Clinical trial results:
An Eighteen-Month, 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 Macular Edema secondary to Central Retinal Vein Occlusion (RAVEN)

Summary

EudraCT number	2018-001788-21
Trial protocol	CZ DE HU NL GR FI ES GB IT
Global end of trial date	26 July 2021

Results information

Result version number	v1 (current)
This version publication date	28 July 2022
First version publication date	28 July 2022

Trial information

Trial identification

Sponsor protocol code	CRTH258C2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03810313
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	26 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in best-corrected visual acuity from baseline up to Month 6

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.
At the investigator's discretion, treatment with macular laser photocoagulation (focal or grid) for the study eye from Week 24 onwards was allowed in case macular edema worsened, resulting in a ≥ 10-letter loss in BCVA at 2 consecutive visits, or in a ≥ 15-letter loss in BCVA at 1 visit in the study eye, compared to best previous measurement, and the study eye BCVA value was not better than the baseline value.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2019
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	Australia: 25
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	China: 71
Country: Number of subjects enrolled	Czechia: 32
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 41
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Malaysia: 15
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Thailand: 8

Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 97
Worldwide total number of subjects	493
EEA total number of subjects	178

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)	236
From 65 to 84 years	238
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 132 sites in 19 countries

Pre-assignment

Screening details:

The study comprised a screening period of 28 days

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brolucizumab 6 mg

Arm description:

1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)

Arm type	Experimental
Investigational medicinal product name	Brolucizumab
Investigational medicinal product code	RTH258
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Brolucizumab 6 mg intravitreal injection

Arm title	Aflibercept 2 mg

Arm description:

1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Aflibercept 2 mg intravitreal injection

Number of subjects in period 1	Brolucizumab 6 mg	Aflibercept 2 mg
Started	247	246
Completed	66	70
Not completed	181	176
Adverse event, serious fatal	2	1
Physician decision	-	1
Subject decision	10	11
Adverse event, non-fatal	2	1
Study terminated by sponsor	164	159
Lost to follow-up	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 6 mg
Reporting group description:	
1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	

Reporting group values	Brolucizumab 6 mg	Aflibercept 2 mg	Total
Number of subjects	247	246	493
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	123	113	236
From 65-84 years	118	120	238
85 years and over	6	13	19
Age Continuous Units: Years			
arithmetic mean	63.0	65.2	
standard deviation	± 13.69	± 12.66	-
Sex: Female, Male Units: Participants			
Female	96	96	192
Male	151	150	301
Race/Ethnicity, Customized Units: Subjects			
White	176	178	354
Black or African American	7	8	15
Asian	62	58	120
Native Hawaiian or Other Pacific Islander	2	0	2
American Indian or Alaska Native	0	1	1
Unknown	0	1	1

End points

End points reporting groups

Reporting group title	Brolucizumab 6 mg
Reporting group description:	
1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	

Primary: Change from baseline in best-corrected visual acuity (BCVA) at Week 24

End point title	Change from baseline in best-corrected visual acuity (BCVA) at Week 24
End point description:	
BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters. Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning. Missing and censored BCVA values were imputed by Last observation carried forward (LOCF) as the primary approach. Observed values from both scheduled and unscheduled post-baseline visits were used for the LOCF imputation. For subjects with no post-baseline BCVA value, the baseline value was carried forward.	
End point type	Primary
End point timeframe:	
Baseline, Week 24	

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Letters read				
least squares mean (standard error)	13.2 (± 0.85)	16.0 (± 0.85)		

Statistical analyses

Statistical analysis title	Change from baseline at BCVA at week 24
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	493
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.173
Method	ANOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-2.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.2
upper limit	-0.5
Variability estimate	Standard error of the mean
Dispersion value	1.2

Notes:

[1] - Non-inferiority was considered to be established if the lower limit of the corresponding 95% CI for the estimated between group difference (brolucizumab vs. aflibercept) on change from baseline in BCVA at Week 24 is > -4 letters.

Secondary: Change from baseline in BCVA averaged over Week 40 to Week 52

End point title	Change from baseline in BCVA averaged over Week 40 to Week 52

End point description:

An average BCVA over week 40 to week 52 was calculated.
BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters.
Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Week 40 to Week 52

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	120		
Units: Letters read				
arithmetic mean (standard deviation)	13.4 (± 15.73)	15.4 (± 13.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BCVA averaged over Week 64 to Week 76

End point title	Change from baseline in BCVA averaged over Week 64 to Week 76

End point description:

An average BCVA over week 64 to week 76 was calculated.
BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters.
Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline, Week 64 to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	113		
Units: Letters read				
arithmetic mean (standard deviation)	14.0 (± 16.39)	16.9 (± 13.60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in BCVA by visit up to Week 76

End point title	Change from baseline in BCVA by visit up to Week 76

End point description:

BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters. Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning.

End point type	Secondary

End point timeframe:

Baseline and every 4 weeks from baseline up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Letters read				
arithmetic mean (standard deviation)				
Week 4 (n= 237, 236)	11.3 (± 12.30)	12.8 (± 11.00)		
Week 8 (n= 212, 212)	13.6 (± 13.77)	15.0 (± 11.78)		
Week 12 (n= 195, 194)	14.1 (± 14.17)	16.3 (± 12.78)		
Week 16 (n= 174, 171)	13.3 (± 15.37)	17.4 (± 13.54)		
Week 20 (n= 164, 156)	13.9 (± 14.17)	17.6 (± 14.68)		
Week 24 (n= 149, 144)	13.6 (± 14.69)	18.1 (± 13.83)		
Week 28 (n= 138, 133)	12.7 (± 15.52)	16.2 (± 13.55)		
Week 32 (n= 130, 123)	11.5 (± 15.96)	15.1 (± 14.58)		
Week 36 (n= 120, 122)	12.6 (± 17.17)	15.3 (± 14.05)		
Week 40 (n= 119, 116)	13.7 (± 15.35)	16.7 (± 12.62)		
Week 44 (n= 112, 116)	13.7 (± 16.59)	15.4 (± 14.50)		
Week 48 (n= 113, 111)	13.5 (± 17.11)	16.2 (± 13.14)		
Week 52 (n= 113, 110)	12.9 (± 18.00)	16.3 (± 14.13)		
Week 56 (n= 107, 111)	13.4 (± 16.98)	14.9 (± 16.43)		
Week 60 (n= 108, 113)	13.1 (± 18.75)	15.7 (± 13.93)		
Week 64 (n= 107, 108)	14.2 (± 17.06)	17.8 (± 13.54)		
Week 68 (n= 93, 101)	14.2 (± 16.75)	17.0 (± 13.88)		

Week 72 (n= 76, 81)	15.8 (± 14.55)	15.2 (± 15.09)		
Week 76 (n= 64, 70)	17.2 (± 13.46)	14.9 (± 13.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

End point title	Proportion of participants with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

End point description:

The summary by visit was conducted based on the BCVA observed from each of the corresponding visits. BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters.
Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning.
Every 5 letters represents 1 line of vision on the reading chart.

End point type	Secondary

End point timeframe:

Baseline and every 4 weeks from baseline up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Participants				
Week4; BCVA gain from baseline >=5 (n= 237, 236)	181	189		
Week4; BCVA gain from baseline >=10 (n= 237, 236)	138	132		
Week4; BCVA gain from baseline >=15 (n= 237, 236)	92	86		
Week8; BCVA gain from baseline >=5 (n= 212, 212)	177	183		
Week8; BCVA gain from baseline >=10 (n= 212, 212)	143	151		
Week8; BCVA gain from baseline >=15 (n= 212, 212)	103	95		
Week12; BCVA gain from baseline >=5 (n= 195, 194)	161	164		
Week12; BCVA gain from baseline >=10 (n= 195, 194)	134	141		
Week12; BCVA gain from baseline >=15 (n= 195, 194)	101	109		
Week16; BCVA gain from baseline >=5 (n= 174, 152)	144	152		
Week16; BCVA gain from baseline >=10 (n= 174, 152)	121	134		
Week16; BCVA gain from baseline >=15 (n= 174, 152)	91	104		

Week20; BCVA gain from baseline >=5 (n= 164, 156)	135	136		
Week20; BCVA gain from baseline >=10 (n= 164, 156)	114	122		
Week20; BCVA gain from baseline >=15 (n= 164, 156)	83	101		
Week24; BCVA gain from baseline >=5 (n= 149, 144)	125	130		
Week24; BCVA gain from baseline >=10 (n= 149, 144)	101	115		
Week24; BCVA gain from baseline >=15 (n= 149, 144)	78	97		
Week28; BCVA gain from baseline >=5 (n= 138, 133)	112	116		
Week28; BCVA gain from baseline >=10 (n= 138, 133)	91	104		
Week28; BCVA gain from baseline >=15 (n= 138, 133)	69	83		
Week32; BCVA gain from baseline >=5 (n= 130, 123)	100	100		
Week32; BCVA gain from baseline >=10 (n= 130, 123)	78	89		
Week32; BCVA gain from baseline >=15 (n= 130, 123)	58	76		
Week36; BCVA gain from baseline >=5 (n= 120, 122)	101	104		
Week36; BCVA gain from baseline >=10 (n= 120, 122)	86	84		
Week36; BCVA gain from baseline >=15 (n= 120, 122)	61	69		
Week40; BCVA gain from baseline >=5 (n= 119, 116)	101	98		
Week40; BCVA gain from baseline >=10 (n= 119, 116)	85	85		
Week40; BCVA gain from baseline >=15 (n= 119, 116)	59	71		
Week44; BCVA gain from baseline >=5 (n= 112, 116)	89	99		
Week44; BCVA gain from baseline >=10 (n= 112, 116)	75	82		
Week44; BCVA gain from baseline >=15 (n= 112, 116)	59	67		
Week48; BCVA gain from baseline >=5 (n= 113, 111)	92	89		
Week48; BCVA gain from baseline >=10 (n= 113, 111)	72	79		
Week48; BCVA gain from baseline >=15 (n= 113, 111)	56	63		
Week52; BCVA gain from baseline >=5 (n= 113, 110)	89	92		
Week52; BCVA gain from baseline >=10 (n= 113, 110)	71	81		
Week52; BCVA gain from baseline >=15 (n= 113, 110)	58	67		
Week56; BCVA gain from baseline >=5 (n= 107, 111)	88	92		
Week56; BCVA gain from baseline >=10 (n= 107, 111)	70	82		
Week56; BCVA gain from baseline >=15 (n= 107, 111)	58	64		
Week60; BCVA gain from baseline >=5 (n= 108, 113)	88	91		

Week 60; BCVA gain from baseline >=10(n= 108, 113)	72	80		
Week60; BCVA gain from baseline >=15(n= 108, 113)	60	69		
Week64; BCVA gain from baseline >=5(n= 107, 108)	88	89		
Week64; BCVA gain from baseline >=10(n= 107, 108)	73	81		
Week64; BCVA gain from baseline >=15 (n= 107, 108)	59	65		
Week68; BCVA gain from baseline >=5 (n= 93, 101)	76	84		
Week68; BCVA gain from baseline >=10 (n= 93, 101)	61	72		
Week68; BCVA gain from baseline >=15 (n= 93, 101)	52	62		
Week72; BCVA gain from baseline >=5 (n= 76, 81)	65	63		
Week72; BCVA gain from baseline >=10 (n= 76, 81)	53	60		
Week72; BCVA gain from baseline >=15 (n= 76, 81)	46	50		
Week76; BCVA gain from baseline >=5 (n= 64, 70)	54	56		
Week76; BCVA gain from baseline >=10 (n= 64, 70)	47	49		
Week76; BCVA gain from baseline >=15 (n= 64, 70)	36	41		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of participants with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

End point title	Proportion of participants with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

End point description:

The summary by visit was conducted based on the BCVA observed from each of the corresponding visit. BCVA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts at an initial testing distance of 4 meters.
Min and max possible scores are 0-100 letters read respectively. A higher score represents better visual functioning.
Every 5 letters represents 1 line of vision on the reading chart.

End point type	Secondary

End point timeframe:

Baseline and every 4 weeks from baseline up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Participants				
Week4; BCVA loss from baseline >=5 (n= 237, 236)	10	7		
Week4; BCVA loss from baseline >=10 (n= 237, 236)	8	3		
Week4; BCVA loss from baseline >=15 (n= 237, 236)	5	2		
Week8; BCVA loss from baseline >=5 (n= 212, 212)	9	6		
Week8; BCVA loss from baseline >=10 (n= 212, 212)	7	3		
Week8; BCVA loss from baseline >=15 (n= 212, 212)	6	2		
Week12; BCVA loss from baseline >=5 (n= 195, 194)	9	7		
Week12; BCVA loss from baseline >=10 (n= 195, 194)	6	5		
Week12; BCVA loss from baseline >=15 (n= 195, 194)	5	1		
Week16; BCVA loss from baseline >=5 (n= 174, 171)	11	7		
Week16; BCVA loss from baseline >=10 (n= 174, 171)	8	5		
Week16; BCVA loss from baseline >=15 (n= 174, 171)	8	2		
Week20; BCVA loss from baseline >=5 (n= 164, 156)	6	8		
Week20; BCVA loss from baseline >=10 (n= 164, 156)	5	5		
Week20; BCVA loss from baseline >=15 (n= 164, 156)	5	5		
Week24; BCVA loss from baseline >=5 (n= 149, 144)	10	7		
Week24; BCVA loss from baseline >=10 (n= 149, 144)	8	5		
Week24; BCVA loss from baseline >=15 (n= 149, 144)	7	4		
Week28; BCVA loss from baseline >=5 (n= 138, 133)	10	7		
Week28; BCVA loss from baseline >=10(n= 138, 133)	6	6		
Week28; BCVA loss from baseline >=15(n= 138, 133)	6	5		
Week32; BCVA loss from baseline >=5(n= 130, 123)	11	11		
Week32; BCVA loss from baseline >=10(n= 130, 123)	9	8		
Week32; BCVA loss from baseline >=15(n= 130, 123)	5	4		
Week36; BCVA loss from baseline >=5(n= 120, 122)	9	7		
Week36; BCVA loss from baseline >=10(n= 120, 122)	8	6		
Week36; BCVA loss from baseline >=15(n= 120, 122)	6	5		
Week40; BCVA loss from baseline >=5(n= 119, 116)	7	5		

Week40; BCVA loss from baseline >=10(n= 119, 116)	6	3		
Week40; BCVA loss from baseline >=15(n= 119, 116)	4	2		
Week44; BCVA loss from baseline >=5(n= 112, 116)	8	9		
Week44; BCVA loss from baseline >=10(n= 112, 116)	7	5		
Week44; BCVA loss from baseline >=15(n= 112, 116)	6	5		
Week48; BCVA loss from baseline >=5(n= 113, 111)	9	6		
Week48; BCVA loss from baseline >=10(n= 113, 111)	7	4		
Week48; BCVA loss from baseline >=15(n= 113, 111)	6	3		
Week52; BCVA loss from baseline >=5(n= 113, 110)	9	7		
Week52; BCVA loss from baseline >=10(n= 113, 110)	7	6		
Week52; BCVA loss from baseline >=15(n= 113, 110)	7	5		
Week56; BCVA loss from baseline >=5(n= 107, 111)	9	9		
Week56; BCVA loss from baseline >=10(n= 107, 111)	6	7		
Week56; BCVA loss from baseline >=15(n= 107, 111)	5	6		
Week60; BCVA loss from baseline >=5(n= 108, 113)	11	10		
Week 60; BCVA loss from baseline >=10(n= 108, 113)	8	6		
Week60; BCVA loss from baseline >=15(n= 108, 113)	6	3		
Week64; BCVA loss from baseline >=5(n= 107, 108)	8	4		
Week64; BCVA loss from baseline >=10(n= 107, 108)	6	2		
Week64; BCVA loss from baseline >=15(n= 107, 108)	6	2		
Week68; BCVA loss from baseline >=5(n= 93, 101)	5	6		
Week68; BCVA loss from baseline >=10(n= 93, 101)	5	3		
Week68; BCVA loss from baseline >=15(n= 93, 101)	3	1		
Week72; BCVA loss from baseline >=5(n= 76, 81)	3	7		
Week72; BCVA loss from baseline >=10(n= 76, 81)	3	5		
Week72; BCVA loss from baseline >=15(n= 76, 81)	3	3		
Week76; BCVA loss from baseline >=5(n= 64, 70)	1	3		
Week 76; BCVA loss from baseline >=10(n= 64, 70)	1	3		
Week 76; BCVA loss from baseline >=15(n= 64, 70)	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CSFT averaged over Week 40 to Week 52

End point title	Change from baseline in CSFT averaged over Week 40 to Week 52

End point description:

Change from baseline in central subfield thickness (CSFT) averaged over Week 40 to Week 52, measured in µm by Spectral Domain Optical Coherence Tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Baseline, Week 40 to Week 52

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	120		
Units: µm				
arithmetic mean (standard deviation)	-399.9 (± 259.22)	-434.6 (± 261.71)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CSFT averaged over Week 64 to Week 76

End point title	Change from baseline in CSFT averaged over Week 64 to Week 76

End point description:

Change from baseline in central subfield thickness (CSFT) averaged over Week 64 to Week 76, measured in µm by Spectral Domain Optical Coherence Tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Baseline, Week 64 to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	112		
Units: µm				
arithmetic mean (standard deviation)	-411.6 (± 259.16)	-445.7 (± 259.73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CSFT by visit up to Week 76

End point title	Change from baseline in CSFT by visit up to Week 76

End point description:

Change from baseline in central subfield thickness (CSFT) measured in µm by Spectral Domain Optical Coherence Tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Baseline, and every 4 weeks from baseline up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: µm				
arithmetic mean (standard deviation)				
Week 4 (n= 235, 235)	-429.5 (± 254.32)	-420.6 (± 242.68)		
Week 8 (n= 210, 213)	-448.8 (± 265.16)	-436.1 (± 255.53)		
Week 12 (n= 194, 194)	-468.3 (± 269.55)	-440.7 (± 251.74)		
Week 16 (n= 174, 170)	-450.1 (± 278.67)	-470.7 (± 255.64)		
Week 20 (n= 163, 156)	-458.1 (± 270.26)	-470.2 (± 260.46)		
Week 24 (n= 149, 142)	-446.8 (± 274.39)	-472.4 (± 249.20)		
Week 28 (n= 137, 132)	-383.2 (± 248.81)	-417.9 (± 269.03)		
Week 32 (n= 129, 122)	-323.5 (± 322.95)	-395.8 (± 299.16)		
Week 36 (n= 116, 122)	-387.8 (± 280.75)	-406.5 (± 265.67)		
Week 40 (n= 118, 116)	-403.9 (± 269.68)	-446.6 (± 270.47)		
Week 44 (n= 111, 116)	-404.0 (± 311.37)	-418.4 (± 271.33)		
Week 48 (n= 112, 111)	-411.5 (± 281.09)	-457.8 (± 261.08)		
Week 52 (n= 112, 110)	-411.3 (± 276.21)	-457.0 (± 256.40)		
Week 56 (n= 106, 111)	-384.6 (± 313.93)	-400.8 (± 298.50)		
Week 60 (n= 107, 113)	-396.1 (± 295.96)	-438.8 (± 254.36)		
Week 64 (n= 105, 107)	-425.2 (± 266.66)	-462.3 (± 258.08)		
Week 68 (n= 91, 99)	-396.3 (± 282.85)	-416.1 (± 260.79)		
Week 72 (n= 72, 79)	-401.5 (± 276.50)	-419.0 (± 252.10)		

Week 76 (n= 63, 69)	-421.9 (± 261.63)	-408.5 (± 251.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with presence of retinal fluid (intra- and/or subretinal fluid) in the study eye by visit up to Week 76

End point title	Proportion of subjects with presence of retinal fluid (intra- and/or subretinal fluid) in the study eye by visit up to Week 76

End point description:

Presence of retinal fluid (intra- and/or subretinal fluid) assessed by Spectral Domain Optical Coherence Tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Every 4 weeks from week 4 up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Participants				
Week 4 (n= 236, 235)	101	105		
Week 8 (n= 212, 213)	54	68		
Week 12 (n= 195, 194)	38	54		
Week 16 (n= 175, 170)	37	43		
Week 20 (n= 164, 156)	34	31		
Week 24 (n= 150, 144)	26	30		
Week 28 (n= 138, 133)	44	56		
Week 32 (n= 130, 122)	63	55		
Week 36 (n= 120, 122)	43	59		
Week 40 (n= 119, 116)	32	40		
Week 44 (n= 112, 116)	38	48		
Week 48 (n= 113, 111)	36	40		
Week 52 (n= 113, 110)	35	40		
Week 56 (n= 107, 111)	42	48		
Week 60 (n= 108, 113)	36	39		
Week 64 (n= 106, 108)	29	41		
Week 68 (n= 93, 100)	36	40		
Week 72 (n= 76, 80)	25	27		
Week 76 (n= 64, 70)	24	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects with a CSFT < 300 µm for the study eye by visit up to Week 76

End point title	Proportion of subjects with a CSFT < 300 µm for the study eye by visit up to Week 76

End point description:

Central subfield thickness (CSFT) is measured in µm by Spectral Domain Optical Coherence Tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Every 4 weeks from week 4 up to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Participants				
Week 4 (n=236 , 235)	157	137		
Week 8 (n= 211, 213)	168	155		
Week 12 (n= 195, 194)	172	149		
Week 16 (n= 175, 170)	153	141		
Week 20 (n= 164, 156)	147	135		
Week 24 (n= 150, 142)	135	123		
Week 28 (n= 138, 132)	107	90		
Week 32 (n= 130, 122)	81	74		
Week 36 (n= 117, 122)	83	77		
Week 40 (n= 119, 116)	94	86		
Week 44 (n= 112, 116)	83	79		
Week 48 (n= 113, 111)	82	83		
Week 52 (n= 113, 110)	85	82		
Week 56 (n= 107, 111)	74	71		
Week 60 (n= 108, 113)	81	79		
Week 64 (n= 106, 107)	85	80		
Week 68 (n= 92, 99)	65	69		
Week 72 (n= 73, 79)	59	56		
Week 76 (n= 64, 69)	51	45		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of injections between Week 24 and Week 52 and between Week 24 and Week 72

End point title	Number of injections between Week 24 and Week 52 and between Week 24 and Week 72

End point description:

Number of administered injections during the individualized flexible treatment (IFT) period, between Week 24 and Week 52 and between Week 24 and Week 72 are presented

End point type	Secondary

End point timeframe:

Week 24 to Week 52 and Week 24 to Week 72

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	115		
Units: Injections				
arithmetic mean (standard deviation)				
Between Week 24 and Week 52 (n= 114, 115)	2.4 (± 1.69)	2.6 (± 2.02)		
Between Week 24 and Week 72 (n=58, 67)	4.1 (± 3.08)	4.4 (± 3.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recurrence after Week 20 and up to Week 76

End point title	Time to recurrence after Week 20 and up to Week 76

End point description:

Recurrence is defined as the need for injection while showing a lack of disease stability for the first time after Week 20 and up to Week 76.
For subjects with recurrence after the Week 20 visit, time-to-event is calculated as (first time with the lack of disease stability – the injection date on Week 20 visit + 1). For subjects without recurrence after Week 20, the censoring time will be calculated as (last visit with disease stability assessment – the injection date on Week 20 visit + 1).

End point type	Secondary

End point timeframe:

Week 20 to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160	163		
Units: Weeks				
median (confidence interval 95%)	12.1 (12.1 to 12.4)	12.1 (11.4 to 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with ocular and non-ocular AEs up to Week 52 and Week 76

End point title	Number of subjects with ocular and non-ocular AEs up to Week 52 and Week 76

End point description:

Number of subjects with at least one ocular or non-ocular Adverse Events (AEs).

End point type	Secondary

End point timeframe:

Baseline to Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Participants				
Ocular AEs up to week 52	105	77		
Non-Ocular AEs up to week 52	103	107		
Ocular AEs up to week 76	111	89		
Non-Ocular AEs up to week 76	119	117		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76

End point title	Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures a patient's subjective assessment of vision-related Quality of Life (QoL).
The 11 subscales in the VFQ-25 are general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The scores on the subscales were added together for a total score, which ranged from 0 to 100. A higher score indicated better vision-related quality of life.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 52 and Week 76

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	247	246		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n= 217, 211)	5.3 (± 13.08)	7.4 (± 12.46)		
Week 52 (n= 128, 128)	6.0 (± 14.83)	9.0 (± 11.10)		
Week 76 (n= 104, 111)	7.4 (± 14.44)	9.4 (± 11.66)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects according to their Anti-drug antibody (ADA) titer at screening and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76

End point title	Number of subjects according to their Anti-drug antibody (ADA) titer at screening and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76[2]

End point description:

Anti-drug antibodies (ADA) levels were assessed from subjects assigned to brolucizumab treatment only.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary outcome.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	247			
Units: Participants				
Baseline|Negative (n= 244)	105			
Week 4|Negative (n= 226)	101			
Week 12|Negative (n= 187)	77			
Week 24|Negative (n= 146)	51			
Week 36|Negative (n= 114)	35			
Week 52|Negative (n= 114)	37			
Week 76|Negative (n= 67)	25			
Baseline|40 (n= 244)	23			
Week 4|40 (n= 226)	26			
Week 12|40 (n= 187)	15			
Week 24|40 (n= 146)	16			
Week 36|40 (n= 114)	8			
Week 52|40 (n= 114)	15			
Week 76|40 (n= 67)	8			
Baseline|120 (n= 244)	35			
Week 4|120 (n= 226)	30			

Week 12|120 (n= 187)	38			
Week 24|120 (n= 146)	32			
Week 36|120 (n= 114)	20			
Week 52|120 (n= 114)	22			
Week 76|120 (n= 67)	14			
Baseline|360 (n= 244)	34			
Week 4|360 (n= 226)	35			
Week 12|360 (n= 187)	28			
Week 24|360 (n= 146)	21			
Week 36|360 (n= 114)	28			
Week 52|360 (n= 114)	16			
Week 76|360 (n= 67)	7			
Baseline|1080 (n= 244)	29			
Week 4|1080 (n= 226)	21			
Week 12|1080 (n= 187)	12			
Week 24|1080 (n= 146)	15			
Week 36|1080 (n= 114)	11			
Week 52|1080 (n= 114)	14			
Week 76|1080 (n= 67)	7			
Baseline|3240 (n= 244)	13			
Week 4|3240 (n= 226)	8			
Week 12|3240 (n= 187)	14			
Week 24|3240 (n= 146)	8			
Week 36|3240 (n= 114)	9			
Week 52|3240 (n= 114)	9			
Week 76|3240 (n= 67)	5			
Baseline|9720 (n= 244)	4			
Week 4|9720 (n= 226)	5			
Week 12|9720 (n= 187)	3			
Week 24|9720 (n= 146)	3			
Week 36|9720 (n= 114)	3			
Week 52|9720 (n= 114)	1			
Week 76|9720 (n= 67)	1			
Baseline|29200 (n= 244)	1			
Week 4|29200 (n= 226)	0			
Week 12|29200 (n= 187)	0			
Week 24|29200 (n= 146)	0			
Week 36|29200 (n= 114)	0			
Week 52|29200 (n= 114)	0			
Week 76|29200 (n= 67)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post treatment, up to maximum duration of 76 weeks	
Adverse event reporting additional description:	
Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Brolucizumab 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	36 / 247 (14.57%)	55 / 493 (11.16%)	19 / 246 (7.72%)
number of deaths (all causes)	2	3	1
number of deaths resulting from adverse events	1	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Prostate cancer			

subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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			
Aneurysm			
subjects affected / exposed	2 / 247 (0.81%)	2 / 493 (0.41%)	0 / 246 (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
Peripheral ischaemia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Varicose vein			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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			
Cervical dysplasia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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			
Acute respiratory failure			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Subdural haematoma			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			

subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive heart disease			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Myocardial infarction			
subjects affected / exposed	1 / 247 (0.40%)	2 / 493 (0.41%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Hemiparesis			

subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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 / 247 (0.40%)	2 / 493 (0.41%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract - Study eye			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiretinal membrane - Fellow eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Ocular hypertension - Study eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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	2 / 247 (0.81%)	2 / 493 (0.41%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal ischaemia - Study eye			

subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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 vasculitis - Study eye			
subjects affected / exposed	2 / 247 (0.81%)	2 / 493 (0.41%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis - Study eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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 vein occlusion - Study eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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			
Ascites			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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			
Diabetic nephropathy			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Spinal osteoarthritis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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			
COVID-19			
subjects affected / exposed	4 / 247 (1.62%)	6 / 493 (1.22%)	2 / 246 (0.81%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	2 / 247 (0.81%)	2 / 493 (0.41%)	0 / 246 (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
Cellulitis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dacryocystitis - Study eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Emphysematous cystitis			

subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Endocarditis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis - Study eye			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Pneumonia			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
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 cyst infection			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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
Vestibular neuronitis			
subjects affected / exposed	1 / 247 (0.40%)	1 / 493 (0.20%)	0 / 246 (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			
Hyponatraemia			
subjects affected / exposed	0 / 247 (0.00%)	1 / 493 (0.20%)	1 / 246 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
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	104 / 247 (42.11%)	191 / 493 (38.74%)	87 / 246 (35.37%)
Investigations			
Intraocular pressure increased - Study eye			
subjects affected / exposed	10 / 247 (4.05%)	23 / 493 (4.67%)	13 / 246 (5.28%)
occurrences (all)	14	37	23
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 247 (7.69%)	29 / 493 (5.88%)	10 / 246 (4.07%)
occurrences (all)	19	29	10
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 247 (1.21%)	11 / 493 (2.23%)	8 / 246 (3.25%)
occurrences (all)	3	13	10
Eye disorders			
Cataract - Study eye			
subjects affected / exposed	8 / 247 (3.24%)	12 / 493 (2.43%)	4 / 246 (1.63%)
occurrences (all)	9	13	4
Conjunctival haemorrhage - Study eye			

subjects affected / exposed	16 / 247 (6.48%)	27 / 493 (5.48%)	11 / 246 (4.47%)
occurrences (all)	25	49	24
Dry eye - Fellow eye			
subjects affected / exposed	5 / 247 (2.02%)	10 / 493 (2.03%)	5 / 246 (2.03%)
occurrences (all)	6	11	5
Eye pain - Study eye			
subjects affected / exposed	9 / 247 (3.64%)	15 / 493 (3.04%)	6 / 246 (2.44%)
occurrences (all)	12	18	6
Dry eye - Study eye			
subjects affected / exposed	6 / 247 (2.43%)	12 / 493 (2.43%)	6 / 246 (2.44%)
occurrences (all)	7	13	6
Glaucoma - Fellow eye			
subjects affected / exposed	5 / 247 (2.02%)	10 / 493 (2.03%)	5 / 246 (2.03%)
occurrences (all)	5	10	5
Glaucoma - Study eye			
subjects affected / exposed	5 / 247 (2.02%)	10 / 493 (2.03%)	5 / 246 (2.03%)
occurrences (all)	5	10	5
Macular oedema - Study eye			
subjects affected / exposed	18 / 247 (7.29%)	29 / 493 (5.88%)	11 / 246 (4.47%)
occurrences (all)	27	41	14
Ocular hypertension - Study eye			
subjects affected / exposed	6 / 247 (2.43%)	9 / 493 (1.83%)	3 / 246 (1.22%)
occurrences (all)	7	10	3
Retinal ischaemia - Study eye			
subjects affected / exposed	6 / 247 (2.43%)	7 / 493 (1.42%)	1 / 246 (0.41%)
occurrences (all)	6	7	1
Retinal vein occlusion - Study eye			
subjects affected / exposed	7 / 247 (2.83%)	8 / 493 (1.62%)	1 / 246 (0.41%)
occurrences (all)	7	8	1
Uveitis - Study eye			
subjects affected / exposed	8 / 247 (3.24%)	8 / 493 (1.62%)	0 / 246 (0.00%)
occurrences (all)	10	10	0
Vitreous detachment - Study eye			
subjects affected / exposed	11 / 247 (4.45%)	22 / 493 (4.46%)	11 / 246 (4.47%)
occurrences (all)	11	22	11
Visual acuity reduced - Study eye			

subjects affected / exposed	22 / 247 (8.91%)	31 / 493 (6.29%)	9 / 246 (3.66%)
occurrences (all)	33	47	14
Vitreous floaters - Study eye			
subjects affected / exposed	5 / 247 (2.02%)	16 / 493 (3.25%)	11 / 246 (4.47%)
occurrences (all)	6	19	13
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 247 (0.40%)	6 / 493 (1.22%)	5 / 246 (2.03%)
occurrences (all)	1	7	6
Arthralgia			
subjects affected / exposed	9 / 247 (3.64%)	16 / 493 (3.25%)	7 / 246 (2.85%)
occurrences (all)	9	16	7
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 247 (2.02%)	11 / 493 (2.23%)	6 / 246 (2.44%)
occurrences (all)	5	11	6
Nasopharyngitis			
subjects affected / exposed	8 / 247 (3.24%)	14 / 493 (2.84%)	6 / 246 (2.44%)
occurrences (all)	9	16	7
Tooth abscess			
subjects affected / exposed	1 / 247 (0.40%)	6 / 493 (1.22%)	5 / 246 (2.03%)
occurrences (all)	1	7	6
Urinary tract infection			
subjects affected / exposed	7 / 247 (2.83%)	10 / 493 (2.03%)	3 / 246 (1.22%)
occurrences (all)	8	13	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 June 2020	The main purpose of this amendment is to provide clarification and guidance on safety assessments in accordance to the urgent safety measure regarding the post-marketing reports with brolucizumab (Beovu®) in the treatment of neovascular age-related macular degeneration (nAMD), which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, that may result in severe vision loss. In addition, the amendment includes modifications due to the Coronavirus disease 2019 (COVID-19) pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was terminated by sponsor due to increased incidences of AEs of special interest (intraocular inflammation including retinal vasculitis and retinal vascular occlusion), in patients dosed brolucizumab 6mg every 4 weeks beyond 3 initial doses

Notes: