Clinical trial results:
A 64-week, two-arm, randomized, double-masked, multicenter, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular agerelated macular degeneration (TALON)

Summary

EudraCT number	2019-000716-28
Trial protocol	PT IT CZ SE GB ES BE DE NL
Global end of trial date	09 September 2022

Results information

Result version number	v1
This version publication date	16 September 2023
First version publication date	16 September 2023

Trial information

Trial identification

Sponsor protocol code	CRTH258A2303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04005352
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	09 September 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2022
Global end of trial reached?	Yes
Global end of trial date	09 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of this study were:

-Distribution of the last interval with no disease activity up to Week 32 (if there was disease activity, the last interval would be shortened by 4 weeks, down to a minimum of 4 weeks)

-Average change in Best-corrected visual acuity (BCVA) from baseline at Weeks 28 and 32

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 56
Country: Number of subjects enrolled	Australia: 36
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	Czechia: 54
Country: Number of subjects enrolled	France: 100
Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Korea, Republic of: 52
Country: Number of subjects enrolled	Malaysia: 24
Country: Number of subjects enrolled	Netherlands: 2

Country: Number of subjects enrolled	Portugal: 25
Country: Number of subjects enrolled	Spain: 98
Country: Number of subjects enrolled	Sweden: 7
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 29
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	734
EEA total number of subjects	396

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)	69
From 65 to 84 years	570
85 years and over	95

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

734 participants were treated.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brolucizumab 6 mg

Arm description:

Intra-vitreal injection

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

Dosage and administration details:

Brolucizumab 6 mg Intravitreal injection

Arm title	Aflibercept 2 mg

Arm description:

Intra-vitreal injection

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	J0178
Other name	Eylea and Zaltrap
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Aflibercept 2 mg

Number of subjects in period 1	Brolucizumab 6 mg	Aflibercept 2 mg
Started	366	368
Completed	317	307
Not completed	49	61
Adverse event, serious fatal	4	2
Physician decision	7	13

Consent withdrawn by subject	28	38
Adverse event, non-fatal	4	5
Lost to follow-up	6	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 6 mg
Reporting group description: Intra-vitreal injection	
Reporting group title	Aflibercept 2 mg
Reporting group description: Intra-vitreal injection	

Reporting group values	Brolucizumab 6 mg	Aflibercept 2 mg	Total
Number of subjects	366	368	734
Age Categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 65 years	32	37	69
>=65 years	334	331	665
Age Continuous Units: years			
arithmetic mean	75.5	75.5	
standard deviation	± 7.85	± 8.41	-
Sex: Female, Male Units: Participants			
Female	216	204	420
Male	150	164	314
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	55	55	110
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	310	312	622
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Brolucizumab 6 mg
Reporting group description: Intra-vitreal injection	
Reporting group title	Aflibercept 2 mg
Reporting group description: Intra-vitreal injection	

Primary: Distribution of the last interval with no disease activity up to Week 32 - study eye

End point title	Distribution of the last interval with no disease activity up to Week 32 - study eye

End point description:

No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. Intraretinal Fluid (IRF), Subretinal Fluid (SRF), hemorrhage, leakage, etc.).

Treatment interval distribution. Number (%) of subjects at 12/8/4-weeks intervals up to Week 32 for the study eye.

If the study treatment is discontinued before Week 16, then the treatment interval is 4 weeks; otherwise. the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks).

If the duration of the last interval falls within the following ranges of (4-week, 8-week) or (8-week, 12-week) or ≥12-week then the floor value of these ranges was used.

End point type	Primary
End point timeframe: Up to Week 32	

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
12 weeks	141	73		
8 weeks	131	147		
4 weeks	94	148		

Statistical analyses

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

Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - with significance level of 0.025

Primary: Average change from baseline at Week 28 and Week 32 in Best-corrected visual acuity (BCVA) - study eye

End point title	Average change from baseline at Week 28 and Week 32 in Best-corrected visual acuity (BCVA) - study eye

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.
Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

End point type	Primary

End point timeframe:

Baseline, Week 28 and Week 32

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Scores on a scale				
least squares mean (standard error)	5.2 (± 0.51)	5.1 (± 0.51)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.73

Secondary: Distribution of the maximal intervals with no disease activity up to Week 64 - study eye

End point title	Distribution of the maximal intervals with no disease activity up to Week 64 - study eye

End point description:

No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

Maximal interval distribution. Number of subjects at 16/12/8/4-weeks intervals as the last interval with no disease activity.

If the study treatment is discontinued before Week 16 included, then the treatment interval is 4 weeks; otherwise, the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks).

If the duration of the maximal interval falls within the following ranges of [4-weeks, 8-weeks) or [8-weeks, 12-weeks) or [12-weeks, 16-weeks] or ≥16-weeks then the floor value of these ranges is used.

End point type	Secondary

End point timeframe:

Up to Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
16 Weeks	117	57		
12 Weeks	96	92		
8 Weeks	94	114		
4 Weeks	59	105		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Distribution of the last interval with no disease activity up to Week 64 - study eye

End point title	Distribution of the last interval with no disease activity up to

	Week 64 - study eye

End point description:

No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

Treatment interval distribution. The number of subjects at 16/12/8/4-weeks intervals as the last interval with no disease activity.

If the study treatment is discontinued before Week 16, then the treatment interval is 4 weeks; otherwise. the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks).

If the duration of the last interval falls within the following ranges of (4-week, 8-week) or (8-week, 12-week) or (12-weeks, 16-weeks) or ≥16-week then the floor value of these ranges was used.

End point type	Secondary

End point timeframe:

Up to Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
16 Weeks	104	45		
12 Weeks	82	88		
8 Weeks	95	81		
4 Weeks	85	154		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Time from the last loading injection to the first visit with no disease activity - study eye

End point title	Time from the last loading injection to the first visit with no disease activity - study eye

End point description:

Disease activity assessment as determined by visual acuity and assessment of other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

End point type	Secondary

End point timeframe:

Up to Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Days				
number (not applicable)				

Notes:

[2] - The flexible dosing rendered this endpoint as not applicable.

[3] - The flexible dosing rendered this endpoint as not applicable.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with no disease activity - study eye

End point title	Number of participants with no disease activity - study eye

End point description:

Disease activity assessment as determined by visual acuity and assessment of other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

End point type	Secondary

End point timeframe:

Weeks 14 and 16

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	296		
Units: Participants				
Week 14 (n=118, 137)	87	88		
Week 16 (n=301,296)	260	211		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	2.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	3.9

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	597
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.051
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.7

Secondary: Time-to-first dry retina - time to the first visit with no Intraretinal Fluid (IRF) or Subretinal Fluid (SRF) - study eye

End point title	Time-to-first dry retina - time to the first visit with no Intraretinal Fluid (IRF) or Subretinal Fluid (SRF) - study eye

End point description:

Intraretinal fluid (IRF) and subretinal fluid (SRF) were assessed by Spectral Domain Optical Coherence Tomography (SD-OCT) (study eye).

End point type	Secondary

End point timeframe:

Up to Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
0 Week	330	337		
4 Week	144	138		
8 Week	70	86		
12 Week	70	86		
16 Week	37	67		
20 Week	34	55		
24 Week	30	47		
28 Week	28	38		

32 Week	20	25		
36 Week	20	23		
40 Week	18	22		
44 Week	18	22		
48 Week	17	20		
52 Week	17	20		
56 Week	17	20		
60 Week	11	14		
64 Week	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with best-corrected visual acuity improvements of ≥ 15 letters in BCVA from baseline or reached BCVA ≥ 84 letters up to Week 32/64 per treatment arm - study eye

End point title	Number of participants with best-corrected visual acuity improvements of ≥ 15 letters in BCVA from baseline or reached BCVA ≥ 84 letters up to Week 32/64 per treatment arm - study eye

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.
Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: participants				
Week 32	88	92		
Week 64	89	91		

Statistical analyses

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

Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4667
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.4

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4106
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.3

Secondary: Average change from baseline at Week 60 and Week 64 in Best-corrected visual acuity (BCVA) - study eye

End point title	Average change from baseline at Week 60 and Week 64 in Best-corrected visual acuity (BCVA) - study eye

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.
Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Week 60 and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Scores on a scale				
least squares mean (standard error)	4.7 (± 0.60)	4.9 (± 0.60)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8137 [4]
Method	ANOVA
Parameter estimate	Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	0.84

Notes:

[4] - p-value for treatment difference

Secondary: Number of participants with best-corrected visual acuity ≥ 69 letters - study eye

End point title	Number of participants with best-corrected visual acuity ≥ 69 letters - study eye

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.
Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Week 32 and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
Week 32	244	228		
Week 64	240	219		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.115
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2397
Method	likelihood ratio test
Parameter estimate	Odds ratio (OR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.7

Secondary: Average change from baseline in Central Subfield Thickness (CSFT) - study eye

End point title	Average change from baseline in Central Subfield Thickness (CSFT) - study eye
End point description:	
CSFT was measured by Spectral Domain Optical Coherence Tomography	
End point type	Secondary

End point timeframe:
Baseline, Weeks 28 and 32 and at Weeks 60 and 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: micrometers				
least squares mean (standard error)				
Weeks 28 and 32 (average)	-166.9 (± 6.97)	-140.0 (± 6.96)		
Weeks 60 and 64 (average)	-182.9 (± 7.72)	-167.5 (± 8.16)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1714
Method	ANOVA
Parameter estimate	Difference
Point estimate	-15.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37.6
upper limit	6.7
Variability estimate	Standard error of the mean
Dispersion value	11.26

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	734
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0066
Method	ANOVA
Parameter estimate	Difference
Point estimate	-26.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.3
upper limit	-7.5
Variability estimate	Standard error of the mean
Dispersion value	9.87

Secondary: Number of participants with presence of sub-Retinal Pigment Epithelium fluid in the central subfield - study eye

End point title	Number of participants with presence of sub-Retinal Pigment Epithelium fluid in the central subfield - study eye

End point description:

Sub-Retinal Pigment Epithelium fluid status was measured by Spectral Domain Optical Coherence Tomography (SD-OCT).

End point type	Secondary

End point timeframe:

At Weeks 28, 32, 60 and 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	288	289		
Units: Participants				
Week 28 (n=288,289)	173	208		
Week 32 (n=288, 266)	156	175		
Week 60 (n=271,244)	27	31		
Week 64 (n=271, 242)	34	43		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of Intraretinal Fluid and/or Subretinal Fluid in the central subfield - study eye

End point title	Number of participants with presence of Intraretinal Fluid and/or Subretinal Fluid in the central subfield - study eye

End point description:

Intraretinal Fluid and/or Subretinal Fluid status was measured by Spectral Domain Optical Coherence Tomography (SD-OCT).

End point type	Secondary

End point timeframe:

At Weeks 28, 32, 60 and 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	286	289		
Units: Participants				
Week 28 (n=285,289)	175	198		
Week 32 (n=286, 267)	144	152		
Week 60 (n=269,244)	60	69		
Week 64 (n=271, 241)	72	83		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - Composite scores - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - Composite scores - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	4.09 (-999 to 999)	3.72 (-999 to 999)		
Week 64 (n=248, 224)	2.8 (-999 to 999)	4.7 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.193
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.9

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.052
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	0

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - General Vision - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - General Vision - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	7.94 (-999 to 999)	5.79 (-999 to 999)		
Week 64 (n=248, 224)	7.3 (-999 to 999)	8.0 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.59
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	1.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.081
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	4.6

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Ocular Pain - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Ocular Pain - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	3.55 (-999 to 999)	2.78 (-999 to 999)		
Week 64 (n=248, 224)	3.1 (-999 to 999)	5.0 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.138
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	0.6

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.558
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	3.4

Secondary: Change from baseline n Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Near Activities - study eye

End point title	Change from baseline n Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Near Activities - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	7.46 (-999 to 999)	5.86 (-999 to 999)		
Week 64 (n=248, 224)	4.9 (-999 to 999)	7.9 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.07
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	0.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.287
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	4.6

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Distance Activities - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Distance Activities - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	3.06 (-999 to 999)	3.78 (-999 to 999)		
Week 64 (n=248, 224)	2.5 (-999 to 999)	5.0 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.086
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.3
upper limit	0.4

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.602
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	2

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Social Functioning - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Social Functioning - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	1.99 (-999 to 999)	0.43 (-999 to 999)		
Week 64 (n=248, 224)	0.2 (-999 to 999)	1.7 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.21
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	0.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.174
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.8

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Mental Health - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Mental Health - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	5.83 (-999 to 999)	6.79 (-999 to 999)		
Week 64 (n=248, 224)	5.0 (-999 to 999)	7.2 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.147
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	0.8

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.499
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.8

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Role Difficulties - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Role Difficulties - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	5.17 (-999 to 999)	4.30 (-999 to 999)		
Week 64 (n=248, 224)	4.7 (-999 to 999)	5.9 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.507
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	2.5

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.643
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	4.6

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Driving - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Driving - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	4.92 (-999 to 999)	4.19 (-999 to 999)		
Week 64 (n=248, 224)	1.3 (-999 to 999)	3.0 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.494
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	3.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.741
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	5.1

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Dependency - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Dependency - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	2.71 (-999 to 999)	2.22 (-999 to 999)		
Week 64 (n=248, 224)	-0.6 (-999 to 999)	2.2 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.07
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	0.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	3

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Color Vision - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Color Vision - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	1.78 (-999 to 999)	0.02 (-999 to 999)		
Week 64 (n=248, 224)	0.1 (-999 to 999)	1.2 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.331
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	1.2

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.054
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	3.5

Secondary: Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Peripheral Vision - study eye

End point title	Change from baseline in Visual Function Questionnnaire-25 (VFQ-25) - subscale score - Peripheral Vision - study eye

End point description:

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

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

End point type	Secondary

End point timeframe:

Baseline, Week 32, and Week 64

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	261		
Units: Composite score				
least squares mean (confidence interval 95%)				
Week 32 (n-278, 261)	3.24 (-999 to 999)	2.00 (-999 to 999)		
Week 64 (n=248, 224)	2.5 (-999 to 999)	3.0 (-999 to 999)		

Statistical analyses

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.728
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.6
upper limit	2.5

Statistical analysis title	Brolucizumab 6 mg v Aflibercept 2 mg
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	539
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.394
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.1

Secondary: Number of participants with treatment emergent ocular adverse events (greater than or equal to 1% in any treatment arm) by preferred term for the study eye

End point title	Number of participants with treatment emergent ocular adverse events (greater than or equal to 1% in any treatment arm) by preferred term for the study eye

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject.

End point type	Secondary

End point timeframe:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants				
Number of subjects with at least one event	114	102		
Conjunctival haemorrhage	23	13		
Visual acuity reduced	16	18		
Eye pain	17	13		
Vitreous floaters	12	6		
Intraocular pressure increased	5	11		
Subretinal fluid	5	11		
Vitreous detachment	10	3		
Retinal haemorrhage	4	7		

Cataract	5	5		
Foreign body sensation in eyes	4	6		
Intra-ocular injection complication	6	3		
Retinal pigment epithelial tear	5	4		
Macular oedema	3	4		
Posterior capsule opacification	2	5		
Dry eye	2	4		
Hordeolum	4	2		
Neovascular age-related macular degeneration	2	4		
Retinal oedema	1	4		
Uveitis	4	1		
Vision blurred	4	1		
Detachment of retinal pigment epithelium	0	4		
Retinal artery occlusion	4	0		
Subretinal fibrosis	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent non-ocular adverse events (greater than or equal to 2% in any treatment arm) - summary table

End point title	Number of participants with treatment emergent non-ocular adverse events (greater than or equal to 2% in any treatment arm) - summary table

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject.

End point type	Secondary

End point timeframe:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	366	368		
Units: Participants	182	185		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Brolucizumab 6mg

Reporting group description:

Brolucizumab 6mg

Reporting group title	All Patients

Reporting group description:

All Patients

Reporting group title	Aflibercept 2mg

Reporting group description:

Aflibercept 2mg

Serious adverse events	Brolucizumab 6mg	All Patients	Aflibercept 2mg
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 366 (15.85%)	111 / 734 (15.12%)	53 / 368 (14.40%)
number of deaths (all causes)	4	6	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Neoplasm			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal cancer			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 366 (0.27%)	3 / 734 (0.41%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic squamous cell carcinoma			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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 neoplasm			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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 arterial occlusive disease			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm rupture			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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 respiratory failure			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Dyspnoea exertional			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Epistaxis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Hypercapnia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Pneumonitis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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 / 366 (0.00%)	2 / 734 (0.27%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Abnormal behaviour			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder due to a general medical condition			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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			
Intraocular pressure increased - Study Eye			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Face injury			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Concussion			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 366 (0.00%)	2 / 734 (0.27%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	2 / 366 (0.55%)	3 / 734 (0.41%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 366 (0.00%)	2 / 734 (0.27%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Hip fracture			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			

subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Meniscus injury			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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	2 / 366 (0.55%)	2 / 734 (0.27%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 366 (0.27%)	3 / 734 (0.41%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Coronary artery disease			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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 failure			
subjects affected / exposed	3 / 366 (0.82%)	4 / 734 (0.54%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Atrial flutter			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Atrial fibrillation			
subjects affected / exposed	2 / 366 (0.55%)	2 / 734 (0.27%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 366 (0.55%)	2 / 734 (0.27%)	0 / 368 (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
Tachycardia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Sinus node dysfunction			

subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Myocardial infarction			
subjects affected / exposed	2 / 366 (0.55%)	3 / 734 (0.41%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia infarction			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Cerebral infarction			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Speech disorder			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ocular discomfort			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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 artery occlusion - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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 vascular occlusion - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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

Macular hole - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Iridocyclitis - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma - Study Eye			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye inflammation - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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 vein occlusion - Study Eye			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis - Study Eye			
subjects affected / exposed	3 / 366 (0.82%)	3 / 734 (0.41%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Ileus paralytic			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Abdominal adhesions			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Ureterolithiasis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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			
Spondylolisthesis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Osteoarthritis			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 366 (0.27%)	2 / 734 (0.27%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Endophthalmitis - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Diverticulitis			
subjects affected / exposed	0 / 366 (0.00%)	2 / 734 (0.27%)	2 / 368 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	5 / 366 (1.37%)	6 / 734 (0.82%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
COVID-19			
subjects affected / exposed	2 / 366 (0.55%)	2 / 734 (0.27%)	0 / 368 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0

Urosepsis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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 viral			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
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	2 / 366 (0.55%)	2 / 734 (0.27%)	0 / 368 (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
Herpes zoster			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Escherichia sepsis			
subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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
Hyponatraemia			

subjects affected / exposed	0 / 366 (0.00%)	1 / 734 (0.14%)	1 / 368 (0.27%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 366 (0.27%)	1 / 734 (0.14%)	0 / 368 (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: 1 %

Non-serious adverse events	Brolucizumab 6mg	All Patients	Aflibercept 2mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	168 / 366 (45.90%)	338 / 734 (46.05%)	170 / 368 (46.20%)
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 366 (4.92%)	35 / 734 (4.77%)	17 / 368 (4.62%)
occurrences (all)	18	35	17
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 366 (1.09%)	7 / 734 (0.95%)	3 / 368 (0.82%)
occurrences (all)	4	7	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 366 (1.37%)	5 / 734 (0.68%)	0 / 368 (0.00%)
occurrences (all)	5	5	0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 366 (1.09%)	7 / 734 (0.95%)	3 / 368 (0.82%)
occurrences (all)	4	7	3
Intraocular pressure increased - Study Eye			
subjects affected / exposed	5 / 366 (1.37%)	15 / 734 (2.04%)	10 / 368 (2.72%)
occurrences (all)	5	15	10
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	6 / 366 (1.64%)	15 / 734 (2.04%)	9 / 368 (2.45%)
occurrences (all)	6	15	9
Intra-ocular injection complication - Study Eye			
subjects affected / exposed	6 / 366 (1.64%)	9 / 734 (1.23%)	3 / 368 (0.82%)
occurrences (all)	6	9	3
Vaccination complication			
subjects affected / exposed	3 / 366 (0.82%)	7 / 734 (0.95%)	4 / 368 (1.09%)
occurrences (all)	3	7	4
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 366 (1.64%)	7 / 734 (0.95%)	1 / 368 (0.27%)
occurrences (all)	6	7	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 366 (1.09%)	6 / 734 (0.82%)	2 / 368 (0.54%)
occurrences (all)	4	6	2
Carpal tunnel syndrome			
subjects affected / exposed	4 / 366 (1.09%)	4 / 734 (0.54%)	0 / 368 (0.00%)
occurrences (all)	4	4	0
Headache			
subjects affected / exposed	10 / 366 (2.73%)	21 / 734 (2.86%)	11 / 368 (2.99%)
occurrences (all)	10	21	11
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 366 (0.00%)	4 / 734 (0.54%)	4 / 368 (1.09%)
occurrences (all)	0	4	4
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 366 (1.09%)	8 / 734 (1.09%)	4 / 368 (1.09%)
occurrences (all)	4	8	4
Eye disorders			
Conjunctival haemorrhage - Nonstudy Eye			
subjects affected / exposed	3 / 366 (0.82%)	7 / 734 (0.95%)	4 / 368 (1.09%)
occurrences (all)	3	7	4
Choroidal neovascularisation - Nonstudy Eye			

subjects affected / exposed	5 / 366 (1.37%)	12 / 734 (1.63%)	7 / 368 (1.90%)
occurrences (all)	5	12	7
Cataract - Study Eye			
subjects affected / exposed	5 / 366 (1.37%)	10 / 734 (1.36%)	5 / 368 (1.36%)
occurrences (all)	5	10	5
Foreign body sensation in eyes - Study Eye			
subjects affected / exposed	4 / 366 (1.09%)	10 / 734 (1.36%)	6 / 368 (1.63%)
occurrences (all)	4	10	6
Macular oedema - Study Eye			
subjects affected / exposed	3 / 366 (0.82%)	7 / 734 (0.95%)	4 / 368 (1.09%)
occurrences (all)	3	7	4
Neovascular age-related macular degeneration - Nonstudy Eye			
subjects affected / exposed	21 / 366 (5.74%)	38 / 734 (5.18%)	17 / 368 (4.62%)
occurrences (all)	21	38	17
Neovascular age-related macular degeneration - Study Eye			
subjects affected / exposed	2 / 366 (0.55%)	6 / 734 (0.82%)	4 / 368 (1.09%)
occurrences (all)	2	6	4
Posterior capsule opacification - Study Eye			
subjects affected / exposed	2 / 366 (0.55%)	7 / 734 (0.95%)	5 / 368 (1.36%)
occurrences (all)	2	7	5
Retinal haemorrhage - Study Eye			
subjects affected / exposed	4 / 366 (1.09%)	11 / 734 (1.50%)	7 / 368 (1.90%)
occurrences (all)	4	11	7
Retinal oedema - Study Eye			
subjects affected / exposed	1 / 366 (0.27%)	5 / 734 (0.68%)	4 / 368 (1.09%)
occurrences (all)	1	5	4
Retinal pigment epithelial tear - Study Eye			
subjects affected / exposed	5 / 366 (1.37%)	9 / 734 (1.23%)	4 / 368 (1.09%)
occurrences (all)	5	9	4
Subretinal fibrosis - Study Eye			
subjects affected / exposed	4 / 366 (1.09%)	4 / 734 (0.54%)	0 / 368 (0.00%)
occurrences (all)	4	4	0
Subretinal fluid - Study Eye			

subjects affected / exposed	5 / 366 (1.37%)	16 / 734 (2.18%)	11 / 368 (2.99%)
occurrences (all)	5	16	11
Vision blurred - Study Eye			
subjects affected / exposed	4 / 366 (1.09%)	5 / 734 (0.68%)	1 / 368 (0.27%)
occurrences (all)	4	5	1
Visual acuity reduced - Study Eye			
subjects affected / exposed	16 / 366 (4.37%)	34 / 734 (4.63%)	18 / 368 (4.89%)
occurrences (all)	16	34	18
Vitreous detachment - Nonstudy Eye			
subjects affected / exposed	4 / 366 (1.09%)	5 / 734 (0.68%)	1 / 368 (0.27%)
occurrences (all)	4	5	1
Eye pain - Study Eye			
subjects affected / exposed	17 / 366 (4.64%)	30 / 734 (4.09%)	13 / 368 (3.53%)
occurrences (all)	17	30	13
Eye pain - Nonstudy Eye			
subjects affected / exposed	1 / 366 (0.27%)	5 / 734 (0.68%)	4 / 368 (1.09%)
occurrences (all)	1	5	4
Dry eye - Study Eye			
subjects affected / exposed	2 / 366 (0.55%)	6 / 734 (0.82%)	4 / 368 (1.09%)
occurrences (all)	2	6	4
Dry eye			
subjects affected / exposed	6 / 366 (1.64%)	20 / 734 (2.72%)	14 / 368 (3.80%)
occurrences (all)	6	20	14
Detachment of retinal pigment epithelium - Study Eye			
subjects affected / exposed	0 / 366 (0.00%)	4 / 734 (0.54%)	4 / 368 (1.09%)
occurrences (all)	0	4	4
Conjunctival haemorrhage - Study Eye			
subjects affected / exposed	23 / 366 (6.28%)	36 / 734 (4.90%)	13 / 368 (3.53%)
occurrences (all)	23	36	13
Vitreous detachment - Study Eye			
subjects affected / exposed	10 / 366 (2.73%)	13 / 734 (1.77%)	3 / 368 (0.82%)
occurrences (all)	10	13	3
Vitreous floaters - Study Eye			

subjects affected / exposed	12 / 366 (3.28%)	18 / 734 (2.45%)	6 / 368 (1.63%)
occurrences (all)	12	18	6
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 366 (1.09%)	4 / 734 (0.54%)	0 / 368 (0.00%)
occurrences (all)	4	4	0
Diarrhoea			
subjects affected / exposed	7 / 366 (1.91%)	9 / 734 (1.23%)	2 / 368 (0.54%)
occurrences (all)	7	9	2
Vomiting			
subjects affected / exposed	5 / 366 (1.37%)	5 / 734 (0.68%)	0 / 368 (0.00%)
occurrences (all)	5	5	0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	6 / 366 (1.64%)	8 / 734 (1.09%)	2 / 368 (0.54%)
occurrences (all)	6	8	2
Back pain			
subjects affected / exposed	8 / 366 (2.19%)	16 / 734 (2.18%)	8 / 368 (2.17%)
occurrences (all)	8	16	8
Infections and infestations			
COVID-19			
subjects affected / exposed	9 / 366 (2.46%)	25 / 734 (3.41%)	16 / 368 (4.35%)
occurrences (all)	9	25	16
Conjunctivitis			
subjects affected / exposed	4 / 366 (1.09%)	7 / 734 (0.95%)	3 / 368 (0.82%)
occurrences (all)	4	7	3
Cystitis			
subjects affected / exposed	3 / 366 (0.82%)	8 / 734 (1.09%)	5 / 368 (1.36%)
occurrences (all)	3	8	5
Hordeolum - Study Eye			
subjects affected / exposed	4 / 366 (1.09%)	6 / 734 (0.82%)	2 / 368 (0.54%)
occurrences (all)	4	6	2
Nasopharyngitis			
subjects affected / exposed	12 / 366 (3.28%)	23 / 734 (3.13%)	11 / 368 (2.99%)
occurrences (all)	12	23	11
Urinary tract infection			

subjects affected / exposed	11 / 366 (3.01%)	21 / 734 (2.86%)	10 / 368 (2.72%)
occurrences (all)	11	21	10
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	4 / 366 (1.09%)	5 / 734 (0.68%)	1 / 368 (0.27%)
occurrences (all)	4	5	1
Hypercholesterolaemia			
subjects affected / exposed	4 / 366 (1.09%)	10 / 734 (1.36%)	6 / 368 (1.63%)
occurrences (all)	4	10	6
Hyperuricaemia			
subjects affected / exposed	1 / 366 (0.27%)	5 / 734 (0.68%)	4 / 368 (1.09%)
occurrences (all)	1	5	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 June 2020	To provide clarification and guidance on safety assessments in accordance to the USM regarding the post-marketing reports with brolucizumab (Beovu ®) in the treatment of nAMD, which were identified as retinal vasculitis (RV) and/or retinal vascular occlusion (RO), typically in the presence of IOI, that may result in severe vision loss. In addition, the amendment included the modifications due to COVID-19 pandemic.
13 August 2021	To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects who were currently on q4w dosing beyond the first 3 monthly loading doses ("loading phase") or would need q4w dosing beyond the "loading phase" based on the investigator's assessment. This was as per the USM dated 27-May- 2021 (based on CTH258AUS04 (MERLIN) Year 1 FIR indicating a higher frequency of IOI including RV, and RO in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%, respectively). To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects with RV and RO events. This was as per the USM dated 10-Aug-2021 (based on the results of the mechanistic study BASICHR0049 which identified a causal link with an immune-mediated mechanism of the previously identified risk of RV and/or RO, typically in the presence of IOI). To update safety sections throughout the protocol including updates to the Risks and Benefits section and the creation of a new section under Safety Monitoring which consolidated all risk mitigation information into one section of the protocol.
23 September 2021	To include information on the gender imbalance in the reported rates of IOI-related adverse events following brolucizumab treatment.

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: