NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Aflibercept

Trial Indication(s)

Macular Edema secondary to Branch Retinal Vein Occlusion

Protocol Number

CRTH258C2301

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 Branch 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 subjects with q4w 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 CRTH258C2301 (RAPTOR) study in the context of CRTH258AUS04 first interpretable results because it had 6 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 CRTH258C2301 study.

Study Design/Methodology

The study was an 18-month, randomized, double-masked, multi-center, active-controlled, noninferiority, 2-arm study in subjects with visual impairment due to macular edema secondary to Branch retinal vein occlusion.
Subjects who met all the inclusion and none of the exclusion criteria were randomized in a 1:1 ratio to one of the two treatment arms as following:

- 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 comprised of a 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

103 centers in 18 countries/regions: United Kingdom(5), United States(27), France(8), Germany(10), Slovakia (Slovak Republic)(3), Switzerland(2), Taiwan(2), Hong Kong(1), Russia(4), China(12), Israel(3), Spain(5), Canada(5), Italy(5), Austria(1), Denmark(1), Japan(6), Czech Republic(3)

Objectives:

Primary objective:

- To demonstrate that brolucizumab is non-inferior to aflibercept with respect to the change in BCVA frombaseline 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 BRVO 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 BRVO, retinal detachment, macular hole, or choroidal neovascularization of any cause, diabetic retinopathy (except mild non-proliferative) and diabetic macular edema). Hemiretinal vein occlusion should be excluded.
-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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)	
Started	226	224	450
Completed	73	76	149
Not Completed	153	148	301
Study terminated by sponsor	130	134	264
Subject decision	16	9	25

Adverse Event	3	1	4
Lost to Follow-up	2	2	4
Physician Decision	2	0	2
Death	0	2	2

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)	
Number of Participants [units: participants]	226	224	450
Age Continuous (units: Years) Mean ± Standard Deviation			
	65.4±11.05	65.0±10.92	65.2±10.97
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			

Female	117	125	242
Male	109	99	208
Race/Ethnicity, Customized (units: Participants)			
White	154	153	307
Black or African American	8	4	12
Asian	65	67	132

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224

Change from baseline in best-corrected visual acuity (BCVA) at Week 24 (units: Letters read) Least Squares Mean ± Standard Error		
	13.1 ± 0.71	15.0 ± 0.71

Statistical Analysis

Groups	Brolucizumab 6 mg, Aflibercept 2 mg	
Non-Inferiority/Equivalence Test	Non-Inferiority	Non-inferiority was considered 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 greater than -4 letters.
P Value	0.018	
Method	ANOVA	
Other Least Square Mean Difference	-1.9	
Standard Error of the mean	1.01	
95 % Confidence Interval 2-Sided	-3.9 to 0.1	

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	123	132
Change from baseline in BCVA averaged over Week 40 to Week 52 (units: Letters read) Mean ± Standard Deviation		
Week 40 through Week 52	12.9 ± 12.81	16.9 ± 10.63

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	1 intravitreal injection every

	4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)	4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	110	121
Change from baseline in BCVA averaged over Week 64 to Week 76 (units: Letters read) Mean ± Standard Deviation		
Week 64 through Week 76	13.7 ± 13.33	17.9 ± 10.65

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 weeks of individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)

Number of Participants Analyzed [units: participants]	226	224
Change from baseline in BCVA by visit up to Week 76 (units: Letters read) Mean ± Standard Deviation		
Week 4	9.2 ± 8.22	10.3 ± 10.13
Week 8	11.9 ± 10.68	12.8 ± 10.84
Week 12	13.2 ± 10.22	14.8 ± 11.23
Week 16	12.2 ± 12.59	16.3 ± 11.58
Week 20	13.5 ± 10.83	16.3 ± 12.15
Week 24	12.7 ± 12.36	16.6 ± 11.35
Week 28	12.1 ± 13.88	16.4 ± 10.62
Week 32	12.2 ± 13.24	15.7 ± 10.94
Week 36	11.8 ± 14.75	16.9 ± 10.95
Week 40	12.7 ± 12.89	16.9 ± 10.74
Week 44	13.5 ± 13.28	17.2 ± 11.37
Week 48	13.3 ± 13.38	17.7 ± 10.79
Week 52	13.5 ± 13.42	17.2 ± 10.46
Week 56	14.9 ± 10.86	17.7 ± 10.62
Week 60	13.7 ± 13.67	17.7 ± 10.33
Week 64	14.1 ± 13.72	18.0 ± 10.54
Week 68	13.9 ± 13.83	17.7 ± 10.75
Week 72	13.9 ± 13.38	18.4 ± 11.44
Week 76	14.4 ± 13.72	18.1 ± 11.19

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	154 (69.06%)	150 (69.12%)
Week 4; BCVA gain from baseline >=10	102 (45.74%)	110 (50.69%)
Week 4; BCVA gain from baseline >=15	64 (28.7%)	79 (36.41%)
Week 8; BCVA gain from baseline >=5	158 (77.45%)	155 (77.89%)
Week 8; BCVA gain from baseline >=10	117 (57.35%)	118 (59.3%)
Week 8; BCVA gain from baseline >=15	92 (45.1%)	93 (46.73%)
Week 12; BCVA gain from baseline >=5	156 (84.32%)	156 (85.71%)

Week 12; BCVA gain from baseline >=10	114 (61.62%)	125 (68.68%)
Week 12; BCVA gain from baseline >=15	90 (48.65%)	102 (56.04%)
Week 16; BCVA gain from baseline >=5	127 (79.38%)	143 (89.38%)
Week 16; BCVA gain from baseline >=10	95 (59.38%)	118 (73.75%)
Week 16; BCVA gain from baseline >=15	73 (45.63%)	100 (62.5%)
Week 20; BCVA gain from baseline >=5	119 (82.64%)	131 (87.92%)
Week 20; BCVA gain from baseline >=10	96 (66.67%)	108 (72.48%)
Week 20; BCVA gain from baseline >=15	74 (51.39%)	92 (61.74%)
Week 24; BCVA gain from baseline >=5	122 (82.99%)	126 (87.5%)
Week 24; BCVA gain from baseline >=10	90 (61.22%)	109 (75.69%)
Week 24; BCVA gain from baseline >=15	75 (51.02%)	91 (63.19%)
Week 28; BCVA gain from baseline >=5	108 (80%)	121 (88.97%)
Week 28; BCVA gain from baseline >=10	89 (65.93%)	107 (78.68%)
Week 28; BCVA gain from baseline >=15	75 (55.56%)	87 (63.97%)
Week 32; BCVA gain from baseline >=5	97 (78.23%)	110 (85.94%)
Week 32; BCVA gain from baseline >=10	79 (63.71%)	94 (73.44%)

Week 32; BCVA gain from baseline >=15	60 (48.39%)	78 (60.94%)
Week 36; BCVA gain from baseline >=5	100 (81.3%)	112 (89.6%)
Week 36; BCVA gain from baseline >=10	81 (65.85%)	98 (78.4%)
Week 36; BCVA gain from baseline >=15	62 (50.41%)	83 (66.4%)
Week 40; BCVA gain from baseline >=5	96 (80.67%)	114 (91.94%)
Week 40; BCVA gain from baseline >=10	79 (66.39%)	98 (79.03%)
Week 40; BCVA gain from baseline >=15	65 (54.62%)	85 (68.55%)
Week 44; BCVA gain from baseline >=5	94 (81.03%)	111 (92.5%)
Week 44; BCVA gain from baseline >=10	78 (67.24%)	97 (80.83%)
Week 44; BCVA gain from baseline >=15	64 (55.17%)	88 (73.33%)
Week 48; BCVA gain from baseline >=5	92 (80.7%)	112 (93.33%)
Week 48; BCVA gain from baseline >=10	76 (66.67%)	95 (79.17%)
Week 48; BCVA gain from baseline >=15	61 (53.51%)	80 (66.67%)
Week 52; BCVA gain from baseline >=5	87 (82.08%)	117 (93.6%)
Week 52; BCVA gain from baseline >=10	75 (70.75%)	99 (79.2%)
Week 52; BCVA gain from baseline >=15	64 (60.38%)	87 (69.6%)

Week 56; BCVA gain from baseline >=5	90 (84.91%)	113 (92.62%)
Week 56; BCVA gain from baseline >=10	76 (71.7%)	106 (86.89%)
Week 56; BCVA gain from baseline >=15	58 (54.72%)	84 (68.85%)
Week 60; BCVA gain from baseline >=5	86 (81.9%)	116 (94.31%)
Week 60; BCVA gain from baseline >=10	71 (67.62%)	104 (84.55%)
Week 60; BCVA gain from baseline >=15	62 (59.05%)	88 (71.54%)
Week 64; BCVA gain from baseline >=5	86 (84.31%)	112 (95.73%)
Week 64; BCVA gain from baseline >=10	74 (72.55%)	98 (83.76%)
Week 64; BCVA gain from baseline >=15	58 (56.86%)	82 (70.09%)
Week 68; BCVA gain from baseline >=5	79 (84.04%)	103 (93.64%)
Week 68; BCVA gain from baseline >=10	67 (71.28%)	88 (80%)
Week 68; BCVA gain from baseline >=15	55 (58.51%)	76 (69.09%)
Week 72; BCVA gain from baseline >=5	68 (81.93%)	89 (96.74%)
Week 72; BCVA gain from baseline >=10	56 (67.47%)	75 (81.52%)
Week 72; BCVA gain from baseline >=15	45 (54.22%)	63 (68.48%)
Week 76; BCVA gain from baseline >=5	62 (91.18%)	67 (90.54%)

Week 76; BCVA gain from baseline >=10	52 (76.47%)	61 (82.43%)
Week 76; BCVA gain from baseline >=15	43 (63.24%)	53 (71.62%)

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	6 (2.69%)	7 (3.23%)
Week 4; BCVA loss from baseline >=10	1 (.45%)	3 (1.38%)
Week 4; BCVA loss from baseline >=15	0 (%)	0 (%)

Week 8; BCVA loss from baseline >=5	2 (.98%)	4 (2.01%)
Week 8; BCVA loss from baseline >=10	1 (.49%)	2 (1.01%)
Week 8; BCVA loss from baseline >=15	1 (.49%)	0 (%)
Week 12; BCVA loss from baseline >=5	3 (1.62%)	2 (1.1%)
Week 12; BCVA loss from baseline >=10	2 (1.08%)	1 (.55%)
Week 12; BCVA loss from baseline >=15	1 (.54%)	0 (%)
Week 16; BCVA loss from baseline >=5	9 (5.63%)	4 (2.5%)
Week 16; BCVA loss from baseline >=10	5 (3.13%)	2 (1.25%)
Week 16; BCVA loss from baseline >=15	3 (1.88%)	2 (1.25%)
Week 20; BCVA loss from baseline >=5	6 (4.17%)	4 (2.68%)
Week 20; BCVA loss from baseline >=10	2 (1.39%)	3 (2.01%)
Week 20; BCVA loss from baseline >=15	2 (1.39%)	1 (.67%)
Week 24; BCVA loss from baseline >=5	8 (5.44%)	3 (2.08%)
Week 24; BCVA loss from baseline >=10	3 (2.04%)	3 (2.08%)
Week 24; BCVA loss from baseline >=15	3 (2.04%)	1 (.69%)
Week 28; BCVA loss from baseline >=5	9 (6.67%)	2 (1.47%)

Week 28; BCVA loss from baseline >=10	6 (4.44%)	1 (.74%)
Week 28; BCVA loss from baseline >=15	6 (4.44%)	1 (.74%)
Week 32; BCVA loss from baseline >=5	8 (6.45%)	3 (2.34%)
Week 32; BCVA loss from baseline >=10	5 (4.03%)	2 (1.56%)
Week 32; BCVA loss from baseline >=15	3 (2.42%)	0 (%)
Week 36; BCVA loss from baseline >=5	9 (7.32%)	2 (1.6%)
Week 36; BCVA loss from baseline >=10	7 (5.69%)	1 (.8%)
Week 36; BCVA loss from baseline >=15	5 (4.07%)	1 (.8%)
Week 40; BCVA loss from baseline >=5	5 (4.2%)	4 (3.23%)
Week 40; BCVA loss from baseline >=10	4 (3.36%)	1 (.81%)
Week 40; BCVA loss from baseline >=15	2 (1.68%)	1 (.81%)
Week 44; BCVA loss from baseline >=5	4 (3.45%)	5 (4.17%)
Week 44; BCVA loss from baseline >=10	3 (2.59%)	3 (2.5%)
Week 44; BCVA loss from baseline >=15	2 (1.72%)	2 (1.67%)
Week 48; BCVA loss from baseline >=5	5 (4.39%)	3 (2.5%)
Week 48; BCVA loss from baseline >=10	3 (2.63%)	1 (.83%)

Week 48; BCVA loss from baseline >=15	1 (.88%)	1 (.83%)
Week 52; BCVA loss from baseline >=5	5 (4.72%)	2 (1.6%)
Week 52; BCVA loss from baseline >=10	3 (2.83%)	1 (.8%)
Week 52; BCVA loss from baseline >=15	2 (1.89%)	1 (.8%)
Week 56; BCVA loss from baseline >=5	3 (2.83%)	3 (2.46%)
Week 56; BCVA loss from baseline >=10	1 (.94%)	1 (.82%)
Week 56; BCVA loss from baseline >=15	0 (%)	0 (%)
Week 60; BCVA loss from baseline >=5	7 (6.67%)	2 (1.63%)
Week 60; BCVA loss from baseline >=10	3 (2.86%)	0 (%)
Week 60; BCVA loss from baseline >=15	1 (.95%)	0 (%)
Week 64; BCVA loss from baseline >=5	5 (4.9%)	2 (1.71%)
Week 64; BCVA loss from baseline >=10	1 (.98%)	1 (.85%)
Week 64; BCVA loss from baseline >=15	1 (.98%)	1 (.85%)
Week 68; BCVA loss from baseline >=5	6 (6.38%)	3 (2.73%)
Week 68; BCVA loss from baseline >=10	3 (3.19%)	1 (.91%)
Week 68; BCVA loss from baseline >=15	1 (1.06%)	0 (%)

Week 72; BCVA loss from baseline >=5	1 (1.2%)	2 (2.17%)
Week 72; BCVA loss from baseline >=10	1 (1.2%)	2 (2.17%)
Week 72; BCVA loss from baseline >=15	1 (1.2%)	1 (1.09%)
Week 76; BCVA loss from baseline >=5	2 (2.94%)	2 (2.7%)
Week 76; BCVA loss from baseline >=10	1 (1.47%)	0 (%)
Week 76; BCVA loss from baseline >=15	1 (1.47%)	0 (%)

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	123	132
Change from baseline in CSFT averaged over Week 40 to Week 52 (units: µm)		

Mean ± Standard Deviation		
Week 40 through Week 52	-231.8 ± 188.97	-259.2 ± 190.69

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	110	121
Change from baseline in CSFT averaged over Week 64 to Week 76 (units: µm) Mean ± Standard Deviation		
Week 64 through Week 76	-243.6 ± 201.61	-272.6 ± 194.29

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
Change from baseline in CSFT by visit up to Week 76 (units: µm) Mean ± Standard Deviation		
Week 4	-247.1 ± 197.99	-259.4 ± 185.11
Week 8	-255.9 ± 206.00	-270.7 ± 195.49
Week 12	-264.5 ± 208.70	-271.9 ± 194.99
Week 16	-271.1 ± 209.38	-276.1 ± 209.70
Week 20	-257.1 ± 197.31	-285.2 ± 210.32
Week 24	-254.9 ± 203.29	-286.6 ± 207.67
Week 28	-245.4 ± 197.62	-263.6 ± 197.11

Week 32	-231.1 ± 208.02	-262.1 ± 193.80
Week 36	-234.1 ± 199.02	-260.8 ± 195.03
Week 40	-224.7 ± 190.50	-259.0 ± 189.01
Week 44	-242.8 ± 197.34	-264.1 ± 192.06
Week 48	-237.1 ± 200.64	-279.4 ± 193.41
Week 52	-243.0 ± 203.87	-263.4 ± 190.36
Week 56	-249.2 ± 206.54	-271.4 ± 198.09
Week 60	-238.3 ± 185.78	-265.3 ± 187.29
Week 64	-249.8 ± 207.86	-266.1 ± 199.79
Week 68	-247.5 ± 217.61	-261.1 ± 192.30
Week 72	-253.4 ± 211.06	-279.4 ± 185.21
Week 76	-255.6 ± 184.22	-283.7 ± 197.29

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 baseline up to Week 76)

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

	total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)	total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	83 (37.22%)	101 (46.54%)
Week 8	56 (27.45%)	68 (33.83%)
Week 12	41 (22.28%)	49 (26.92%)
Week 16	34 (21.12%)	50 (31.25%)
Week 20	33 (22.92%)	45 (30.2%)
Week 24	35 (23.81%)	42 (29.37%)
Week 28	47 (35.07%)	56 (41.18%)
Week 32	58 (46.77%)	50 (39.06%)
Week 36	48 (39.02%)	57 (45.6%)

Week 40	42 (35.29%)	56 (45.16%)
Week 44	43 (37.07%)	54 (45%)
Week 48	44 (38.6%)	49 (40.83%)
Week 52	34 (32.08%)	57 (45.6%)
Week 56	34 (32.08%)	54 (44.26%)
Week 60	39 (37.14%)	63 (51.22%)
Week 64	31 (30.39%)	52 (44.44%)
Week 68	34 (36.56%)	52 (47.27%)
Week 72	33 (39.76%)	39 (42.39%)
Week 76	16 (23.53%)	38 (51.35%)

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 injections, followed by 48 weeks of individualized flexible	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible

	treatment (IFT)	treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	167 (74.89%)	153 (70.51%)
Week 8	172 (84.73%)	166 (82.59%)
Week 12	156 (84.78%)	155 (85.16%)
Week 16	137 (85.09%)	131 (81.88%)
Week 20	120 (83.92%)	118 (80.27%)
Week 24	127 (86.39%)	114 (79.72%)
Week 28	109 (81.34%)	103 (75.74%)
Week 32	92 (74.19%)	97 (75.78%)
Week 36	96 (78.05%)	91 (72.8%)
Week 40	94 (78.99%)	92 (74.19%)
Week 44	95 (81.9%)	93 (77.5%)
Week 48	89 (78.07%)	97 (80.83%)

Week 52	86 (81.13%)	95 (76%)
Week 56	86 (81.13%)	91 (74.59%)
Week 60	83 (79.05%)	90 (73.17%)
Week 64	85 (83.33%)	90 (76.92%)
Week 68	82 (88.17%)	79 (71.82%)
Week 72	70 (84.34%)	76 (82.61%)
Week 76	59 (86.76%)	59 (79.73%)

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	111	126
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	2.2 ± 1.69	2.5 ± 2.17
Between Week 24 and Week 72	3.2 ± 2.54	4.0 ± 3.28

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	157	159
Time to recurrence after Week 20 and up to Week 76 (units: Weeks) Median (95% Confidence Interval)		
	12.9 (12.1 to 14.4)	13.1 (11.3 to 17.4)

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	93 (41.15%)	72 (32.14%)
Non-Ocular AEs up to week 52	94 (41.59%)	112 (50%)
Ocular AEs up to week 76	98 (43.36%)	75 (33.48%)
Non-Ocular AEs up to week 76	103 (45.58%)	120 (53.57%)

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 individualized flexible treatment (IFT)	1 intravitreal injection every 4 weeks for a total of 6 injections, followed by 48 weeks of individualized flexible treatment (IFT)
Number of Participants Analyzed [units: participants]	226	224
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	5.6 ± 11.51	6.4 ± 11.92
Week 52	6.9 ± 13.21	7.6 ± 10.47
Week 76	8.6 ± 13.89	7.5 ± 11.55

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 individualized flexible

	treatment (IFT)
Number of Participants Analyzed [units: participants]	226
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	67 (30.59%)
Baseline : 40	29 (13.24%)
Baseline : 120	33 (15.07%)
Baseline : 360	37 (16.89%)
Baseline : 1080	31 (14.16%)
Baseline : 3240	15 (6.85%)
Baseline : 9720	1 (.46%)
Baseline : 29200	6 (2.74%)
Week 4 : Negative	76 (36.54%)
Week 4 : 40	29 (13.94%)
Week 4 : 120	31 (14.9%)

Week 4 : 360	28 (13.46%)
Week 4 : 1080	27 (12.98%)
Week 4 : 3240	9 (4.33%)
Week 4 : 9720	6 (2.88%)
Week 4 : 29200	2 (.96%)
Week 12 : Negative	58 (34.12%)
Week 12 : 40	17 (10%)
Week 12 : 120	31 (18.24%)
Week 12 : 360	25 (14.71%)
Week 12 : 1080	19 (11.18%)
Week 12 : 3240	11 (6.47%)
Week 12 : 9720	7 (4.12%)
Week 12 : 29200	2 (1.18%)
Week 24 : Negative	44 (32.84%)
Week 24 : 40	14 (10.45%)
Week 24 : 120	23 (17.16%)

Week 24 : 360	17 (12.69%)
Week 24 : 1080	19 (14.18%)
Week 24 : 3240	11 (8.21%)
Week 24 : 9720	5 (3.73%)
Week 24 : 29200	1 (.75%)
Week 36 : Negative	33 (28.95%)
Week 36 : 40	18 (15.79%)
Week 36 : 120	19 (16.67%)
Week 36 : 360	17 (14.91%)
Week 36 : 1080	17 (14.91%)
Week 36 : 3240	8 (7.02%)
Week 36 : 9720	1 (.88%)
Week 36 : 29200	1 (.88%)
Week 52 : Negative	28 (27.72%)
Week 52 : 40	18 (17.82%)
Week 52 : 120	19 (18.81%)

Week 52 : 360	16 (15.84%)
Week 52 : 1080	14 (13.86%)
Week 52 : 3240	5 (4.95%)
Week 52 : 9720	1 (.99%)
Week 52 : 29200	0 (%)
Week 76 : Negative	17 (25%)
Week 76 : 40	6 (8.82%)
Week 76 : 120	18 (26.47%)
Week 76 : 360	14 (20.59%)
Week 76 : 1080	10 (14.71%)
Week 76 : 3240	2 (2.94%)
Week 76 : 9720	1 (1.47%)
Week 76 : 29200	0 (%)

Safety Results

All-Cause Mortality

	Brolucizumab 6mg N = 226	Aflibercept 2mg N = 224	Overall N = 450
Arm/Group Description	Brolucizumab 6mg	Aflibercept 2mg	Overall
Total participants affected	0 (0.00%)	2 (0.89%)	2 (0.44%)

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 = 226	Aflibercept 2mg N = 224	Overall N = 450

Arm/Group Description	Brolucizumab 6mg	Aflibercept 2mg	Overall
Total participants affected	32 (14.16%)	16 (7.14%)	48 (10.67%)
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cardiac disorders			
Angina pectoris	1 (0.44%)	0 (0.00%)	1 (0.22%)
Atrial fibrillation	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cardiac arrest	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cardiac failure	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cardiac failure congestive	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cardiac valve disease	0 (0.00%)	1 (0.45%)	1 (0.22%)
Myocardial infarction	0 (0.00%)	1 (0.45%)	1 (0.22%)
Palpitations	1 (0.44%)	0 (0.00%)	1 (0.22%)
Congenital, familial and genetic disorders			
Atrial septal defect	1 (0.44%)	0 (0.00%)	1 (0.22%)
Ear and labyrinth disorders			
Vertigo	0 (0.00%)	1 (0.45%)	1 (0.22%)
Eye disorders			
Cataract - Fellow eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Cataract - Study eye	2 (0.88%)	0 (0.00%)	2 (0.44%)
Glaucoma - Fellow eye	1 (0.44%)	0 (0.00%)	1 (0.22%)

Glaucoma - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Iridocyclitis - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Retinal aneurysm - Study eye	0 (0.00%)	1 (0.45%)	1 (0.22%)
Retinal artery occlusion - Fellow eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Retinal artery occlusion - Study eye	2 (0.88%)	0 (0.00%)	2 (0.44%)
Retinal detachment - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Retinal occlusive vasculitis - Study eye	2 (0.88%)	0 (0.00%)	2 (0.44%)
Retinal vascular occlusion - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Retinal vasculitis - Study eye	2 (0.88%)	0 (0.00%)	2 (0.44%)
Uveitis - Study eye	3 (1.33%)	0 (0.00%)	3 (0.67%)
Vitreous haemorrhage - Study eye	0 (0.00%)	1 (0.45%)	1 (0.22%)
Vitreous opacities - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Vitritis - Study eye	1 (0.44%)	0 (0.00%)	1 (0.22%)
Gastrointestinal disorders			
Mallory-Weiss syndrome	0 (0.00%)	1 (0.45%)	1 (0.22%)
Pancreatitis acute	1 (0.44%)	0 (0.00%)	1 (0.22%)
General disorders and administration site conditions			
Chest pain	1 (0.44%)	1 (0.45%)	2 (0.44%)

Hepatobiliary disorders			
Cholecystitis acute	0 (0.00%)	1 (0.45%)	1 (0.22%)
Infections and infestations			
Bronchitis	1 (0.44%)	1 (0.45%)	2 (0.44%)
COVID-19	2 (0.88%)	0 (0.00%)	2 (0.44%)
COVID-19 pneumonia	1 (0.44%)	0 (0.00%)	1 (0.22%)
Endophthalmitis - Study eye	2 (0.88%)	0 (0.00%)	2 (0.44%)
Injury, poisoning and procedural complications			
Dislocation of vertebra	0 (0.00%)	1 (0.45%)	1 (0.22%)
Fall	1 (0.44%)	0 (0.00%)	1 (0.22%)
Subdural haemorrhage	1 (0.44%)	0 (0.00%)	1 (0.22%)
Investigations			
Weight increased	1 (0.44%)	0 (0.00%)	1 (0.22%)
Musculoskeletal and connective tissue disorders			
Muscular weakness	1 (0.44%)	0 (0.00%)	1 (0.22%)
Osteoarthritis	1 (0.44%)	1 (0.45%)	2 (0.44%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm	0 (0.00%)	1 (0.45%)	1 (0.22%)

Eyelid seborrhoeic keratosis - Fellow eye	0 (0.00%)	1 (0.45%)	1 (0.22%)
Prostate cancer	2 (0.88%)	0 (0.00%)	2 (0.44%)
Nervous system disorders			
Cerebral infarction	0 (0.00%)	1 (0.45%)	1 (0.22%)
Cerebrovascular accident	0 (0.00%)	1 (0.45%)	1 (0.22%)
Ischaemic stroke	1 (0.44%)	0 (0.00%)	1 (0.22%)
Syncope	1 (0.44%)	0 (0.00%)	1 (0.22%)
Transient ischaemic attack	1 (0.44%)	0 (0.00%)	1 (0.22%)
Product issues			
Device dislocation	0 (0.00%)	1 (0.45%)	1 (0.22%)
Psychiatric disorders			
Depression	1 (0.44%)	0 (0.00%)	1 (0.22%)
Renal and urinary disorders			
Urinary retention	1 (0.44%)	0 (0.00%)	1 (0.22%)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	1 (0.44%)	0 (0.00%)	1 (0.22%)
Respiratory, thoracic and mediastinal disorders			
Pleural mass	0 (0.00%)	1 (0.45%)	1 (0.22%)

Vascular disorders			
Aortic stenosis	1 (0.44%)	0 (0.00%)	1 (0.22%)
Vasospasm	0 (0.00%)	1 (0.45%)	1 (0.22%)

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 = 226	**Aflibercept 2mg N = 224**	**Overall N = 450**
Arm/Group Description	Brolucizumab 6mg	Aflibercept 2mg	Overall
Total participants affected	109 (48.23%)	95 (42.41%)	204 (45.33%)
Eye disorders			
Cataract - Study eye	9 (3.98%)	2 (0.89%)	11 (2.44%)
Conjunctival haemorrhage - Study eye	11 (4.87%)	12 (5.36%)	23 (5.11%)
Dry eye - Fellow eye	5 (2.21%)	9 (4.02%)	14 (3.11%)

Dry eye - Study eye	6 (2.65%)	9 (4.02%)	15 (3.33%)
Eye pain - Study eye	4 (1.77%)	11 (4.91%)	15 (3.33%)
Foreign body sensation in eyes - Study eye	5 (2.21%)	1 (0.45%)	6 (1.33%)
Macular oedema - Study eye	15 (6.64%)	10 (4.46%)	25 (5.56%)
Retinal exudates - Study eye	5 (2.21%)	8 (3.57%)	13 (2.89%)
Retinal haemorrhage - Study eye	2 (0.88%)	8 (3.57%)	10 (2.22%)
Uveitis - Study eye	5 (2.21%)	0 (0.00%)	5 (1.11%)
Visual acuity reduced - Study eye	15 (6.64%)	12 (5.36%)	27 (6.00%)
Vitreous detachment - Study eye	5 (2.21%)	5 (2.23%)	10 (2.22%)
Vitreous floaters - Study eye	11 (4.87%)	5 (2.23%)	16 (3.56%)
Vitreous opacities - Study eye	5 (2.21%)	1 (0.45%)	6 (1.33%)
Vitritis - Study eye	5 (2.21%)	0 (0.00%)	5 (1.11%)
Gastrointestinal disorders			
Toothache	5 (2.21%)	3 (1.34%)	8 (1.78%)
Infections and infestations			
COVID-19	7 (3.10%)	7 (3.13%)	14 (3.11%)
Nasopharyngitis	6 (2.65%)	7 (3.13%)	13 (2.89%)
Upper respiratory tract infection	2 (0.88%)	7 (3.13%)	9 (2.00%)
Urinary tract infection	5 (2.21%)	6 (2.68%)	11 (2.44%)

Injury, poisoning and procedural complications			
Fall	3 (1.33%)	5 (2.23%)	8 (1.78%)
Investigations			
Intraocular pressure increased - Fellow eye	3 (1.33%)	6 (2.68%)	9 (2.00%)
Intraocular pressure increased - Study eye	4 (1.77%)	8 (3.57%)	12 (2.67%)
Metabolism and nutrition disorders			
Hypercholesterolaemia	5 (2.21%)	3 (1.34%)	8 (1.78%)
Type 2 diabetes mellitus	5 (2.21%)	0 (0.00%)	5 (1.11%)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (0.88%)	6 (2.68%)	8 (1.78%)
Back pain	2 (0.88%)	7 (3.13%)	9 (2.00%)
Osteoarthritis	6 (2.65%)	2 (0.89%)	8 (1.78%)
Nervous system disorders			
Dizziness	4 (1.77%)	7 (3.13%)	11 (2.44%)
Vascular disorders			
Hypertension	26 (11.50%)	19 (8.48%)	45 (10.00%)

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 the aflibercept in patients with macular edema due to Branch retinal vein occlusion (BRVO) was established based on the primary method.
- Higher incidences of ocular Serious adverse events (SAEs) and Adverse events of special interest (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

26 April 2022