Clinical trial results:
An Eighteen-Month, Two-Arm, Randomized, Double- Masked, Multi-center, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Branch Retinal Vein Occlusion (RAPTOR)

Summary

EudraCT number	2018-001842-33
Trial protocol	DE AT DK ES GB IT CZ
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	CRTH258C2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03802630
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 BCVA 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	02 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	Austria: 3
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	China: 85
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 37
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Switzerland: 10
Country: Number of subjects enrolled	Taiwan: 10

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 119
Worldwide total number of subjects	450
EEA total number of subjects	143

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)	214
From 65 to 84 years	220
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 103 sites in 18 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 individualized 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 individualized 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	226	224
Completed	73	76
Not completed	153	148
Adverse event, serious fatal	-	2
Physician decision	2	-
Subject decision	16	9
Adverse event, non-fatal	3	1
Study terminated by sponsor	130	134
Lost to follow-up	2	2

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 individualized 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 individualized flexible treatment (IFT)	

Reporting group values	Brolucizumab 6 mg	Aflibercept 2 mg	Total
Number of subjects	226	224	450
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)	106	108	214
From 65-84 years	113	107	220
85 years and over	7	9	16
Age Continuous Units: Years			
arithmetic mean	65.4	65.0	
standard deviation	± 11.05	± 10.92	-
Sex: Female, Male Units: Participants			
Female	117	125	242
Male	109	99	208
Race/Ethnicity, Customized Units: Subjects			
White	153	153	306
Black or African American	7	4	11
Asian	65	67	132
White/Black or African American	1	0	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 individualized 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 individualized 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	226	224		
Units: Letters read				
least squares mean (standard error)	13.1 (± 0.71)	15.0 (± 0.71)		

Statistical analyses

Statistical analysis title	Change from BCVA at week 24
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg

Number of subjects included in analysis	450
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.018
Method	ANOVA
Parameter estimate	Least Square Mean Difference
Point estimate	-1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	1.01

Notes:

[1] - Non-inferiority was considered 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 greater than -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	123	132		
Units: Letters read				
arithmetic mean (standard deviation)	12.9 (± 12.81)	16.9 (± 10.63)		

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	110	121		
Units: Letters read				
arithmetic mean (standard deviation)	13.7 (± 13.33)	17.9 (± 10.65)		

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	226	224		
Units: Letters read				
arithmetic mean (standard deviation)				
Week 4 (n=223, 217)	9.2 (± 8.22)	10.3 (± 10.13)		
Week 8 (n=204, 199)	11.9 (± 10.68)	12.8 (± 10.84)		
Week 12 (n=185, 182)	13.2 (± 10.22)	14.8 (± 11.23)		
Week 16 (n=160, 160)	12.2 (± 12.59)	16.3 (± 11.58)		
Week 20 (n=144, 149)	13.5 (± 10.83)	16.3 (± 12.15)		
Week 24 (n=147, 144)	12.7 (± 12.36)	16.6 (± 11.35)		
Week 28 (n=135, 136)	12.1 (± 13.88)	16.4 (± 10.62)		
Week 32 (n=124, 128)	12.2 (± 13.24)	15.7 (± 10.94)		
Week 36 (n=123, 125)	11.8 (± 14.75)	16.9 (± 10.95)		
Week 40 (n=119, 124)	12.7 (± 12.89)	16.9 (± 10.74)		

Week 44 (n=116, 120)	13.5 (± 13.28)	17.2 (± 11.37)		
Week 48 (n=114, 120)	13.3 (± 13.38)	17.7 (± 10.79)		
Week 52 (n=106, 125)	13.5 (± 13.42)	17.2 (± 10.46)		
Week 56 (n=106, 122)	14.9 (± 10.86)	17.7 (± 10.62)		
Week 60 (n=105, 123)	13.7 (± 13.67)	17.7 (± 10.33)		
Week 64 (n=102, 117)	14.1 (± 13.72)	18.0 (± 10.54)		
Week 68 (n=94, 110)	13.9 (± 13.83)	17.7 (± 10.75)		
Week 72 (n=83, 92)	13.9 (± 13.38)	18.4 (± 11.44)		
Week 76 (n=68, 74)	14.4 (± 13.72)	18.1 (± 11.19)		

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	226	224		
Units: Participants				
Week 4; BCVA gain from baseline >=5 (n=223, 217)	154	150		
Week 4; BCVA gain from baseline >=10 (n=223, 217)	102	110		
Week4; BCVA gain from baseline >=15(n=223, 217)	64	79		
Week8; BCVA gain from baseline >=5(n=204, 199)	158	155		
Week8; BCVA gain from baseline >=10(n=204, 199)	117	118		
Week8; BCVA gain from baseline >=15(n=204, 199)	92	93		
Week 12; BCVA gain from baseline >=5(n=185, 182)	156	156		
Week 12; BCVA gain from baseline >=10(n=185, 182)	114	125		

Week 12; BCVA gain from baseline >=15(n=185, 182)	90	102		
Week 16; BCVA gain from baseline >=5(n=160, 160)	127	143		
Week 16; BCVA gain from baseline >=10(n=160, 160)	95	118		
Week 16; BCVA gain from baseline >=15(n=160, 160)	73	100		
Week 20; BCVA gain from baseline >=5(n=144, 149)	119	131		
Week 20; BCVA gain from baseline >=10(n=144, 149)	96	108		
Week20; BCVA gain from baseline >=15 (n=144, 149)	74	92		
Week24; BCVA gain from baseline >=5 (n=147, 144)	122	126		
Week24; BCVA gain from baseline >=10 (n=147, 144)	90	109		
Week24; BCVA gain from baseline >=15 (n=147, 144)	75	91		
Week28; BCVA gain from baseline >=5 (n=135, 136)	108	121		
Week28; BCVA gain from baseline >=10 (n=135, 136)	89	107		
Week28; BCVA gain from baseline >=15 (n=135, 136)	75	87		
Week32; BCVA gain from baseline >=5 (n=124, 128)	97	110		
Week32; BCVA gain from baseline >=10 (n=124, 128)	79	94		
Week32; BCVA gain from baseline >=15 (n=124, 128)	60	78		
Week36; BCVA gain from baseline >=5 (n=123, 125)	100	112		
Week36; BCVA gain from baseline >=10 (n=123, 125)	81	98		
Week36; BCVA gain from baseline >=15 (n=123, 125)	62	83		
Week40; BCVA gain from baseline >=5 (n=119, 124)	96	114		
Week40; BCVA gain from baseline >=10 (n=119, 124)	79	98		
Week40; BCVA gain from baseline >=15 (n=119, 124)	65	85		
Week44; BCVA gain from baseline >=5 (n=116, 120)	94	111		
Week44; BCVA gain from baseline >=10 (n=116, 120)	78	97		
Week44; BCVA gain from baseline >=15 (n=116, 120)	64	88		
Week48; BCVA gain from baseline >=5 (n=114, 120)	92	112		
Week48; BCVA gain from baseline >=10 (n=114, 120)	76	95		
Week48; BCVA gain from baseline >=15 (n=114, 120)	61	80		
Week52; BCVA gain from baseline >=5 (n=106, 125)	87	117		
Week52; BCVA gain from baseline >=10 (n=106, 125)	75	99		
Week52; BCVA gain from baseline >=15 (n=106, 125)	64	87		

Week56; BCVA gain from baseline >=5 (n=106, 122)	90	113		
Week56; BCVA gain from baseline >=10 (n=106, 122)	76	106		
Week56; BCVA gain from baseline >=15 (n=106, 122)	58	84		
Week60; BCVA gain from baseline >=5 (n=105, 123)	86	116		
Week60; BCVA gain from baseline >=10 (n=105, 123)	71	104		
Week60; BCVA gain from baseline >=15 (n=105, 123)	62	88		
Week64; BCVA gain from baseline >=5 (n=102, 117)	86	112		
Week64; BCVA gain from baseline >=10 (n=102, 117)	74	98		
Week64; BCVA gain from baseline >=15 (n=102, 117)	58	82		
Week68; BCVA gain from baseline >=5 (n=94, 110)	79	103		
Week68; BCVA gain from baseline >=10 (n=94, 110)	67	88		
Week68; BCVA gain from baseline >=15 (n=94, 110)	55	76		
Week72; BCVA gain from baseline >=5 (n=83, 92)	68	89		
Week72; BCVA gain from baseline >=10 (n=83, 92)	56	75		
Week72; BCVA gain from baseline >=15 (n=83, 92)	45	63		
Week76; BCVA gain from baseline >=5 (n=68, 74)	62	67		
Week76; BCVA gain from baseline >=10 (n=68, 74)	52	61		
Week76; BCVA gain from baseline >=15 (n=68, 74)	43	53		

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	226	224		
Units: Participants				
Week4; BCVA loss from baseline >=5 (n=223, 217)	6	7		
Week4; BCVA loss from baseline >=10 (n=223, 217)	1	3		
Week4; BCVA loss from baseline >=15 (n=223, 217)	0	0		
Week8; BCVA loss from baseline >=5 (n=204, 199)	2	4		
Week8; BCVA loss from baseline >=10 (n=204, 199)	1	2		
Week8; BCVA loss from baseline >=15 (n=204, 199)	1	0		
Week12; BCVA loss from baseline >=5 (n=185,182)	3	2		
Week12; BCVA loss from baseline >=10 (n=185,182)	2	1		
Week12; BCVA loss from baseline >=15 (n=185,182)	1	0		
Week16; BCVA loss from baseline >=5 (n=160,160)	9	4		
Week16; BCVA loss from baseline >=10 (n=160,160)	5	2		
Week16; BCVA loss from baseline >=15 (n=160,160)	3	2		
Week20; BCVA loss from baseline >=5 (n=144,149)	6	4		
Week20; BCVA loss from baseline >=10 (n=144,149)	2	3		
Week20; BCVA loss from baseline >=15 (n=144,149)	2	1		
Week24; BCVA loss from baseline >=5 (n=147,144)	8	3		
Week24; BCVA loss from baseline >=10 (n=147,144)	3	3		
Week24; BCVA loss from baseline >=15 (n=147,144)	3	1		
Week28; BCVA loss from baseline >=5 (n=135,136)	9	2		
Week28; BCVA loss from baseline >=10 (n=135,136)	6	1		
Week28; BCVA loss from baseline >=15 (n=135,136)	6	1		
Week32; BCVA loss from baseline >=5 (n=124,128)	8	3		
Week32; BCVA loss from baseline >=10 (n=124,128)	5	2		
Week32; BCVA loss from baseline >=15 (n=124,128)	3	0		
Week36; BCVA loss from baseline >=5 (n=123,125)	9	2		
Week36; BCVA loss from baseline >=10 (n=123,125)	7	1		

Week36; BCVA loss from baseline >=15 (n=123,125)	5	1		
Week40; BCVA loss from baseline >=5 (n=119,124)	5	4		
Week40; BCVA loss from baseline >=10 (n=119,124)	4	1		
Week40; BCVA loss from baseline >=15 (n=119,124)	2	1		
Week44; BCVA loss from baseline >=5 (n=116,120)	4	5		
Week44; BCVA loss from baseline >=10 (n=116,120)	3	3		
Week44; BCVA loss from baseline >=15 (n=116,120)	2	2		
Week48; BCVA loss from baseline >=5 (n=114,120)	5	3		
Week48; BCVA loss from baseline >=10 (n=114,120)	3	1		
Week48; BCVA loss from baseline >=15 (n=114,120)	1	1		
Week52; BCVA loss from baseline >=5 (n=106,125)	5	2		
Week52; BCVA loss from baseline >=10 (n=106,125)	3	1		
Week52; BCVA loss from baseline >=15 (n=106,125)	2	1		
Week56; BCVA loss from baseline >=5 (n=106,122)	3	3		
Week56; BCVA loss from baseline >=10 (n=106,122)	1	1		
Week56; BCVA loss from baseline >=15 (n=106,122)	0	0		
Week60; BCVA loss from baseline >=5 (n=105, 123)	7	2		
Week60; BCVA loss from baseline >=10 (n=105, 123)	3	0		
Week60; BCVA loss from baseline >=15 (n=105, 123)	1	0		
Week64; BCVA loss from baseline >=5 (n=102, 117)	5	2		
Week64; BCVA loss from baseline >=10 (n=102, 117)	1	1		
Week64; BCVA loss from baseline >=15 (n=102, 117)	1	1		
Week68; BCVA loss from baseline >=5 (n=94, 110)	6	3		
Week68; BCVA loss from baseline >=10 (n=94, 110)	3	1		
Week68; BCVA loss from baseline >=15 (n=94, 110)	1	0		
Week72; BCVA loss from baseline >=5 (n=83, 92)	1	2		
Week72; BCVA loss from baseline >=10 (n=83, 92)	1	2		
Week72; BCVA loss from baseline >=15 (n=83, 92)	1	1		
Week76; BCVA loss from baseline >=5 (n=68, 74)	2	2		
Week76; BCVA loss from baseline >=10 (n=68, 74)	1	0		
Week76; BCVA loss from baseline >=15 (n=68, 74)	1	0		

