NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Aflibercept

Trial Indication(s)

Macular Edema secondary to Central Retinal Vein Occlusion

Protocol Number

CRTH258C2302

Protocol Title

An Eighteen-Month, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Macular Edema secondary to Central Retinal Vein Occlusion

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: July 2019 (Actual)

Primary Completion Date: July 2021 (Actual)
Study Completion Date: July 2021 (Actual)

Reason for Termination (If applicable)

Based on CRTH258AUS04 (MERLIN) first interpretable results, an increased incidence of intraocular inflammation (IOI) and related AEs, including retinal vasculitis and retinal vascular occlusion, in patients with q4 week dosing beyond the three monthly "loading phase" in nAMD has been observed. On 26-May-2021, the Data Monitoring Committee (DMC) reviewed the safety data of the CRTH258C2302 (RAVEN) study in the context of CRTH258AUS04 first interpretable results because it had six, monthly loading treatments. The DMC detected a similarly increased incidence of relevant AEs. Therefore, Novartis decided to initiate an urgent safety measure which included early termination of the CRTH258C2302 study.

Study Design/Methodology

The study was an 18-month, randomized, double-masked, multicenter, active-controlled, noninferiority, 2-arm study in subjects with visual impairment due to macular edema secondary to Central retinal vein occlusion.
Eligible subjects were randomly assigned via Interactive Response Technology at Baseline/Day 1 to one of the following two treatment arms in a 1:1 ratio:

- Brolucizumab 6 mg: 6 x q4w followed by 48 weeks of Individualized flexible treatment (IFT) from Week 24 onwards
- Aflibercept 2 mg: 6 x q4w followed by 48 weeks of IFT from Week 24 onwards

The study included Screening Period (Day -28 to Day -1), double-masked treatment period (Day 1 to Week 72), and post-treatment follow-up period (Week 72 to Week 76)

The IFT phase is defined as follows:

- The assessment of disease stability is performed at each visit by the masked investigator as of Week 24, and is guided by the stability of visual acuity and/or anatomical parameters (e.g. subretinal fluid, intraretinal fluid, retinal thickness (CSFT)), within the previous 3 visits.
- As long as there is no disease stability, subjects will receive active injections every 4 weeks.

- When disease stability is reached, treatment is interrupted.

Centers

132 centers in 19 countries: United States(34), United Kingdom(7), Australia(7), Germany(11), France(7), Hungary(5), Czech Republic(4), Italy(4), Malaysia(2), China(14), Spain(6), Israel(4), Russia(4), Greece(2), Canada(5), Netherlands(1), Japan(11), Thailand(3), Turkey(1)

Objectives:

Primary objective:

- To demonstrate that brolucizumab is noninferior to aflibercept with respect to the change in best-corrected visual acuity from baseline up to Month 6

Secondary objectives:

- To assess the effect of brolucizumab as compared to aflibercept on BCVA
- To evaluate the anatomical outcome with brolucizumab relative to aflibercept
- To evaluate the treatment frequency with brolucizumab during the individualized flexible treatment (IFT) period relative to aflibercept
- To assess the safety and tolerability of brolucizumab relative to aflibercept
- To evaluate the effect of brolucizumab relative to aflibercept on patient-reported vision-related quality of life
- To assess the immunogenicity of brolucizumab

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

- Brolucizumab: single use, sterile glass vial to deliver a 6 mg dose when administering a volume of 0.05 mL Intravitreal injection.
- Aflibercept: single use, sterile glass vial to deliver a 2 mg dose when administering a volume of 0.05 mL Intravitreal injection.

Statistical Methods

The objective related to the primary endpoint was to demonstrate non-inferiority of brolucizumab versus aflibercept with respect to the change from baseline in BCVA at Week 24, assuming a non-inferiority margin of 4 ETDRS letters. An analysis of variance (ANOVA) model was used to test non-inferiority. Missing/censored BCVA values were imputed/replaced by LOCF as the primary approach for the primary estimand. Observed values from both scheduled and unscheduled post-baseline visits were used for the LOCF imputation. For subjects with no post-baseline BCVA value, the baseline values were carried forward.

Summary statistics were presented by treatment group unless otherwise specified.

All safety analyses were descriptive and performed based on observed data using the SAF.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Signed informed consent must be obtained prior to participation in the study.
-Patients with visual impairment due to ME secondary to CRVO diagnosed < 6 months prior to screening.
-BCVA score between 78 and 23 letters, inclusive, using ETDRS visual acuity testing charts (approximate Snellen equivalent of 20/32 to 20/320) at both screening and baseline visits.

Exclusion criteria
-Concomitant conditions or ocular disorders in the study eye at screening or baseline which could, in the opinion of the investigator, prevent response to study treatment or may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the first 12-month study period (e.g. structural damage of the fovea, vitreous hemorrhage, retinal vascular occlusion other than CRVO, retinal detachment, macular hole, or choroidal neovascularization of any cause, diabetic retinopathy (except mild non-proliferative) and diabetic macular edema).
-Any active intraocular or periocular infection or active intraocular inflammation (e.g. infectious conjunctivitis, keratitis, scleritis, endophthalmitis, infectious blepharitis, uveitis) in study eye at screening or baseline
-Uncontrolled glaucoma in the study eye defined as intraocular pressure (IOP) > 25 mmHg on medication, or according to investigator’s judgment, at screening or baseline

-Presence of amblyopia, amaurosis or ocular disorders in the fellow eye with BCVA < 20/200 at screening (except when due to conditions whose surgery may improve VA, e.g. cataract)
-Previous treatment with any anti-VEGF therapy or investigational drugs in the study eye at any time prior to baseline
-Previous use of intraocular or periocular steroids in study eye at any time prior to baseline
-Macular laser photocoagulation (focal/grid) in the study eye at any time prior to baseline and peripheral laser photocoagulation in the study eye within 3 months prior to the baseline
-Intraocular surgery in the study eye during the 3-month period prior to baseline
-Vitreoretinal surgery in the study eye at any time prior to baseline
-Aphakia with the absence of posterior capsule in the study eye

Participant Flow Table

Overall Study

	Brolucizumab 6 mg	Aflibercept 2 mg	Total
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	
Started	247	246	493
Completed	66	70	136
Not Completed	181	176	357
Study terminated by sponsor	164	159	323

Subject decision	10	11	21
Lost to Follow-up	3	3	6
Adverse Event	2	1	3
Death	2	1	3
Physician Decision	0	1	1

Baseline Characteristics

	Brolucizumab 6 mg	**Aflibercept 2 mg**	**Total**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	
Number of Participants [units: participants]	247	246	493
Age Continuous (units: Years) Mean ± Standard Deviation			
	63.0±13.69	65.2±12.66	64.1±13.22

Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	96	96	192
Male	151	150	301
Race/Ethnicity, Customized (units: Participants)			
White	176	178	354
Black or African American	7	8	15
Asian	62	58	120
Native Hawaiian or Other Pacific Islander	2	0	2
American Indian or Alaska Native	0	1	1
Unknown	0	1	1

Primary Outcome Result(s)

Change from baseline in best-corrected visual acuity (BCVA) at Week 24

(Time Frame: Baseline, Week 24)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual

	flexible treatment (IFT)	flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Change from baseline in best-corrected visual acuity (BCVA) at Week 24 (units: Letters read) Least Squares Mean ± Standard Error		
	13.2 ± 0.85	16.0 ± 0.85

Statistical Analysis

Groups	Brolucizumab 6 mg, Aflibercept 2 mg	
Non-Inferiority/Equivalence Test	Non-Inferiority	Non-inferiority was considered to be established if the lower limit of the corresponding 95% CI for the estimated between group difference (brolucizumab vs. aflibercept) on change from baseline in BCVA at Week 24 is > -4 letters.
P Value	0.173	
Method	ANOVA	
Other Least Square Mean Difference	-2.9	

Standard Error of the mean	1.20
95 % Confidence Interval 2-Sided	-5.2 to -0.5

Secondary Outcome Result(s)

Change from baseline in BCVA averaged over Week 40 to Week 52

(Time Frame: Baseline, Week 40 to Week 52)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	120	120
Change from baseline in BCVA averaged over Week 40 to Week 52 (units: Letters read) Mean ± Standard Deviation		
	13.4 ± 15.73	15.4 ± 13.96

Change from baseline in BCVA averaged over Week 64 to Week 76

(Time Frame: Baseline, Week 64 to Week 76)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	109	113
Change from baseline in BCVA averaged over Week 64 to Week 76 (units: Letters read) Mean ± Standard Deviation		
	14.0 ± 16.39	16.9 ± 13.60

Change from baseline in BCVA by visit up to Week 76

(Time Frame: Baseline and every 4 weeks from baseline up to Week 76)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48

	weeks of individual flexible treatment (IFT)	weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Change from baseline in BCVA by visit up to Week 76 (units: Letters read) Mean ± Standard Deviation		
Week 4	11.3 ± 12.30	12.8 ± 11.00
Week 8	13.6 ± 13.77	15.0 ± 11.78
Week 12	14.1 ± 14.17	16.3 ± 12.78
Week 16	13.3 ± 15.37	17.4 ± 13.54
Week 20	13.9 ± 14.17	17.6 ± 14.68
Week 24	13.6 ± 14.69	18.1 ± 13.83
Week 28	12.7 ± 15.52	16.2 ± 13.55
Week 32	11.5 ± 15.96	15.1 ± 14.58
Week 36	12.6 ± 17.17	15.3 ± 14.05
Week 40	13.7 ± 15.35	16.7 ± 12.62
Week 44	13.7 ± 16.59	15.4 ± 14.50
Week 48	13.5 ± 17.11	16.2 ± 13.14
Week 52	12.9 ± 18.00	16.3 ± 14.13
Week 56	13.4 ± 16.98	14.9 ± 16.43
Week 60	13.1 ± 18.75	15.7 ± 13.93
Week 64	14.2 ± 17.06	17.8 ± 13.54
Week 68	14.2 ± 16.75	17.0 ± 13.88
Week 72	15.8 ± 14.55	15.2 ± 15.09

Week 76	17.2 ± 13.46	14.9 ± 13.76

Proportion of participants with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

(Time Frame: Baseline and every 4 weeks from baseline up to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Proportion of participants with a gain ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline (units: Participants) Count of Participants (Not Applicable)		
Week 4; BCVA gain from baseline >=5	181 (76.37%)	189 (80.08%)
Week 4; BCVA gain from baseline >=10	138 (58.23%)	132 (55.93%)
Week 4; BCVA gain from baseline >=15	92 (38.82%)	86 (36.44%)
Week 8; BCVA gain from baseline >=5	177 (83.49%)	183 (86.32%)
Week 8; BCVA gain from baseline >=10	143 (67.45%)	151 (71.23%)

Week 8; BCVA gain from baseline >=15	103 (48.58%)	95 (44.81%)
Week 12; BCVA gain from baseline >=5	161 (82.56%)	164 (84.54%)
Week 12; BCVA gain from baseline >=10	134 (68.72%)	141 (72.68%)
Week 12; BCVA gain from baseline >=15	101 (51.79%)	109 (56.19%)
Week 16; BCVA gain from baseline >=5	144 (82.76%)	152 (88.89%)
Week 16; BCVA gain from baseline >=10	121 (69.54%)	134 (78.36%)
Week 16; BCVA gain from baseline >=15	91 (52.3%)	104 (60.82%)
Week 20; BCVA gain from baseline >=5	135 (82.32%)	136 (87.18%)
Week 20; BCVA gain from baseline >=10	114 (69.51%)	122 (78.21%)
Week 20; BCVA gain from baseline >=15	83 (50.61%)	101 (64.74%)
Week 24; BCVA gain from baseline >=5	125 (83.89%)	130 (90.28%)
Week 24; BCVA gain from baseline >=10	101 (67.79%)	115 (79.86%)
Week 24; BCVA gain from baseline >=15	78 (52.35%)	97 (67.36%)
Week 28; BCVA gain from baseline >=5	112 (81.16%)	116 (87.22%)
Week 28; BCVA gain from baseline >=10	91 (65.94%)	104 (78.2%)
Week 28; BCVA gain from baseline >=15	69 (50%)	83 (62.41%)

Week 32; BCVA gain from baseline >=5	100 (76.92%)	100 (81.3%)
Week 32; BCVA gain from baseline >=10	78 (60%)	89 (72.36%)
Week 32; BCVA gain from baseline >=15	58 (44.62%)	76 (61.79%)
Week 36; BCVA gain from baseline >=5	101 (84.17%)	104 (85.25%)
Week 36; BCVA gain from baseline >=10	86 (71.67%)	84 (68.85%)
Week 36; BCVA gain from baseline >=15	61 (50.83%)	69 (56.56%)
Week 40; BCVA gain from baseline >=5	101 (84.87%)	98 (84.48%)
Week 40; BCVA gain from baseline >=10	85 (71.43%)	85 (73.28%)
Week 40; BCVA gain from baseline >=15	59 (49.58%)	71 (61.21%)
Week 44; BCVA gain from baseline >=5	89 (79.46%)	99 (85.34%)
Week 44; BCVA gain from baseline >=10	75 (66.96%)	82 (70.69%)
Week 44; BCVA gain from baseline >=15	59 (52.68%)	67 (57.76%)
Week 48; BCVA gain from baseline >=5	92 (81.42%)	89 (80.18%)
Week 48; BCVA gain from baseline >=10	72 (63.72%)	79 (71.17%)
Week 48; BCVA gain from baseline >=15	56 (49.56%)	63 (56.76%)
Week 52; BCVA gain from baseline >=5	89 (78.76%)	92 (83.64%)

Week 52; BCVA gain from baseline >=10	71 (62.83%)	81 (73.64%)
Week 52; BCVA gain from baseline >=15	58 (51.33%)	67 (60.91%)
Week 56; BCVA gain from baseline >=5	88 (82.24%)	92 (82.88%)
Week 56; BCVA gain from baseline >=10	70 (65.42%)	82 (73.87%)
Week 56; BCVA gain from baseline >=15	58 (54.21%)	64 (57.66%)
Week 60; BCVA gain from baseline >=5	88 (81.48%)	91 (80.53%)
Week 60; BCVA gain from baseline >=10	72 (66.67%)	80 (70.8%)
Week 60; BCVA gain from baseline >=15	60 (55.56%)	69 (61.06%)
Week 64; BCVA gain from baseline >=5	88 (82.24%)	89 (82.41%)
Week 64; BCVA gain from baseline >=10	73 (68.22%)	81 (75%)
Week 64; BCVA gain from baseline >=15	59 (55.14%)	65 (60.19%)
Week 68; BCVA gain from baseline >=5	76 (81.72%)	84 (83.17%)
Week 68; BCVA gain from baseline >=10	61 (65.59%)	72 (71.29%)
Week 68; BCVA gain from baseline >=15	52 (55.91%)	62 (61.39%)
Week 72; BCVA gain from baseline >=5	65 (85.53%)	63 (77.78%)
Week 72; BCVA gain from baseline >=10	53 (69.74%)	60 (74.07%)

Week 72; BCVA gain from baseline >=15	46 (60.53%)	50 (61.73%)
Week 76; BCVA gain from baseline >=5	54 (84.38%)	56 (80%)
Week 76; BCVA gain from baseline >=10	47 (73.44%)	49 (70%)
Week 76; BCVA gain from baseline >=15	36 (56.25%)	41 (58.57%)

Proportion of participants with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline

(Time Frame: Baseline and every 4 weeks from baseline up to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Proportion of participants with a loss ≥ 5, 10 and 15 letters in BCVA by visit compared to baseline (units: Participants) Count of Participants (Not Applicable)		
Week 4; BCVA loss from baseline >=5	10 (4.22%)	7 (2.97%)

Week 4; BCVA loss from baseline >=10	8 (3.38%)	3 (1.27%)
Week 4; BCVA loss from baseline >=15	5 (2.11%)	2 (.85%)
Week 8; BCVA loss from baseline >=5	9 (4.25%)	6 (2.83%)
Week 8; BCVA loss from baseline >=10	7 (3.3%)	3 (1.42%)
Week 8; BCVA loss from baseline >=15	6 (2.83%)	2 (.94%)
Week 12; BCVA loss from baseline >=5	9 (4.62%)	7 (3.61%)
Week 12; BCVA loss from baseline >=10	6 (3.08%)	5 (2.58%)
Week 12; BCVA loss from baseline >=15	5 (2.56%)	1 (.52%)
Week 16; BCVA loss from baseline >=5	11 (6.32%)	7 (4.09%)
Week 16; BCVA loss from baseline >=10	8 (4.6%)	5 (2.92%)
Week 16; BCVA loss from baseline >=15	8 (4.6%)	2 (1.17%)
Week 20; BCVA loss from baseline >=5	6 (3.66%)	8 (5.13%)
Week 20; BCVA loss from baseline >=10	5 (3.05%)	5 (3.21%)
Week 20; BCVA loss from baseline >=15	5 (3.05%)	5 (3.21%)
Week 24; BCVA loss from baseline >=5	10 (6.71%)	7 (4.86%)
Week 24; BCVA loss from baseline >=10	8 (5.37%)	5 (3.47%)

Week 24; BCVA loss from baseline >=15	7 (4.7%)	4 (2.78%)
Week 28; BCVA loss from baseline >=5	10 (7.25%)	7 (5.26%)
Week 28; BCVA loss from baseline >=10	6 (4.35%)	6 (4.51%)
Week 28; BCVA loss from baseline >=15	6 (4.35%)	5 (3.76%)
Week 32; BCVA loss from baseline >=5	11 (8.46%)	11 (8.94%)
Week 32; BCVA loss from baseline >=10	9 (6.92%)	8 (6.5%)
Week 32; BCVA loss from baseline >=15	5 (3.85%)	4 (3.25%)
Week 36; BCVA loss from baseline >=5	9 (7.5%)	7 (5.74%)
Week 36; BCVA loss from baseline >=10	8 (6.67%)	6 (4.92%)
Week 36; BCVA loss from baseline >=15	6 (5%)	5 (4.1%)
Week 40; BCVA loss from baseline >=5	7 (5.88%)	5 (4.31%)
Week 40; BCVA loss from baseline >=10	6 (5.04%)	3 (2.59%)
Week 40; BCVA loss from baseline >=15	4 (3.36%)	2 (1.72%)
Week 44; BCVA loss from baseline >=5	8 (7.14%)	9 (7.76%)
Week 44; BCVA loss from baseline >=10	7 (6.25%)	5 (4.31%)
Week 44; BCVA loss from baseline >=15	6 (5.36%)	5 (4.31%)

Week 48; BCVA loss from baseline >=5	9 (7.96%)	6 (5.41%)
Week 48; BCVA loss from baseline >=10	7 (6.19%)	4 (3.6%)
Week 48; BCVA loss from baseline >=15	6 (5.31%)	3 (2.7%)
Week 52; BCVA loss from baseline >=5	9 (7.96%)	7 (6.36%)
Week 52; BCVA loss from baseline >=10	7 (6.19%)	6 (5.45%)
Week 52; BCVA loss from baseline >=15	7 (6.19%)	5 (4.55%)
Week 56; BCVA loss from baseline >=5	9 (8.41%)	9 (8.11%)
Week 56; BCVA loss from baseline >=10	6 (5.61%)	7 (6.31%)
Week 56; BCVA loss from baseline >=15	5 (4.67%)	6 (5.41%)
Week 60; BCVA loss from baseline >=5	11 (10.19%)	10 (8.85%)
Week 60; BCVA loss from baseline >=10	8 (7.41%)	6 (5.31%)
Week 60; BCVA loss from baseline >=15	6 (5.56%)	3 (2.65%)
Week 64; BCVA loss from baseline >=5	8 (7.48%)	4 (3.7%)
Week 64; BCVA loss from baseline >=10	6 (5.61%)	2 (1.85%)
Week 64; BCVA loss from baseline >=15	6 (5.61%)	2 (1.85%)
Week 68; BCVA loss from baseline >=5	5 (5.38%)	6 (5.94%)

Week 68; BCVA loss from baseline >=10	5 (5.38%)	3 (2.97%)
Week 68; BCVA loss from baseline >=15	3 (3.23%)	1 (.99%)
Week 72; BCVA loss from baseline >=5	3 (3.95%)	7 (8.64%)
Week 72; BCVA loss from baseline >=10	3 (3.95%)	5 (6.17%)
Week 72; BCVA loss from baseline >=15	3 (3.95%)	3 (3.7%)
Week 76; BCVA loss from baseline >=5	1 (1.56%)	3 (4.29%)
Week 76; BCVA loss from baseline >=10	1 (1.56%)	3 (4.29%)
Week 76; BCVA loss from baseline >=15	1 (1.56%)	3 (4.29%)

Change from baseline in CSFT averaged over Week 40 to Week 52

(Time Frame: Baseline, Week 40 to Week 52)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)

Number of Participants Analyzed [units: participants]	119	120
Change from baseline in CSFT averaged over Week 40 to Week 52 (units: µm) Mean ± Standard Deviation		
	-399.9 ± 259.22	-434.6 ± 261.71

Change from baseline in CSFT averaged over Week 64 to Week 76

(Time Frame: Baseline, Week 64 to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	108	112
Change from baseline in CSFT averaged over Week 64 to Week 76 (units: µm) Mean ± Standard Deviation		

	-411.6 ± 259.16	-445.7 ± 259.73

Change from baseline in CSFT by visit up to Week 76

(Time Frame: Baseline, and every 4 weeks from baseline up to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Change from baseline in CSFT by visit up to Week 76 (units: µm) Mean ± Standard Deviation		
Week 4	-429.5 ± 254.32	-420.6 ± 242.68
Week 8	-448.8 ± 265.16	-436.1 ± 255.53
Week 12	-468.3 ± 269.55	-440.7 ± 251.74
Week 16	-450.1 ± 278.67	-470.7 ± 255.64
Week 20	-458.1 ± 270.26	-470.2 ± 260.46

Week 24	-446.8 ± 274.39	-472.4 ± 249.20
Week 28	-383.2 ± 248.81	-417.9 ± 269.03
Week 32	-323.5 ± 322.95	-395.8 ± 299.16
Week 36	-387.8 ± 280.75	-406.5 ± 265.67
Week 40	-403.9 ± 269.68	-446.6 ± 270.47
Week 44	-404.0 ± 311.37	-418.4 ± 271.33
Week 48	-411.5 ± 281.09	-457.8 ± 261.08
Week 52	-411.3 ± 276.21	-457.0 ± 256.40
Week 56	-384.6 ± 313.93	-400.8 ± 298.50
Week 60	-396.1 ± 295.96	-438.8 ± 254.36
Week 64	-425.2 ± 266.66	-462.3 ± 258.08
Week 68	-396.3 ± 282.85	-416.1 ± 260.79
Week 72	-401.5 ± 276.50	-419.0 ± 252.10
Week 76	-421.9 ± 261.63	-408.5 ± 251.12

Proportion of subjects with presence of retinal fluid (intra- and/or subretinal fluid) in the study eye by visit up to Week 76

(Time Frame: Every 4 weeks from week 4 up to Week 76)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Proportion of subjects with presence of retinal fluid (intra- and/or subretinal fluid) in the study eye by visit up to Week 76 (units: Participants) Count of Participants (Not Applicable)		
Week 4	101 (42.8%)	105 (44.68%)
Week 8	54 (25.47%)	68 (31.92%)
Week 12	38 (19.49%)	54 (27.84%)
Week 16	37 (21.14%)	43 (25.29%)
Week 20	34 (20.73%)	31 (19.87%)
Week 24	26 (17.33%)	30 (20.83%)
Week 28	44 (31.88%)	56 (42.11%)

Week 32	63 (48.46%)	55 (45.08%)
Week 36	43 (35.83%)	59 (48.36%)
Week 40	32 (26.89%)	40 (34.48%)
Week 44	38 (33.93%)	48 (41.38%)
Week 48	36 (31.86%)	40 (36.04%)
Week 52	35 (30.97%)	40 (36.36%)
Week 56	42 (39.25%)	48 (43.24%)
Week 60	36 (33.33%)	39 (34.51%)
Week 64	29 (27.36%)	41 (37.96%)
Week 68	36 (38.71%)	40 (40%)
Week 72	25 (32.89%)	27 (33.75%)
Week 76	24 (37.5%)	31 (44.29%)

Proportion of subjects with a CSFT < 300 µm for the study eye by visit up to Week 76

(Time Frame: Every 4 weeks from week 4 up to Week 76)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6	1 intravitreal injection every 4 weeks for a total of 6

	injections, followed by 48 weeks of individual flexible treatment (IFT)	injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Proportion of subjects with a CSFT < 300 µm for the study eye by visit up to Week 76 (units: Participants) Count of Participants (Not Applicable)		
Week 4	157 (66.53%)	137 (58.3%)
Week 8	168 (79.62%)	155 (72.77%)
Week 12	172 (88.21%)	149 (76.8%)
Week 16	153 (87.43%)	141 (82.94%)
Week 20	147 (89.63%)	135 (86.54%)
Week 24	135 (90%)	123 (86.62%)
Week 28	107 (77.54%)	90 (68.18%)
Week 32	81 (62.31%)	74 (60.66%)
Week 36	83 (70.94%)	77 (63.11%)
Week 40	94 (78.99%)	86 (74.14%)

Week 44	83 (74.11%)	79 (68.1%)
Week 48	82 (72.57%)	83 (74.77%)
Week 52	85 (75.22%)	82 (74.55%)
Week 56	74 (69.16%)	71 (63.96%)
Week 60	81 (75%)	79 (69.91%)
Week 64	85 (80.19%)	80 (74.77%)
Week 68	65 (70.65%)	69 (69.7%)
Week 72	59 (80.82%)	56 (70.89%)
Week 76	51 (79.69%)	45 (65.22%)

Number of injections between Week 24 and Week 52 and between Week 24 and Week 72

(Time Frame: Week 24 to Week 52 and Week 24 to Week 72)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)

Number of Participants Analyzed [units: participants]	114	115
Number of injections between Week 24 and Week 52 and between Week 24 and Week 72 (units: Injections) Mean ± Standard Deviation		
Between Week 24 and Week 52	2.4 ± 1.69	2.6 ± 2.02
Between Week 24 and Week 72	4.1 ± 3.08	4.4 ± 3.25

Time to recurrence after Week 20 and up to Week 76

(Time Frame: Week 20 to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	160	163
Time to recurrence after Week 20 and up to Week 76 (units: Weeks)		

Median (95% Confidence Interval)		
	12.1 (12.1 to 12.4)	12.1 (11.4 to 13.4)

Number of subjects with ocular and non-ocular AEs up to Week 52 and Week 76

(Time Frame: Baseline to Week 76)

	Brolucizumab 6 mg	**Aflibercept 2 mg**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Number of subjects with ocular and non-ocular AEs up to Week 52 and Week 76 (units: Participants) Count of Participants (Not Applicable)		
Ocular AEs up to week 52	105 (42.51%)	77 (31.3%)
Non-Ocular AEs up to week 52	103 (41.7%)	107 (43.5%)
Ocular AEs up to week 76	111 (44.94%)	89 (36.18%)
Non-Ocular AEs up to week 76	119 (48.18%)	117 (47.56%)

Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76

(Time Frame: Baseline, Week 24, Week 52 and Week 76)

	Brolucizumab 6 mg	Aflibercept 2 mg
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247	246
Change from baseline in patient reported outcomes (NEI VFQ-25) at Week 24, Week 52 and Week 76 (units: Score on a scale) Mean ± Standard Deviation		
Week 24	5.3 ± 13.08	7.4 ± 12.46
Week 52	6.0 ± 14.83	9.0 ± 11.10
Week 76	7.4 ± 14.44	9.4 ± 11.66

Number of subjects according to their Anti-drug antibody (ADA) titer at screening and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76

(Time Frame: Baseline, Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76)

	Brolucizumab 6 mg
Arm/Group Description	1 intravitreal injection every

	4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	247
Number of subjects according to their Anti-drug antibody (ADA) titer at screening and Week 4, Week 12, Week 24, Week 36, Week 52 and Week 76 (units: Participants) Count of Participants (Not Applicable)	
Baseline : Negative	105 (43.03%)
Baseline : 40	23 (9.43%)
Baseline : 120	35 (14.34%)
Baseline : 360	34 (13.93%)
Baseline : 1080	29 (11.89%)
Baseline : 3240	13 (5.33%)
Baseline : 9720	4 (1.64%)
Baseline : 29200	1 (.41%)
Week 4 : Negative	101 (44.69%)

Week 4 : 40	26 (11.5%)
Week 4 : 120	30 (13.27%)
Week 4 : 360	35 (15.49%)
Week 4 : 1080	21 (9.29%)
Week 4 : 3240	8 (3.54%)
Week 4 : 9720	5 (2.21%)
Week 4 : 29200	0 (%)
Week 12 : Negative	77 (41.18%)
Week 12 : 40	15 (8.02%)
Week 12 : 120	38 (20.32%)
Week 12 : 360	28 (14.97%)
Week 12 : 1080	12 (6.42%)
Week 12 : 3240	14 (7.49%)
Week 12 : 9720	3 (1.6%)
Week 12 : 29200	0 (%)
Week 24 : Negative	51 (34.93%)

Week 24 : 40	16 (10.96%)
Week 24 : 120	32 (21.92%)
Week 24 : 360	21 (14.38%)
Week 24 : 1080	15 (10.27%)
Week 24 : 3240	8 (5.48%)
Week 24 : 9720	3 (2.05%)
Week 24 : 29200	0 (%)
Week 36 : Negative	35 (30.7%)
Week 36 : 40	8 (7.02%)
Week 36 : 120	20 (17.54%)
Week 36 : 360	28 (24.56%)
Week 36 : 1080	11 (9.65%)
Week 36 : 3240	9 (7.89%)
Week 36 : 9720	3 (2.63%)
Week 36 : 29200	0 (%)
Week 52 : Negative	37 (32.46%)

Week 52 : 40	15 (13.16%)
Week 52 : 120	22 (19.3%)
Week 52 : 360	16 (14.04%)
Week 52 : 1080	14 (12.28%)
Week 52 : 3240	9 (7.89%)
Week 52 : 9720	1 (.88%)
Week 52 : 29200	0 (%)
Week 76 : Negative	25 (37.31%)
Week 76 : 40	8 (11.94%)
Week 76 : 120	14 (20.9%)
Week 76 : 360	7 (10.45%)
Week 76 : 1080	7 (10.45%)
Week 76 : 3240	5 (7.46%)
Week 76 : 9720	1 (1.49%)
Week 76 : 29200	0 (%)

Safety Results

All-Cause Mortality

	Brolucizumab 6mg N = 247	Aflibercept 2mg N = 246	Overall N = 493
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	Overall
Total participants affected	2 (0.81%)	1 (0.41%)	3 (0.61%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post treatment, up to maximum duration of 76 weeks
Additional Description	Any sign or symptom that occurs during the study treatment plus the 4 weeks post treatment
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment

	Brolucizumab 6mg N = 247	Aflibercept 2mg N = 246	Overall N = 493
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual flexible treatment (IFT)	Overall
Total participants affected	36 (14.57%)	19 (7.72%)	55 (11.16%)
Cardiac disorders			
Cardiac failure congestive	1 (0.40%)	0 (0.00%)	1 (0.20%)
Hypertensive heart disease	1 (0.40%)	0 (0.00%)	1 (0.20%)
Myocardial infarction	1 (0.40%)	1 (0.41%)	2 (0.41%)
Ear and labyrinth disorders			
Sudden hearing loss	1 (0.40%)	0 (0.00%)	1 (0.20%)
Endocrine disorders			
Adrenal mass	1 (0.40%)	0 (0.00%)	1 (0.20%)
Eye disorders			
Cataract - Fellow eye	0 (0.00%)	1 (0.41%)	1 (0.20%)

Cataract - Study eye	0 (0.00%)	1 (0.41%)	1 (0.20%)
Epiretinal membrane - Fellow eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Ocular hypertension - Study eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Retinal artery occlusion - Study eye	2 (0.81%)	0 (0.00%)	2 (0.41%)
Retinal ischaemia - Study eye	0 (0.00%)	1 (0.41%)	1 (0.20%)
Retinal vasculitis - Study eye	2 (0.81%)	0 (0.00%)	2 (0.41%)
Retinal vein occlusion - Study eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Uveitis - Study eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Gastrointestinal disorders			
Ascites	1 (0.40%)	0 (0.00%)	1 (0.20%)
Infections and infestations			
Cellulitis	0 (0.00%)	1 (0.41%)	1 (0.20%)
COVID-19	4 (1.62%)	2 (0.81%)	6 (1.22%)
COVID-19 pneumonia	2 (0.81%)	0 (0.00%)	2 (0.41%)
Dacryocystitis - Study eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Emphysematous cystitis	1 (0.40%)	0 (0.00%)	1 (0.20%)
Endocarditis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Endophthalmitis - Study eye	1 (0.40%)	0 (0.00%)	1 (0.20%)
Gastroenteritis viral	0 (0.00%)	1 (0.41%)	1 (0.20%)

Pneumonia	1 (0.40%)	0 (0.00%)	1 (0.20%)
Renal cyst infection	1 (0.40%)	0 (0.00%)	1 (0.20%)
Staphylococcal sepsis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Subcutaneous abscess	0 (0.00%)	1 (0.41%)	1 (0.20%)
Urosepsis	1 (0.40%)	0 (0.00%)	1 (0.20%)
Vestibular neuronitis	1 (0.40%)	0 (0.00%)	1 (0.20%)
Injury, poisoning and procedural complications			
Femoral neck fracture	1 (0.40%)	0 (0.00%)	1 (0.20%)
Head injury	1 (0.40%)	0 (0.00%)	1 (0.20%)
Subdural haematoma	0 (0.00%)	1 (0.41%)	1 (0.20%)
Metabolism and nutrition disorders			
Hyponatraemia	0 (0.00%)	1 (0.41%)	1 (0.20%)
Musculoskeletal and connective tissue disorders			
Osteoarthritis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Osteoporotic fracture	0 (0.00%)	1 (0.41%)	1 (0.20%)
Rotator cuff syndrome	1 (0.40%)	0 (0.00%)	1 (0.20%)
Spinal osteoarthritis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer	1 (0.40%)	0 (0.00%)	1 (0.20%)
Diffuse large B-cell lymphoma	0 (0.00%)	1 (0.41%)	1 (0.20%)

Prostate cancer	0 (0.00%)	1 (0.41%)	1 (0.20%)
Squamous cell carcinoma	1 (0.40%)	0 (0.00%)	1 (0.20%)
Waldenstrom's macroglobulinaemia	1 (0.40%)	0 (0.00%)	1 (0.20%)
Nervous system disorders			
Carotid artery stenosis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Cerebral haemorrhage	1 (0.40%)	0 (0.00%)	1 (0.20%)
Cerebral infarction	0 (0.00%)	1 (0.41%)	1 (0.20%)
Cerebrovascular accident	0 (0.00%)	1 (0.41%)	1 (0.20%)
Hemiparesis	0 (0.00%)	1 (0.41%)	1 (0.20%)
Syncope	1 (0.40%)	0 (0.00%)	1 (0.20%)
Transient ischaemic attack	1 (0.40%)	1 (0.41%)	2 (0.41%)
Psychiatric disorders			
Suicidal ideation	1 (0.40%)	0 (0.00%)	1 (0.20%)
Renal and urinary disorders			
Diabetic nephropathy	1 (0.40%)	0 (0.00%)	1 (0.20%)
Reproductive system and breast disorders			
Cervical dysplasia	0 (0.00%)	1 (0.41%)	1 (0.20%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	1 (0.40%)	0 (0.00%)	1 (0.20%)

Dyspnoea	1 (0.40%)	0 (0.00%)	1 (0.20%)
Pulmonary embolism	0 (0.00%)	1 (0.41%)	1 (0.20%)
Vascular disorders			
Aneurysm	2 (0.81%)	0 (0.00%)	2 (0.41%)
Hypertensive crisis	1 (0.40%)	0 (0.00%)	1 (0.20%)
Peripheral ischaemia	1 (0.40%)	0 (0.00%)	1 (0.20%)
Varicose vein	1 (0.40%)	0 (0.00%)	1 (0.20%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were collected from first dose of study treatment until end of study treatment plus 4 weeks post treatment, up to maximum duration of 76 weeks
Additional Description	Any sign or symptom that occurs during the study treatment plus the 4 weeks post treatment
Source Vocabulary for Table Default	MedDRA (24.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Brolucizumab 6mg N = 247	**Aflibercept 2mg N = 246**	**Overall N = 493**
Arm/Group Description	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individual	Overall

	flexible treatment (IFT)	flexible treatment (IFT)	
Total participants affected	104 (42.11%)	87 (35.37%)	191 (38.74%)
Eye disorders			
Cataract - Study eye	8 (3.24%)	4 (1.63%)	12 (2.43%)
Conjunctival haemorrhage - Study eye	16 (6.48%)	11 (4.47%)	27 (5.48%)
Dry eye - Fellow eye	5 (2.02%)	5 (2.03%)	10 (2.03%)
Dry eye - Study eye	6 (2.43%)	6 (2.44%)	12 (2.43%)
Eye pain - Study eye	9 (3.64%)	6 (2.44%)	15 (3.04%)
Glaucoma - Fellow eye	5 (2.02%)	5 (2.03%)	10 (2.03%)
Glaucoma - Study eye	5 (2.02%)	5 (2.03%)	10 (2.03%)
Macular oedema - Study eye	18 (7.29%)	11 (4.47%)	29 (5.88%)
Ocular hypertension - Study eye	6 (2.43%)	3 (1.22%)	9 (1.83%)
Retinal ischaemia - Study eye	6 (2.43%)	1 (0.41%)	7 (1.42%)
Retinal vein occlusion - Study eye	7 (2.83%)	1 (0.41%)	8 (1.62%)
Uveitis - Study eye	8 (3.24%)	0 (0.00%)	8 (1.62%)
Visual acuity reduced - Study eye	22 (8.91%)	9 (3.66%)	31 (6.29%)
Vitreous detachment - Study eye	11 (4.45%)	11 (4.47%)	22 (4.46%)
Vitreous floaters - Study eye	5 (2.02%)	11 (4.47%)	16 (3.25%)

Infections and infestations			
COVID-19	5 (2.02%)	6 (2.44%)	11 (2.23%)
Nasopharyngitis	8 (3.24%)	6 (2.44%)	14 (2.84%)
Tooth abscess	1 (0.40%)	5 (2.03%)	6 (1.22%)
Urinary tract infection	7 (2.83%)	3 (1.22%)	10 (2.03%)
Investigations			
Intraocular pressure increased - Study eye	10 (4.05%)	13 (5.28%)	23 (4.67%)
Musculoskeletal and connective tissue disorders			
Arthralgia	9 (3.64%)	7 (2.85%)	16 (3.25%)
Back pain	1 (0.40%)	5 (2.03%)	6 (1.22%)
Nervous system disorders			
Headache	3 (1.21%)	8 (3.25%)	11 (2.23%)
Vascular disorders			
Hypertension	19 (7.69%)	10 (4.07%)	29 (5.88%)

Other Relevant Findings

NA

Conclusion:

- The primary hypothesis of non-inferiority of brolucizumab in improving the Best-corrected visual acuity (BCVA) at Week 24 as compared to aflibercept in patients with macular edema due to Central retinal vein occlusion (CRVO) was not established based on the primary method.
- Higher incidences of ocular SAEs and AESIs in the study eye were reported in the brolucizumab arm compared to the aflibercept arm and support the decision of early study termination.

Date of Clinical Trial Report

4 May 2022