Clinical trial results:
A one-year, single-arm, open-label, multicenter study assessing the effect of brolucizumab 6 mg on disease control in adult patients with suboptimal anatomically controlled neovascular age-related macular degeneration (SWIFT)

Summary

EudraCT number	2019-004145-33
Trial protocol	FR
Global end of trial date	03 May 2023

Results information

Result version number	v2 (current)
This version publication date	07 April 2024
First version publication date	12 October 2023
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CRTH258AFR03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04264819
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	03 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2022
Global end of trial reached?	Yes
Global end of trial date	03 May 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Primary objective is to evaluate the effect of brolucizumab 6 mg on disease control.

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	14 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	France: 295
Worldwide total number of subjects	295
EEA total number of subjects	295

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)	22
From 65 to 84 years	217
85 years and over	56

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Before inclusion, patients underwent a 4-to-8-Week Washout Period (from 26 to 62 days) from the last administration of a licensed anti-VEGF drug (i.e., Lucentis®, Eylea®).

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	RTH258/Brolucizumab

Arm description:

This is a single arm study in which all patients are treated with brolucizumab 6mg; 3 loading injections (at Screening/Baseline, week 4 and week 8) followed by treat-to-control phase with adjustable treatment frequency based on disease activity from every 8 to up to 16 weeks; last treatment at week 44/46 based on the treatment regimen.

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 (RTH258 6 mg /0.05 mL)

Number of subjects in period 1	RTH258/Brolucizumab
Started	295
Full Analysis Set (FAS)	289
Completed	249
Not completed	46
Adverse event, serious fatal	2
Physician decision	19
Consent withdrawn by subject	11
Adverse event, non-fatal	12
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	RTH258/Brolucizumab

Reporting group description:

This is a single arm study in which all patients are treated with brolucizumab 6mg; 3 loading injections (at Screening/Baseline, week 4 and week 8) followed by treat-to-control phase with adjustable treatment frequency based on disease activity from every 8 to up to 16 weeks; last treatment at week 44/46 based on the treatment regimen.

Reporting group values	RTH258/Brolucizumab	Total	
Number of subjects	295	295	
Age Categorical Units: Participants			
<=18 years	0	0	
Between 18 and 65 years	22	22	
>=65 years	273	273	
Age Continuous Units: Years			
arithmetic mean	76.2		
standard deviation	± 8.13	-	
Sex: Female, Male Units: Participants			
Female	183	183	
Male	112	112	

End points

End points reporting groups

Reporting group title	RTH258/Brolucizumab

Reporting group description:

This is a single arm study in which all patients are treated with brolucizumab 6mg; 3 loading injections (at Screening/Baseline, week 4 and week 8) followed by treat-to-control phase with adjustable treatment frequency based on disease activity from every 8 to up to 16 weeks; last treatment at week 44/46 based on the treatment regimen.

Primary: Number of patients with no disease activity at Week 16

End point title	Number of patients with no disease activity at Week 16[1]

End point description:

Disease activity criteria were assessed by the Investigator based on whether neovascular age-related macular degeneration (nAMD) was still active or had been re-activated. The disease was defined as active if at least one of the following
criteria was observed:
- Best-corrected visual acuity (BCVA) decrease ≥ 5 letters from the best value since Baseline due to disease activity
- Any significant increase in central retinal thickness (CRT)
- Retinal hemorrhage
- Intraretinal fluid or sub-retinal fluid (SRF) due to disease activity (degenerative cysts allowed)
- Increase of sub-retinal pigmented epithelium (RPE) fluid
These criteria were for guidance only, Investigators could define disease activity based on their own assessment.

End point type	Primary

End point timeframe:

Week 16

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.

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	217			
Units: Participants	89			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in CFST (Central Sub-Field Retinal Thickness) as assessed by OCT (Optical Coherence Tomography) over time up to Week 48

End point title	Change from Baseline in CFST (Central Sub-Field Retinal Thickness) as assessed by OCT (Optical Coherence Tomography) over time up to Week 48

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

End point type	Secondary
End point timeframe: Baseline, Weeks 4,8,16, 48	

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	258			
Units: µm				
arithmetic mean (standard deviation)				
Week 4	-79.19 (± 79.874)			
Week 8 (n=227)	-88.08 (± 91.505)			
Week 16 (n=220)	-48.87 (± 84.345)			
Week 48 (n = 195)	-66.75 (± 101.496)			

Statistical analyses

No statistical analyses for this end point

Secondary: Absence of IRF (Intraretinal Fluid), SRF (Subretinal Fluid), and sub-RPE (Retinal Pigmented Epithelium) fluid as assessed by OCT over time up to Week 48

End point title	Absence of IRF (Intraretinal Fluid), SRF (Subretinal Fluid), and sub-RPE (Retinal Pigmented Epithelium) fluid as assessed by OCT over time up to Week 48

End point description:

Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

At week 8, for 1 patient, the fluid assessment was performed, but result is unknown;
at week 16, for 1 patient, the fluid assessment was performed, but result is unknown;
at week 48, for 2 patients, the fluid assessment was performed, but result is unknown.

End point type	Secondary
End point timeframe: Baseline, Week 4, 8, 16, 48	

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	289			
Units: Participants				
Baseline - Intraretinal fluid	104			
Baseline - Subretinal fluid	245			
Baseline - Sub-RPE fluid	204			
Baseline - Without any fluid (IRF/SRF)	4			

Baseline - With any fluid (IRF/SRF)	285			
Week 4 - Intraretinal fluid (n=260)	61			
Week 4 - Subretinal fluid (n=260)	102			
Week 4 - Sub-RPE fluid (n=260)	102			
Week 4 - Without any fluid (IRF/SRF) (n=260)	114			
Week 4 - With any fluid (IRF/SRF) (n=260)	146			
Week 8 - Intraretinal fluid (n=229)	50			
Week 8 - Subretinal fluid (n=229)	72			
Week 8 - Sub-RPE fluid (n=229)	74			
Week 8 - Without any fluid (IRF/SRF) (n=229)	122			
Week 8 - With any fluid (IRF/SRF) (n=229)	106			
Week 16 - Intraretinal fluid (n=222)	70			
Week 16 - Subretinal fluid (n=222)	117			
Week 16 - Sub-RPE fluid (n=222)	99			
Week 16 - Without any fluid (IRF/SRF) (n=222)	69			
Week 16 - With any fluid (IRF/SRF) (n=222)	152			
Week 48 - Intraretinal fluid (n=198)	64			
Week 48 - Subretinal fluid (n=198)	84			
Week 48 - Sub-RPE fluid (n=198)	85			
Week 48 - Without any fluid (IRF/SRF) (n=198)	80			
Week 48 - With any fluid (IRF/SRF) (n=198)	116			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with no disease activity at Week 48

End point title	Number of patients with no disease activity at Week 48

End point description:

Disease activity criteria were assessed by the Investigator based on whether neovascular age-related macular degeneration (nAMD) was still active or had been re-activated. The disease was defined as active if at least one of the following
criteria was observed:
- Best-corrected visual acuity (BCVA) decrease ≥ 5 letters from the best value since Baseline due to disease activity
- Any significant increase in central retinal thickness (CRT)
- Retinal hemorrhage
- Intraretinal fluid or sub-retinal fluid (SRF) due to disease activity (degenerative cysts allowed)
- Increase of sub-retinal pigmented epithelium (RPE) fluid
These criteria were for guidance only, Investigators could define disease activity based on their own assessment.

End point type	Secondary

End point timeframe:

Week 48

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	196			
Units: Participants	102			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with a dry retina (neither IRF nor SRF) up to Week 48

End point title	Number of patients with a dry retina (neither IRF nor SRF) up to Week 48

End point description:

Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16, 48

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	289			
Units: Participants				
Baseline	4			
Week 4 (n=260)	114			
Week 8 (n=229)	122			
Week 16 (n=222)	69			
Week 48 (n=198)	80			

Statistical analyses

No statistical analyses for this end point

Secondary: Distribution of the last interval with no disease activity up to Week 48

End point title	Distribution of the last interval with no disease activity up to Week 48

End point description:

Disease activity criteria were assessed by the Investigator based on whether neovascular age-related macular degeneration (nAMD) was still active or had been re-activated. The disease was defined as active if at least one of the following

criteria was observed:
- Best-corrected visual acuity (BCVA) decrease ≥ 5 letters from the best value since Baseline due to disease activity
- Any significant increase in central retinal thickness (CRT)
- Retinal hemorrhage
- Intraretinal fluid or sub-retinal fluid (SRF) due to disease activity (degenerative cysts allowed)
- Increase of sub-retinal pigmented epithelium (RPE) fluid
These criteria were for guidance only, Investigators could define disease activity based on their own assessment.

End point type	Secondary

End point timeframe:

Intervals of 0,4,5,6,7,8,9,10,11,12,13,14,15,16,17 Weeks

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	289			
Units: Participants				
q0wk	10			
q4wk	24			
q5wk	13			
q6wk	7			
q7wk	19			
q8wk	102			
q9wk	28			
q10wk	10			
q11wk	13			
q12wk	29			
q13wk	10			
q14wk	3			
q15wk	4			
q16wk	13			
q17wk	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Distribution of the maximal intervals with no disease activity up to Week 48

End point title	Distribution of the maximal intervals with no disease activity up to Week 48

End point description:

Disease activity criteria were assessed by the Investigator based on whether neovascular age-related macular degeneration (nAMD) was still active or had been re-activated. The disease was defined as active if at least one of the following
criteria was observed:
- Best-corrected visual acuity (BCVA) decrease ≥ 5 letters from the best value since Baseline due to disease activity
- Any significant increase in central retinal thickness (CRT)
- Retinal hemorrhage

- Intraretinal fluid or sub-retinal fluid (SRF) due to disease activity (degenerative cysts allowed)
- Increase of sub-retinal pigmented epithelium (RPE) fluid
These criteria were for guidance only, Investigators could define disease activity based on their own assessment.

End point type	Secondary

End point timeframe:

Intervals of 0,4,5,6,7,8,9,10,11,12,13,14,15,16,17 Weeks

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	289			
Units: Participants				
q0wk	10			
q4wk	19			
q5wk	18			
q6wk	3			
q7wk	6			
q8wk	51			
q9wk	48			
q10wk	19			
q11wk	14			
q12wk	56			
q13wk	16			
q14wk	3			
q15wk	5			
q16wk	16			
q17wk	4			
q20wk	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Average change in BCVA (Best-Corrected Visual Acuity) from Baseline up to Week 48

End point title	Average change in BCVA (Best-Corrected Visual Acuity) from Baseline up to Week 48

End point description:

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.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 16, 48

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	259			
Units: Letters read				
arithmetic mean (standard deviation)				
Week 4	2.6 (± 6.09)			
Week 8 (n=231)	4.1 (± 6.68)			
Week 16 (n=218)	4.1 (± 7.41)			
Week 48 (n=199)	3.2 (± 9.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of treatment-emergent adverse events – Overall

End point title	Summary of treatment-emergent adverse events – Overall

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 were reported from first dose of study treatment until Week 48, plus 30 days post treatment, up to a maximum duration of 52 weeks.

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: Participants				
Any adverse event (AE)	165			
Any AE - Treatment-related	34			
Any AE - Procedure-related	33			
Serious adverse events (SAEs)	28			
SAE s- Treatment-related	14			
SAEs - Procedure-related	4			
Fatal SAEs	2			
Fatal SAEs - Treatment-related	0			
Fatal SAEs - Procedure-related	0			
AEs causing treatment disc.	39			
AEs causing treatment disc. - Treatment-related	30			
AEs causing treatment disc. - Procedure-related	5			

AEs leading to treatment interruption	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of treatment-emergent adverse events regardless of study treatment relationship by primary system organ class, preferred term, and maximum severity - Ocular (study eye)

End point title	Summary of treatment-emergent adverse events regardless of study treatment relationship by primary system organ class, preferred term, and maximum severity - Ocular (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 were reported from first dose of study treatment until Week 48, plus 30 days post treatment, up to a maximum duration of 52 weeks.

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: Participants				
Number of patients with at least one AE	100			
Eye disorders	92			
Eye disorders-Vitreous floaters	15			
Eye disorders-Ocular hypertension	11			
Eye disorders-Vitreous detachment	9			
Eye disorders-Uveitis	8			
Eye disorders-Vitritis	8			
Eye disorders-Cataract	5			
Eye disorders-Iridocyclitis	5			
Eye disorders-Dry eye	4			
Eye disorders-Eye inflammation	4			
Eye disorders-Eye irritation	4			
Eye disorders-Eye pain	4			
Eye disorders-Posterior capsule opacification	4			
Eye disorders-Retinal hemorrhage	4			
Eye disorders-Vision blurred	4			
Eye disorders-Conjunctival hemorrhage	2			
Eye disorders-Ocular vasculitis	2			
Eye disorders-Retinal artery occlusion	2			

Eye disorders-Retinal occlusive vasculitis	2			
Eye disorders-Retinal pigment epithelial tear	2			
Eye disorders-Retinal tear	2			
Eye disorders-Retinal vasculitis	2			
Eye disorders-Visual acuity reduced	2			
Eye disorders-Anterior chamber cell	1			
Eye disorders-Cyclitis	1			
Eye disorders-Diplopia	1			
Eye disorders-Dyschromatopsia	1			
Eye disorders-Eye hematoma	1			
Eye disorders-Eye pruritus	1			
Eye disorders-Glaucoma	1			
Eye disorders-Keratitis	1			
Eye disorders-Lacrimation increased	1			
Eye disorders-Macular hole	1			
Eye disorders-Ocular hyperemia	1			
Eye disorders-Ocular ischemic syndrome	1			
Eye disorders-Retinal aneurysm	1			
Eye disorders-Retinal degeneration	1			
Eye disorders-Retinal detachment	1			
Eye disorders-Retinal drusen	1			
Eye disorders-Retinal perivascular sheathing	1			
Eye disorders-Serous retinal detachment	1			
Eye disorders-Swelling of eyelid	1			
Eye disorders-Visual field defect	1			
Eye disorders-Vitreous hemorrhage	1			
Eye disorders-Vitreous opacities	1			
Infections and infestations	3			
Infections and infestations-Conjunctivitis	2			
Infections and infestations-Herpes ophthalmic	1			
Injury, poisoning and procedural complications	3			
- Foreign body in eye	1			
- Procedural pain	1			
- Thermal burn	1			
Investigations	7			
Investigations-Intraocular pressure increased	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of treatment-emergent adverse events regardless of study treatment relationship by primary system organ class, preferred term, and maximum severity – Non-ocular

End point title	Summary of treatment-emergent adverse events regardless of study treatment relationship by primary system organ class, preferred term, and maximum severity – Non-ocular

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 were reported from first dose of study treatment until Week 48, plus 30 days post treatment, up to a maximum duration of 52 weeks.

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: Participants	90			

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 – up to 52 weeks; Post-treatment - greater than 30 days after last treatment, up to a maximum timeframe of 81 days after treatment

End point type	Post-hoc

End point timeframe:

On-treatment – up to 52 weeks; Post-treatment - greater than 30 days after last treatment, up to 81 days post-treatment

End point values	RTH258/Brolucizumab			
Subject group type	Reporting group			
Number of subjects analysed	295			
Units: Participants				
On-Treatment Deaths	0			
Post-Treatment Deaths	2			
All Deaths	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until Week 48, plus 30 days post treatment, up to a maximum duration of 52 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	26.0

Reporting groups

Reporting group title	RTH258/Brolucizumab

Reporting group description:

This is a single arm study in which all patients are treated with brolucizumab 6mg; 3 loading injections (at Screening/Baseline, week 4 and week 8) followed by treat-to-control phase with adjustable treatment frequency based on disease activity from every 8 to up to 16 weeks; last treatment at week 44/46 based on the treatment regimen.

Serious adverse events	RTH258/Brolucizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 295 (9.49%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cancer			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Lung adenocarcinoma			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Traumatic intracranial haematoma			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 295 (0.68%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Headache			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			

subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subarachnoid haemorrhage				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cyclitis - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye haematoma - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye inflammation - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Iridocyclitis - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal artery occlusion - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

Retinal occlusive vasculitis - Study eye			
subjects affected / exposed	2 / 295 (0.68%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Uveitis - Study eye			
subjects affected / exposed	7 / 295 (2.37%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Vitritis - Study eye			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	RTH258/Brolucizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	154 / 295 (52.20%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Uterine leiomyoma subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Vascular disorders Phlebitis subjects affected / exposed occurrences (all) White coat hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Arterial stenosis subjects affected / exposed occurrences (all)	 1 / 295 (0.34%) 1 1 / 295 (0.34%) 1 1 / 295 (0.34%) 1 11 / 295 (3.73%) 12 1 / 295 (0.34%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 1 / 295 (0.34%) 1		
Immune system disorders Allergy to arthropod sting subjects affected / exposed occurrences (all) Allergy to synthetic fabric subjects affected / exposed occurrences (all) Drug hypersensitivity subjects affected / exposed occurrences (all) Seasonal allergy subjects affected / exposed occurrences (all)	 1 / 295 (0.34%) 1 1 / 295 (0.34%) 1 1 / 295 (0.34%) 1 1 / 295 (0.34%) 1		

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Psychiatric disorders			
Hallucination			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Investigations			
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Prostatic specific antigen increased			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Intraocular pressure increased - Study eye			
subjects affected / exposed	6 / 295 (2.03%)		
occurrences (all)	8		
Intraocular pressure increased - Both eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Foreign body in eye - Both eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Upper limb fracture			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		

Thermal burn - Both eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Spinal fracture subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Procedural pain - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Radius fracture subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Head injury subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Limb injury subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Arrhythmia subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2		
Arrhythmia supraventricular subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Nervous system disorders Tremor subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Sciatica subjects affected / exposed occurrences (all)	3 / 295 (1.02%) 3		
Psychomotor skills impaired			

subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Amnesia			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	2		
Eye disorders			
Age-related macular degeneration - Fellow eye			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Keratitis - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Neovascular age-related macular degeneration - Fellow eye			
subjects affected / exposed	12 / 295 (4.07%)		
occurrences (all)	12		
Glaucoma - Both eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Eyelid irritation			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Eye pruritus - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Eye pain - Study eye			
subjects affected / exposed	4 / 295 (1.36%)		
occurrences (all)	4		
Eye irritation - Study eye			

subjects affected / exposed	3 / 295 (1.02%)			
occurrences (all)	3			
Eye irritation - Both eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Eye inflammation - Study eye				
subjects affected / exposed	3 / 295 (1.02%)			
occurrences (all)	3			
Dyschromatopsia - Both eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Dry eye - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Dry eye - Both eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Diplopia - Both eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Conjunctival haemorrhage - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Chalazion				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Cataract - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Cataract - Fellow eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Cataract - Both eye				
subjects affected / exposed	4 / 295 (1.36%)			
occurrences (all)	4			

Blepharitis subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Anterior chamber cell - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Lacrimation increased - Both eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Macular hole - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Iridocyclitis - Study eye subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4			
Vitreous floaters - Study eye subjects affected / exposed occurrences (all)	14 / 295 (4.75%) 15			
Vitreous haemorrhage - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Vitreous floaters - Both eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Vitreous detachment - Study eye subjects affected / exposed occurrences (all)	9 / 295 (3.05%) 9			
Visual field defect - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1			
Visual acuity reduced - Study eye subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2			
Vision blurred - Study eye subjects affected / exposed occurrences (all)	3 / 295 (1.02%) 3			

Vision blurred - Fellow eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Vision blurred - Both eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Uveitis - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Swelling of eyelid				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Serous retinal detachment - Fellow eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal vasculitis - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Retinal tear - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Retinal pigment epithelial tear - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Retinal perivascular sheathing - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal perivascular sheathing - Fellow eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal haemorrhage - Study eye				
subjects affected / exposed	4 / 295 (1.36%)			
occurrences (all)	5			
Retinal haemorrhage - Fellow eye				

subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal drusen - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal detachment - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Retinal degeneration - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Posterior capsule opacification - Study eye				
subjects affected / exposed	3 / 295 (1.02%)			
occurrences (all)	3			
Posterior capsule opacification - Fellow eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Posterior capsule opacification - Both eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Ocular vasculitis - Study eye				
subjects affected / exposed	2 / 295 (0.68%)			
occurrences (all)	2			
Ocular hypertension - Study eye				
subjects affected / exposed	10 / 295 (3.39%)			
occurrences (all)	14			
Ocular hypertension - Fellow eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Vitreous opacities - Study eye				
subjects affected / exposed	1 / 295 (0.34%)			
occurrences (all)	1			
Ocular hyperaemia - Study eye				

subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Ocular hypertension - Both eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Vitritis - Study eye			
subjects affected / exposed	5 / 295 (1.69%)		
occurrences (all)	6		
Swelling of eyelid - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Serous retinal detachment - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Retinal aneurysm - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Ocular ischaemic syndrome - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 295 (0.68%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Gingival erosion			

subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Inguinal hernia subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Irritable bowel syndrome subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Nausea subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2		
Rectal polyp subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Skin and subcutaneous tissue disorders			
Rash subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Purpura subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Psoriasis subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Erythema subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Eczema subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Dermatitis allergic subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		

Alopecia			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Hydronephrosis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Urinary tract polyp			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Renal cyst			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Tendonitis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Osteoporosis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		

Osteoarthritis subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2		
Myalgia subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Limb discomfort subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Intervertebral disc protrusion subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Back pain subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4		
Arthralgia subjects affected / exposed occurrences (all)	2 / 295 (0.68%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	4 / 295 (1.36%) 4		
COVID-19 subjects affected / exposed occurrences (all)	9 / 295 (3.05%) 9		
Conjunctivitis - Both eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Conjunctivitis - Study eye subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Dermatophytosis			

subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Herpes ophthalmic - Study eye			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Onychomycosis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Otitis externa			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Periodontitis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	3 / 295 (1.02%)		
occurrences (all)	3		
Tooth abscess			
subjects affected / exposed	1 / 295 (0.34%)		
occurrences (all)	1		
Metabolism and nutrition disorders			

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Hyperuricaemia subjects affected / exposed occurrences (all)	1 / 295 (0.34%) 1		
Diabetes mellitus subjects affected / exposed occurrences (all)	3 / 295 (1.02%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2020	The purpose of this amendment was to incorporate changes requested by Regulatory Authorities. Clarification of the washout period between the last dose of the anti-VEGF treatment received by the patient prior to be included in the study and the first dose of brolucizumab 6 mg administrated in the study. Clarification on the number of mandatory visits and on the data to collect for the fellow eye.
21 October 2020	The purpose was to provide clarification and guidance on safety assessments in accordance to the urgent safety measures regarding the post-marketing reports with brolucizumab 6 mg (Beovu®) in the treatment of nAMD. Restrictions in the use of corticosteroids were removed to provide flexibility using systemic steroids for the treatment of AEs at the Investigator's discretion. Additional guidance was added to emphasize that if any sign of IOI was present, an IVT injection were not to be performed and patients were to be treated for IOI according to clinical practice. Additional examinations and assessments were included to fully characterize cases of IOI. The number of study sites was increased from 50 to 75 to ensure the feasibility of patient recruitment in a 9-month period. Instructions on ophthalmic examinations in case of symptoms of IOI were added.
01 September 2021	As per the urgent safety measures, clarification and guidance were provided on the early discontinuation of study treatment required for those patients who were on q4w dosing beyond the first 3-monthly loading phase or would need q4w dosing beyond the "loading phase" based on the Investigator's assessment. Discontinuation of study treatment for patients who develop RV and/or RVO was added in line with the urgent safety measures. The safety sections were updated throughout the protocol including updating the Risks and Benefits section and creating a new section under Safety Monitoring to consolidate all the information regarding the risk mitigation into one section in the protocol and require close monitoring of patients with IOI. Clarification was provided on record of prior Intraocular or periocular use of corticosteroids in the study eye and remove of the study timelines and number of sites.
25 November 2021	The optional Patient reported outcome (PRO) self-assessment of BCNVA by the patient at home was removed because of the scarce use by the elderly population of the study, which would not allow valid conclusions from data collected. The Warnings and Precautions for Use section of the Beovu® brolucizumab 6 mg EU SmPC was updated to indicate that patients treated with Beovu with a medical history of IOI and/or RVO should be closely monitored, and for patients who develop IOI, even if not associated with RV and/or RVO, treatment with Beovu should be discontinued and the events promptly managed. Information on gender imbalance on IOI following brolucizumab 6 mg treatment was added.
05 April 2022	Due to COVID-19 and the urgent safety measures, the originally planned number of patients could not be achieved. Thus, the sample size was reassessed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported