Clinical trial results:
One year, single arm, open label, multicenter, phase IV study using multimodal imaging to guide disease activity assessment through innovative early predictive anatomical biomarkers of fluid resolution in wAMD patients treated with brolucizumab– IMAGINE study

Summary

EudraCT number	2020-002452-20
Trial protocol	IT
Global end of trial date	04 October 2023

Results information

Result version number	v1
This version publication date	04 October 2024
First version publication date	04 October 2024

Trial information

Trial identification

Sponsor protocol code	CRTH258AIT04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 Pharmaceuticals , 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	04 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 October 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to identify innovative early imaging parameters as predictors of the long-term clinical response to brolucizumab in terms of fluid resolution in patients with wAMD to evaluate their potential in supporting the choice of treatment regimen (q12w or q8w).

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	15 October 2021
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	Italy: 122
Worldwide total number of subjects	122
EEA total number of subjects	122

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)	10
From 65 to 84 years	99
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

There were 122 patients in the safety set and the enrolled set.

Pre-assignment

Screening details:

There were 120 patients in the Full Analysis Set (FAS).

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

Arm description:

Participants received 3 monthly ocular injections followed by a q12w or q8w maintenance phase based on patient's disease activity (DA).

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 -
Participants received 3 monthly ocular injections followed by a q12w or q8w maintenance phase based on patient's disease activity (DA).

Number of subjects in period 1	Brolucizumab 6 mg
Started	122
Completed	91
Not completed	31
Physician decision	6
Consent withdrawn by subject	3
Adverse event, non-fatal	15
Investigator resigned without a replacement	4
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 6 mg
Reporting group description:	
Participants received 3 monthly ocular injections followed by a q12w or q8w maintenance phase based on patient's disease activity (DA).	

Reporting group values	Brolucizumab 6 mg	Total	
Number of subjects	122	122	
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)	10	10	
From 65-84 years	99	99	
85 years and over	13	13	
Age Continuous Units: Years			
arithmetic mean	76.1		
standard deviation	± 7.88	-	
Sex: Female, Male Units: Participants			
Female	72	72	
Male	50	50	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	122	122	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Brolucizumab 6 mg

Reporting group description:

Participants received 3 monthly ocular injections followed by a q12w or q8w maintenance phase based on patient's disease activity (DA).

Primary: Potential predictor factors of fluid-free response: Type of predominant Basal Choroidal Neovascularization (CNV) lesion type, as assessed by SD-OCT at Baseline

End point title	Potential predictor factors of fluid-free response: Type of predominant Basal Choroidal Neovascularization (CNV) lesion type, as assessed by SD-OCT at Baseline[1]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within 'No' and 'Yes' groups according to q12w fluid free.

Type 1 neovascularization arises when CNV proliferation occurs below the Retinal Pigment Epithelium (RPE) and corresponds to occult CNV with a poorly defined pattern of leakage on fluorescein angiography (FA). Type 2 neovascularization refers to CNV proliferation above the RPE in the subretinal space and corresponds to classic CNV with intense fluorescein leakage. Type 3 neovascularization (or retinal angiomatous proliferation [RAP]) occurs when retinal circulation is involved, with an anastomosis between the choroidal and retinal circulations.

PCV = Polypoidal Choroidal Vasculopathy

End point type	Primary

End point timeframe:

Baseline

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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
TYPE I + PCV - No	61			
TYPE I + PCV - Yes	19			
TYPE II - No	21			
TYPE II - Yes	4			
TYPE III - No	53			
TYPE III - Yes	3			
Missing- No	6			
Missing - Yes	1			

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients classified as q12w fluid-free or not q12w fluid-free

End point title	Number of patients classified as q12w fluid-free or not q12w fluid-free[2]

End point description:

Early predictive factors of fluid-free response is defined as the absence of retinal fluid at Week 48 in patients with a stable q12w treatment regimen up to Week 48 after the loading phase, As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

q12w fluid-free: pts completing the treatment and the study maintaining a stable q12w regimen assigned at Wk 16 up to Wk 48 and without the presence of IRF and SRF at Wk 48.

not q12w fluid-free:
-Pt who completed treatment and the study with the presence of IRF or SRF at Wk 48
-Pt who followed the q8w regimen of treatment at any time during the study (considering also who started with q12w regimen but then due to disease activity shifted to q8w regimen)
-Pt who discontinued treatment at any time after b/l since treatment disc. was considered as intercurrent event and a 'failure'.
-Pt who dropped out at any time after b/l since study disc. was considered as intercurrent event and a 'failure'.

End point type	Primary

End point timeframe:

Up to Week 48

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.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
q12w fluid free - NO	93			
q12w fluid free - YES	27			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Sub-retinal pigment epithelium (sub-RPE) fluid

End point title	Potential predictor factors of fluid-free response: Sub-retinal pigment epithelium (sub-RPE) fluid[3]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within ‘No’ and ‘Yes’ groups according to q12w fluid free.

Of note, the category 'Stable absent' is considered also for cases with baseline and last measurement collected equal to 'No' even if there are at least one 'Yes' in one of the other collected measurements. Similarly, the category 'Stable present' is considered also for cases with baseline and last measurement collected equal to 'Yes' even if there are at least one 'No' in one of the other collected measurements.

Stable absent (i.e., all measurements 'No),
Stable present (i.e., all measurements 'Yes'),
Improved (i.e., last measurement collected as 'No' and baseline 'Yes'),
Worsened (i.e., last measurement collected 'Yes' and baseline 'No').

End point type	Primary

End point timeframe:

Baseline to Week 16

Notes:

[3] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Stable absent - No	39			
Stable absent - Yes	12			
Stable present - No	32			
Stable present - Yes	7			
Improved - No	20			
Improved - Yes	8			
Worsened - No	2			
Worsened - Yes	0			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM)

End point title	Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM)[4]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within 'No' and 'Yes' groups according to q12w fluid free.

Of note, the category 'Stable absent' is considered also for cases with baseline and last measurement collected equal to 'No' even if there are at least one 'Yes' in one of the other collected measurements. Similarly, the category 'Stable present' is considered also for cases with baseline and last measurement collected equal to 'Yes' even if there are at least one 'No' in one of the other collected measurements.

Stable absent (i.e., all measurements 'No),
Stable present (i.e., all measurements 'Yes'),
Improved (i.e., last measurement collected as 'No' and baseline 'Yes'),
Worsened (i.e., last measurement collected 'Yes' and baseline 'No').

End point type	Primary

End point timeframe:

Baseline to Week 16

Notes:

[4] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Stable absent - No	41			
Stable absent - Yes	11			
Stable present - No	33			
Stable present - Yes	7			
Improved - No	7			
Improved - Yes	4			
Worsened - No	12			
Worsened - Yes	5			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT)

End point title	Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT)[5]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within ‘No’ and ‘Yes’ groups according to q12w fluid free.

Of note, the category 'Stable absent' is considered also for cases with baseline and last measurement collected equal to 'No' even if there are at least one 'Yes' in one of the other collected measurements. Similarly, the category 'Stable present' is considered also for cases with baseline and last measurement collected equal to 'Yes' even if there are at least one 'No' in one of the other collected measurements.

Stable absent (i.e., all measurements ‘No),
Stable present (i.e., all measurements ‘Yes’),
Improved (i.e., last measurement collected as ‘No’ and baseline ‘Yes’),
Worsened (i.e., last measurement collected ‘Yes’ and baseline ‘No’).

End point type	Primary

End point timeframe:

Baseline to Week 16

Notes:

[5] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Stable absent - No	84			
Stable absent - Yes	25			
Stable present - No	1			
Stable present - Yes	2			
Improved - No	3			
Improved - Yes	0			
Worsened - No	5			
Worsened - Yes	0			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: External Limiting Membrane (ELM) integrity loss in center 1 mm

End point title	Potential predictor factors of fluid-free response: External Limiting Membrane (ELM) integrity loss in center 1 mm[6]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within 'No' and 'Yes' groups according to q12w fluid free.

Of note, the category 'Stable absent' is considered also for cases with baseline and last measurement collected equal to 'No' even if there are at least one 'Yes' in one of the other collected measurements. Similarly, the category 'Stable present' is considered also for cases with baseline and last measurement collected equal to 'Yes' even if there are at least one 'No' in one of the other collected measurements.

Stable absent (i.e., all measurements 'No),
Stable present (i.e., all measurements 'Yes'),
Improved (i.e., last measurement collected as 'No' and baseline 'Yes'),
Worsened (i.e., last measurement collected 'Yes' and baseline 'No').

End point type	Primary

End point timeframe:

Baseline to Week 16

Notes:

[6] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Stable absent - No	25			
Stable absent - Yes	8			
Stable present - No	43			
Stable present - Yes	13			

Improved - No	11			
Improved - Yes	3			
Worsened - No	14			
Worsened - Yes	3			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Type of Pigment Epithelium Detachment (PED)

End point title	Potential predictor factors of fluid-free response: Type of Pigment Epithelium Detachment (PED)[7]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Percentages were computed on Safety Population within 'No' and 'Yes' groups according to q12w fluid free.

-Stable Fibrovascular only (i.e., all measurements 'Fibrovascular only').
-Stable not only fibrovascular (i.e., all measurements 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid Pigment Epithelial Detachment (PED)').
- From not only fibrovascular to Fibrovascular only (i.e., last measurement collected 'Fibrovascular only' and baseline 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid PED').
-From Fibrovascular only to not only fibrovascular (i.e., last measurement collected 'Predominantly fibrovascular' or 'Predominantly serous' or 'Drusenoid PED' and baseline 'Fibrovascular only').

FV = fibrovascular

End point type	Primary

End point timeframe:

Baseline to Week 16

Notes:

[7] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Stable Fibrovascular only - No	38			
Stable Fibrovascular only - Yes	13			
Stable not only fibrovascular - No	28			
Stable not only fibrovascular - Yes	7			
From not only FV to FV only - No	24			
From not only FV to FV only - Yes	7			
From FV only to not only FV - No	3			
From FV only to not only FV - Yes	0			

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Percentage Changes in Central Subfield Thickness (CST) from Baseline at Week 16

End point title	Potential predictor factors of fluid-free response: Percentage Changes in Central Subfield Thickness (CST) from Baseline at Week 16[8]

End point description:

As assessed by Spectral Domain Optical Coherence Tomography (SD-OCT).

Mean (SD) was computed on the Safety Population within 'No' and 'Yes' groups according to q12w fluid free.

End point type	Primary

End point timeframe:

Baseline, Week 16

Notes:

[8] - 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	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Percentage change				
arithmetic mean (standard deviation)				
Mean - no	-31.7 (± 18.28)			
Mean - yes	-36.4 (± 16.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Branching Vessels

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Branching Vessels

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD)

The morphology of the Neovascularization (CNV) complex was evaluated qualitatively by assessing the presence/absence of branching vessels. The presence of tiny vessels branching from bigger vessels is indicative of an active CNV lesion.

UNG/P = Ungradable due to pathology
UNG/Q = Ungradable due to Quality

BV = Branching Vessels

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
BV - Increased from prior - Week 16	11			
BV - Increased from prior - Week 48 (n=91)	4			
BV - Decreased from prior - Week 16	2			
BV - Decreased from prior - Week 48 (n=91)	11			
Branching Vessels - Stable - Week 16	26			
BV - Stable - Week 48 (n=91)	20			
Branching Vessels - UNG/P - Week 16	9			
Branching Vessels - UNG/P - Week 48 (n=91)	21			
Branching Vessels - UNG/Q - Week 16	66			
Branching Vessels - UNG/Q - Week 48 (n=91)	35			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Total CNV Lesion Area (mm*2)

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Total CNV Lesion Area (mm*2)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The total Basal Choroidal Neovascularization (CNV) lesion area (mm^2) and greatest linear diameter of lesion (mm) are the parameters related to CNV flow size.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: mm^2				
arithmetic mean (standard deviation)				
Week 16 (n=27)	0.476 (± 1.0012)			
Week 48 (n=20)	0.533 (± 0.9053)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Choroidal Neovascularization (CNV) Vascular Density (%)

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Choroidal Neovascularization (CNV) Vascular Density (%)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The Choroidal Neovascularization (CNV) vascular density (%) is calculated as a ratio of the area occupied by vessels and the total area of the lesion and multiplied by 100.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: % CNV Vascular Density				
arithmetic mean (standard deviation)				
Week 16	1.326 (± 35.6003)			
Week 48 (n=8)	29.900 (± 52.3079)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Lesion Greatest Linear Diameter (mm)

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Change from baseline of Lesion Greatest Linear Diameter (mm)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The total Basal Choroidal Neovascularization (CNV) lesion area (mm^2) and greatest linear diameter of lesion (mm) are the parameters related to CNV flow size.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	27			
Units: mm				
arithmetic mean (standard deviation)				
Week 16	-0.211 (± 0.5416)			
Week 48 (n=20)	-0.147 (± 0.5837)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Peripheral Anastomotic Arcades

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Peripheral Anastomotic Arcades

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The morphology of the Choroidal Neovascularization (CNV) complex was evaluated qualitatively by assessing the peripheral anastomotic arcades. The presence of peripheral anastomotic arcades at the vessel termini is indicative of an active CNV lesion.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: Participants				
No at Baseline and No at Week 16	14			
Yes at Baseline and No at Week 16	1			
No at Baseline and Yes at Week 16	4			
Yes at Baseline and Yes at Week 16	6			
No at Baseline and No at Week 48 (n=21)	7			
Yes at Baseline and No at Week 48 (n=21)	2			
No at Baseline and Yes at Week 48 (n=21)	8			
Yes at Baseline and Yes at Week 48 (n=21)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Vascular Loops

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Vascular Loops

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The morphology of the Choroidal Neovascularization (CNV) complex was evaluated qualitatively by assessing the vascular loops. The presence of vascular loops is indicative of an active CNV lesion.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Participants				
No at Baseline and No at Week 16	12			
Yes at Baseline and No at Week 16	1			
No at Baseline and Yes at Week 16	3			
Yes at Baseline and Yes at Week 16	10			
No at Baseline and No at Week 48 (n=22)	4			
Yes at Baseline and No at Week 48 (n=22)	3			
No at Baseline and Yes at Week 48 (n=22)	7			

Yes at Baseline and Yes at Week 48 (n=22)	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Dark Halo

End point title	Change in Optical Coherence Tomography (OCTA) features Baseline up to Week 48 - Dark Halo

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD).

The morphology of the Choroidal Neovascularization (CNV) complex was evaluated qualitatively by assessing the dark halo. The presence of dark halo is considered a region of choriocapillaris alteration corresponding to local flow impairment and is indicative of an active CNV lesion.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Participants				
No at Baseline and No at Week 16 (n=15)	9			
Yes at Baseline and No at Week 16 (n=15)	2			
No at Baseline and Yes at Week 16 (n=15)	0			
Yes at Baseline and Yes at Week 16 (n=15)	4			
No at Baseline and No at Week 48 (n=17)	6			
Yes at Baseline and No at Week 48 (n=17)	5			
No at Baseline and Yes at Week 48 (n=17)	2			
Yes at Baseline and Yes at Week 48 (n=17)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Spectral Domain Optical Coherence Tomography (SD-OCT) features Baseline up to Week 48 - Pigment Epithelial Detachment (PED)

End point title	Spectral Domain Optical Coherence Tomography (SD-OCT) features Baseline up to Week 48 - Pigment Epithelial Detachment (PED)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD)

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Participants				
Yes - Baseline	120			
Yes - Week 16 (n=114)	114			
Yes - Week 48 (n=93)	92			
Missing - Week 48 (n=93)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Spectral Domain Optical Coherence Tomography (SD-OCT) features Baseline up to Week 48 - Central Subfield Thickness (CST) (µm)

End point title	Spectral Domain Optical Coherence Tomography (SD-OCT) features Baseline up to Week 48 - Central Subfield Thickness (CST) (µm)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

The central retina thickness (CRT) evaluated in this study represents the average retinal thickness of the circular area within 1 mm diameter around the foveal center and was called Center Subfield Thickness (CST), also known as foveal thickness.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: micrometers				
arithmetic mean (standard deviation)				
Baseline	482.6 (± 177.40)			
Week 16 (n=114)	309.2 (± 107.69)			
Week 48 (n=93)	307.9 (± 118.05)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative OCTA parameters of wet Age-related Macular Degeneration (wAMD)

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	76			
Units: micrometers				
arithmetic mean (standard deviation)				
Week 16	-188.4 (± 142.79)			
Week 48 (n=60)	-197.6 (± 152.63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - subretinal fluid (SRF)

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - subretinal fluid (SRF)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

SRF is the fluid that commonly accumulates between the neurosensory retina and the retinal pigment epithelium (RPE) due to the profuse leakage from blood vessels of the Choroidal Neovascularization (CNV) complex.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
No at Baseline and No at Week 16	7			
Yes at Baseline and No at Week 16	75			
No at Baseline and Yes at Week 16	1			
Yes at Baseline and Yes at Week 16	31			
No at Baseline and No at Week 48 (n=92)	6			
Yes at Baseline and No at Week 48 (n=92)	57			
No at Baseline and Yes at Week 48 (n=92)	0			
Yes at Baseline and Yes at Week 48 (n=92)	29			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - Intraretinal Fluid (IRF) Cystoid edema

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - Intraretinal Fluid (IRF) Cystoid edema

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

IRF is the fluid that accumulates within the neurosensory retina due to the disruption of the external limiting membrane (ELM)-photoreceptor complex in the outer retina by the active Choroidal Neovascularization (CNV) membrane.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
No at Baseline and No at Week 16	46			
Yes at Baseline and No at Week 16	38			
No at Baseline and Yes at Week 16	4			
Yes at Baseline and Yes at Week 16	26			
No at Baseline and No at Week 48 (n=92)	40			
Yes at Baseline and No at Week 48 (n=92)	30			
No at Baseline and Yes at Week 48 (n=92)	1			
Yes at Baseline and Yes at Week 48 (n=92)	21			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - sub retinal pigment epithelium (sub RPE) fluid

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - sub retinal pigment epithelium (sub RPE) fluid

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

Sub-RPE fluid, i.e., the fluid that accumulates under the RPE, thus often leading to Pigment Epithelial Detachments (PEDs).

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
No at Baseline and No at Week 16	49			
Yes at Baseline and No at Week 16	26			
No at Baseline and Yes at Week 16	1			
Yes at Baseline and Yes at Week 16	38			
No at Baseline and No at Week 48 (n=92)	36			
Yes at Baseline and No at Week 48 (n=92)	26			

No at Baseline and Yes at Week 48 (n=92)	2			
Yes at Baseline and Yes at Week 48 (n=92)	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - subretinal hyperreflective material (SHRM)

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - subretinal hyperreflective material (SHRM)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

SHRM, i.e., a poorly defined, medium-to-hyperreflective mass between the neurosensory layers and the sub retinal pigment epithelium (RPE) on SD-OCT, which is indicative of the neurovascular membrane, particularly in type II Choroidal Neovascularization (CNV) lesions, and of disciform scar formation

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
No at Baseline and No at Week 16	50			
Yes at Baseline and No at Week 16	11			
No at Baseline and Yes at Week 16	16			
Yes at Baseline and Yes at Week 16	37			
No at Baseline and No at Week 48 (n=92)	45			
Yes at Baseline and No at Week 48 (n=92)	14			
No at Baseline and Yes at Week 48 (n=92)	8			
Yes at Baseline and Yes at Week 48 (n=92)	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT)

features from Baseline up to Week 48 - outer retinal tubulation (ORT)

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - outer retinal tubulation (ORT)

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

ORT, i.e., branching tubular structures located in the outer nuclear layer of the retina, which seems to be indicative of a rearrangement of degenerating photoreceptors in a variety of retinal diseases, including wAMD. On SD-OCT, ORT appears as well-defined round or ovoid hyporeflective spaces with hyperreflective borders.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	114			
Units: Participants				
No at Baseline and No at Week 16	103			
Yes at Baseline and No at Week 16	3			
No at Baseline and Yes at Week 16	5			
Yes at Baseline and Yes at Week 16	3			
No at Baseline and No at Week 48 (n=92)	77			
Yes at Baseline and No at Week 48 (n=92)	3			
No at Baseline and Yes at Week 48 (n=92)	10			
Yes at Baseline and Yes at Week 48 (n=92)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Best-corrected visual acuity (BCVA) from Baseline up to Week 48

End point title	Change in Best-corrected visual acuity (BCVA) 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. Participants with a BCVA ETDRS letter score of >= 34 ETDRS letters (Snellen equivalent 20/200) at Screening / Baseline in the study eye were included.

Min and max possible scores are 0-100 respectively. A higher score represents better functioning.

Last observation carried forward (LOCF) was used for the imputation of missing values.

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	120			
Units: Letters read				
median (inter-quartile range (Q1-Q3))				
Week 16	4.0 (0.0 to 10.0)			
Week 48	5.5 (-0.5 to 12.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - External Limiting Membrane (ELM) integrity loss

End point title	Change in Spectral Domain Optical Coherence Tomography (SD-OCT) features from Baseline up to Week 48 - External Limiting Membrane (ELM) integrity loss

End point description:

Evaluate the effect of brolucizumab on the evolution of qualitative and quantitative SCD-OCT parameters of wet Age-related Macular Degeneration (wAMD).

Status of the ELM as an indicator of retinal integrity was evaluated focusing on ELM integrity loss in center 1 mm (i.e., considering the central 1 x 1-mm subfield).

End point type	Secondary

End point timeframe:

Baseline, Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Participants				
No at Baseline and No at Week 16	30			
Yes at Baseline and No at Week 16	14			
No at Baseline and Yes at Week 16	15			
Yes at Baseline and Yes at Week 16	54			
No at Baseline and No at Week 48 (n=91)	24			
Yes at Baseline and No at Week 48 (n=91)	9			

No at Baseline and Yes at Week 48 (n=91)	15			
Yes at Baseline and Yes at Week 48 (n=91)	43			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with fluid resolution of the study eye

End point title	Number of patients with fluid resolution of the study eye

End point description:

Evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48.

Among patients with fluid present at Baseline, patients with fluid resolution were identified in case of absence of IRF and SRF and patients without fluid resolution were categorized in 'only IRF present', 'only SRF present', 'both IRF and SRF present' at each post-baseline timepoint.

IRF = Intraretinal Fluid
SRF = Subretinal Fluid

FR = fluid resolution
Pts = patients

End point type	Secondary

End point timeframe:

Week 16, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: Participants				
Patients with fluid resolution - Week 16	64			
Patients without fluid resolution - Week 16	49			
Pts without FR- Only IRF present-Wk 16 (n=49)	18			
Pts without FR-Only SRF present-Wk 16 (n=49)	19			
Pts without FR-Both IRF & SRF present-Wk 16 (n=49)	12			
Patients with fluid resolution - Wk 48 (n=92)	49			
Unknown- Wk 48 (n=92)	1			
Patients without fluid resolution - Wk 48 (n=92)	42			
Pts without FR -Only IRF present - Wk 48 (n=42)	13			
Pts without FR -Only SRF present-Wk 48 (n=42)	20			
Pts without FR-Both IRF & SRF present-Wk 48 (n=42)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: Sustained Dryness of the study eye - Kaplan-Meier estimates - Median time to the achievement of sustained dryness

End point title	Sustained Dryness of the study eye - Kaplan-Meier estimates - Median time to the achievement of sustained dryness

End point description:

Evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48.

Patients who achieved sustained dryness were identified considering those with fluid resolution for at least 2/3 consecutive visits.
Median time to the achievement of sustained dryness was calculated by the Kaplan-Meier method.

Sustained dryness of the study eye, is defined by the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits.

IRF = Intraretinal Fluid
SRF = Subretinal Fluid

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: weeks				
median (confidence interval 95%)	16.43 (12.86 to 31.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Determinants in the Investigator’s choice of brolucizumab dosing regimen (q8w) at Week 16

End point title	Determinants in the Investigator’s choice of brolucizumab dosing regimen (q8w) at Week 16

End point description:

Evaluate the reasons underlying the Investigators’ choice of brolucizumab treatment regimen (q8w)

BVCA=Best-Corrected Visual Acuity, CFP=Color Fundus Photography; CNV=Choroidal Neovascularization; FA=Fluorescein Angiography; ICGA=IndoCyanine Green Angiography;

OCTA=Optical Coherence Tomography Angiography; SD-OCT=Spectral Domain Optical Coherence Tomography

sub-RPE = Subretinal pigment epithelium
SHRM = Subretinal hyperreflective material
RPE = Retina Pigment Epithelial
SD-OCT = Domain Optical Coherence Tomography

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: Participants				
Intraretinal fluid (IRF) at SD-OCT	17			
Subretinal fluid (SRF) at SD-OCT	21			
Central Subfield Thickness (CST) at SD-OCT	15			
Best-corrected visual acuity (BCVA)	13			
sub-RPE fluid at SD-OCT	4			
Central Retinal Thickness (CRT)	4			
SHRM at SD-OCT	6			
RPE Detachment volume at SD-OCT	3			
CNV size at OCTA	2			
Hemorrhage at CFP	2			
Vessel morphology at OCTA	2			
Vessel density at OCTA	3			
Other - investigator's discretion	2			
Leakage at FA/ICGA	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of patients with sustained dryness of the study eye

End point title	Cumulative incidence of patients with sustained dryness of the study eye

End point description:

Evaluate the effect of brolucizumab on sustained dryness from Baseline to Week 48.

Sustained dryness of the study eye, is defined by the absence of IRF and SRF for at least 2 consecutive visits and for at least 3 consecutive visits.

IRF = Intraretinal Fluid
SRF = Subretinal Fluid

End point type	Secondary

End point timeframe:

Weeks 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: Participants				
Patients with sustained dryness - Week 8	36			
Patients with sustained dryness - Week 12	54			
Patients with sustained dryness - Week 16	64			
Patients with sustained dryness - Week 20	68			
Patients with sustained dryness - Week 24	68			
Patients with sustained dryness - Week 28	68			
Patients with sustained dryness - Week 32	73			
Patients with sustained dryness - Week 36	76			
Patients with sustained dryness - Week 40	77			
Patients with sustained dryness - Week 44	77			
Patients with sustained dryness - Week 48	78			

Statistical analyses

No statistical analyses for this end point

Secondary: Determinants in the Investigator’s choice of brolucizumab dosing regimen (q12w) at Week 16

End point title	Determinants in the Investigator’s choice of brolucizumab dosing regimen (q12w) at Week 16

End point description:

Evaluate the reasons underlying the Investigators’ choice of brolucizumab treatment regimen (q12w)

BVCA=Best-Corrected Visual Acuity, CFP=Color Fundus Photography; CNV=Choroidal Neovascularization; FA=Fluorescein Angiography; ICGA=IndoCyanine Green Angiography; OCTA=Optical Coherence Tomography Angiography; SD-OCT=Spectral Domain Optical Coherence Tomography
sub-RPE = Subretinal pigment epithelium
SHRM = Subretinal hyperreflective material
RPE = Retina Pigment Epithelial

End point type	Secondary

End point timeframe:

Up to Week 16

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	68			
Units: Participants				
Intraretinal fluid (IRF) at SD-OCT	46			
Subretinal fluid (SRF) at SD-OCT	41			
Central Subfield Thickness (CST) at SD-OCT	35			
BCVA	29			
sub-RPE fluid at SD-OCT	26			
Central Retinal Thickness (CRT)	26			
SHRM at SD-OCT	22			
RPE Detachment volume at SD-OCT	19			
CNV size at OCTA	18			
Hemorrhage at CFP	17			
Vessel morphology at OCTA	13			
Vessel density at OCTA	11			
Other - investigator's discretion	11			
Leakage at FA/ICGA	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Hospital Anxiety and Depression Scale (HADS) scores

End point title	Change in Hospital Anxiety and Depression Scale (HADS) scores

End point description:

Evaluate anxiety/depression in patients with wAMD treated with brolucizumab. The Hospital Anxiety and Depression Scale (HADS) is a fourteen-item scale that generates ordinal data. Seven items relate to anxiety and seven relate to depression. This patient-reported outcome measure was specifically developed to avoid reliance on anxiety/depression aspects which are also common somatic symptoms of illness, such as fatigue and insomnia or hypersomnia. Calculations of scores: each item is rated on a 4-point scale. The HADS consists of two sub-scores: the HAD-A for anxiety and HAD-D for depression. Each sub-score ranges from 0 to 21 points: scores ≥11 indicate the presence of an anxious or depressive disorder, scores between 8-10 points are borderline abnormal, and scores ≤7 indicate that an anxious or depressive disorder is not present.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Scores on a scale				
arithmetic mean (standard deviation)				
HAD-A - Absolute change from baseline at Week 48	-0.78 (± 3.258)			
HAD-D - Absolute change from baseline at Week 48	-0.10 (± 3.049)			

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Emergent Adverse Events

End point title	Treatment Emergent Adverse Events

End point description:

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

Pts = patients
w/ = with
trt = treatment
temp = temporary
disc = discontinuation

End point type	Secondary

End point timeframe:

AEs are reported from first dose of study treatment until 4 weeks after last treatment, for a maximum time frame of approx. 48 weeks.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Participants				
Patients with TEAEs	59			
Patients with Serious TEAEs	14			
Patients with Ocular TEAEs	33			
Patients with non-ocular TEAEs	40			
Patients with suspected drug-related TEAEs	13			
Pts w/ TEAEs related to Ocular injection procedure	4			
Pts w/ TEAEs leading to temp. interruption of trt.	2			
Pts w/ TEAEs leading to withdrawn of treatment	15			
Pts w/ TEAEs leading to study disc.	7			
Patients with TEAEs with fatal outcome	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in European Quality of Life-5D-5L (EQ-5D-5L) scores

End point title	Change in European Quality of Life-5D-5L (EQ-5D-5L) scores

End point description:

Evaluate quality of life in patients with wAMD treated with brolucizumab. The EQ-5D-5L is a standardized widely used instrument for measuring generic health status. It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels. i.e. no problems, slight problems, moderate problems, severe problems and extreme problems, corresponding to digit numbers ranging from 1 to 5. The EQ-5D-5L total score is determined through a Visual Analogue Scale (VAS) and ranges from 0 to 100 with higher scores indicative of a better health status.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.00 (± 0.147)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular Treatment Emergent Adverse Events - study eye

End point title	Ocular Treatment Emergent Adverse Events - study eye

End point description:

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

Pts = patients
w/ = with
trt = treatment
temp = temporary
disc = discontinuation
int = interruption
inj = injection
proc = procedure

End point type	Secondary

End point timeframe:

AEs are reported from first dose of study treatment until 4 weeks after last treatment, for a maximum time frame of approx. 48 weeks.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Participants				
Patients with Ocular TEAEs	25			
Patients with Serious Ocular TEAEs	1			
Pts w/ suspected drug-related Ocular TEAEs	11			
Pts w/ Ocular TEAEs related to Ocular inj. proc	3			
Pts w/ Ocular TEAEs leading to temp inter of trt	1			
Pts w/ Ocular TEAEs leading to withdrawn of trt	10			
Pts w/ Ocular TEAEs leading to study disc.	5			
Pts w/ Ocular TEAEs with fatal outcome	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Ocular Treatment Emergent Adverse Events - by System Organ Class (SOC) and Preferred Term (PT)

End point title	Ocular Treatment Emergent Adverse Events - by System Organ Class (SOC) and Preferred Term (PT)

End point description:

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

End point type	Secondary

End point timeframe:

AEs are reported from first dose of study treatment until 4 weeks after last treatment, for a maximum time frame of approx. 48 weeks.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	122			
Units: Participants				
Eye disorders	30			
-Cataract	3			
-Conjunctival haemorrhage	1			

-Eye haemorrhage	1			
-Eye inflammation	2			
-Iridocyclitis	1			
-Macular degeneration	1			
-Macular detachment	1			
-Macular fibrosis	2			
-Macular hole	3			
-Maculopathy	1			
-Neovascular age-related macular degeneration	3			
-Ocular hypertension	2			
-Retinal haemorrhage	1			
-Retinal occlusive vasculitis	1			
-Retinal pigment epithelial tear	3			
-Retinal tear	2			
-Retinal vascular disorder	1			
-Retinal vasculitis	1			
-Uveitis	1			
-Vision blurred	1			
-Visual impairment	1			
-Vitreous floaters	1			
-Vitritis	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are reported from first dose of study treatment until 4 weeks after last treatment, for a maximum time frame of approx. 48 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Brolucizumab 6 mg

Reporting group description:

Participants received 3 monthly ocular injections followed by a q12w or q8w maintenance phase based on patient's disease activity (DA).

Serious adverse events	Brolucizumab 6 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 122 (11.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute undifferentiated leukaemia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Joint dislocation			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebellar ischaemia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	2 / 122 (1.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Condition aggravated			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis- Study eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal occlusive vasculitis- Study eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 122 (0.82%)		
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	Brolucizumab 6 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 122 (42.62%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Squamous cell carcinoma			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Vascular disorders			
Vasculitis- Study eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Epistaxis- Fellow eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Investigations			
Blood pressure abnormal			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Head injury			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Diastolic dysfunction			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Defect conduction intraventricular			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Conduction disorder			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Cardiac failure			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nervous system disorders			
Arachnoid cyst			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Ataxia			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Gliosis			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Nystagmus- Fellow eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Eye disorders			
Macular detachment- Fellow eye			
subjects affected / exposed	1 / 122 (0.82%)		
occurrences (all)	1		
Macular degeneration- Fellow eye			

subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Iridocyclitis- Study eye				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Eye inflammation- Study eye				
subjects affected / exposed	2 / 122 (1.64%)			
occurrences (all)	2			
Eye haemorrhage- Fellow eye				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Conjunctival haemorrhage- Study eye				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Cataract- Study eye				
subjects affected / exposed	2 / 122 (1.64%)			
occurrences (all)	2			
Cataract- Fellow eye				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Cataract- Both				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			
Macular hole- Study eye				
subjects affected / exposed	3 / 122 (2.46%)			
occurrences (all)	3			
Macular fibrosis- Study eye				
subjects affected / exposed	2 / 122 (1.64%)			
occurrences (all)	2			
Vitritis- Study eye				
subjects affected / exposed	5 / 122 (4.10%)			
occurrences (all)	5			
Vitreous floaters- Study eye				
subjects affected / exposed	1 / 122 (0.82%)			
occurrences (all)	1			

Visual impairment- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Vision blurred- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Retinal vasculitis- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Retinal vascular disorder- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Retinal tear- Study eye subjects affected / exposed occurrences (all)	2 / 122 (1.64%) 2		
Retinal pigment epithelial tear- Study eye subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3		
Retinal haemorrhage- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 2		
Ocular hypertension- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Ocular hypertension- Both subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Neovascular age-related macular degeneration- Fellow eye subjects affected / exposed occurrences (all)	3 / 122 (2.46%) 3		
Maculopathy- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Gastrointestinal disorders			

Toothache subjects affected / exposed occurrences (all) Colitis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1		
Renal and urinary disorders Renal colic subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Spinal osteoarthritis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1 1 / 122 (0.82%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1 4 / 122 (3.28%) 4		

Gastroenteritis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Conjunctivitis- Study eye subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
COVID-19 subjects affected / exposed occurrences (all)	13 / 122 (10.66%) 13		
Bronchitis subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Post procedural infection subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Conjunctivitis bacterial- Both subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	1 / 122 (0.82%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2020	Information was added to describe new safety signal from post- marketing case reports. Added CFP for basal lesion type definition. Added specification of other imaging modalities. 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 this section emphasizing that if any sign of intraocular inflammation was present, an IVT injection could not be performed and patients should be treated for IOI according to clinical practice. Additional examination and assessments were included to fully characterize cases of intraocular inflammation. Changes were incorporated to address the COVID-19 pandemic. Clarification on timing for post-injection IOP measurement. Added clarification about discontinuation. Added specification on the anonymization of the images sent to the CRC.
11 November 2021	Information added to describe Urgent Safety Measures. Information added to describe Urgent Safety Measures and additional information on gender imbalance on IOI following brolucizumab treatment. Recommendations on the time window for a study subject to receive the COVID-19 vaccine or vitrectomy were added. Requirement of treatment discontinuation for brolucizumab was added if subject developed RV and/or RO. Clarified that when serum pregnancy test is positive brolucizumab treatment must be discontinued. Changes were made as follows: Subject developing retinal a vasculitis and/or a retinal vascular occlusion event with brolucizumab. Requirement of treatment discontinuation for brolucizumab was added if subject developed RV and/or RO. Clarified the definition of Withdrawal of Consent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported