



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 | v2 (current) |
| This version publication date | 23 February 2025 |
| First version publication date | 04 October 2024 |
| Version creation reason | |

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 Pharmaceuticals |
| 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 brolocizumab 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: -

Pre-assignment

Screening details:

If both eyes were eligible as per the inclusion and exclusion criteria, only one eye was treated during the study, with the eye with the worse visual acuity (BCVA) at Baseline selected as the study eye. If both eyes had the same BCVA, the right eye was chosen as the study eye.

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 monthlyocular injections followed by aq12w or q8w maintenancephase based on patient'sdisease 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: 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 ^[1] |
|-----------------|--|

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:

[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 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 - patients classified as not q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Sub-retinal pigment epithelium (sub-RPE) fluid - patients classified as not q12w fluid-free ^[2] |
|-----------------|--|

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:

[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 single arm study

| End point values | Brolucizumab 6 mg | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - No | 39 | | | |
| Stable present; q12w fluid free - No | 32 | | | |
| Improved; q12w fluid free - No | 20 | | | |
| Worsened; q12w fluid free - No | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Type of predominant Basal Choroidal Neovascularization (CNV) lesion type, as assessed by SD-OCT at Baseline - patients classified as not q12w fluid-free

| | |
|-----------------|---|
| 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 - patients classified as not q12w fluid-free ^[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.

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.

Types 1-3 classification is a classification according to the type of anatomical lesion and is determined

by multimodal imaging characteristics. Please note that by design, this is not a grading nor scores on a scale.

PCV = Polypoidal Choroidal Vasculopathy

| | |
|---|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline | |
| 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 single arm study | |

| | | | | |
|------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| TYPE I + PCV; q12w fluid free - No | 61 | | | |
| TYPE II; q12w fluid free - No | 21 | | | |
| TYPE III; q12w fluid free - No | 5 | | | |
| Missing; q12w fluid free - No | 6 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Type of predominant Basal Choroidal Neovascularization (CNV) lesion type, as assessed by SD-OCT at Baseline - patients classified as q12w fluid-free

| | |
|-----------------|---|
| 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 - patients classified as q12w fluid-free ^[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.

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.

Types 1-3 classification is a classification according to the type of anatomical lesion and is determined by multimodal imaging characteristics. Please note that by design, this is not a grading nor scores on a scale.

PCV = Polypoidal Choroidal Vasculopathy

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| Baseline | |

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 single arm study

| End point values | Brolucizumab 6 mg | | | |
|-------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| TYPE I + PCV; q12w fluid free - Yes | 19 | | | |
| TYPE II; q12w fluid free - Yes | 4 | | | |
| TYPE III; q12w fluid free - Yes | 3 | | | |
| Missing; q12w fluid free- Yes | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM) - patients classified as not q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM) - patients classified as not q12w fluid-free ^[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 single arm study

| End point values | Brolucizumab 6 mg | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - No | 41 | | | |
| Stable present; q12w fluid free - No | 33 | | | |
| Improved; q12w fluid free - No | 7 | | | |

| | | | | |
|--------------------------------|----|--|--|--|
| Worsened; q12w fluid free - No | 12 | | | |
|--------------------------------|----|--|--|--|

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Sub-retinal pigment epithelium (sub-RPE) fluid - patients classified as q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Sub-retinal pigment epithelium (sub-RPE) fluid - patients classified as q12w fluid-free ^[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 single arm study

| End point values | Brolucizumab 6 mg | | | |
|---------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - Yes | 12 | | | |
| Stable present; q12w fluid free - Yes | 7 | | | |
| Improved; q12w fluid free - Yes | 8 | | | |
| Worsened; q12w fluid free - Yes | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM) - patients classified as q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Subretinal Hyperreflective Material (SHRM) - patients classified as q12w fluid-free ^[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.

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:

[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 single arm study

| | | | | |
|---------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - Yes | 11 | | | |
| Stable present; q12w fluid free - Yes | 7 | | | |
| Improved; q12w fluid free - Yes | 4 | | | |
| Worsened; q12w fluid free - Yes | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT) - patients classified as not q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT) - patients classified as not q12w fluid-free ^[8] |
|-----------------|--|

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:

[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 single arm study

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - No | 84 | | | |
| Stable present; q12w fluid free - No | 1 | | | |
| Improved; q12w fluid free - No | 3 | | | |
| Worsened; q12w fluid free - No | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT) - patients classified as q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Outer Retinal Tubulation (ORT) - patients classified as q12w fluid-free ^[9] |
|-----------------|--|

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:

[9] - 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 single arm study

| | | | | |
|---------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - Yes | 25 | | | |
| Stable present; q12w fluid free - Yes | 2 | | | |
| Improved; q12w fluid free - Yes | 0 | | | |
| Worsened; q12w fluid free - 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 - patients classified as not q12w fluid-free

| | |
|-----------------|---|
| End point title | Potential predictor factors of fluid-free response: External Limiting Membrane (ELM) integrity loss in center 1 mm - patients classified as not q12w fluid-free ^[10] |
|-----------------|---|

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:

[10] - 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 single arm study

| | | | | |
|-------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - No | 25 | | | |
| Stable present; q12w fluid free- No | 43 | | | |
| Improved; q12w fluid free - No | 11 | | | |
| Worsened; q12w fluid free - No | 14 | | | |

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 - patients classified as q12w fluid-free

| | |
|-----------------|---|
| End point title | Potential predictor factors of fluid-free response: External Limiting Membrane (ELM) integrity loss in center 1 mm - patients classified as q12w fluid-free ^[11] |
|-----------------|---|

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:

[11] - 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 single arm study

| | | | | |
|---------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| Stable absent; q12w fluid free - Yes | 8 | | | |
| Stable present; q12w fluid free - Yes | 13 | | | |
| Improved; q12w fluid free - Yes | 3 | | | |
| Worsened; q12w fluid free - 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) - patients classified as not q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Type of Pigment Epithelium Detachment (PED) - patients classified as not q12w fluid-free ^[12] |
|-----------------|--|

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:

[12] - 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 single arm study

| | | | | |
|---|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 93 | | | |
| Units: Participants | | | | |
| Stable FV only; q12w fluid free - No | 38 | | | |
| Stable not only FV; q12w fluid free - No | 28 | | | |
| From not only FV to FV only; q12w fluid free - No | 24 | | | |
| From FV only to not only FV; q12w fluid free - No | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Potential predictor factors of fluid-free response: Type of Pigment Epithelium Detachment (PED) - patients classified as q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Type of Pigment Epithelium Detachment (PED) - patients classified as q12w fluid-free ^[13] |
|-----------------|--|

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:

[13] - 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 single arm study

| | | | | |
|--|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Participants | | | | |
| Stable FV only; q12w fluid free - Yes | 13 | | | |
| Stable not only FV; q12w fluid free - Yes | 7 | | | |
| From not only FV to FV only; q12w fluid free - Yes | 7 | | | |
| From FV only to not only FV; q12w fluid free - 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 - patients classified as not q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Percentage Changes in Central Subfield Thickness (CST) from Baseline at Week 16 - patients classified as not q12w fluid-free ^[14] |
|-----------------|--|

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:

[14] - 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 single arm study

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 92 | | | |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | -31.7 (± 18.28) | | | |

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 - patients classified as q12w fluid-free

| | |
|-----------------|--|
| End point title | Potential predictor factors of fluid-free response: Percentage Changes in Central Subfield Thickness (CST) from Baseline at Week 16 - patients classified as q12w fluid-free ^[15] |
|-----------------|--|

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:

[15] - 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 single arm study

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Brolucizumab 6 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 27 | | | |
| Units: Percentage change | | | | |
| arithmetic mean (standard deviation) | -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 | | | | |
| Branching Vessels - 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 | | | |
| BV - Stable - Week 16 | 26 | | | |
| BV - Stable - Week 48 (n=91) | 20 | | | |
| BV - UNG/P - Week 16 | 9 | | | |
| BV - UNG/P - Week 48 (n=91) | 21 | | | |
| BV - UNG/Q - Week 16 | 66 | | | |
| BV - 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 (mm²) 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 (mm²) 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 - 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

| | |
|---|--|
| 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 (\pm 142.79) | | | |
| Week 48 (n=60) | -197.6 (\pm 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 - 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 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 - 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 brolocizumab 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 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: 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: 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

Wk = Week

| | |
|----------------|-----------|
| 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 | | | |
| Pts 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 FR - Wk 48 (n=92) | 49 | | | |
| Unknown- Week 48 (n=92) | 1 | | | |
| Patients without FR - Week 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: 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: 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 | 119 | | | |
| 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: 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: 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: 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 | | | |
| Patients w/ TEAEs leading to study disc. | 7 | | | |
| Patients with TEAEs with fatal outcome | 0 | | | |

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/h suspected drug-related Ocular TEAEs | 11 | | | |
| Pts w/h 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 |
|-----------------------|--------------|

Reporting group description:

Brolucizumab

| Serious adverse events | Brolucizumab | | |
|---|-------------------|--|--|
| 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) | | | |
| 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 | | |
| 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 | | |

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

| | | | |
|--|----------------------|--|--|
| Conduction disorder subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Defect conduction intraventricular subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Diastolic dysfunction subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Cardiac failure subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Ataxia subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Arachnoid cyst subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Nystagmus- Fellow eye subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Gliososis subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Eye disorders | | | |
| Retinal tear- Study eye subjects affected / exposed occurrences (all) | 2 / 122 (1.64%) 2 | | |
| Cataract- Both subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Cataract- Fellow eye | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Cataract- Study eye | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | | |
| occurrences (all) | 2 | | |
| Retinal vascular disorder- Study 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 | | |
| Eye haemorrhage- Fellow 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 | | |
| Iridocyclitis- Study 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 | | |
| Macular detachment- Fellow eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Macular fibrosis- Study eye | | | |
| subjects affected / exposed | 2 / 122 (1.64%) | | |
| occurrences (all) | 2 | | |
| Macular hole- Study eye | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | | |
| occurrences (all) | 3 | | |
| Maculopathy- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|-----------------|--|--|
| Neovascular age-related macular degeneration- Fellow eye | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | | |
| occurrences (all) | 3 | | |
| Ocular hypertension- Both | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Ocular hypertension- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Retinal haemorrhage- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 2 | | |
| Retinal pigment epithelial tear- Study eye | | | |
| subjects affected / exposed | 3 / 122 (2.46%) | | |
| occurrences (all) | 3 | | |
| Retinal vasculitis- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Vision blurred- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Visual impairment- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Vitreous floaters- Study eye | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Vitritis- Study eye | | | |
| subjects affected / exposed | 5 / 122 (4.10%) | | |
| occurrences (all) | 5 | | |
| Gastrointestinal disorders | | | |
| Toothache | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Colitis | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Aphthous ulcer subjects affected / exposed occurrences (all) | 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 Spinal osteoarthritis subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Myalgia subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| COVID-19 subjects affected / exposed occurrences (all) | 13 / 122 (10.66%) 13 | | |
| Conjunctivitis- Study eye subjects affected / exposed occurrences (all) | 1 / 122 (0.82%) 1 | | |
| Cystitis | | | |

| | | | |
|------------------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 4 / 122 (3.28%) | | |
| occurrences (all) | 4 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Post procedural infection | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis bacterial- Both | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 1 | | |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 1 / 122 (0.82%) | | |
| occurrences (all) | 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