Sponsor

Novartis

Generic Drug Name

Brolucizumab

Trial Indications

Neovascular age-related macular degeneration (nAMD)

Protocol Number

CRTH258AGB02

Protocol Title

Brolucizumab Treatment Experience Study of Patients with Neovascular Age-related Macular Degeneration (nAMD) in UK routine clinical practice (BESRA)

Clinical Trial Phase

Not applicable

Phase of Drug Development

Not applicable

Study Start/End Dates

Study Start Date: 19 November 2021

Study Completion Date: 08 September 2022

Reason for Termination

Sponsor decision

Study Design/Methodology

The BESRA study was a national, multi-centre, prospective, observational study conducted to assess the effectiveness of brolucizumab intravitreal injections in patients with nAMD treated in the UK. Data was collected in a standardised manner from hospital medical records at participating sites, with most data collected prospectively over time as patients attended their routine clinical visits for nAMD. In addition to the collection of data from medical records, retinal optical coherence tomography (OCT) images were also planned to be collected during the first two years of treatment and transferred to a central reading centre for independent grading and interpretation, in order to support the validity of anatomical measurements relevant to the primary and secondary study objectives.

Centers

17 sites in the United Kingdom

Objectives:

Primary objectives

- The primary objective was to assess retinal fluid resolution (disease control) as measured by OCT after initiation of brolucizumab at the end of the first year.

Secondary objectives

- To describe the characteristics of patients with nAMD who initiate treatment with brolucizumab.
- To evaluate anatomical parameters during treatment with brolucizumab.
- To evaluate visual acuity (VA) change from baseline during treatment with brolucizumab.
- To evaluate the number of anti-vascular endothelial growth factor (anti-VEGF) injection visits, number of non-injection visits and total number of visits during treatment with brolucizumab, as well as the duration of intervals between brolucizumab injections.
- To evaluate the number of OCTs performed during treatment with brolucizumab, including the number of visits with/without OCT and the association between frequency of OCT measurement and choroidal neovascularisation (CNV) activity (i.e. presence/absence of intra-retinal fluid [IRF] and sub-retinal fluid [SRF]) and VA change from baseline.
- To explore the predictive value of the following factors on anatomical and functional outcomes at Months 12 and 24 of treatment with brolucizumab; age, baseline VA, baseline CNV activity (IRF or SRF), complete loading phase (yes/no), VA at the end of the loading phase (Month 3), CNV activity at the end of the loading phase (IRF or SRF), number of anti-VEGF injections (maintenance phase), geographic atrophy (yes/no), sub-retinal fibrosis (yes/no).
- To assess physician-reported retreatment criteria i.e. the factors influencing decisions to treat / not treat patients at each visit.
- To estimate the percentage (%) of patients that switched to another anti-VEGF during treatment with brolucizumab and characterise switchers with respect to their baseline characteristics and characteristics at switch.
- To evaluate the discontinuation rate of patients receiving brolucizumab and the time to discontinuation (persistence).
- To characterise the safety of brolucizumab treatment.

- To assess anatomical outcomes relating to disease control following initiation of brolucizumab, as assessed by an independent central reading centre.

Test Product, Dose, and Mode of Administration

Patients had received at least one injection of brolucizumab prior to this observational study. This criterion was verified during the eligibility period.

Statistical Methods

All analyses were performed by OPEN Health. The proposed analyses were planned to be conducted for all patients meeting the eligibility criteria, except for endpoints relating to outcomes at specified time-points (e.g. Month 3, 6, 9, 12, 24, 36, 48, and 60), which were only evaluated in those eyes with available follow-up at that time point unless otherwise specified.

All percentages were reported with decimals and the percentages were added up to 100%. For total group/subgroup sizes of less than 10, percentages were reported, except under exceptional circumstances. Consideration was given during data analysis as to whether reporting any of the planned analyses might identify individuals from combinations of variables occurring in very small groups. To preserve participant anonymity, such results were suppressed in the study report.

This was a descriptive study, and there was no a priori hypothesis to be tested. Due to early termination of the study and availability of limited data, not all of the planned analyses could be performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Diagnosis of nAMD.
- ≥ 50 years of age at index date.
- Receipt of at least one injection of brolucizumab during the eligibility period.
- Able and willing to provide signed informed consent.

Exclusion Criteria

- Received treatment for retinal vein occlusion, diabetic macular edema (DME) and/or myopic choroidal neovascularisation (mCNV), and/or has received a new diagnosis of diabetes-related macular degeneration in the index eye within 6 months prior to the index date.
- Receipt of anti-VEGF treatment other than brolucizumab in the index eye at index date.
- Any active intraocular or periocular infection or active intraocular inflammation in the index eye at index date.

- Had a contraindication and was not eligible for treatment with brolucizumab according to the Beovu® (brolucizumab) Summary of Product Characteristics (SmPC) ("Beovu 120 mg/ml solution for injection in pre-filled syringe – Summary of Product Characteristics (SmPC)" 2020).
- Any medical or psychological condition in the treating physician's opinion which might have prevented the patient from participating in the study.
- Participating in a parallel interventional clinical study.
- Participating in a parallel non-interventional study (NIS) generating primary data for an anti-VEGF drug.

Participant Flow Table

Screened	Eligible	Enrolled	Included in analysis*
435	374	294	285

*Patients who had index date available and records in the treatment table

Baseline Characteristics

	n	Percentage
Age (n) (years)	285	100
Mean (SD)	78.23 (7.9)	NA

	n	Percentage
Min – Max	50-97	NA
Median	79	NA
Lq	74	NA
Uq	84	NA
Age group (years)		
50-59	6	2.1%
60-69	29	10.2%
70-79	122	42.8%
80-89	111	38.9%
90+	17	6.0%
Sex		
Female	162	56.8%
Male	123	43.2%
Ethnicity		
Mixed/Multiple ethnic groups/Other	1	0.4%
Not recorded	21	7.4%
South Asian/Far East Asian/ Asian British	5	1.8%
White/White British	258	90.5%
Smoking status		
Current smoker	25	8.8%
Non-smoker - former smoker - stopping duration not known	25	8.8%
Non-smoker - former smoker ≤6 months	1	0.4%
Non-smoker - former smoker >6 months	26	9.1%
Non-smoker - never smoked	96	33.7%
Not recorded	112	39.3%
Driver		
Current driver	94	33.0%
Ex-driver	26	9.1%
Never driven	20	7.0%
Not known	145	50.8%
Index eye		

Left	162	56.8%
Right	123	43.2%
Uni/bilateral		
Bilateral	42	14.7%
Unilateral	240	84.2%
Not-known	3	1.1%
Total	**285**	**100%**

	n	**Percentage**
If Bilateral, is your index eye the best or worst seeing eye?		
Best seeing eye	7	16.7%
Worst seeing eye	33	78.6%
Not known	1	2.4%
Not recorded	1	2.4%
Total	**42**	**100%**

LQ- lower quartile, NA- Not applicable, UQ- upper quartile

Primary Outcome Results

Percentage (%) of patients with absence of retinal fluid (no SRF and no IRF as documented in medical records by the treating physician in relation to OCT results) at 12 months

IRF/SRF	n	Percent
At least one present	29	10.2%
Both absent	7	2.5%
Not available at timepoint	242	84.9%
One or both not recorded	7	2.5%
Total	285	100.0%

SRF=Sub-retinal fluid, IRF= Intra retinal fluid, OCT=Optical coherence tomography

Secondary Outcome Results

Absence of IRF and SRF by central reading centre by 12-month timepoint

IRF/SRF	n	percent
At least one present	3	75.0%
Both absent	1	25.0%
Total	4	100.0%

IRF = Intra retinal fluid, SRF = Sub-retinal fluid

Difference IRF macular volume at 12 months from baseline

Missing (n)	Available (n)	Difference
284	1	0.034

IRF = Intra retinal fluid

Percentage (%) of patients with absence of SRF at Month 3, 6 and 12

SRF	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
Absent	66	23.3%	43	15.1%	11	3.9%
Present	48	16.8%	39	13.7%	19	6.7%
No data available at timepoint	129	45.3%	185	64.9%	242	84.9%
Not recorded	42	14.7%	18	6.3%	13	4.6%
Total	285	100.0%	285	100.0%	285	100.0%

SRF- Sub-retinal fluid

Percentage (%) of patients with absence of IRF at Month 3, 6 and 12

IRF	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
Absent	84	29.5%	53	18.6%	19	6.7%
Present	28	9.8%	25	8.8%	13	4.6%
No data available at timepoint	129	45.3%	185	64.9%	242	84.9%
Not recorded	44	15.4%	21	7.4%	11	3.9%
Not routinely collected	NA	NA	1	0.4%	NA	NA
Total	285	100.0%	285	100.0%	285	100.0%

IRF = Intra retinal fluid

Percentage of patients with absence of sub-RPE at Month 3, 6 and 12

Sub-RPE	3 months		6 months		12 months	
	n	percent	n	Percent	n	percent
Absent	32	11.2%	6	2.1%	4	1.4%
Present	17	6.0%	13	4.6%	1	0.4%
No data available at timepoint	129	45.3%	185	64.9%	242	84.9%
Not recorded	65	22.8%	44	15.4%	25	8.8%
Not routinely collected	42	14.7%	37	13.0%	13	4.6%
Total	285	100.0%	285	100.0%	285	100.0%

RPE=Retinal pigment epithelium

Percentage (%) of patients with absence of PED at Month 3, 6 and 12

PED	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
Absent	11	3.9%	13	4.6%	5	1.8%
Present	49	17.2%	35	12.3	7	2.5%
No data available at timepoint	129	45.3%	185	64.9%	242	84.9%
Not recorded	55	19.3%	31	10.9%	24	8.4%
Not routinely collected	36	12.6%	17	6.0%	5	1.8%
Observed flattening	5	1.8%	4	1.4%	2	0.7%
Total	285	100.0%	285	100.0%	285	100.0%

PED=Pigment epithelial detachment

CRT recording at 3 months

CRT recorded at baseline	CRT recorded	Not recorded	Total (%)
CRT recorded	1 (6.7%)	14 (93.3%)	15 (100.0)
Not recorded	0 (0.0%)	260 (100.0%)	260 (100.0)
Not routinely collected at this centre	1 (10.0%)	9 (90.0%)	10 (100.0)

Note: The protocol included separate secondary endpoints for change in CRT and CST from Baseline. However, a decision was made by Novartis and the chief investigator for the study to only record CST (as it was confirmed CRT and CST values would always be the same). Therefore, CRT is shown above, which corresponds to both CST and CRT secondary outcomes as per protocol.

CRT recording at 6 months

CRT recorded at baseline	CRT recorded	Not recorded	Total (%)
CRT recorded	1 (6.7%)	14 (93.3%)	15 (100.0)
Not recorded	0 (0.0%)	260 (100%)	260 (100.0)
Not routinely collected at this centre	0 (0.0%)	10 (100.0%)	10 (100.0)

Note: The protocol included separate secondary endpoints for change in CRT and CST from Baseline. However, a decision was made by Novartis and the chief investigator for the study to only record CST (as it was confirmed CRT and CST values would always be the same). Therefore, CRT is shown above, which corresponds to both CST and CRT secondary outcomes as per protocol.

CRT recording at 12 months

CRT recorded at baseline	Not recorded	Total (%)
CRT recorded	15 (100.0%)	15 (100.0)
Not recorded	260 (100.0%)	260 (100.0)
Not routinely collected at this centre	10 (100.0%)	10 (100.0)

Note: The protocol included separate secondary endpoints for change in CRT and CST from Baseline. However, a decision was made by Novartis and the chief investigator for the study to only record CST (as it was confirmed CRT and CST values would always be the same). Therefore, CRT is shown above, which corresponds to both CST and CRT secondary outcomes as per protocol.

Percentage (%) of patients with BCVA (≥ 70 ETDRS)

BCVA ≥ 70 ETDRS	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
<70	16	5.6%	12	4.2%	9	3.2%
≥70	70	24.6%	32	11.2%	15	5.3%
No BCVA recorded at timepoint	11	3.9%	6	2.1%	1	0.4%
No data available at timepoint	104	36.5%	177	62.1%	241	84.6%
Not recorded	84	29.5%	58	20.4%	19	6.7%

BCVA ≥ 70 ETDRS	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
Total	285	100.0	285	100.0	285	100.0

BCVA=Best corrected visual acuity, ETDRS=Early Treatment Diabetic Retinopathy Study

BCVA change from Baseline

	3 months	6 months	12 months
Available (n)	88	19	19
Mean	-0.12	-12.53	-11.37
SD	14.64	15.73	20.7
Range	-40 to 55	-58 to 4	-53 to 27
Median	-1	-9	-5
LQ	-9	-16	-26
UQ	7.25	-1	2
Missing (n)	197	266	266

BCVA=Best corrected visual acuity

Number of injections received up to each visit

No of Injections by visit	3 months		6 months		12 months	
	n	percent	n	percent	n	percent
1	9	3.2%	1	0.4%	-	-
2	16	5.7%	3	1.1%	-	-
3	148	52.5%	9	3.2%	-	-
4	37	13.1%	37	13.1%	-	-
5	1	0.4%	64	22.7%	8	2.8%
6	-	-	1	0.4%	16	5.7%
7	-	-	-	-	12	4.3%
8	-	-	-	-	10	3.5%
No timepoint	71	25.2%	167	59.2%	236	83.7%
Total	282	100%	282	100%	282	100%

Percentage (%) of patients with more than 3 brolucizumab injections by timepoint

	3 months		6 months		12 months	
	n	Percent	n	Percent	n	Percent
< 3	173	60.7%	13	4.5%	NA	NA
≥ 3	38	13.30%	102	35.7%	46	16.1%
No timepoint	71	24.9%	170	59.6%	239	83.8%
Patients with no recorded injections	3	1.1%	3	1.1%	3	1.1%
Total	285	100%	285	100%	285	100%

NA- Not available

Number of injections after 3 month and 6 month timepoints

No of injections	After 3-month timepoint and up to and including 6-month timepoint		After 6-month timepoint and up to and including 12-month timepoint	
0	11	3.9%	3	1.1%
1	61	21.6%	8	2.8%
2	37	13.1%	14	5.0%
3			10	3.5%
4			1	0.4%
No 3-month timepoint	6	2.1%	NA	NA
No 6-month timepoint	102	36.2%	10	3.5%
No 12-month timepoint	NA	NA	79	28.0%
Neither 3 or 6 month timepoint	65	23.0%	NA	NA
Neither 6 or 12 month timepoint	NA	NA	157	55.7%
Total	282	100%	282	100%

NA=Not available

Percentage (%) of patients with more than 3 brolucizumab injections after 3 and 6 month timepoints

	After 3 month and up to 6-month timepoint		After 6 month and up to 12-month timepoint	
< 3	109	38.2%	35	12.2%
≥3	NA	NA	1	0.4%
No 3 month timepoint	6	2.1%	NA	NA
No 6 month timepoint	102	35.7%	10	3.5%
No 12 month timepoint	NA	NA	79	27.7%
Neither 3 or 6 month timepoint	65	22.8%	NA	NA
Neither 6 or 12 month timepoint	NA	NA	157	55.1%
Patients with no recorded injections	3	1.1%	3	1.1%
Total	**285**	**100%**	**285**	**100%**

Duration of injection intervals per patient (days)

	3 months	6 months	12 months
Count available	202	114	46
Mean	38.00	50.36	58.24
SD	12.91	20.93	9.06
Range	27-105	28-190	46-81
Median	35.5	46.58	56
LQ	30.5	43.8	51.6
UQ	39.6	50.9	63.8
Count missing	80	168	236

Duration of injection intervals after 6- and 12-month timepoint (days)

	After 3 month and up to 6-month timepoint	After 6 month and up to 12-month timepoint
Count available	98	33
Mean	70.73	79.52
SD	21.83	23.98
Range	42-190	56-149
Median	64	74.5
LQ	58.1	60.6
UQ	73.6	85
Count missing	184	249

Percentage (%) of patients who switched from brolucizumab to another anti-VEGF treatment (For all enrolled patients)

	n	Percent
Switched	21	7.4%
Did not switch	264	92.6%
Total	285	100%

Percentage (%) of patients who discontinued brolucizumab (For all enrolled patients)

	n	Percent
Discontinued	21	7.4%
Did not discontinue	264	92.6%
Total	285	100%

Percentage (%) of patients with IOI (including RV and RVO)

	n	Percent
Had IOI	14	4.9%
Did not have IOI	271	95.1%
Total	285	100%

IOI-Intraocular inflammation, RV= Retinal vasculitis, RVO= Retinal vascular occlusion.

Safety Results

Adverse Events (AEs)

Summary of AEs

Ocular	**71**
Endophthalmitis	1
Intraocular inflammation (IOI)	14
Other ocular	54
Retinal vasculitis (RV)	2
Non-Ocular	**8**
Total	**79**

Most Frequently Reported AEs Overall by Preferred Term n (%)

Not applicable

Serious Adverse Events (SAEs) and Deaths

Summary of SAEs	
Ocular	**44**
Endophthalmitis	1
Intraocular inflammation (IOI)	8
Other ocular	33
Retinal vasculitis (RV)	2
Non-Ocular	**3**
Total	**47**

Deaths: One patient was diagnosed with cervical cancer and died due to kidney injury.

Other Relevant Findings

Not applicable

Conclusion

Due to early termination of the study, available data are insufficient to draw any significant conclusions in terms of the study objectives. No significant additional safety signals for brolucizumab were identified.

Date of Clinical Study Report

04 September 2024