Clinical trial results:
56-week, phase IIIb/IV, open-label, one-arm extension study to assess the efficacy and safety of brolucizumab 6 mg in a Treat-to-Control regimen with maximum treatment intervals up to 20 weeks for the treatment of subjects with neovascular age-related macular degeneration who have completed the CRTH258A2303 (TALON) study

Summary

EudraCT number	2020-002349-40
Trial protocol	NL PT CZ SE BE DE IT
Global end of trial date	28 March 2023

Results information

Result version number	v2 (current)
This version publication date	18 April 2024
First version publication date	16 March 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRTH258A2303E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04597632
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	28 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the extended durability of brolucizumab in a treat-to-control (TtC) regimen with respect to the duration of treatment intervals at Week 56.

To evaluate the functional outcomes of brolucizumab in a TtC regimen with respect to average change in best-corrected visual acuity (BCVA) at Week 52 and Week 56.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czechia: 25
Country: Number of subjects enrolled	France: 62
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Malaysia: 4
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Korea, Republic of: 42
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Taiwan: 13

Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	248
EEA total number of subjects	149

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)	14
From 65 to 84 years	199
85 years and over	35

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 248 participants who were treated in this trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	brolucizumab 6 mg (Extension study total)

Arm description:

Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.

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

Dosage and administration details:

brolucizumab 6 mg that was administered via intravitreal treatment (IVT) injection. This was a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.

Number of subjects in period 1	brolucizumab 6 mg (Extension study total)
Started	248
Completed	231
Not completed	17
Adverse event, serious fatal	1
Consent withdrawn by subject	10
Adverse event, non-fatal	5
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	brolucizumab 6 mg (Extension study total)
Reporting group description:	
Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	

Reporting group values	brolucizumab 6 mg (Extension study total)	Total	
Number of subjects	248	248	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	199	199	
85 years and over	35	35	
Age Continuous Units: Years			
arithmetic mean	75.9		
standard deviation	± 7.90	-	
Sex: Female, Male Units: Participants			
Female	129	129	
Male	119	119	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	61	61	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	187	187	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	23	23	
Not Hispanic or Latino	219	219	
Unknown or Not Reported	6	6	

End points

End points reporting groups

Reporting group title	brolucizumab 6 mg (Extension study total)
Reporting group description:	
Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Subject analysis set title	brolucizumab 6 mg
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Subject analysis set title	Brolucizumab 6 mg (Core Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	
Subject analysis set title	Aflibercept 2 mg (Core Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study	
Subject analysis set title	brolucizumab 6 mg (Extension study total)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Subject analysis set title	Brolucizumab 6 mg (Core Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	
Subject analysis set title	Aflibercept 2 mg (Core Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study	
Subject analysis set title	brolucizumab 6 mg (Extension study total)
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Subject analysis set title	Brolucizumab 6 mg (Core Study)
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	
Subject analysis set title	Aflibercept 2 mg (Core Study)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study

Subject analysis set title	brolucizumab 6 mg (Extension study total)
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.

Subject analysis set title	Brolucizumab 6 mg (Core Study)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study

Subject analysis set title	Aflibercept 2 mg (Core Study)
Subject analysis set type	Full analysis

Subject analysis set description:

Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study

Subject analysis set title	brolucizumab 6 mg
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.

Primary: Duration of the last interval with no disease activity up to Week 56 - study eye

End point title	Duration of the last interval with no disease activity up to Week 56 - study eye[1]

End point description:

Number of subjects in every 4 weeks (q4w), every 8 weeks (q8w), every 12 weeks (q12w) and every 20 weeks (q20w) intervals at last interval with no disease activity up to Week 56. Last interval with no disease activity (number of weeks): Number of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the extension study

End point type	Primary

End point timeframe:

Up to Week 56

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable for a single arm study (for this extension study).

End point values	brolucizumab 6 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	237			
Units: Participants				
20 weeks	68			
16 weeks	59			
12 weeks	47			
8 weeks	49			
4 weeks	14			

Statistical analyses

No statistical analyses for this end point

Primary: Average change in BCVA from baseline to Week 52 and Week 56 for the study eye

End point title	Average change in BCVA from baseline to Week 52 and Week 56 for the study eye[2]

End point description:

Best-Corrected Visual Acuity (BCVA) was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. Visual Function of the study eye was assessed using the ETDRS protocol. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning. The average change in BCVA from Baseline of the extension study at Week 52 and Week 56 was estimated by an analysis of variance (ANOVA) with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects. Last observation carried forward (LOCF) was used to impute missing BCVA values.

End point type	Primary

End point timeframe:

Extension study baseline, average of Week 52 and Week 56

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not applicable for a single arm study (for this extension study).

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)	brolucizumab 6 mg (Extension study total)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	135	113	248	
Units: Letters read				
arithmetic mean (standard deviation)	-1.8 (± 8.29)	-2.9 (± 7.33)	-2.3 (± 7.88)	

Statistical analyses

No statistical analyses for this end point

Secondary: Average change in central subfield thickness (CSFT) from baseline to Week 52 and Week 56 - study eye

End point title	Average change in central subfield thickness (CSFT) from baseline to Week 52 and Week 56 - study eye

End point description:

Central Subfield Thickness (µm): Analysis of Variance (ANOVA) results for the average change from extension study Baseline at Week 52 and Week 56 for the study eye in the extension study by core study treatment arm. Central Subfield Thickness was assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

End point type	Secondary

End point timeframe:

Extension study baseline, average of Week 52 and Week 56

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)	brolucizumab 6 mg (Extension study total)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	105	89	194	
Units: µm				
arithmetic mean (standard deviation)	5.9 (± 24.43)	-14.1 (± 60.67)	-3.3 (± 45.83)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of subjects with presence of IRF and/or SRF, and sub-RPE fluid in the study eye at Week 52 and Week 56 overall and by core study treatment arm

End point title	Number (%) of subjects with presence of IRF and/or SRF, and sub-RPE fluid in the study eye at Week 52 and Week 56 overall and by core study treatment arm

End point description:

Intraretinal Fluid (IRF) and Subretinal Fluid (SRF) status in the central subfield as assessed by Spectral Domain Ocular Coherence Tomography (SD-OCT): Number (%) of subjects with presence of IRF and/or SRF, and sub-Retinal Pigment Epithelium (RPE) fluid in the study eye at Week 52 and Week 56 overall and by core study treatment arm

End point type	Secondary

End point timeframe:

Weeks 52 and 56

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)	brolucizumab 6 mg (Extension study total)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	106	94	200	
Units: Participants				
Week 52 IRF assessment - Present (n=103,90,193)	10	14	24	
Week 52 IRF assessment - Absent (n=103,90,193)	93	76	169	
Week 52 SRF assessment - Present (n=103,90,193)	14	9	23	
Week 52 SRF assessment - Absent (n=103,90,193)	89	81	170	
Week 52 Sub-RPE fluid - Present (n=103,90,193)	52	44	96	
Week 52 Sub-RPE fluid - Absent (n=103,90,193)	51	46	97	

Week 52 IRF and/or SRF - Present (n=103,90,193)	23	22	45	
Week 52 IRF and/or SRF - Absent (n=103,90,193)	102	89	191	
Week 52 IRF and SRF - Present (n=103,90,193)	1	1	2	
Week 52 IRF and SRF - Absent (n=103,90,193)	80	68	148	
Week 56 IRF assessment - Present	13	12	25	
Week 56 IRF assessment - Absent	93	82	175	
Week 56 SRF assessment - Present	11	7	18	
Week 56 SRF assessment - Absent	95	87	182	
Week 56 Sub-RPE fluid - Present	51	49	100	
Week 56 Sub-RPE fluid - Absent	55	45	100	
Week 56 IRF and/or SRF - Present	23	17	40	
Week 56 IRF and/or SRF - Absent	105	92	197	
Week 56 IRF and SRF - Present	1	2	3	
Week 56 IRF and SRF - Absent	83	77	160	

Statistical analyses

No statistical analyses for this end point

Secondary: Last interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the Extension Study by core study randomized treatment arm

End point title	Last interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the Extension Study by core study randomized treatment arm

End point description:

Duration of the last interval with no disease activity up to Week 52 by core study treatment arm.

End point type	Secondary

End point timeframe:

up to Week 56

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	107		
Units: Participants				
20 Weeks	49	19		
16 Weeks	29	30		
12 Weeks	21	26		
8 Weeks	23	26		
4 Weeks	8	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximal interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the extension study

End point title	Maximal interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the extension study

End point description:

Duration of the maximal intervals with no disease activity up to Week 52 by core study treatment arm.

End point type	Secondary

End point timeframe:

up to Week 56

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	107		
Units: Participants				
20 Weeks	54	20		
16 Weeks	28	31		
12 Weeks	23	34		
8 Weeks	22	18		
4 Weeks	3	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of subjects with change in duration of last interval with no disease activity between Baseline of the extension study and Week 56 by core study treatment arm

End point title	Number (%) of subjects with change in duration of last interval with no disease activity between Baseline of the extension study and Week 56 by core study treatment arm

End point description:

Change in last interval with no disease activity

End point type	Secondary

End point timeframe:

Extension study baseline, up to Week 56

End point values	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	130	107		
Units: Participants				
16 Weeks	0	2		
12 Weeks	8	5		
8 Weeks	21	32		
4 Weeks	49	28		
0 Weeks	41	31		
- 4 Weeks	8	7		
-8 Weeks	2	2		
-12 Weeks	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent ocular adverse events (greater than or equal to 1.0%) by preferred term for the study eye

End point title	Treatment-emergent ocular adverse events (greater than or equal to 1.0%) by preferred term for the study eye

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

End point type	Secondary

End point timeframe:

Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.

End point values	brolucizumab 6 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	248			
Units: Participants				
Number of subjects with at least one AE	63			
Cataract	9			
Eye pain	6			
Visual acuity reduced	6			
Intraocular pressure increased	5			
Retinal haemorrhage	4			

Ocular discomfort	3			
Vitreous floaters	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment-emergent non-ocular adverse events (greater than or equal to 2%) by preferred term

End point title	Treatment-emergent non-ocular adverse events (greater than or equal to 2%) by preferred term

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.

End point type	Secondary

End point timeframe:

Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.

End point values	brolucizumab 6 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	248			
Units: Participants				
Number of subjects with at least one AE	82			
COVID-19	10			
Nasopharyngitis	8			
Fall	7			
Basal cell carcinoma	5			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

On treatment death monitoring occurred after the first dose of study drug in the extension study until 30 days after the last administration of study drug for a maximum timeframe of approximately 56 weeks. Post-treatment death monitoring occurred greater than 30 days after the last administration of study drug.

End point type	Post-hoc

End point timeframe:

On-treatment death reporting - from first dose until 30 days after last dose for a maximum timeframe of approximately 56 weeks. Post-treatment death reporting - greater than 30 days after the last dose of

study drug.

End point values	brolucizumab 6 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	248			
Units: Participants				
On-treatment Deaths	0			
Post-treatment Deaths	1			
Total Deaths	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from the first dose of study-drug until the end of the treatment period (at Week 208) plus 16 weeks additional follow up reporting, for a maximum timeframe of approximately 224 weeks.

Adverse event reporting additional description:

Treatment emergent adverse events in this study are events that started after the first dose of study treatment and until 84 days after the last study treatment, or events present prior to the first dose of treatment which increased in severity based on preferred term within 84 days after the last study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Brolucizumab 6mg

Reporting group description:

Brolucizumab 6mg

Serious adverse events	Brolucizumab 6mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 248 (10.48%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	5 / 248 (2.02%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			

subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Spinal compression fracture				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Contusion				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 248 (0.81%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Procedural vomiting				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				

subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	2 / 248 (0.81%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Seizure				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Retinal detachment - Fellow eye				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal occlusive vasculitis - Study eye				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreal cells - Study eye				
subjects affected / exposed	1 / 248 (0.40%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Vitreal cells - Fellow eye			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis - Study eye			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory arrest			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Calculus urinary			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			

Chondropathy			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Whipple's disease			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			
subjects affected / exposed	1 / 248 (0.40%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brolucizumab 6mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 248 (23.39%)		
Investigations			
Intraocular pressure increased - Study eye			
subjects affected / exposed	5 / 248 (2.02%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Fall			

subjects affected / exposed	7 / 248 (2.82%)		
occurrences (all)	7		
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	7 / 248 (2.82%)		
occurrences (all)	7		
Cataract - Study eye			
subjects affected / exposed	9 / 248 (3.63%)		
occurrences (all)	9		
Eye pain - Study eye			
subjects affected / exposed	6 / 248 (2.42%)		
occurrences (all)	6		
Neovascular age-related macular degeneration - Fellow eye			
subjects affected / exposed	10 / 248 (4.03%)		
occurrences (all)	10		
Visual acuity reduced - Study eye			
subjects affected / exposed	6 / 248 (2.42%)		
occurrences (all)	6		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 248 (3.23%)		
occurrences (all)	8		
COVID-19			
subjects affected / exposed	10 / 248 (4.03%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2021	To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects who were currently on q4w dosing beyond the first 3 monthly loading doses ("loading phase") or would need q4w dosing beyond the "loading phase" based on the Investigator's assessment. This was as per the USM dated 27-May-2021 (based on CTH258AUS04 (MERLIN) Year 1 first interpretable results (FIR) indicating a higher frequency of intraocular inflammation (IOI) including retinal vasculitis (RV), and retinal vascular occlusion (RO) in brolucizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%, respectively). To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects with RV and RO events. This was as per the USM dated 10-Aug-2021 (based on the results of the mechanistic study BASICHR0049 which identified a causal link with an immune-mediated mechanism of the previously identified risk of RV and/or RO, typically in the presence of IOI). To update safety sections throughout the protocol including updates to the Risks and Benefits section and the creation of a new section under Safety Monitoring which consolidated all risk mitigation information into one section of the protocol.
20 October 2021	The main purpose of this amendment was to reduce the sample size for this study. The initial sample size calculation for this open-label, one-arm extension study was mainly based on the assumption that all eligible subjects completing the core study could be enrolled. Following the USM dated 27-May-2021, subjects requiring study treatment every 4 weeks were discontinued, therefore, the originally planned number of subjects transitioning from the core study into the extension study was reduced. Consequently, the sample size was re-assessed with the focus on the estimation of subjects who would be on a q20w interval. This estimation could be achieved with acceptable precision with a sample size of 250. The study objectives were still assessed with the revised sample size. In addition, information was included on the gender imbalance in the reported rates of IOI-related adverse events following brolucizumab treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported