-assigned and maintained on q12w up to Week 100 within the patients on q8w at Week 68 and on q12w at Week 80

End point title	(Brolucizumab treatment arm only): Percentage of participants re-assigned and maintained on q12w up to Week 100 within

	the patients on q8w at Week 68 and on q12w at Week 80

End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.
The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

End point type	Secondary

End point timeframe:

Week 68, Week 80, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	0[7]		
Units: Percentage of participants				
number (confidence interval 95%)	73.1 (54.5 to 85.0)	(to)		

Notes:

[7] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: (Brolucizumab treatment arm only): Number of participants with injections per planned dosing regimen (every 8, 12 or 16 weeks)

End point title	(Brolucizumab treatment arm only): Number of participants with injections per planned dosing regimen (every 8, 12 or 16 weeks)

End point description:

Reported categorically for the subjects who completed the study treatment period: every 8 weeks (q8w), Every 12 weeks (q12w), Every 16 weeks (q16w)

End point type	Secondary

End point timeframe:

Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	0[8]		
Units: Participants				
q8w	74			
q12w	32			
q16w	35			

Notes:

[8] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Best Corrected Visual Acuity (BCVA) at each visit up to Week 100 for the study eye

End point title	Mean change from Baseline in Best Corrected Visual Acuity (BCVA) at each visit up to Week 100 for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The BCVA score is the number of letters read correctly by the patient, hence an increase in score indicates improvement in acuity. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
Week 4	5.1 (4.3 to 6.0)	4.2 (3.4 to 5.1)		
Week 6	6.8 (5.9 to 7.6)	5.9 (5.0 to 6.7)		
Week 8	7.8 (6.9 to 8.7)	6.7 (5.8 to 7.5)		
Week 12	8.6 (7.6 to 9.5)	7.7 (6.7 to 8.6)		
Week 16	9.0 (7.9 to 10.1)	8.3 (7.2 to 9.5)		
Week 18	9.2 (8.0 to 10.3)	9.2 (8.0 to 10.3)		
Week 20	9.6 (8.4 to 10.8)	9.4 (8.2 to 10.6)		
Week 24	10.0 (8.8 to 11.2)	8.7 (7.5 to 9.9)		
Week 28	9.8 (8.6 to 11.1)	9.4 (8.2 to 10.6)		
Week 32	10.3 (9.1 to 11.5)	8.9 (7.7 to 10.1)		
Week 36	9.6 (8.4 to 10.9)	9.4 (8.2 to 10.7)		

Week 40	9.9 (8.7 to 11.2)	9.2 (7.9 to 10.4)		
Week 44	10.6 (9.3 to 11.8)	9.5 (8.3 to 10.8)		
Week 48	10.1 (8.8 to 11.3)	9.6 (8.3 to 10.9)		
Week 52	10.6 (9.3 to 11.9)	9.4 (8.1 to 10.7)		
Week 56	10.7 (9.3 to 12.0)	9.5 (8.2 to 10.9)		
Week 60	10.5 (9.1 to 11.9)	9.3 (8.0 to 10.7)		
Week 64	11.0 (9.7 to 12.3)	9.5 (8.2 to 10.8)		
Week 68	11.0 (9.6 to 12.3)	9.5 (8.2 to 10.8)		
Week 72	11.0 (9.6 to 12.3)	9.4 (8.1 to 10.8)		
Week 76	10.5 (9.2 to 11.8)	9.8 (8.4 to 11.1)		
Week 80	10.2 (8.9 to 11.6)	9.4 (8.1 to 10.8)		
Week 84	10.9 (9.4 to 12.4)	8.9 (7.4 to 10.4)		
Week 88	10.7 (9.1 to 12.4)	8.6 (7.0 to 10.2)		
Week 92	10.7 (9.1 to 12.2)	9.3 (7.7 to 10.8)		
Week 96	10.7 (9.1 to 12.3)	8.5 (6.8 to 10.1)		
Week 100	10.9 (9.3 to 12.6)	8.4 (6.7 to 10.1)		

Statistical analyses

Statistical analysis title	BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	LS mean difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	3.1
Variability estimate	Standard error of the mean
Dispersion value	0.94

Notes:

[9] - Treatment Difference

Statistical analysis title	BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	LS mean difference
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	4.9
Variability estimate	Standard error of the mean
Dispersion value	1.21

Notes:

[10] - Treatment Difference

Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 4 to Week 52/100 for the study eye

End point title	Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 4 to Week 52/100 for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the periods: Week 4 through Week 52, Week 4 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, period Week 4 through Week 52, period Week 4 through Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
period Week 4 through Week 52	9.1 (8.2 to 10.1)	8.4 (7.4 to 9.3)		
period Week 4 through Week 100	9.8 (8.8 to 10.9)	8.7 (7.7 to 9.8)		

Statistical analyses

Statistical analysis title	BCVA over period Week 4 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	LS mean difference
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.6
Variability estimate	Standard error of the mean
Dispersion value	0.78

Notes:

[11] - Treatment difference

Statistical analysis title	BCVA over period Week 4 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	LS mean difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	2.1
Variability estimate	Standard error of the mean
Dispersion value	0.7

Notes:

[12] - Treatment difference

Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 20 to Week 52/100 and Week 28 to Week 52/100 for the study eye

End point title	Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 20 to Week 52/100 and Week 28 to Week 52/100 for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the periods: Week 20 through Week 52, Week 20 through Week 100, Week 28 through Week 52, Week 28 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, period Week 20 through Week 52, period Week 20 through Week 100, period Week 28 through Week 52, period Week 28 through Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)				
period Week 20 through Week 52	10.1 (8.9 to 11.2)	9.3 (8.1 to 10.4)		
period Week 20 through Week 100	10.4 (9.2 to 11.7)	9.2 (8.0 to 10.4)		
period Week 28 through Week 52	10.1 (9.0 to 11.3)	9.4 (8.2 to 10.5)		
period Week 28 through Week 100	10.5 (9.3 to 11.7)	9.2 (8.0 to 10.5)		

Statistical analyses

Statistical analysis title	BCVA over period Week 20 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	LS mean difference
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2.4
Variability estimate	Standard error of the mean
Dispersion value	0.83

Notes:

[13] - Treatment difference

Statistical analysis title	BCVA over period Week 28 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	LS mean difference
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	2.5
Variability estimate	Standard error of the mean
Dispersion value	0.85

Notes:

[14] - Treatment difference

Statistical analysis title	BCVA over period Week 20 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[15]
Parameter estimate	LS mean difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	2.9
Variability estimate	Standard error of the mean
Dispersion value	0.87

Notes:

[15] - Treatment difference

Statistical analysis title	BCVA over period Week 28 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[16]
Parameter estimate	LS mean difference
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	3
Variability estimate	Standard error of the mean
Dispersion value	0.89

Notes:

[16] - Treatment difference

Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 88 to 100 for the study eye

End point title	Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 88 to 100 for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the period Week 88 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, period Week 88 through Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Scores on a scale				
least squares mean (confidence interval 95%)	10.8 (9.2 to 12.3)	8.7 (7.1 to 10.2)		

Statistical analyses

Statistical analysis title	BCVA over period Week 88 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[17]
Parameter estimate	LS mean difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	4.3
Variability estimate	Standard error of the mean
Dispersion value	1.12

Notes:

[17] - Treatment difference

Secondary: Percentage of participants who gained >= 5 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-baseline visit for the study eye

End point title	Percentage of participants who gained >= 5 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity

testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	49.2 (41.6 to 56.7)	46.4 (39.0 to 54.0)		
Week 6	62.0 (54.5 to 69.1)	62.4 (54.9 to 69.5)		
Week 8	67.6 (60.2 to 74.4)	63.5 (56.1 to 70.5)		
Week 12	70.9 (63.7 to 77.5)	73.5 (66.4 to 79.8)		
Week 16	71.5 (64.3 to 78.0)	73.5 (66.4 to 79.8)		
Week 18	77.7 (70.8 to 83.5)	77.9 (71.1 to 83.7)		
Week 20	79.3 (72.7 to 85.0)	76.2 (69.4 to 82.2)		
Week 24	79.9 (73.3 to 85.5)	77.9 (71.1 to 83.7)		
Week 28	75.4 (68.4 to 81.5)	77.9 (71.1 to 83.7)		
Week 32	77.1 (70.2 to 83.0)	80.7 (74.1 to 86.1)		
Week 36	74.3 (67.2 to 80.5)	80.7 (74.1 to 86.1)		
Week 40	74.9 (67.8 to 81.0)	79.6 (72.9 to 85.2)		
Week 44	74.3 (67.2 to 80.5)	80.7 (74.1 to 86.1)		
Week 48	76.0 (69.0 to 82.0)	79.0 (72.3 to 84.7)		
Week 52	77.7 (70.8 to 83.5)	79.0 (72.3 to 84.7)		
Week 56	77.7 (70.8 to 83.5)	80.7 (74.1 to 86.1)		
Week 60	76.0 (69.0 to 82.0)	79.0 (72.3 to 84.7)		
Week 64	78.2 (71.4 to 84.0)	79.0 (72.3 to 84.7)		
Week 68	77.7 (70.8 to 83.5)	76.8 (70.0 to 82.7)		
Week 72	79.9 (73.3 to 85.5)	77.3 (70.6 to 83.2)		

Week 76	74.3 (67.2 to 80.5)	77.3 (70.6 to 83.2)		
Week 80	74.3 (67.2 to 80.5)	75.7 (68.8 to 81.7)		
Week 84	78.2 (71.4 to 84.0)	73.5 (66.4 to 79.8)		
Week 88	77.7 (70.8 to 83.5)	75.7 (68.8 to 81.7)		
Week 92	79.3 (72.7 to 85.0)	74.0 (67.0 to 80.3)		
Week 96	78.8 (72.0 to 84.5)	73.5 (66.4 to 79.8)		
Week 100	77.1 (70.2 to 83.0)	73.5 (66.4 to 79.8)		

Statistical analyses

Statistical analysis title	Gain of >= 5 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[18]
Parameter estimate	Clopper-Pearson exact method
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	14.5

Notes:

[18] - Treatment difference

Statistical analysis title	Gain of >= 5 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[19]
Parameter estimate	Clopper-Pearson exact method
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	8.9

Notes:

[19] - Treatment difference

Secondary: Percentage of participants who gained >= 10 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-baseline visit for the study eye

End point title	Percentage of participants who gained >= 10 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-

	baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	22.9 (17.0 to 29.8)	23.8 (17.8 to 30.6)		
Week 6	34.6 (27.7 to 42.1)	31.5 (24.8 to 38.8)		
Week 8	39.7 (32.4 to 47.2)	36.5 (29.5 to 43.9)		
Week 12	43.0 (35.7 to 50.6)	45.9 (39.4 to 53.4)		
Week 16	44.1 (36.7 to 51.7)	49.7 (42.2 to 57.2)		
Week 18	47.5 (40.0 to 55.1)	53.0 (45.5 to 60.5)		
Week 20	53.1 (45.5 to 60.6)	56.9 (49.4 to 64.2)		
Week 24	56.4 (48.8 to 63.8)	53.6 (46.0 to 61.0)		
Week 28	55.3 (47.7 to 62.7)	55.2 (47.7 to 62.6)		
Week 32	58.7 (51.1 to 66.0)	51.9 (44.4 to 59.4)		
Week 36	57.5 (49.9 to 64.9)	55.2 (47.7 to 62.6)		
Week 40	58.1 (50.5 to 65.4)	52.5 (44.9 to 59.9)		
Week 44	61.5 (53.9 to 68.6)	56.9 (49.4 to 64.2)		
Week 48	60.9 (53.3 to 68.1)	53.0 (45.5 to 60.5)		
Week 52	61.5 (53.9 to 68.6)	58.6 (51.0 to 65.8)		
Week 56	62.0 (54.5 to 69.1)	54.1 (46.6 to 61.6)		
Week 60	61.5 (53.9 to 68.6)	54.7 (47.1 to 62.1)		
Week 64	63.7 (56.2 to 70.7)	56.9 (49.4 to 64.2)		

Week 68	62.0 (54.5 to 69.1)	57.5 (49.9 to 64.8)		
Week 72	63.7 (56.2 to 70.7)	56.4 (48.8 to 63.7)		
Week 76	60.9 (53.3 to 68.1)	56.9 (49.4 to 64.2)		
Week 80	57.5 (49.9 to 64.9)	55.8 (48.2 to 63.2)		
Week 84	63.7 (56.2 to 70.7)	58.6 (51.0 to 65.8)		
Week 88	61.5 (53.9 to 68.6)	58.0 (50.5 to 65.3)		
Week 92	63.7 (56.2 to 70.7)	58.6 (51.0 to 65.8)		
Week 96	62.6 (55.0 to 69.7)	56.9 (49.4 to 64.2)		
Week 100	61.5 (53.9 to 68.6)	54.1 (46.6 to 61.6)		

Statistical analyses

Statistical analysis title	Gain of >= 10 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[20]
Parameter estimate	Clopper-Pearson exact method
Point estimate	9.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	19.4

Notes:

[20] - Treatment difference

Statistical analysis title	Gain of >= 10 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[21]
Parameter estimate	Clopper-Pearson exact method
Point estimate	5.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	14.7

Notes:

[21] - Treatment difference

Secondary: Percentage of participants who gained >= 15 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-baseline visit for the study eye

End point title	Percentage of participants who gained >= 15 letters in BCVA from Baseline or reached BCVA >= 84 letters at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	12.3 (7.9 to 18.0)	9.4 (5.6 to 14.6)		
Week 6	13.4 (8.8 to 19.3)	13.8 (9.1 to 19.7)		
Week 8	25.1 (19.0 to 32.2)	16.0 (11.0 to 22.2)		
Week 12	25.1 (19.0 to 32.2)	22.1 (16.3 to 28.9)		
Week 16	33.5 (26.7 to 40.9)	25.4 (19.2 to 32.4)		
Week 18	31.8 (25.1 to 39.2)	33.1 (26.3 to 40.5)		
Week 20	34.6 (27.7 to 42.1)	32.6 (25.8 to 39.9)		
Week 24	41.9 (34.6 to 49.5)	30.9 (24.3 to 38.2)		
Week 28	40.2 (33.0 to 47.8)	37.0 (30.0 to 44.5)		
Week 32	44.1 (36.7 to 51.7)	30.4 (23.8 to 37.6)		
Week 36	45.3 (37.8 to 52.8)	32.6 (25.8 to 39.9)		
Week 40	44.7 (37.3 to 52.3)	31.5 (24.8 to 38.8)		
Week 44	50.3 (42.7 to 57.8)	35.4 (28.4 to 42.8)		
Week 48	41.9 (34.6 to 49.5)	37.0 (30.0 to 44.5)		
Week 52	46.4 (38.9 to 54.0)	37.6 (30.5 to 45.1)		

Week 56	46.4 (38.9 to 54.0)	35.9 (28.9 to 43.4)		
Week 60	46.9 (39.4 to 54.5)	38.7 (31.5 to 46.2)		
Week 64	50.3 (42.7 to 57.8)	36.5 (29.5 to 43.9)		
Week 68	48.6 (41.1 to 56.2)	35.9 (28.9 to 43.4)		
Week 72	48.0 (40.5 to 55.6)	35.4 (28.4 to 42.8)		
Week 76	46.4 (38.9 to 54.0)	40.9 (33.6 to 48.4)		
Week 80	43.6 (36.2 to 51.2)	37.6 (30.5 to 45.1)		
Week 84	46.4 (38.9 to 54.0)	37.0 (30.0 to 44.5)		
Week 88	47.5 (40.0 to 55.1)	40.9 (33.6 to 48.4)		
Week 92	44.7 (37.3 to 52.3)	40.3 (33.1 to 47.9)		
Week 96	46.9 (39.4 to 54.5)	38.1 (31.0 to 45.6)		
Week 100	49.7 (42.2 to 57.3)	37.6 (30.5 to 45.1)		

Statistical analyses

Statistical analysis title	Gain of >= 15 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[22]
Parameter estimate	Clopper-Pearson exact method
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	20.2

Notes:

[22] - Treatment difference

Statistical analysis title	Gain of >= 15 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[23]
Parameter estimate	Clopper-Pearson exact method
Point estimate	13.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.3
upper limit	23.5

Notes:

[23] - Treatment difference

Secondary: Percentage of participants who lost >= 5 ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point title	Percentage of participants who lost >= 5 ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	3.4 (1.2 to 7.2)	4.4 (1.9 to 8.5)		
Week 6	1.7 (0.3 to 4.8)	3.3 (1.2 to 7.1)		
Week 8	1.1 (0.1 to 4.0)	2.8 (0.9 to 6.3)		
Week 12	1.1 (0.1 to 4.0)	2.2 (0.6 to 5.6)		
Week 16	0.6 (0.0 to 3.1)	2.2 (0.6 to 5.6)		
Week 18	1.1 (0.1 to 4.0)	1.1 (0.1 to 3.9)		
Week 20	2.2 (0.6 to 5.6)	2.8 (0.9 to 6.3)		
Week 24	1.7 (0.3 to 4.8)	3.3 (1.2 to 7.1)		
Week 28	1.7 (0.3 to 4.8)	2.2 (0.6 to 5.6)		
Week 32	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		
Week 36	4.5 (1.9 to 8.6)	1.1 (0.1 to 3.9)		
Week 40	3.9 (1.6 to 7.9)	2.2 (0.6 to 5.6)		
Week 44	2.8 (0.9 to 6.4)	2.2 (0.6 to 5.6)		
Week 48	2.8 (0.9 to 6.4)	2.8 (0.9 to 6.3)		
Week 52	3.4 (1.2 to 7.2)	3.3 (1.2 to 7.1)		
Week 56	5.0 (2.3 to 9.3)	3.3 (1.2 to 7.1)		
Week 60	3.9 (1.6 to 7.9)	4.4 (1.9 to 8.5)		

Week 64	2.8 (0.9 to 6.4)	3.3 (1.2 to 7.1)		
Week 68	3.9 (1.6 to 7.9)	2.8 (0.9 to 6.3)		
Week 72	4.5 (1.9 to 8.6)	5.0 (2.3 to 9.2)		
Week 76	3.4 (1.2 to 7.2)	4.4 (1.9 to 8.5)		
Week 80	2.8 (0.9 to 6.4)	6.1 (3.1 to 10.6)		
Week 84	3.4 (1.2 to 7.2)	7.7 (4.3 to 12.6)		
Week 88	3.9 (1.6 to 7.9)	7.2 (3.9 to 12.0)		
Week 92	3.4 (1.2 to 7.2)	6.6 (3.5 to 11.3)		
Week 96	3.9 (1.6 to 7.9)	7.2 (3.9 to 12.0)		
Week 100	2.8 (0.9 to 6.4)	8.3 (4.7 to 13.3)		

Statistical analyses

Statistical analysis title	Loss of >= 5 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[24]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	2.9

Notes:

[24] - Treatment difference

Statistical analysis title	Loss of >= 5 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[25]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	-1.7

Notes:

[25] - Treatment difference

Secondary: Percentage of participants who lost >= 10 ETDRS letters in Best

Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point title	Percentage of participants who lost >= 10 ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	999 (999 to 999)	1.1 (0.1 to 3.9)		
Week 6	1.1 (0.1 to 4.0)	0.6 (0.0 to 3.0)		
Week 8	1.1 (0.1 to 4.0)	999 (999 to 999)		
Week 12	999 (999 to 999)	0.6 (0.0 to 3.0)		
Week 16	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 18	1.1 (0.1 to 4.0)	999 (999 to 999)		
Week 20	1.7 (0.3 to 4.8)	999 (999 to 999)		
Week 24	1.7 (0.3 to 4.8)	1.1 (0.1 to 3.9)		
Week 28	1.7 (0.3 to 4.8)	999 (999 to 999)		
Week 32	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 36	3.4 (1.2 to 7.2)	999 (999 to 999)		
Week 40	2.8 (0.9 to 6.4)	999 (999 to 999)		
Week 44	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 48	2.2 (0.6 to 5.6)	0.6 (0.0 to 3.0)		
Week 52	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		
Week 56	2.2 (0.6 to 5.6)	1.1 (0.1 to 3.9)		
Week 60	1.7 (0.3 to 4.8)	1.7 (0.3 to 4.8)		
Week 64	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 68	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 72	2.2 (0.6 to 5.6)	1.7 (0.3 to 4.8)		

Week 76	2.2 (0.6 to 5.6)	0.6 (0.0 to 3.0)		
Week 80	1.7 (0.3 to 4.8)	1.7 (0.3 to 4.8)		
Week 84	2.2 (0.6 to 5.6)	4.4 (1.9 to 8.5)		
Week 88	2.8 (0.9 to 6.4)	3.9 (1.6 to 7.8)		
Week 92	2.8 (0.9 to 6.3)	2.8 (0.9 to 6.3)		
Week 96	2.2 (0.6 to 5.6)	3.9 (1.6 to 7.8)		
Week 100	2.2 (0.6 to 5.6)	6.1 (3.1 to 10.6)		

Statistical analyses

Statistical analysis title	Loss of >= 10 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[26]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	2.4

Notes:

[26] - Treatment difference

Statistical analysis title	Loss of >= 10 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[27]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	-0.1

Notes:

[27] - Treatment difference

Secondary: Percentage of participants who lost >= 15 ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point title	Percentage of participants who lost >= 15 ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were

taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	999 (999 to 999)	0.6 (0.0 to 3.0)		
Week 6	1.1 (0.1 to 4.0)	999 (999 to 999)		
Week 8	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 12	999 (999 to 999)	0.6 (0.0 to 3.0)		
Week 16	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 18	1.1 (0.1 to 4.0)	999 (999 to 999)		
Week 20	1.7 (0.3 to 4.8)	999 (999 to 999)		
Week 24	1.1 (0.1 to 4.0)	0.6 (0.0 to 3.0)		
Week 28	1.7 (0.3 to 4.8)	999 (999 to 999)		
Week 32	1.7 (0.3 to 4.8)	999 (999 to 999)		
Week 36	2.8 (0.9 to 6.4)	999 (999 to 999)		
Week 40	2.2 (0.6 to 5.6)	999 (999 to 999)		
Week 44	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 48	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 52	1.1 (0.1 to 4.0)	1.7 (0.3 to 4.8)		
Week 56	1.7 (0.3 to 4.8)	1.1 (0.1 to 3.9)		
Week 60	1.7 (0.3 to 4.8)	1.7 (0.3 to 4.8)		
Week 64	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 68	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 72	2.2 (0.6 to 5.6)	1.1 (0.1 to 3.9)		
Week 76	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 80	1.7 (0.3 to 4.8)	0.6 (0.0 to 3.0)		
Week 84	1.7 (0.3 to 4.8)	2.2 (0.6 to 5.6)		
Week 88	1.7 (0.3 to 4.8)	2.2 (0.6 to 5.6)		
Week 92	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		
Week 96	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		

Week 100	2.2 (0.6 to 5.6)	3.3 (1.2 to 7.1)		

Statistical analyses

Statistical analysis title	Loss of >= 15 letters in BCVA at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[28]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.6

Notes:

[28] - Treatment difference

Statistical analysis title	Loss of >= 15 letters in BCVA at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[29]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	2

Notes:

[29] - Treatment difference

Secondary: Percentage of participants with an Absolute Best Corrected Visual Acuity (BCVA) >= 73 ETDRS letters at each post-baseline visit for the study eye

End point title	Percentage of participants with an Absolute Best Corrected Visual Acuity (BCVA) >= 73 ETDRS letters at each post-baseline visit for the study eye

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	55.3 (47.7 to 62.7)	42.5 (35.2 to 50.1)		
Week 6	64.8 (57.3 to 71.8)	49.7 (42.2 to 57.2)		
Week 8	66.5 (59.1 to 73.3)	50.8 (43.3 to 58.3)		
Week 12	66.5 (59.1 to 73.3)	59.7 (52.1 to 66.9)		
Week 16	69.8 (62.5 to 76.5)	60.8 (53.3 to 67.9)		
Week 18	71.5 (64.3 to 78.0)	64.6 (57.2 to 71.6)		
Week 20	71.5 (64.3 to 78.0)	61.3 (53.8 to 68.5)		
Week 24	73.2 (66.1 to 79.5)	60.2 (52.7 to 67.4)		
Week 28	72.6 (65.5 to 79.0)	61.9 (54.4 to 69.0)		
Week 32	73.7 (66.7 to 80.0)	59.1 (51.6 to 66.4)		
Week 36	70.4 (63.1 to 77.0)	65.2 (57.8 to 72.1)		
Week 40	69.8 (62.5 to 76.5)	60.2 (52.7 to 67.4)		
Week 44	73.7 (66.7 to 80.0)	63.5 (56.1 to 70.5)		
Week 48	70.9 (63.7 to 77.5)	61.3 (53.8 to 68.5)		
Week 52	73.7 (66.7 to 80.0)	64.6 (57.2 to 71.6)		
Week 56	72.6 (65.5 to 79.0)	66.9 (59.5 to 73.7)		
Week 60	70.9 (63.7 to 77.5)	66.9 (59.5 to 73.7)		
Week 64	74.3 (67.2 to 80.5)	68.5 (61.2 to 75.2)		
Week 68	71.5 (64.3 to 78.0)	66.3 (58.9 to 73.1)		
Week 72	73.7 (66.7 to 80.0)	65.2 (57.8 to 72.1)		
Week 76	72.6 (65.5 to 79.0)	66.9 (59.5 to 73.7)		
Week 80	70.9 (63.7 to 77.5)	64.1 (56.6 to 71.1)		
Week 84	70.9 (63.7 to 77.5)	65.2 (57.8 to 72.1)		

Week 88	72.6 (65.5 to 79.0)	63.5 (56.1 to 70.5)		
Week 92	71.5 (64.3 to 78.0)	63.5 (56.1 to 70.5)		
Week 96	70.4 (63.1 to 77.0)	62.4 (54.9 to 69.5)		
Week 100	70.9 (63.7 to 77.5)	62.4 (54.9 to 69.5)		

Statistical analyses

Statistical analysis title	Absolute BCVA >= 73 letters at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[30]
Parameter estimate	Clopper-Pearson exact method
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	12.6

Notes:

[30] - Treatment difference

Statistical analysis title	Absolute BCVA >= 73 letters at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[31]
Parameter estimate	Clopper-Pearson exact method
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	12

Notes:

[31] - Treatment difference

Secondary: Mean change from Baseline in Central Subfield Thickness (CSFT) at each post-baseline visit for the study eye

End point title	Mean change from Baseline in Central Subfield Thickness (CSFT) at each post-baseline visit for the study eye

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were

censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Micrometers				
arithmetic mean (standard deviation)				
Week 4	-128.2 (± 131.47)	-113.9 (± 123.20)		
Week 6	-136.9 (± 135.57)	-126.0 (± 124.82)		
Week 8	-155.4 (± 139.09)	-130.8 (± 124.71)		
Week 12	-160.8 (± 137.23)	-137.9 (± 132.30)		
Week 16	-179.1 (± 137.26)	-145.3 (± 132.63)		
Week 18	-175.8 (± 139.10)	-149.0 (± 132.28)		
Week 20	-183.7 (± 139.76)	-151.0 (± 130.98)		
Week 24	-183.3 (± 143.14)	-134.0 (± 136.67)		
Week 28	-192.0 (± 145.85)	-161.4 (± 131.27)		
Week 32	-178.6 (± 138.5)	-144.9 (± 135.93)		
Week 36	-163.5 (± 144.34)	-162.9 (± 135.19)		
Week 40	-183.3 (± 139.84)	-149.9 (± 132.66)		
Week 44	-193.3 (± 144.12)	-163.5 (± 133.01)		
Week 48	-172.8 (± 141.83)	-154.6 (± 130.54)		
Week 52	-196.5 (± 144.44)	-165.0 (± 134.77)		
Week 56	-191.08 (± 148.02)	-162.4 (± 132.53)		
Week 60	-189.8 (± 147.93)	-166.2 (± 132.61)		
Week 64	-193.2 (± 143.36)	-160.2 (± 137.83)		
Week 68	-194.5 (± 141.47)	-169.8 (± 143.97)		
Week 72	-190.4 (± 142.25)	-165.1 (± 141.38)		
Week 76	-185.6 (± 143.68)	-174.7 (± 138.70)		
Week 80	-185.7 (± 145.52)	-171.1 (± 138.53)		

Week 84	-193.5 (± 142.53)	-175.1 (± 139.76)		
Week 88	-191.0 (± 141.29)	-172.2 (± 138.08)		
Week 92	-193.8 (± 142.07)	-180.1 (± 138.88)		
Week 96	-197.2 (± 144.29)	-170.2 (± 154.37)		
Week 100	-201.4 (± 142.90)	-173.9 (± 152.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average mean change from Baseline in Central Subfield Thickness (CSFT) over the period Week 40 through Week 52 / Week 88 through Week 100 for the study eye

End point title	Average mean change from Baseline in Central Subfield Thickness (CSFT) over the period Week 40 through Week 52 / Week 88 through Week 100 for the study eye

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment. For each participants, this endpoint was derived as the average of the changes from Baseline to Weeks 40, 44, 48, 52. Then the same was derived over the period Week 88 through Week 100, considering the average of the changes from Baseline to Weeks 88, 92, 96, 100. This endpoint was only assessed in the year-2 analysis (Week 100).

End point type	Secondary

End point timeframe:

Baseline, period Week 40 through Week 52, period Week 88 through Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Micrometers				
least squares mean (confidence interval 95%)				
period Week 40 through Week 52	-187.1 (-200.7 to -173.5)	-157.7 (-171.2 to -144.1)		
period Week 88 through Week 100	-196.6 (-210.9 to -182.3)	-173.4 (-187.6 to -159.1)		

Statistical analyses

Statistical analysis title	CSFT over period Week 40 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.003
Method	ANOVA
Parameter estimate	LS mean difference
Point estimate	-29.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.6
upper limit	-10.2
Variability estimate	Standard error of the mean
Dispersion value	9.76

Notes:

[32] - Treatment difference

Statistical analysis title	CSFT over period Week 40 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	ANOVA

Statistical analysis title	CSFT over period Week 88 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[33]
Parameter estimate	LS mean difference
Point estimate	-23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.5
upper limit	-3
Variability estimate	Standard error of the mean
Dispersion value	10.28

Notes:

[33] - Treatment difference

Secondary: Average mean change from baseline in CSFT over the period Week 4 to Week 52 / 100 for the study eye

End point title	Average mean change from baseline in CSFT over the period Week 4 to Week 52 / 100 for the study eye

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, period Week 4 through Week 52, period Week 4 through Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Micrometers				
least squares mean (confidence interval 95%)				
period Week 4 through Week 52	-172.8 (-185.8 to -159.8)	-145.4 (-158.4 to -132.4)		
period Week 4 through Week 100	-181.8 (-194.7 to -168.9)	-156.1 (-169.0 to -143.2)		

Statistical analyses

Statistical analysis title	CSFT over period Week 4 through Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[34]
Parameter estimate	LS mean difference
Point estimate	-27.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.8
upper limit	-9
Variability estimate	Standard error of the mean
Dispersion value	9.35

Notes:

[34] - Treatment difference

Statistical analysis title	CSFT over period Week 4 through Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[35]
Parameter estimate	LS mean difference
Point estimate	-25.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44
upper limit	-7.5
Variability estimate	Standard error of the mean
Dispersion value	9.29

Notes:

[35] - Treatment difference

Secondary: Percentage of participants with normal CSFT thickness (<280 micrometers) at each post-baseline visit for the study eye

End point title	Percentage of participants with normal CSFT thickness (<280 micrometers) at each post-baseline visit for the study eye

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	12.8 (8.3 to 18.7)	13.3 (8.7 to 19.2)		
Week 6	16.8 (11.6 to 23.1)	14.4 (9.7 to 20.4)		
Week 8	22.9 (17.0 to 29.8)	16.7 (11.5 to 22.9)		
Week 12	30.2 (23.5 to 37.5)	24.4 (18.4 to 31.4)		
Week 16	36.9 (29.8 to 44.4)	29.4 (22.9 to 36.7)		
Week 18	39.1 (31.9 to 46.7)	30.0 (23.4 to 37.3)		
Week 20	42.5 (35.1 to 50.1)	31.1 (24.4 to 38.4)		
Week 24	48.6 (41.1 to 56.2)	29.4 (22.9 to 36.7)		

Week 28	50.3 (42.7 to 57.8)	33.9 (27.0 to 41.3)		
Week 32	48.0 (40.5 to 55.6)	30.6 (23.9 to 37.8)		
Week 36	38.5 (31.4 to 46.1)	38.9 (31.7 to 46.4)		
Week 40	51.4 (43.8 to 58.9)	37.2 (30.1 to 44.7)		
Week 44	51.4 (43.8 to 58.9)	38.9 (31.7 to 46.4)		
Week 48	49.7 (42.2 to 57.3)	37.2 (30.1 to 44.7)		
Week 52	57.5 (49.9 to 64.9)	41.4 (34.2 to 49.0)		
Week 56	57.5 (49.9 to 64.9)	40.3 (33.1 to 47.9)		
Week 60	53.1 (45.5 to 60.6)	40.3 (33.1 to 47.9)		
Week 64	54.2 (46.6 to 61.6)	38.1 (31.0 to 45.6)		
Week 68	53.6 (46.0 to 61.1)	41.4 (34.2 to 49.0)		
Week 72	56.4 (48.8 to 63.8)	38.7 (31.5 to 46.2)		
Week 76	55.3 (47.7 to 62.7)	42.5 (35.2 to 50.1)		
Week 80	57.0 (49.4 to 64.3)	39.8 (32.6 to 47.3)		
Week 84	57.0 (49.4 to 64.3)	43.1 (35.8 to 50.6)		
Week 88	56.4 (48.8 to 63.8)	41.4 (34.2 to 49.0)		
Week 92	57.0 (49.4 to 64.3)	45.9 (38.4 to 53.4)		
Week 96	59.8 (52.2 to 67.0)	43.6 (36.3 to 51.2)		
Week 100	62.0 (54.5 to 69.1)	47.0 (39.5 to 54.5)		

Statistical analyses

Statistical analysis title	CSFT thickness (<280 micrometers) at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[36]
Parameter estimate	Clopper-Pearson exact method
Point estimate	14.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.2
upper limit	24.9

Notes:
[36] - Treatment difference

Statistical analysis title	CSFT thickness (<280 micrometers) at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[37]
Parameter estimate	Clopper-Pearson exact method
Point estimate	16.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	25.9

Notes:
[37] - Treatment difference

Secondary: Percentage of patients with presence of Subretinal Fluid (SRF) in the study eye at each post-baseline visit

End point title	Percentage of patients with presence of Subretinal Fluid (SRF) in the study eye at each post-baseline visit

End point description:

Presence of Subretinal Fluid (SRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Subretinal fluid status assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	12.3 (7.9 to 18.0)	19.3 (13.9 to 25.9)		
Week 6	10.1 (6.1 to 15.4)	13.8 (9.1 to 19.7)		
Week 8	5.6 (2.7 to 10.0)	12.2 (7.8 to 17.8)		
Week 12	3.9 (1.6 to 7.9)	7.7 (4.3 to 12.6)		
Week 16	1.7 (0.3 to 4.8)	3.9 (1.6 to 7.8)		
Week 18	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		
Week 20	1.7 (0.3 to 4.8)	3.3 (1.2 to 7.1)		

Week 24	2.2 (0.6 to 5.6)	6.6 (3.5 to 11.3)		
Week 28	2.2 (0.6 to 5.6)	2.8 (0.9 to 6.3)		
Week 32	5.0 (2.3 to 9.3)	3.9 (1.6 to 7.8)		
Week 36	6.7 (3.5 to 11.4)	1.7 (0.3 to 4.8)		
Week 40	4.5 (1.9 to 8.6)	2.8 (0.9 to 6.3)		
Week 44	2.2 (0.6 to 5.6)	2.8 (0.9 to 6.3)		
Week 48	6.1 (3.1 to 10.7)	5.0 (2.3 to 9.2)		
Week 52	1.7 (0.3 to 4.8)	3.3 (1.2 to 7.1)		
Week 56	2.8 (0.9 to 6.4)	2.2 (0.6 to 5.6)		
Week 60	2.8 (0.9 to 6.4)	2.2 (0.6 to 5.6)		
Week 64	2.2 (0.6 to 5.6)	3.9 (1.6 to 7.8)		
Week 68	3.4 (1.2 to 7.2)	4.4 (1.9 to 8.5)		
Week 72	3.4 (1.2 to 7.2)	2.8 (0.9 to 6.3)		
Week 76	3.9 (1.6 to 7.9)	2.2 (0.6 to 5.6)		
Week 80	4.5 (1.9 to 8.6)	2.2 (0.6 to 5.6)		
Week 84	2.2 (0.6 to 5.6)	2.2 (0.6 to 5.6)		
Week 88	3.4 (1.2 to 7.2)	2.2 (0.6 to 5.6)		
Week 92	1.7 (0.3 to 4.8)	1.1 (0.1 to 3.9)		
Week 96	2.2 (0.6 to 5.6)	2.8 (0.9 to 6.3)		
Week 100	2.2 (0.6 to 5.6)	2.8 (0.9 to 6.3)		

Statistical analyses

Statistical analysis title	Subretinal Fluid (SRF) at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[38]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	2.1

Notes:

[38] - Treatment Difference

Statistical analysis title	Subretinal Fluid (SRF) at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[39]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.4

Notes:

[39] - Treatment Difference

Secondary: Percentage of patients with presence of Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

End point title	Percentage of patients with presence of Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

End point description:

Presence of Intraretinal Fluid (IRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Intraretinal fluid status assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	88.3 (82.6 to 92.6)	89.0 (83.5 to 93.1)		
Week 6	85.5 (79.4 to 90.3)	86.2 (80.3 to 90.9)		
Week 8	87.2 (81.3 to 91.7)	84.5 (78.4 to 89.5)		
Week 12	83.8 (77.6 to 88.9)	85.6 (79.7 to 90.4)		
Week 16	76.0 (69.0 to 82.0)	84.0 (77.8 to 89.0)		
Week 18	77.7 (70.8 to 83.5)	81.2 (74.8 to 86.6)		
Week 20	72.6 (65.5 to 79.0)	79.6 (72.9 to 85.2)		
Week 24	69.8 (62.5 to 76.5)	82.3 (76.0 to 87.6)		
Week 28	67.6 (60.2 to 74.4)	75.1 (68.2 to 81.3)		
Week 32	67.6 (60.2 to 74.4)	76.8 (70.0 to 82.7)		
Week 36	73.2 (66.1 to 79.5)	72.4 (65.3 to 78.7)		
Week 40	57.5 (49.9 to 64.9)	74.0 (67.0 to 80.3)		
Week 44	56.4 (48.8 to 63.8)	71.3 (64.1 to 77.7)		

Week 48	60.9 (53.3 to 68.1)	75.7 (68.8 to 81.7)		
Week 52	53.6 (46.0 to 61.1)	72.9 (65.8 to 79.3)		
Week 56	51.4 (43.8 to 58.9)	70.2 (62.9 to 76.7)		
Week 60	55.3 (47.7 to 62.7)	69.1 (61.8 to 75.7)		
Week 64	48.6 (41.1 to 56.2)	69.6 (62.4 to 76.2)		
Week 68	47.5 (40.0 to 55.1)	66.9 (59.5 to 73.7)		
Week 72	45.8 (38.4 to 53.4)	66.9 (59.5 to 73.7)		
Week 76	50.3 (42.7 to 57.8)	63.0 (55.5 to 70.0)		
Week 80	45.8 (38.4 to 53.4)	65.7 (58.3 to 72.6)		
Week 84	40.2 (33.0 to 47.8)	63.0 (55.5 to 70.0)		
Week 88	48.0 (40.5 to 55.6)	64.1 (56.6 to 71.1)		
Week 92	44.7 (37.3 to 52.3)	59.1 (51.6 to 66.4)		
Week 96	41.3 (34.0 to 48.9)	61.9 (54.4 to 69.0)		
Week 100	40.8 (33.5 to 48.4)	56.9 (49.4 to 64.2)		

Statistical analyses

Statistical analysis title	Intraretinal Fluid (IRF) at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[40]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-16.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.3
upper limit	-5.7

Notes:

[40] - Treatment Difference

Statistical analysis title	Intraretinal Fluid (IRF) at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[41]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-19.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.9
upper limit	-9.2

Notes:

[41] - Treatment Difference

Secondary: Percentage of patients with presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

End point title	Percentage of patients with presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

End point description:

Presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Fluid status (SRF and/or IRF) assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 4	90.5 (85.2 to 94.4)	90.6 (85.4 to 94.4)		
Week 6	86.6 (80.7 to 91.2)	88.4 (82.8 to 92.7)		
Week 8	87.2 (81.3 to 91.7)	85.6 (79.7 to 90.4)		
Week 12	83.8 (77.6 to 88.9)	86.2 (80.3 to 90.9)		
Week 16	76.0 (69.0 to 82.0)	84.0 (77.8 to 89.0)		
Week 18	78.2 (71.4 to 84.0)	81.2 (74.8 to 86.6)		
Week 20	73.2 (66.1 to 79.5)	79.6 (72.9 to 85.2)		
Week 24	70.4 (63.1 to 77.0)	82.3 (76.0 to 87.6)		
Week 28	68.7 (61.4 to 75.4)	75.1 (68.2 to 81.3)		

Week 32	68.7 (61.4 to 75.4)	76.8 (70.0 to 82.7)		
Week 36	73.7 (66.7 to 80.0)	72.4 (65.3 to 78.7)		
Week 40	58.1 (50.5 to 65.4)	74.0 (67.0 to 80.3)		
Week 44	57.0 (49.4 to 64.3)	71.3 (64.1 to 77.7)		
Week 48	61.5 (53.9 to 68.6)	75.7 (68.8 to 81.7)		
Week 52	54.2 (46.6 to 61.6)	72.9 (65.8 to 79.3)		
Week 56	52.0 (44.4 to 59.5)	70.2 (62.9 to 76.7)		
Week 60	55.3 (47.7 to 62.7)	69.1 (61.8 to 75.7)		
Week 64	49.2 (41.6 to 56.7)	69.6 (62.4 to 76.2)		
Week 68	48.0 (40.5 to 55.6)	68.0 (60.6 to 74.7)		
Week 72	46.9 (39.4 to 54.5)	66.9 (59.5 to 73.7)		
Week 76	50.8 (43.3 to 58.4)	63.0 (55.5 to 70.0)		
Week 80	46.4 (38.9 to 54.0)	65.7 (58.3 to 72.6)		
Week 84	40.8 (33.5 to 48.4)	63.0 (55.5 to 70.0)		
Week 88	48.6 (41.1 to 56.2)	64.1 (56.6 to 71.1)		
Week 92	45.3 (37.8 to 52.8)	59.1 (51.6 to 66.4)		
Week 96	41.3 (34.0 to 48.9)	61.9 (54.4 to 69.0)		
Week 100	40.8 (33.5 to 48.4)	56.9 (49.4 to 64.2)		

Statistical analyses

Statistical analysis title	SRF and/or IRF at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-18.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.5
upper limit	-8.3

Notes:

[42] - Treatment Difference

Statistical analysis title	SRF and/or IRF at Week 100

Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-16.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-5.9

Notes:

[43] - Treatment difference

Secondary: Percentage of participants with presence of leakage on Fluorescein Angiography (FA) at Weeks 52 and 100

End point title	Percentage of participants with presence of leakage on Fluorescein Angiography (FA) at Weeks 52 and 100

End point description:

Presence of leakage on Fluorescein Angiography as assessed by fluorescein angiography. Leakage on FA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Week 52, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 52	54.7 (47.2 to 62.2)	79.4 (72.8 to 85.1)		
Week 100	46.9 (39.4 to 54.5)	65.6 (58.1 to 72.5)		

Statistical analyses

Statistical analysis title	Fluorescein Angiography (FA) at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[44]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-19.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.1
upper limit	-8.2

Notes:

[44] - Treatment difference

Statistical analysis title	Fluorescein Angiography (FA) at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[45]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-25.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.4
upper limit	-16.3

Notes:

[45] - Treatment difference

Secondary: Percentage of Participants with with >=2-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point title	Percentage of Participants with with >=2-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 28	25.0 (18.8 to 32.1)	20.9 (15.2 to 27.6)		
Week 52	29.0 (22.4 to 36.3)	27.7 (21.2 to 34.9)		
Week 76	30.1 (23.4 to 37.5)	30.5 (23.8 to 37.9)		
Week 100	35.8 (28.7 to 43.4)	31.1 (24.3 to 38.5)		

Statistical analyses

Statistical analysis title	>=2-step improvement in ETDRS-DRSS at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[46]
Parameter estimate	Clopper-Pearson exact method
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	10.8

Notes:

[46] - Treatment difference

Statistical analysis title	>=2-step improvement in ETDRS-DRSS at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[47]
Parameter estimate	Clopper-Pearson exact method
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.6
upper limit	7.8

Notes:

[47] - Treatment difference

Secondary: Percentage of Participants with with >=3-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point title	Percentage of Participants with with >=3-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 28	13.1 (8.5 to 19.0)	11.3 (7.0 to 16.9)		
Week 52	14.8 (9.9 to 20.9)	15.3 (10.3 to 21.4)		
Week 76	18.8 (13.3 to 25.3)	15.3 (10.3 to 21.4)		
Week 100	21.0 (15.3 to 27.8)	16.9 (11.7 to 23.3)		

Statistical analyses

Statistical analysis title	>=3-step improvement in ETDRS-DRSS at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[48]
Parameter estimate	Clopper-Pearson exact method
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	10

Notes:

[48] - Treatment difference

Statistical analysis title	>=3-step improvement in ETDRS-DRSS at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[49]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	5.7

Notes:

[49] - Treatment difference

Secondary: Percentage of Participants with with >=2-step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point title	Percentage of Participants with with >=2-step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 28	2.3 (0.6 to 5.7)	0.6 (0.0 to 3.1)		
Week 52	1.7 (0.4 to 4.9)	0.6 (0.0 to 3.1)		
Week 76	3.4 (1.3 to 7.3)	0.6 (0.0 to 3.1)		
Week 100	4.5 (2.0 to 8.8)	1.7 (0.4 to 4.9)		

Statistical analyses

Statistical analysis title	>=2-step worsening in ETDRS-DRSS at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[50]
Parameter estimate	Clopper-Pearson exact method
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	6.9

Notes:

[50] - Treatment difference

Statistical analysis title	>=2-step worsening in ETDRS-DRSS at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[51]
Parameter estimate	Clopper-Pearson exact method
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	3.6

Notes:

[51] - Treatment difference

Secondary: Percentage of Participants with with >=3-step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point title	Percentage of Participants with with >=3-step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)				
Week 28	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 52	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 76	0.6 (0.0 to 3.1)	999 (999 to 999)		
Week 100	0.6 (0.0 to 3.1)	1.1 (0.1 to 4.0)		

Statistical analyses

Statistical analysis title	>=3-step worsening in ETDRS-DRSS at Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[52]
Parameter estimate	Clopper-Pearson exact method
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	1.3

Notes:

[52] - Treatment difference

Statistical analysis title	>=3-step worsening in ETDRS-DRSS at Week 52
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[53]
Parameter estimate	Clopper-Pearson exact method
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.1

Notes:

[53] - Treatment difference

Secondary: Percentage of participants with progression to proliferative diabetic retinopathy (PDR) as assessed by ETDRS-DRSS Score of at least 61 by Week 100

End point title	Percentage of participants with progression to proliferative diabetic retinopathy (PDR) as assessed by ETDRS-DRSS Score of at least 61 by Week 100

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

End point type	Secondary

End point timeframe:

Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Percentage of Participants				
number (confidence interval 95%)	0.6 (0.0 to 3.4)	0.6 (0.0 to 3.4)		

Statistical analyses

Statistical analysis title	PDR of at least 61 by Week 100
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	360
Analysis specification	Pre-specified
Analysis type	other[54]
Parameter estimate	Clopper-Pearson exact method
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.9

Notes:

[54] - Treatment difference

Secondary: Number of Participants with Ocular and Non-ocular Adverse Events (AEs)

End point title	Number of Participants with Ocular and Non-ocular Adverse Events (AEs)

End point description:

The number of participants with ocular and non-ocular adverse events was was assessed by CTCAE and reported categorically: Mild, Moderate, Severe.

End point type	Secondary

End point timeframe:

From randomization till 30 days safety follow-up, assessed up to 35 months.

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Participants				
Ocular adverse events|Mild	52	47		
Non-ocular adverse events|Mild	52	51		
Ocular adverse events|Moderate	15	23		
Non-ocular adverse events|Moderate	51	50		
Ocular adverse events|Severe	6	4		
Non-ocular adverse events|Severe	33	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): composite score

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): composite score

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	5.7 (± 11.91)	6.3 (± 10.19)		
Week 52	8.9 (± 11.67)	6.7 (± 12.12)		
Week 76	9.8 (± 12.22)	7.6 (± 11.81)		
Week 100	9.0 (± 12.94)	6.2 (± 14.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - General Vision

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - General Vision

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	9.0 (± 16.11)	10.2 (± 15.63)		
Week 52	11.2 (± 17.05)	10.5 (± 17.14)		
Week 76	12.4 (± 16.49)	12.0 (± 16.40)		
Week 100	12.0 (± 16.25)	10.1 (± 18.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Ocular Pain

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Ocular Pain

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	4.1 (± 19.52)	4.6 (± 18.48)		
Week 52	4.6 (± 18.75)	4.4 (± 17.92)		
Week 76	6.2 (± 16.95)	4.6 (± 18.68)		
Week 100	4.3 (± 16.60)	5.4 (± 20.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Near Activities

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Near Activities

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	6.4 (± 20.83)	6.3 (± 18.42)		
Week 52	10.5 (± 20.30)	9.3 (± 19.57)		
Week 76	11.0 (± 21.91)	9.2 (± 18.76)		
Week 100	13.0 (± 20.21)	7.3 (± 21.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Distance Activities

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Distance Activities

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	6.2 (± 18.87)	5.6 (± 15.78)		
Week 52	11.7 (± 17.62)	8.2 (± 17.12)		
Week 76	12.1 (± 18.32)	8.1 (± 16.71)		
Week 100	11.4 (± 18.94)	6.6 (± 19.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Social Functioning

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Social Functioning

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	3.3 (± 15.82)	4.4 (± 16.48)		
Week 52	7.1 (± 16.22)	4.9 (± 15.59)		
Week 76	6.3 (± 16.65)	5.0 (± 15.34)		
Week 100	6.1 (± 16.78)	4.1 (± 17.55)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Mental Health

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Mental Health

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	7.9 (± 19.53)	10.1 (± 19.90)		
Week 52	12.6 (± 22.42)	10.1 (± 22.78)		
Week 76	13.5 (± 21.02)	13.1 (± 23.10)		
Week 100	13.3 (± 20.91)	11.6 (± 26.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Role Difficulties

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Role Difficulties

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	6.9 (± 25.13)	9.4 (± 23.41)		
Week 52	12.2 (± 24.76)	8.7 (± 27.21)		
Week 76	14.0 (± 28.44)	11.4 (± 27.83)		
Week 100	12.3 (± 28.14)	10.2 (± 27.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Dependency

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Dependency

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	5.5 (± 19.39)	3.6 (± 20.34)		
Week 52	7.6 (± 19.53)	3.9 (± 22.49)		
Week 76	7.3 (± 20.19)	5.6 (± 23.24)		
Week 100	6.8 (± 19.85)	2.9 (± 24.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Driving

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Driving

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	1.4 (± 18.75)	4.8 (± 12.24)		
Week 52	6.4 (± 14.63)	4.2 (± 12.81)		
Week 76	8.9 (± 15.95)	2.8 (± 15.88)		
Week 100	5.4 (± 15.81)	1.2 (± 16.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Color Vision

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Color Vision

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	3.5 (± 15.10)	4.2 (± 12.50)		
Week 52	5.8 (± 15.08)	3.6 (± 13.09)		
Week 76	5.2 (± 15.73)	3.9 (± 13.79)		
Week 100	4.3 (± 14.70)	3.2 (± 15.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Peripheral Vision

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Peripheral Vision

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	5.3 (± 18.83)	4.0 (± 16.99)		
Week 52	7.2 (± 18.68)	3.2 (± 19.77)		
Week 76	9.3 (± 19.64)	4.3 (± 17.82)		
Week 100	8.5 (± 19.33)	2.3 (± 19.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): General Health Rating

End point title	Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): General Health Rating

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

End point type	Secondary

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	181		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 28	3.9 (± 18.66)	4.3 (± 19.92)		
Week 52	5.8 (± 22.34)	4.8 (± 23.12)		
Week 76	8.9 (± 21.21)	7.1 (± 22.57)		
Week 100	6.7 (± 19.14)	5.7 (± 21.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic brolucizumab concentration

End point title	Systemic brolucizumab concentration

End point description:

Serum samples were taken approximately 24 hours after the first dose and 24 hours after the treatment at Week 24 to confirm the systemic brolucizumab exposure in patients with visual impairment due to diabetic macular edema.

End point type	Secondary

End point timeframe:

Up to Week 24

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[55]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 2	56.2 (± 10.4)	()		
Week 4	0.760 (± 1.98)	()		
Week 12	999 (± 999)	()		
Week 24	999 (± 999)	()		
Week 24 + 1 Day	41.5 (± 80.5)	()		

Notes:

[55] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm

End point title	Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm

End point description:

Integrated ADA Status was categorized: ADA negative or ADA positive with no boost, Induced or Boosted, Missing ADA at pre-dose or no post-dose ADA data.
- ADA negative: (a) ADA negative at all time points (pre-dose and post-dose), (b) ADA negative at pre-dose and no titer values above 40 at all other time points, (c) ADA titer of 40 at pre-dose but negative at all other time points.
- ADA positive with no boost: ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point.
- Induced: ADA negative at pre-dose, post-dose titer value of 120 or more at any time point.
- Boosted: ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point.

End point type	Secondary

End point timeframe:

Up to Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[56]		
Units: Participants				
ADA negative or ADA positive with no boost	146			
Induced or Boosted	27			
Missing ADA at pre-dose or no post-dose ADA data	6			

Notes:

[56] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm - adjusted for pre-existing ADA status

End point title	Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm - adjusted for pre-existing ADA status

End point description:

Integrated ADA Status - adjusted for pre-existing ADA status was categorized: ADA negative, ADA positive with no boost, Induced, Boosted.
- ADA negative: (a) ADA negative at all time points (pre-dose and post-dose), (b) ADA negative at pre-dose and no titer values above 40 at all other time points, (c) ADA titer of 40 at pre-dose but negative at all other time points.
- ADA positive with no boost: ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point.
- Induced: ADA negative at pre-dose, post-dose titer value of 120 or more at any time point.
- Boosted: ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point.

End point type	Secondary

End point timeframe:

Up to Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[57]		
Units: Participants				
ADA Negative and/or titer value of 40 at pre-dose	53			
ADA positive with no boost and/or at pre-dose	93			
Induced/ADA Negative at pre-dose	14			
Boosted/ADA Positive at pre-dose	13			

Notes:

[57] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye

End point title	Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye

End point description:

Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye was categorized: Negative, Positive.

End point type	Secondary

End point timeframe:

Up to Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[58]		
Units: Participants				
Negative|At least 1 AESI	1			
Postive|At least 1 AESI	5			
Negative|No AESI	63			
Postive|No AESI	105			

Notes:

[58] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Secondary: Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye.

End point title	Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye.

End point description:

Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye was categorized: ADA-negative or no boost, Induced or boosted.

End point type	Secondary

End point timeframe:

Up to Week 100

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179	0[59]		
Units: Participants				
ADA-negative or no boost|At least 1 AESI	4			
Induced or boosted|At least 1 AESI	2			
ADA-negative or no boost|No AESI	142			
Induced or boosted|No AESI	25			

Notes:

[59] - Endpoint applicable to Brolucizumab treatment arm only

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study treatment up to 30 days after last dose (maximum 35 months)	
Adverse event reporting additional description:	
Consistent with EudraCTdisclosure 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	53 / 179 (29.61%)	113 / 360 (31.39%)	60 / 181 (33.15%)
number of deaths (all causes)	13	22	9
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign oesophageal neoplasm			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Biliary neoplasm			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Bronchial carcinoma			

subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cholangiocarcinoma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Colon adenoma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage I			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 cancer			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Hepatic cancer			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastasis			

subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Neoplasm malignant			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Pleomorphic adenoma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Arterial stenosis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Arteriovenous fistula			

subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 arterial occlusive disease			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 179 (0.56%)	3 / 360 (0.83%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 2
Mass			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Reproductive system and breast disorders			
Breast hypoplasia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoventilation			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Sleep apnoea syndrome			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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			
Femoral neck fracture			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
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 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Wrist fracture			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	2 / 179 (1.12%)	2 / 360 (0.56%)	0 / 181 (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
Aortic valve stenosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 arrest			

subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 2
Cardiac failure			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences causally related to treatment / all	0 / 3	0 / 10	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Cardiogenic shock			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Cardiopulmonary failure			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 179 (0.56%)	3 / 360 (0.83%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	2 / 179 (1.12%)	3 / 360 (0.83%)	1 / 181 (0.55%)
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 infarction			

subjects affected / exposed	0 / 179 (0.00%)	3 / 360 (0.83%)	3 / 181 (1.66%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Arachnoiditis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bickerstaff's encephalitis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Carotid artery stenosis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Cerebellar haemorrhage			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar stroke			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 179 (1.12%)	4 / 360 (1.11%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Headache			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Hypoglycaemic coma			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ischaemic stroke			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			

subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma - Study eye			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Retinal artery occlusion - Study eye			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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 detachment - Study eye			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear - Study eye			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis - Fellow eye			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis - Study eye			

subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
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	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			

subjects affected / exposed	2 / 179 (1.12%)	2 / 360 (0.56%)	0 / 181 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
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 chronic			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Cholelithiasis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
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	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Chronic kidney disease			
subjects affected / exposed	0 / 179 (0.00%)	3 / 360 (0.83%)	3 / 181 (1.66%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic nephropathy			
subjects affected / exposed	1 / 179 (0.56%)	3 / 360 (0.83%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dysuria			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Nephrotic syndrome			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Renal failure			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Goitre			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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

Osteonecrosis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bone abscess			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	4 / 179 (2.23%)	7 / 360 (1.94%)	3 / 181 (1.66%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Endophthalmitis - Study eye			
subjects affected / exposed	2 / 179 (1.12%)	3 / 360 (0.83%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	1 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal oesophagitis			

subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	3 / 179 (1.68%)	5 / 360 (1.39%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Localised infection			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes zoster - Study eye			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Orchitis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	4 / 179 (2.23%)	7 / 360 (1.94%)	3 / 181 (1.66%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonia viral			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Pyelonephritis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Fluid overload			

subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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
Fluid retention			
subjects affected / exposed	0 / 179 (0.00%)	2 / 360 (0.56%)	2 / 181 (1.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 179 (0.00%)	1 / 360 (0.28%)	1 / 181 (0.55%)
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 / 179 (0.56%)	2 / 360 (0.56%)	1 / 181 (0.55%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 179 (0.56%)	1 / 360 (0.28%)	0 / 181 (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	131 / 179 (73.18%)	265 / 360 (73.61%)	134 / 181 (74.03%)
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 179 (8.38%)	32 / 360 (8.89%)	17 / 181 (9.39%)
occurrences (all)	18	41	23
Peripheral arterial occlusive disease			
subjects affected / exposed	4 / 179 (2.23%)	6 / 360 (1.67%)	2 / 181 (1.10%)
occurrences (all)	4	6	2
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	3 / 179 (1.68%)	10 / 360 (2.78%)	7 / 181 (3.87%)
occurrences (all)	3	10	7
Chest pain			
subjects affected / exposed	4 / 179 (2.23%)	5 / 360 (1.39%)	1 / 181 (0.55%)
occurrences (all)	5	6	1
Peripheral swelling			
subjects affected / exposed	0 / 179 (0.00%)	4 / 360 (1.11%)	4 / 181 (2.21%)
occurrences (all)	0	4	4
Oedema peripheral			
subjects affected / exposed	4 / 179 (2.23%)	6 / 360 (1.67%)	2 / 181 (1.10%)
occurrences (all)	4	6	2
Pyrexia			
subjects affected / exposed	8 / 179 (4.47%)	13 / 360 (3.61%)	5 / 181 (2.76%)
occurrences (all)	10	15	5
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	4 / 179 (2.23%)	7 / 360 (1.94%)	3 / 181 (1.66%)
occurrences (all)	4	7	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 179 (2.79%)	15 / 360 (4.17%)	10 / 181 (5.52%)
occurrences (all)	5	16	11
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 179 (4.47%)	10 / 360 (2.78%)	2 / 181 (1.10%)
occurrences (all)	8	10	2
Blood pressure increased			
subjects affected / exposed	5 / 179 (2.79%)	9 / 360 (2.50%)	4 / 181 (2.21%)
occurrences (all)	5	9	4
Blood triglycerides increased			
subjects affected / exposed	2 / 179 (1.12%)	8 / 360 (2.22%)	6 / 181 (3.31%)
occurrences (all)	2	8	6
Blood urea increased			
subjects affected / exposed	3 / 179 (1.68%)	7 / 360 (1.94%)	4 / 181 (2.21%)
occurrences (all)	3	7	4

Glycosylated haemoglobin increased			
subjects affected / exposed	7 / 179 (3.91%)	12 / 360 (3.33%)	5 / 181 (2.76%)
occurrences (all)	7	12	5
Intraocular pressure increased - Fellow eye			
subjects affected / exposed	2 / 179 (1.12%)	7 / 360 (1.94%)	5 / 181 (2.76%)
occurrences (all)	2	8	6
Intraocular pressure increased - Study eye			
subjects affected / exposed	6 / 179 (3.35%)	10 / 360 (2.78%)	4 / 181 (2.21%)
occurrences (all)	8	13	5
Protein urine present			
subjects affected / exposed	4 / 179 (2.23%)	9 / 360 (2.50%)	5 / 181 (2.76%)
occurrences (all)	4	10	6
White blood cells urine positive			
subjects affected / exposed	1 / 179 (0.56%)	5 / 360 (1.39%)	4 / 181 (2.21%)
occurrences (all)	1	6	5
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 179 (0.56%)	5 / 360 (1.39%)	4 / 181 (2.21%)
occurrences (all)	1	6	5
Headache			
subjects affected / exposed	8 / 179 (4.47%)	12 / 360 (3.33%)	4 / 181 (2.21%)
occurrences (all)	10	14	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 179 (4.47%)	16 / 360 (4.44%)	8 / 181 (4.42%)
occurrences (all)	8	17	9
Eye disorders			
Blepharitis - Fellow eye			
subjects affected / exposed	2 / 179 (1.12%)	7 / 360 (1.94%)	5 / 181 (2.76%)
occurrences (all)	2	7	5
Blepharitis - Study eye			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences (all)	2	6	4
Cataract - Fellow eye			
subjects affected / exposed	11 / 179 (6.15%)	27 / 360 (7.50%)	16 / 181 (8.84%)
occurrences (all)	11	27	16

Cataract - Study eye			
subjects affected / exposed	12 / 179 (6.70%)	31 / 360 (8.61%)	19 / 181 (10.50%)
occurrences (all)	12	32	20
Conjunctival haemorrhage - Fellow eye			
subjects affected / exposed	1 / 179 (0.56%)	10 / 360 (2.78%)	9 / 181 (4.97%)
occurrences (all)	1	11	10
Conjunctival haemorrhage - Study eye			
subjects affected / exposed	9 / 179 (5.03%)	15 / 360 (4.17%)	6 / 181 (3.31%)
occurrences (all)	9	17	8
Diabetic retinal oedema - Fellow eye			
subjects affected / exposed	18 / 179 (10.06%)	34 / 360 (9.44%)	16 / 181 (8.84%)
occurrences (all)	18	35	17
Diabetic retinopathy - Fellow eye			
subjects affected / exposed	5 / 179 (2.79%)	6 / 360 (1.67%)	1 / 181 (0.55%)
occurrences (all)	5	6	1
Dry eye - Fellow eye			
subjects affected / exposed	9 / 179 (5.03%)	16 / 360 (4.44%)	7 / 181 (3.87%)
occurrences (all)	9	16	7
Dry eye - Study eye			
subjects affected / exposed	9 / 179 (5.03%)	18 / 360 (5.00%)	9 / 181 (4.97%)
occurrences (all)	9	18	9
Eye pain - Study eye			
subjects affected / exposed	6 / 179 (3.35%)	10 / 360 (2.78%)	4 / 181 (2.21%)
occurrences (all)	7	14	7
Eye pruritus - Fellow eye			
subjects affected / exposed	5 / 179 (2.79%)	5 / 360 (1.39%)	0 / 181 (0.00%)
occurrences (all)	5	5	0
Eye pruritus - Study eye			
subjects affected / exposed	5 / 179 (2.79%)	5 / 360 (1.39%)	0 / 181 (0.00%)
occurrences (all)	5	5	0
Macular fibrosis - Fellow eye			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences (all)	2	6	4
Macular oedema - Fellow eye			

subjects affected / exposed	5 / 179 (2.79%)	8 / 360 (2.22%)	3 / 181 (1.66%)
occurrences (all)	9	13	4
Vision blurred - Study eye			
subjects affected / exposed	1 / 179 (0.56%)	6 / 360 (1.67%)	5 / 181 (2.76%)
occurrences (all)	1	7	6
Vision blurred - Fellow eye			
subjects affected / exposed	0 / 179 (0.00%)	4 / 360 (1.11%)	4 / 181 (2.21%)
occurrences (all)	0	4	4
Visual acuity reduced - Fellow eye			
subjects affected / exposed	4 / 179 (2.23%)	7 / 360 (1.94%)	3 / 181 (1.66%)
occurrences (all)	5	11	6
Visual acuity reduced - Study eye			
subjects affected / exposed	6 / 179 (3.35%)	12 / 360 (3.33%)	6 / 181 (3.31%)
occurrences (all)	7	18	11
Vitreous floaters - Study eye			
subjects affected / exposed	4 / 179 (2.23%)	8 / 360 (2.22%)	4 / 181 (2.21%)
occurrences (all)	4	9	5
Vitreous haemorrhage - Fellow eye			
subjects affected / exposed	5 / 179 (2.79%)	11 / 360 (3.06%)	6 / 181 (3.31%)
occurrences (all)	5	15	10
Vitreous haemorrhage - Study eye			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences (all)	2	11	9
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 179 (2.23%)	6 / 360 (1.67%)	2 / 181 (1.10%)
occurrences (all)	4	7	3
Diarrhoea			
subjects affected / exposed	3 / 179 (1.68%)	10 / 360 (2.78%)	7 / 181 (3.87%)
occurrences (all)	5	13	8
Nausea			
subjects affected / exposed	5 / 179 (2.79%)	10 / 360 (2.78%)	5 / 181 (2.76%)
occurrences (all)	6	11	5
Vomiting			
subjects affected / exposed	0 / 179 (0.00%)	4 / 360 (1.11%)	4 / 181 (2.21%)
occurrences (all)	0	4	4

Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	4 / 179 (2.23%)	7 / 360 (1.94%)	3 / 181 (1.66%)
occurrences (all)	4	7	3
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	4 / 179 (2.23%)	8 / 360 (2.22%)	4 / 181 (2.21%)
occurrences (all)	4	8	4
Diabetic nephropathy			
subjects affected / exposed	5 / 179 (2.79%)	12 / 360 (3.33%)	7 / 181 (3.87%)
occurrences (all)	5	12	7
Proteinuria			
subjects affected / exposed	6 / 179 (3.35%)	19 / 360 (5.28%)	13 / 181 (7.18%)
occurrences (all)	7	20	13
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 179 (2.23%)	10 / 360 (2.78%)	6 / 181 (3.31%)
occurrences (all)	4	12	8
Back pain			
subjects affected / exposed	7 / 179 (3.91%)	9 / 360 (2.50%)	2 / 181 (1.10%)
occurrences (all)	7	9	2
Pain in extremity			
subjects affected / exposed	0 / 179 (0.00%)	4 / 360 (1.11%)	4 / 181 (2.21%)
occurrences (all)	0	4	4
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 179 (3.91%)	12 / 360 (3.33%)	5 / 181 (2.76%)
occurrences (all)	7	13	6
COVID-19			
subjects affected / exposed	3 / 179 (1.68%)	7 / 360 (1.94%)	4 / 181 (2.21%)
occurrences (all)	3	7	4
Conjunctivitis - Fellow eye			
subjects affected / exposed	4 / 179 (2.23%)	6 / 360 (1.67%)	2 / 181 (1.10%)
occurrences (all)	4	6	2
Conjunctivitis - Study eye			

subjects affected / exposed	6 / 179 (3.35%)	7 / 360 (1.94%)	1 / 181 (0.55%)
occurrences (all)	6	7	1
Gastroenteritis			
subjects affected / exposed	4 / 179 (2.23%)	4 / 360 (1.11%)	0 / 181 (0.00%)
occurrences (all)	4	4	0
Herpes zoster			
subjects affected / exposed	2 / 179 (1.12%)	7 / 360 (1.94%)	5 / 181 (2.76%)
occurrences (all)	2	7	5
Influenza			
subjects affected / exposed	7 / 179 (3.91%)	11 / 360 (3.06%)	4 / 181 (2.21%)
occurrences (all)	8	18	10
Nasopharyngitis			
subjects affected / exposed	16 / 179 (8.94%)	33 / 360 (9.17%)	17 / 181 (9.39%)
occurrences (all)	20	42	22
Pulpitis dental			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences (all)	2	6	4
Rhinitis			
subjects affected / exposed	2 / 179 (1.12%)	6 / 360 (1.67%)	4 / 181 (2.21%)
occurrences (all)	3	8	5
Upper respiratory tract infection			
subjects affected / exposed	5 / 179 (2.79%)	8 / 360 (2.22%)	3 / 181 (1.66%)
occurrences (all)	5	8	3
Urinary tract infection			
subjects affected / exposed	5 / 179 (2.79%)	9 / 360 (2.50%)	4 / 181 (2.21%)
occurrences (all)	7	12	5
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	1 / 179 (0.56%)	8 / 360 (2.22%)	7 / 181 (3.87%)
occurrences (all)	1	12	11
Hyperlipidaemia			
subjects affected / exposed	8 / 179 (4.47%)	10 / 360 (2.78%)	2 / 181 (1.10%)
occurrences (all)	8	10	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2018	Amendment No. 1: ● Definition of "personal data" was added and "withdrawal of study consent (WOC)" was updated. ● Added clarification on the framework of analysis on study information collected from withdrawn subjects. ● The PK of aflibercept was removed from testing and analysis, as the pharmacokinetics data for aflibercept has been available. The PK samples are collected at approximately 24 hours after first dose and the treatment at Week 24. ● Inclusion criteria no. 5 was revised to allow enrollment of subjects with central subfield retinal thickness cutoff value on SDOCT of ≥ 320 µm instead ≥ 340 µm. ● The assessment schedule table was corrected according to protocol body text and adjustment of appearance for clarity. ● The contraception requirement specified in exclusion criteria no. 26 was extended from 40 days to 3 months after last dose, for consistency with the approved label of comparator in EU and US. ● Other minor corrections and clarifications.
11 June 2020	Amendment No. 2: ● 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 ● Aflibercept was removed from ADA and systemic exposure ● 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: