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Sponsor
Novartis Pharmaceuticals

Generic Drug Name
brolucizumab/RTH258

Trial Indication(s)
Neovascular age-related macular degeneration

Protocol Number
CRTH258A2303E1

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

Clinical Trial Phase
Phase 3

Phase of Drug Development
Phase IIIb/ IV

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Study Start/End Dates

Study Start Date: December 16, 2020 (Actual)
Primary Completion Date: March 28, 2023 (Actual)
Study Completion Date: March 28, 2023 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a 56-week, open-label, one-arm extension study in subjects who had completed the CRTH258A2303 (TALON) study, referred to as the core study in this document. Subjects who provided written informed consent and met all the inclusion and none of the exclusion criteria were enrolled into this extension study to receive brolucizumab 6 mg in a treat-to-control (TtC) regimen, irrespective of the treatment received in the core study.

The maximum study duration for a subject was 56 weeks, including post-treatment follow-up.

There were two periods in this study:
• Treat-to-control (TtC) treatment period: from Baseline (Day 1) to Week 52.

• Post-treatment follow-up period: from Week 52 to Week 56.

Treat to control period:
The first injection visit in the extension study was based on the planned treatment interval as decided by the Investigator at the last injection visit of the core study. Treatment intervals were either every 8 weeks (q8w), every 12 weeks (q12w), or every 16 weeks (q16w). Per the original protocol, if it was determined that a subject required more frequent injections than q8w, he/she would be moved to a q4w treatment interval. However, in response to an urgent safety measure (USM), per Protocol amendment 01, dosing intervals shorter than q8w were not permitted.

The treatment interval could then be extended by 4 weeks at a time based on the Investigator's judgment of visual and/or anatomic outcomes, as per guidance provided, for example, no change in visual acuity and in other signs of the disease (e.g. intraretinal fluid (IRF), subretinal fluid (SRF), hemorrhage, leakage, etc.). Subjects who had the last injection interval with no disease activity of q16w in the core study were to be injected at another q16w interval before deciding whether or not to increase the interval in the extension study. The maximal treatment interval was every 20 weeks (q20w). The injection interval could also be maintained if the Investigator deemed that the subject would not benefit from injection interval extension. The interval was to be shortened by 4 weeks at a time if disease activity recurred (down to a minimal interval of 8 weeks). The Investigators had options to plan for an inspection visit prior to the treatment visit when the treatment intervals were extended.

For all subjects, the last potential study treatment was at the Week 52 visit. Subjects who received a study treatment at an inspection visit could have a study visit at Week 54. For those subjects, the Week 54 visit took place in lieu of the visit at Week 52.

Post-treatment follow-up period:
For all subjects completing the study, the End of Study (EOS) (Week 56 ± 21 days) assessments were performed 4 weeks after the last treatment administration (Week 52/Week 54). Subjects withdrawn from the study prior to study completion within less than 4 weeks after the last study treatment were asked to return for an EOS visit, 4 weeks (± 14 days) following their last study treatment administration (End of Treatment).

Sample size and number of subjects:
The initial sample size calculation for this open-label, one-arm extension study was mainly based on the assumption that all eligible subjects completing the core study could be enrolled. Following the Urgent Safety Measure (USM) dated 27-May-2021, subjects requiring study treatment every 4 weeks were discontinued; therefore, the originally planned number of subjects (i.e. 503 subjects) transitioning from the core study into the extension study was reduced. Consequently, the sample size was re-assessed with the focus on the estimation of subjects who would be on a q20w interval. This estimation could be achieved with acceptable precision with a sample size of 250. The study objectives were assessed with the revised sample size. A total of 248 subjects were treated in the study, of which 233 subjects completed the study.

Centers

60 centers in 16 countries: Australia(7), France(10), Belgium(1), Korea, Republic of(6), Spain(8), Netherlands(2), Switzerland(1), Germany(3), Czech Republic(3), Portugal(2), Sweden(2), Taiwan(3), Israel(3), Malaysia(3), United States(5), Italy(1)

Objectives:

The primary objectives were:

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

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

The secondary objectives were:

To evaluate the anatomical outcomes of brolucizumab in all subjects and per randomized arm in the core study.

To assess the durability of brolucizumab in all subjects and/or per randomized arm in the core study.

To assess the functional outcomes of brolucizumab per randomized arm in the core study.

To assess the safety of brolucizumab.

Test Product (s), Dose(s), and Mode(s) of Administration

Brolucizumab solution for Intravitreal injection (IVT) injection, 6 mg/0.05 mL

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Statistical Methods

The analyses of primary endpoints were conducted using the Full Analysis Set (FAS).
• The distribution of the last interval with no disease activity up to Week 56 was described based on counts and proportions of subjects at 4-week, 8-week, 12-week, 16-week, and 20-week intervals. The counts and proportions were accompanied by 2-sided 95% confidence intervals (CIs) inferred based on binomial distribution for each endpoint and 2-sided 95% simultaneous CIs inferred using the Goodman method.
• The average change in Best Corrected Visual Acuity (BCVA) from baseline of the extension study at Week 52 and Week 56 was estimated by an analysis of variance (ANOVA) with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects. The estimate of BCVA change was accompanied by 95% CIs.

Sensitivity analyses for the two co-primary endpoints were performed to examine robustness with respect to protocol deviations (PDs) based on the Per Protocol Set (PPS). To evaluate robustness of the analyses for the co-primary endpoint (change in BCVA from extension baseline at Week 52 and Week 56) that were based on the last observation carried forward (LOCF) method, sensitivity analyses were performed on the observed data in the FAS and mixed models for repeated measures (MMRM). The MMRM model included the change in BCVA as the dependent variable, age categories at baseline, BCVA categories at baseline, treatment arm in the core study, and assessment visit as the fixed effects and subject as a random effect.

Secondary efficacy endpoints: The analyses of secondary endpoints were conducted using the FAS. For the analyses of functional and anatomical outcomes (i.e. change in Central Subfield Thickness (CSFT)) the 95% CIs were inferred based on ANOVA analyses. The same analysis model as used for change from baseline in BCVA was used with the baseline BCVA categories replaced by baseline CSFT categories.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
1. Signed informed consent
2. Successfully completed TALON core study at week 64 (End of Study)

Exclusion Criteria:
1. Medical condition or personal circumstance which precludes study participation or compliance with study procedures, as assessed by the Investigator

2. Discontinued study treatment in the core study
3. Anti-VEGF treatment is futile in the study eye, in the Investigator's opinion.
4. Pregnant or nursing (lactating) women
5. Women of child-bearing potential not using highly effective methods of contraception

Participant Flow Table

Overall Study

	brolucizumab 6 mg (Extension study total)	Total
Arm/Group Description	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Started	248	248
Completed	231	231
Not Completed	17	17
Withdrawal by Subject	10	10
Lost to Follow-up	1	1
Death	1	1
Adverse Event	5	5

Baseline Characteristics

	brolucizumab 6 mg (Extension study total)	Total
Arm/Group Description	Participants received brolucizumab 6 mg/0.05 mL	

	solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.	
Number of Participants [units: participants]	248	248
Baseline Analysis Population Description	Full Analysis Set composed of all subjects who received at least one dose of study treatment in the extension study.	
Age Continuous (units: Years) Analysis Population Type: Participants Mean ± Standard Deviation		
	75.9±7.90	
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Female	129	129
Male	119	119
Race (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
American Indian or Alaska Native	0	0
Asian	61	61
Native Hawaiian or Other Pacific Islander	0	0
Black or African American	0	0
White	187	187
More than one race	0	0

Unknown or Not Reported	0	0
Ethnicity (NIH/OMB) (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)		
Hispanic or Latino	23	23
Not Hispanic or Latino	219	219
Unknown or Not Reported	6	6

Primary Outcome Result(s)

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

Description	Number of subjects in every 4 weeks (q4w), every 8 weeks (q8w), every 12 weeks (q12w) and every 20 weeks (q20w) intervals at last interval with no disease activity up to Week 56. Last interval with no disease activity (number of weeks): Number of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the extension study
Time Frame	Up to Week 56
Analysis Population Description	Full Analyses Set. Subjects with at least two injections in the extension study

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

Number of Participants Analyzed [units: participants]	237

Duration of the last interval with no disease activity up to Week 56 - study eye (units: Participants)	Count of Participants (Not Applicable)
20 weeks	68 (28.69%)
16 weeks	59 (24.89%)
12 weeks	47 (19.83%)
8 weeks	49 (20.68%)
4 weeks	14 (5.91%)

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

Description	Best-Corrected Visual Acuity (BCVA) was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. Visual Function of the study eye was assessed using the ETDRS protocol. Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning. The average change in BCVA from Baseline of the extension study at Week 52 and Week 56 was estimated by an analysis of variance (ANOVA) with baseline age categories, baseline BCVA categories and treatment arm in the core study included as fixed effects. Last observation carried forward (LOCF) was used to impute missing BCVA values.
Time Frame	Extension study baseline, average of Week 52 and Week 56
Analysis Population Description	Full Analyses Set - Last Observation Carried Forward. Participants were analyzed according to the originally assigned treatment arm in the core study (CRTH258A2303, NCT04005352).

	Brolucizumab 6 mg (Core Study)	Aflibercept 2 mg (Core Study)	brolucizumab 6 mg (Extension study total)
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could

			have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	135	113	248
Average change in BCVA from baseline to Week 52 and Week 56 for the study eye (units: Letters read)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	-1.8 ± 8.29	-2.9 ± 7.33	-2.3 ± 7.88

Secondary Outcome Result(s)

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

Description	Central Subfield Thickness (µm): Analysis of Variance (ANOVA) results for the average change from extension study Baseline at Week 52 and Week 56 for the study eye in the extension study by core study treatment arm. Central Subfield Thickness was assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.
Time Frame	Extension study baseline, average of Week 52 and Week 56
Analysis Population Description	Participants in the Full Analysis Set with a valid measurement for the outcome measure. Participants were analyzed according to the originally assigned treatment arm in the core study (CRTH258A2303, NCT04005352).

	Brolucizumab 6 mg (Core Study)	**Aflibercept 2 mg (Core Study)**	**brolucizumab 6 mg (Extension study total)**
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with the	Patients who received aflibercept 2 mg in the core study and switched to	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4

	same treatment in the extension study	brolucizumab 6 mg in the extension study	up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	105	89	194
Average change in central subfield thickness (CSFT) from baseline to Week 52 and Week 56 - study eye (units: µm)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
	5.9 ± 24.43	-14.1 ± 60.67	-3.3 ± 45.83

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

Description	Intraretinal Fluid (IRF) and Subretinal Fluid (SRF) status in the central subfield as assessed by Spectral Domain Ocular Coherence Tomography (SD-OCT): Number (%) of subjects with presence of IRF and/or SRF, and sub-Retinal Pigment Epithelium (RPE) fluid in the study eye at Week 52 and Week 56 overall and by core study treatment arm
Time Frame	Weeks 52 and 56
Analysis Population Description	Full Analyses Set - for subjects with a valid measurement

	Brolucizumab 6 mg (Core Study)	**Aflibercept 2 mg (Core Study)**	**brolucizumab 6 mg (Extension study total)**
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per

			investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	106	94	200
Number (%) of subjects with presence of IRF and/or SRF, and sub-RPE fluid in the study eye at Week 52 and Week 56 overall and by core study treatment arm (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Week 52 IRF assessment - Present (n=103,90,193)	10 (9.71%)	14 (15.56%)	24 (12.44%)
Week 52 IRF assessment - Absent (n=103,90,193)	93 (90.29%)	76 (84.44%)	169 (87.56%)
Week 52 SRF assessment - Present (n=103,90,193)	14 (13.59%)	9 (10%)	23 (11.92%)
Week 52 SRF assessment - Absent (n=103,90,193)	89 (86.41%)	81 (90%)	170 (88.08%)
Week 52 Sub-RPE fluid - Present (n=103,90,193)	52 (50.49%)	44 (48.89%)	96 (49.74%)
Week 52 Sub-RPE fluid - Absent (n=103,90,193)	51 (49.51%)	46 (51.11%)	97 (50.26%)
Week 52 IRF and/or SRF - Present (n=103,90,193)	23 (22.33%)	22 (24.44%)	45 (23.32%)
Week 52 IRF and/or SRF - Absent (n=103,90,193)	102 (99.03%)	89 (98.89%)	191 (98.96%)
Week 52 IRF and SRF - Present (n=103,90,193)	1 (.97%)	1 (1.11%)	2 (1.04%)
Week 52 IRF and SRF - Absent (n=103,90,193)	80 (77.67%)	68 (75.56%)	148 (76.68%)
Week 56 IRF assessment - Present	13 (12.26%)	12 (12.77%)	25 (12.5%)
Week 56 IRF assessment - Absent	93 (87.74%)	82 (87.23%)	175 (87.5%)

Week 56 SRF assessment - Present	11 (10.38%)	7 (7.45%)	18 (9%)
Week 56 SRF assessment - Absent	95 (89.62%)	87 (92.55%)	182 (91%)
Week 56 Sub-RPE fluid - Present	51 (48.11%)	49 (52.13%)	100 (50%)
Week 56 Sub-RPE fluid - Absent	55 (51.89%)	45 (47.87%)	100 (50%)
Week 56 IRF and/or SRF - Present	23 (21.7%)	17 (18.09%)	40 (20%)
Week 56 IRF and/or SRF - Absent	105 (99.06%)	92 (97.87%)	197 (98.5%)
Week 56 IRF and SRF - Present	1 (.94%)	2 (2.13%)	3 (1.5%)
Week 56 IRF and SRF - Absent	83 (78.3%)	77 (81.91%)	160 (80%)

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

Description	Duration of the last interval with no disease activity up to Week 52 by core study treatment arm.
Time Frame	up to Week 56
Analysis Population Description	Full Analyses Set - for Subjects with at least two injections in the extension study

	Brolucizumab 6 mg (Core Study)	**Aflibercept 2 mg (Core Study)**
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with	Patients who received aflibercept 2 mg in the core study and switched to

	the same treatment in the extension study	brolucizumab 6 mg in the extension study
Number of Participants Analyzed [units: participants]	130	107
Last interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the Extension Study by core study randomized treatment arm (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
20 Weeks	49 (37.69%)	19 (17.76%)
16 Weeks	29 (22.31%)	30 (28.04%)
12 Weeks	21 (16.15%)	26 (24.3%)
8 Weeks	23 (17.69%)	26 (24.3%)
4 Weeks	8 (6.15%)	6 (5.61%)

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

Description	Duration of the maximal intervals with no disease activity up to Week 52 by core study treatment arm.
Time Frame	up to Week 56
Analysis Population Description	Full Analyses Set - for Subjects with at least two injections in the extension study

	Brolucizumab 6 mg (Core Study)	**Aflibercept 2 mg (Core Study)**
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with	Patients who received aflibercept 2 mg in the core study and switched to

	the same treatment in the extension study	brolucizumab 6 mg in the extension study
Number of Participants Analyzed [units: participants]	130	107
Maximal interval with no disease activity (number of weeks): Number (%) of subjects at 20/16/12/8/4-weeks intervals up to Week 56 for the study eye in the extension study (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
20 Weeks	54 (41.54%)	20 (18.69%)
16 Weeks	28 (21.54%)	31 (28.97%)
12 Weeks	23 (17.69%)	34 (31.78%)
8 Weeks	22 (16.92%)	18 (16.82%)
4 Weeks	3 (2.31%)	4 (3.74%)

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

Description	Change in last interval with no disease activity
Time Frame	Extension study baseline, up to Week 56
Analysis Population Description	Full Analyses Set - for Subjects with at least two injections in the extension study

	Brolucizumab 6 mg (Core Study)	**Aflibercept 2 mg (Core Study)**
Arm/Group Description	Patients who received brolucizumab 6 mg in the core study and continued with the same treatment in the extension study	Patients who received aflibercept 2 mg in the core study and switched to brolucizumab 6 mg in the extension study

Number of Participants Analyzed [units: participants]	130	107
Number (%) of subjects with change in duration of last interval with no disease activity between Baseline of the extension study and Week 56 by core study treatment arm (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
16 Weeks	0 (%)	2 (1.87%)
12 Weeks	8 (6.15%)	5 (4.67%)
8 Weeks	21 (16.15%)	32 (29.91%)
4 Weeks	49 (37.69%)	28 (26.17%)
0 Weeks	41 (31.54%)	31 (28.97%)
- 4 Weeks	8 (6.15%)	7 (6.54%)
-8 Weeks	2 (1.54%)	2 (1.87%)
-12 Weeks	1 (.77%)	0 (%)

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

Description	An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study.
Time Frame	Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.
Analysis Population Description	Full Analyses Set

	brolucizumab 6 mg
Arm/Group Description	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	248
Treatment-emergent ocular adverse events (greater than or equal to 1.0%) by preferred term for the study eye (units: Participants)	**Count of Participants (Not Applicable)**
Number of subjects with at least one AE	63 (25.4%)
Cataract	9 (3.63%)
Eye pain	6 (2.42%)
Visual acuity reduced	6 (2.42%)
Intraocular pressure increased	5 (2.02%)
Retinal haemorrhage	4 (1.61%)
Ocular discomfort	3 (1.21%)
Vitreous floaters	3 (1.21%)

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

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

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

	brolucizumab 6 mg
Arm/Group Description	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	248
Treatment-emergent non-ocular adverse events (greater than or equal to 2%) by preferred term (units: Participants)	**Count of Participants (Not Applicable)**
Number of subjects with at least one AE	82 (33.06%)
COVID-19	10 (4.03%)
Nasopharyngitis	8 (3.23%)
Fall	7 (2.82%)
Basal cell carcinoma	5 (2.02%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

All Collected Deaths

Description	On treatment death monitoring occurred after the first dose of study drug in the extension study until 30 days after the last administration of study drug for a maximum timeframe of approximately 56 weeks. Post-treatment death monitoring occurred greater than 30 days after the last administration of study drug.
Time Frame	On-treatment death reporting - from first dose until 30 days after last dose for a maximum timeframe of approximately 56 weeks. Post-treatment death reporting - greater than 30 days after the last dose of study drug.
Analysis Population Description	Full Analyses Set

	brolucizumab 6 mg
Arm/Group Description	Participants received brolucizumab 6 mg/0.05 mL solution by intravitreal injection in a Treat-to-Control regimen with injection intervals from 4 up to 20 weeks. Intervals could have changed in steps of 4 weeks at a time per investigators' decisions determined by the disease activity.
Number of Participants Analyzed [units: participants]	248
All Collected Deaths (units: Participants)	**Count of Participants (Not Applicable)**
On-treatment Deaths	0 (%)
Post-treatment Deaths	1 (.4%)
Total Deaths	1 (.4%)

Safety Results

Time Frame	Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.
Additional Description	Adverse events and the death are reported in the Full Analysis Set that includes all participants who received at least one dose of study treatment in the extension study.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Brolucizumab 6mg N = 248
Arm/Group Description	Brolucizumab 6mg
Total Number Affected	1
Total Number At Risk	248

Serious Adverse Events

Time Frame	Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.
Additional Description	Adverse events and the death are reported in the Full Analysis Set that includes all participants who received at least one dose of study treatment in the extension study.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	Brolucizumab 6mg N = 248
Arm/Group Description	Brolucizumab 6mg
Total # Affected by any Serious Adverse Event	26
Total # at Risk by any Serious Adverse Event	248
Cardiac disorders	
Atrial fibrillation	2 (0.81%)
Eye disorders	
Retinal detachment - Fellow eye	1 (0.40%)
Retinal occlusive vasculitis - Study eye	1 (0.40%)
Uveitis - Study eye	1 (0.40%)
Vitreal cells - Fellow eye	1 (0.40%)
Vitreal cells - Study eye	1 (0.40%)
Gastrointestinal disorders	
Inguinal hernia	1 (0.40%)

Infections and infestations	
Pneumonia	1 (0.40%)
Pyelonephritis acute	1 (0.40%)
Urinary tract infection	1 (0.40%)
Whipple's disease	1 (0.40%)
Injury, poisoning and procedural complications	
Contusion	1 (0.40%)
Fall	2 (0.81%)
Lower limb fracture	1 (0.40%)
Meniscus injury	1 (0.40%)
Procedural vomiting	1 (0.40%)
Rib fracture	1 (0.40%)
Spinal compression fracture	1 (0.40%)
Musculoskeletal and connective tissue disorders	
Chondropathy	1 (0.40%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Basal cell carcinoma	5 (2.02%)
Breast cancer	1 (0.40%)
Lung neoplasm	1 (0.40%)
Prostate cancer	1 (0.40%)
Squamous cell carcinoma of skin	1 (0.40%)
Nervous system disorders	
Ischaemic stroke	1 (0.40%)

Seizure	1 (0.40%)
Transient ischaemic attack	1 (0.40%)
Psychiatric disorders	
Delirium	1 (0.40%)
Renal and urinary disorders	
Calculus urinary	1 (0.40%)
Respiratory, thoracic and mediastinal disorders	
Chronic obstructive pulmonary disease	1 (0.40%)
Respiratory arrest	1 (0.40%)

Other (Not Including Serious) Adverse Events

Time Frame	Adverse events are reported from the first dose of study-drug until the end of treatment at week 52, plus 4 weeks safety follow-up, for a maximum timeframe of approximately 56 weeks.
Additional Description	Adverse events and the death are reported in the Full Analysis Set that includes all participants who received at least one dose of study treatment in the extension study.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 2%

	Brolucizumab 6mg N = 248
Arm/Group Description	Brolucizumab 6mg
Total # Affected by any Other Adverse Event	58
Total # at Risk by any Other Adverse Event	248
Eye disorders	
Cataract - Fellow eye	7 (2.82%)
Cataract - Study eye	9 (3.63%)
Eye pain - Study eye	6 (2.42%)
Neovascular age-related macular degeneration - Fellow eye	10 (4.03%)
Visual acuity reduced - Study eye	6 (2.42%)
Infections and infestations	
COVID-19	10 (4.03%)
Nasopharyngitis	8 (3.23%)
Injury, poisoning and procedural complications	
Fall	7 (2.82%)
Investigations	
Intraocular pressure increased - Study eye	5 (2.02%)

Other Relevant Findings

Conclusion:

Brolucizumab 6 mg administered in a treat-to-control (TtC) dosing regimen has demonstrated good durability in terms of sustained disease control and Best Corrected Visual Acuity (BCVA) maintenance up to Week 56 in subjects who continued brolucizumab treatment and those who switched from aflibercept to brolucizumab. The majority of subjects had treatment interval extensions of 4 weeks or more up to Week 56; subjects who switched from aflibercept had longer treatment interval extensions than those who continued on brolucizumab. The safety profile of brolucizumab in the Talon extension study was consistent with that observed in the Talon core study and the previously established profile of brolucizumab in the treatment of neovascular Age-related Macular Degeneration (nAMD). No new or enhanced safety signal was identified.

Date of Clinical Trial Report

30 Jan 2024