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	123	132		
Units: µm				
arithmetic mean (standard deviation)	-231.8 (± 188.97)	-259.2 (± 190.69)		

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	110	121		
Units: µm				
arithmetic mean (standard deviation)	-243.6 (± 201.61)	-272.6 (± 194.29)		

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	226	224		
Units: µm				
arithmetic mean (standard deviation)				
Week 4 (n=223, 217)	-247.1 (± 197.99)	-259.4 (± 185.11)		
Week 8 (n=203, 201)	-255.9 (± 206.00)	-270.7 (± 195.49)		
Week 12 (n=184, 182)	-264.5 (± 208.70)	-271.9 (± 194.99)		
Week 16 (n=161, 160)	-271.1 (± 209.38)	-276.1 (± 209.70)		
Week 20 (n=143, 147)	-257.1 (± 197.31)	-285.2 (± 210.32)		
Week 24 (n=147, 143)	-254.9 (± 203.29)	-286.6 (± 207.67)		
Week 28 (n=134, 136)	-245.4 (± 197.62)	-263.6 (± 197.11)		
Week 32 (n=124, 128)	-231.1 (± 208.02)	-262.1 (± 193.80)		
Week 36 (n=123, 125)	-234.1 (± 199.02)	-260.8 (± 195.03)		
Week 40 (n=119, 124)	-224.7 (± 190.50)	-259.0 (± 189.01)		
Week 44 (n=116, 120)	-242.8 (± 197.34)	-264.1 (± 192.06)		
Week 48 (n=114, 120)	-237.1 (± 200.64)	-279.4 (± 193.41)		

Week 52 (n=106, 125)	-243.0 (± 203.87)	-263.4 (± 190.36)		
Week 56 (n=106, 122)	-249.2 (± 206.54)	-271.4 (± 198.09)		
Week 60 (n=105, 123)	-238.3 (± 185.78)	-265.3 (± 187.29)		
Week 64 (n=102, 117)	-249.8 (± 207.86)	-266.1 (± 199.79)		
Week 68 (n=93, 110)	-247.5 (± 217.61)	-261.1 (± 192.30)		
Week 72 (n=83, 92)	-253.4 (± 211.06)	-279.4 (± 185.21)		
Week 76 (n=68, 74)	-255.6 (± 184.22)	-283.7 (± 197.29)		

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 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	226	224		
Units: Participants				
Week 4 (n=223, 217)	83	101		
Week 8 (n=204, 201)	56	68		
Week 12 (n=184, 182)	41	49		
Week 16 (n=161, 160)	34	50		
Week 20 (n=144, 149)	33	45		
Week 24 (n=147, 143)	35	42		
Week 28 (n=134, 136)	47	56		
Week 32 (n=124, 128)	58	50		
Week 36 (n=123, 125)	48	57		
Week 40 (n=119, 124)	42	56		
Week 44 (n=116, 120)	43	54		
Week 48 (n=114, 120)	44	49		
Week 52 (n=106, 125)	34	57		
Week 56 (n=106, 122)	34	54		
Week 60 (n=105, 123)	39	63		

Week 64 (n=102, 117)	31	52		
Week 68 (n=93, 110)	34	52		
Week 72 (n=83, 92)	33	39		
Week 76 (n=68, 74)	16	38		

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	226	224		
Units: Participants				
Week 4 (n=223, 217)	167	153		
Week 8 (n=203, 201)	172	166		
Week 12 (n=184, 182)	156	155		
Week 16 (n=161, 160)	137	131		
Week 20 (n=143, 147)	120	118		
Week 24 (n=147, 143)	127	114		
Week 28 (n=134, 136)	109	103		
Week 32 (n=124, 128)	92	97		
Week 36 (n=123, 125)	96	91		
Week 40 (n=119, 124)	94	92		
Week 44 (n=116, 120)	95	93		
Week 48 (n=114, 120)	89	97		
Week 52 (n=106, 125)	86	95		
Week 56 (n=106, 122)	86	91		
Week 60 (n=105, 123)	83	90		
Week 64 (n=102, 117)	85	90		
Week 68 (n=93, 110)	82	79		
Week 72 (n=83, 92)	70	76		
Week 76 (n=68, 74)	59	59		

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	111	126		
Units: Injections				
arithmetic mean (standard deviation)				
Between Week 24 and Week 52 (n=111, 126)	2.2 (± 1.69)	2.5 (± 2.17)		
Between Week 24 and Week 72 (n=65, 75)	3.2 (± 2.54)	4.0 (± 3.28)		

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	157	159		
Units: Weeks				
median (confidence interval 95%)	12.9 (12.1 to 14.4)	13.1 (11.3 to 17.4)		

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	226	224		
Units: Participants				
Ocular AEs up to week 52	93	72		
Non-Ocular AEs up to week 52	94	112		
Ocular AEs up to week 76	98	75		
Non-Ocular AEs up to week 76	103	120		

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	226	224		
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 24 (n=193, 192)	5.6 (± 11.51)	6.4 (± 11.92)		
Week 52 (n=119, 125)	6.9 (± 13.21)	7.6 (± 10.47)		
Week 76 (n=95, 114)	8.6 (± 13.89)	7.5 (± 11.55)		

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	226			
Units: Participants				
Baseline|Negative (n=219)	67			
Week 4|Negative (n=208)	76			
Week 12|Negative (n=170)	58			
Week 24|Negative (n=134)	44			
Week 36|Negative (n=114)	33			
Week 52|Negative (n=101)	28			
Week 76|Negative (n=68)	17			
Baseline|40 (n=219)	29			
Week 4|40 (n=208)	29			

Week 12|40 (n=170)	17			
Week 24|40 (n=134)	14			
Week 36|40 (n=114)	18			
Week 52|40 (n=101)	18			
Week 76|40 (n=68)	6			
Baseline|120 (n=219)	33			
Week 4|120 (n=208)	31			
Week 12|120 (n=170)	31			
Week 24|120 (n=134)	23			
Week 36|120 (n=114)	19			
Week 52|120 (n=101)	19			
Week 76|120 (n=68)	18			
Baseline|360 (n=219)	37			
Week 4|360 (n=208)	28			
Week 12|360 (n=170)	25			
Week 24|360 (n=134)	17			
Week 36|360 (n=114)	17			
Week 52|360 (n=101)	16			
Week 76|360 (n=68)	14			
Baseline|1080 (n=219)	31			
Week 4|1080 (n=208)	27			
Week 12|1080 (n=170)	19			
Week 24|1080 (n=134)	19			
Week 36|1080 (n=114)	17			
Week 52|1080 (n=101)	14			
Week 76|1080 (n=68)	10			
Baseline|3240 (n=219)	15			
Week 4|3240 (n=208)	9			
Week 12|3240 (n=170)	11			
Week 24|3240 (n=134)	11			
Week 36|3240 (n=114)	8			
Week 52|3240 (n=101)	5			
Week 76|3240 (n=68)	2			
Baseline|9720 (n=219)	1			
Week 4|9720 (n=208)	6			
Week 12|9720 (n=170)	7			
Week 24|9720 (n=134)	5			
Week 36|9720 (n=114)	1			
Week 52|9720 (n=101)	1			
Week 76|9720 (n=68)	1			
Baseline|29200 (n=219)	6			
Week 4|29200 (n=208)	2			
Week 12|29200 (n=170)	2			
Week 24|29200 (n=134)	1			
Week 36|29200 (n=114)	1			
Week 52|29200 (n=101)	0			
Week 76|29200 (n=68)	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	32 / 226 (14.16%)	48 / 450 (10.67%)	16 / 224 (7.14%)
number of deaths (all causes)	0	2	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid seborrhoeic keratosis - Fellow eye			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Vasospasm			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 226 (0.44%)	2 / 450 (0.44%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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			
Pleural mass			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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			
Depression			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Product issues			

Device dislocation			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Weight increased			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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			
Dislocation of vertebra			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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 haemorrhage			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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			
Angina pectoris			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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 arrest			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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 congestive			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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 valve disease			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Ischaemic stroke			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Syncope			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract - Study eye			
subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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

Glaucoma - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Glaucoma - Fellow eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Iridocyclitis - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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 aneurysm - Study eye			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
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 artery occlusion - Fellow eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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
Retinal detachment - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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 occlusive vasculitis - Study eye			
subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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 vasculitis - Study eye			

subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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 vascular occlusion - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Uveitis - Study eye			
subjects affected / exposed	3 / 226 (1.33%)	3 / 450 (0.67%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage - Study eye			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous opacities - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Vitritis - Study eye			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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			
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis acute			
subjects affected / exposed	0 / 226 (0.00%)	1 / 450 (0.22%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 226 (0.44%)	2 / 450 (0.44%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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
Bronchitis			
subjects affected / exposed	1 / 226 (0.44%)	2 / 450 (0.44%)	1 / 224 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 226 (0.44%)	1 / 450 (0.22%)	0 / 224 (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
Endophthalmitis - Study eye			

subjects affected / exposed	2 / 226 (0.88%)	2 / 450 (0.44%)	0 / 224 (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

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	109 / 226 (48.23%)	204 / 450 (45.33%)	95 / 224 (42.41%)
Investigations			
Intraocular pressure increased - Fellow eye			
subjects affected / exposed	3 / 226 (1.33%)	9 / 450 (2.00%)	6 / 224 (2.68%)
occurrences (all)	3	10	7
Intraocular pressure increased - Study eye			
subjects affected / exposed	4 / 226 (1.77%)	12 / 450 (2.67%)	8 / 224 (3.57%)
occurrences (all)	4	25	21
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 226 (1.33%)	8 / 450 (1.78%)	5 / 224 (2.23%)
occurrences (all)	4	10	6
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 226 (11.50%)	45 / 450 (10.00%)	19 / 224 (8.48%)
occurrences (all)	28	48	20
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 226 (1.77%)	11 / 450 (2.44%)	7 / 224 (3.13%)
occurrences (all)	4	13	9
Eye disorders			
Cataract - Study eye			
subjects affected / exposed	9 / 226 (3.98%)	11 / 450 (2.44%)	2 / 224 (0.89%)
occurrences (all)	9	11	2
Dry eye - Fellow eye			
subjects affected / exposed	5 / 226 (2.21%)	14 / 450 (3.11%)	9 / 224 (4.02%)
occurrences (all)	5	14	9
Dry eye - Study eye			

subjects affected / exposed	6 / 226 (2.65%)	15 / 450 (3.33%)	9 / 224 (4.02%)
occurrences (all)	8	17	9
Eye pain - Study eye			
subjects affected / exposed	4 / 226 (1.77%)	15 / 450 (3.33%)	11 / 224 (4.91%)
occurrences (all)	6	23	17
Conjunctival haemorrhage - Study eye			
subjects affected / exposed	11 / 226 (4.87%)	23 / 450 (5.11%)	12 / 224 (5.36%)
occurrences (all)	11	27	16
Macular oedema - Study eye			
subjects affected / exposed	15 / 226 (6.64%)	25 / 450 (5.56%)	10 / 224 (4.46%)
occurrences (all)	25	38	13
Foreign body sensation in eyes - Study eye			
subjects affected / exposed	5 / 226 (2.21%)	6 / 450 (1.33%)	1 / 224 (0.45%)
occurrences (all)	5	6	1
Retinal haemorrhage - Study eye			
subjects affected / exposed	2 / 226 (0.88%)	10 / 450 (2.22%)	8 / 224 (3.57%)
occurrences (all)	2	10	8
Uveitis - Study eye			
subjects affected / exposed	5 / 226 (2.21%)	5 / 450 (1.11%)	0 / 224 (0.00%)
occurrences (all)	6	6	0
Visual acuity reduced - Study eye			
subjects affected / exposed	15 / 226 (6.64%)	27 / 450 (6.00%)	12 / 224 (5.36%)
occurrences (all)	19	33	14
Retinal exudates - Study eye			
subjects affected / exposed	5 / 226 (2.21%)	13 / 450 (2.89%)	8 / 224 (3.57%)
occurrences (all)	5	13	8
Vitreous detachment - Study eye			
subjects affected / exposed	5 / 226 (2.21%)	10 / 450 (2.22%)	5 / 224 (2.23%)
occurrences (all)	5	12	7
Vitreous floaters - Study eye			
subjects affected / exposed	11 / 226 (4.87%)	16 / 450 (3.56%)	5 / 224 (2.23%)
occurrences (all)	12	18	6
Vitritis - Study eye			

subjects affected / exposed	5 / 226 (2.21%)	5 / 450 (1.11%)	0 / 224 (0.00%)
occurrences (all)	5	5	0
Vitreous opacities - Study eye			
subjects affected / exposed	5 / 226 (2.21%)	6 / 450 (1.33%)	1 / 224 (0.45%)
occurrences (all)	5	6	1
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	5 / 226 (2.21%)	8 / 450 (1.78%)	3 / 224 (1.34%)
occurrences (all)	7	10	3
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	6 / 226 (2.65%)	8 / 450 (1.78%)	2 / 224 (0.89%)
occurrences (all)	7	10	3
Back pain			
subjects affected / exposed	2 / 226 (0.88%)	9 / 450 (2.00%)	7 / 224 (3.13%)
occurrences (all)	2	9	7
Arthralgia			
subjects affected / exposed	2 / 226 (0.88%)	8 / 450 (1.78%)	6 / 224 (2.68%)
occurrences (all)	2	9	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 226 (2.21%)	11 / 450 (2.44%)	6 / 224 (2.68%)
occurrences (all)	5	12	7
COVID-19			
subjects affected / exposed	7 / 226 (3.10%)	14 / 450 (3.11%)	7 / 224 (3.13%)
occurrences (all)	7	14	7
Nasopharyngitis			
subjects affected / exposed	6 / 226 (2.65%)	13 / 450 (2.89%)	7 / 224 (3.13%)
occurrences (all)	6	14	8
Upper respiratory tract infection			
subjects affected / exposed	2 / 226 (0.88%)	9 / 450 (2.00%)	7 / 224 (3.13%)
occurrences (all)	2	11	9
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	5 / 226 (2.21%)	8 / 450 (1.78%)	3 / 224 (1.34%)
occurrences (all)	5	8	3

Type 2 diabetes mellitus subjects affected / exposed occurrences (all)	5 / 226 (2.21%) 5	5 / 450 (1.11%) 5	0 / 224 (0.00%) 0

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 the amendment was to provide clarification and guidance on safety assessments in accordance to the urgent safety measure regarding the postmarketing reports with brolucizumab in the treatment of nAMD, which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI, that may result in severe vision loss. In addition, the amendment included modifications (exclusion criteria, prohibited medications/procedures, informed consent procedures, visit schedule and assessments, safety, laboratory evaluations, data analysis and statistical methods) due to the 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: