Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Brolucizumab

Trial Indication(s)
Age-related macular degeneration (AMD)

Protocol Number
CRTH258AUS12

Protocol Title
Treatment History, Demographic Characteristics, Clinical Characteristics, and Early Treatment Patterns of Patients Who Received Brolucizumab for Neovascular Age-related Macular Degeneration: IRIS Registry Study

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 05 March 2020

Study Completion date: 01 August 2020

Reason for Termination

NA

Study Design/Methodology

This was a retrospective cohort study of patients with wet AMD who received brolucizumab. Evidence was generated from the IRIS registry to describe patient treatment histories, demographic and clinical characteristics, and early treatment patterns.

Setting and study population

IRIS Registry EHR data from 10/08/2018 to the 03/31/2020 from patients with wet AMD who initiated brolucizumab were analyzed.

Identification period of the index date: The patients fulfilling the selection criteria identified during the period from 10/08/2019 to 03/31/2020.

Index date: Defined as the date of the earliest brolucizumab injection.

Study Period: The period from 10/08/2018 to 03/31/2020.

Pre-index period: The period 12 months prior to the index date.

Post-index period: The period 4 months after the index date (not a required selection criterion; only for the assessment of select endpoints in a subgroup of patients).

Centers
IRIS Registry

Objectives:

Primary objective(s)
The primary objective of this study was to describe anti-VEGF treatment status (naive or switcher) in patients with wet AMD who initiated brolucizumab.

Secondary objective(s)
The secondary objective of this study was to describe the demographic and clinical characteristics of patients with wet AMD who initiated brolucizumab, and to describe early treatment patterns of patients with wet AMD who initiated brolucizumab.

Test Product (s), Dose(s), and Mode(s) of Administration
≥1 Brolucizumab Intravitreal injection

Statistical Methods
All analyses were performed by Verana Health (San Francisco, CA 94105, USA). Descriptive statistics have been tabulated for the baseline demographic and clinical characteristics and outcome variables for each of the cohorts. Python was used to run all analyses.
Continuous variables were summarized by providing the number of observations, means, medians, standard deviations, and minimum and maximum values.
Categorical variables were summarized by providing counts and proportions, with missing data considered a separate category.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria
· Patients with ≥1 brolucizumab injection

· Diagnosis of wet AMD on the index date

Exclusion criteria
None

Participant Flow

The cohort included a total of 9,457 patients. Out of 10,594 brolucizumab treated eyes, 9,645 (91%) had switched from prior anti-VEGF treatment. A total of 6,845 (71.3%) eyes switched from aflibercept, 1,388 (14.4%) from bevacizumab, and 1,378 14.3% from ranibizumab.

Baseline Characteristics

Refer to Secondary Outcomes section for baseline characteristics.

Primary Outcome Result(s)

The primary endpoint of the study was the percentage (%) of patient eyes that switched from another anti-VEGF agent. Since this percentage was unknown at the time of study design, precision was calculated based on the following assumptions:

- N = 200
- 80-90% of the patient eyes switched from another anti-VEGF treatment agent (for outcomes addressed as percentages, the confidence interval will be the widest for an observed proportion of 90%).

Secondary Outcome Result(s)

Baseline demographics of the final study cohort

Baseline demographics; N= 9,457	
Age at index (years): average (SD); median	80.5 (8.54); 0.81
Age categories	**Number of patients, n (%)**
18 – 49	19 (0.20)
50 – 64	280 (2.96)
65 – 69	630 (6.66)
70 – 74	1,338 (14.15)
75 – 79	1,882 (19.90)
80 – 84	2,131 (22.53)
≥85	3,177 (33.59)
Sex	
Female	5,485 (58.00)
Male	3,969 (41.97)
Unknown	3 (0.03)
Patient region	
Midwest	617 (6.52)
Northeast	355 (3.75)
South	1,192 (12.60)
West	613 (6.48)
Unknown	6,680 (70.64)
Insurance type	
Commercial	350 (3.70)
Government	60 (0.63)
Medicaid	45 (0.48)
Medicare*	6,394 (67.61)
Medicare Advantage	668 (7.06)
Military	58 (0.61)
Misc.	242 (2.56)
No insurance	4 (0.04)
Unknown	1,636 (17.30)

Laterality (treatment)	
Unilateral	8,320 (87.98)
Bilateral	1,137 (12.02)
Unknown	0 (0.00)
Laterality (wet AMD)	
Unilateral	5,023 (53.11)
Bilateral	4,090 (43.25)
Unknown	344 (3.64)
Race	
Asian	94 (0.99)
Black of African American	56 (0.59)
Caucasian	7,966 (84.23)
Native American and Alaska Native	16 (0.17)
Native Hawaiian and Other Pacific Islander	5 (0.05)
Two or more races	6 (0.06)
Unknown	1,314 (13.89)

Baseline clinical characteristics of the final study cohort

Clinical characteristic	Number of eyes, n (%) N=10,594	Number of patients, n (%) N=9,457
Concurrent eye disease		
Amblyopia	34 (0.32)	-
Cataracts	3,755 (35.44)	-
Diabetic macular edema	79 (0.75)	-
Diabetic retinopathy	309 (2.92)	-
Epiretinal membrane	1,517 (14.32)	-
Glaucoma	1,903 (17.96)	-
Macular hole	175 (1.65)	-
Myopic choroidal neovascularization	49 (0.46)	-
Posterior vitreous detachment	297 (2.80)	-
Pseudophakia	4,720 (44.55)	-
Retinal vein occlusion	215 (2.03)	-
Vitreomacular traction	119 (1.12)	-
Provider specialty		
Retina/vitreous specialist	9,079 (85.70)	8,200 (86.71)
Comprehensive ophthalmology	861 (8.13)	758 (8.02)
Unknown	403 (3.80)	269 (2.84)
Cataract/anterior segment specialist	204 (1.93)	186 (1.97)
Cornea and external diseases specialist	21 (0.20)	20 (0.21)
Glaucoma specialist	17 (0.16)	16 (0.17)
Refractive surgery	3 (0.03)	3 (0.03)
Neuro-ophthalmology specialist	2 (0.02)	2 (0.02)
Pediatric ophthalmology and strabismus specialist	2 (0.02)	1 (0.01)
Oculofacial plastic and reconstructive surgery	1 (0.01)	1 (0.01)
Uveitis and immunology specialist	1 (0.01)	1 (0.01)
Encounter location (practice location on the index date)		
Midwest	-	2,685 (28.39)
Northeast	-	1,323 (13.99)
South	-	2,946 (31.15)
West	-	2,364 (25.00)
Unknown	-	139 (1.47)

Eye location of brolucizumab injections		
OD (Right eye)	5,535 (52.25)	-
OS (Left eye)	5,059 (47.75)	-
Index visual acuity (Snellen)		
20/12 – 20/20	414 (3.91)	-
20/25 – 20/40	3,119 (29.44)	-
20/50 – 20/160	3,059 (28.87)	-
20/200 or worse	867 (8.18)	-
Missing index VA	3,135 (29.59)	-
Index visual acuity (ETDRS)		
Average (SD)	62.47 (17.84)	-
Median	65.00	-
Wet AMD in fellow eye		
Yes	5,702 (53.82)	-
No	4,892 (46.18)	-
Visual acuity in the fellow eye at index (Snellen)	**Number of eyes, n (%) N= 6,692**	
20/12–20/20	1,163 (17.38)	
20/25–20/40	3,095 (46.25)	
20/50–20/160	1,518 (22.68)	
20/200 or worse	916 (13.69)	
Visual acuity in the fellow eye at index (ETDRS)		
Average (SD)	65.35 (22.43)	
Median	75	

Anti-VEGF treatment of the fellow eye

Prior anti-VEGF treatment	Number of fellow eyes, n (%) N= 5,702
Anti-VEGF treatment status for the fellow eye (at index)	
Treatment naive	522 (9.15)
Continuing (same agent)	2,054 (36.02)
Switcher	482 (8.45)
No anti-VEGF treatment	2,644 (46.37)
Index treatment type for the fellow eye	
Bevacizumab	244 (4.28)
Aflibercept	1,929 (33.83)
Ranibizumab	360 (6.31)
Brolucizumab	525 (9.21)
None	2,644 (46.37)
Number of prior anti-VEGF injections for the fellow eye	**Number of prior anti-VEGF treated fellow eyes, n (%) N= 2,536**
1-3	490 (19.32)
4-6	842 (33.20)
6-9	763 (30.09)
≥10	441 (17.39)
Average (SD)	6.38 (3.11)
Median	6

Early treatment patterns

Number of brolucizumab injections received per study eye at ≥4 months follow-up

	Switcher N = 9,645	Naïve N = 949	Total N = 10,594
Number of eyes, n (%)	135 (1.4)	11 (1.16)	146 (1.38)
Total Number of brolucizumab injections per study eye			
Average (SD)	2.47 (0.71)	2 (1.1)	2.44 (0.75)
Median	3	2	3
Number of eyes receiving brolucizumab injections, n (%)			
1 injection	16 (11.85)	5 (45.45)	21 (14.38)
2 injections	40 (29.63)	2 (18.18)	42 (28.77)
3 injections	78 (57.78)	3 (27.27)	81 (55.48)
4 injections	1 (0.74)	1 (9.09)	2 (1.37)

Length of injection interval at ≥4 months follow-up

Length of injection interval (weeks)	Number of eyes (%) ≥4 months follow-up		
	Previous agents used 12+ months	Previous agents used <12 months	Total
2	1 (0.97)	0 (0.00)	1 (0.78)
3	0 (0.00)	0 (0.00)	0 (0.00)
4	35(33.98)	14 (56.00)	49 (38.28)
5	27 (26.21)	6 (24.00)	33 (25.78)
6	8 (7.77)	1 (4.00)	9 (7.03)
7	5 (4.85)	1 (4.00)	6 (4.69)
8	14 (13.59)	1 (4.00)	15 (11.72)
9	5 (4.85)	1 (4.00)	6 (4.69)
10	4 (3.88)	0 (0.00)	4 (3.13)
11	1 (0.97)	1 (4.00)	2 (1.56)
12	3 (2.91)	0 (0.00)	3 (2.34)
Total	**103 (100)**	**25 (100)**	**128 (100)**

First injection interval after switch at ≥4 months follow-up

	Length of treatment	Number of eyes (%) ≥4 months follow-up N = 119
First injection interval after switch compared to last injection interval with prior treatment	Longer	20 (16.81)
	Same	68 (57.14)
	Shorter	31 (26.05)
Length of last injection interval after index brolucizumab injection compared to injection interval directly prior to index brolucizumab injection	Longer	22 (18.49)
	Same	63 (52.94)
	Shorter	34 (28.57)

Type of anti-VEGF agent after brolucizumab switch

Anti-VEGF	Number of eyes, N (%)
Bevacizumab	57 (8.68)
Aflibercept	487 (74.12)
Ranibizumab	113 (17.20)

Safety Results

No safety data was collected or analyzed as part of this retrospective study.

Other Relevant Findings

None

Limitations

This study had certain limitations. The EHR data in the study was from a specific set of providers that treat patients with wet AMD and may limit ability to evaluate other patient characteristics (e.g. comorbidities) or care patterns (e.g. visits to other healthcare providers).

Evaluating the number of all-cause provider visits, for example, would enable improved understanding of the treatment burden for patients with wet AMD in a more holistic manner. This limitation is characteristic of most disease specific EHR databases. Other limitations of data from the IRIS registry include the possibility of a lack of follow-up. In the IRIS registry, patients are followed between practices, only if each practice is participating in the registry. Lastly, no additional attempts (e.g. chart reviews) were made to verify the accuracy or validity of the diagnosis at the point of care or anatomical outcome measurements. Endpoints were collected and no further validations were performed for the study.

Conclusion This study highlights substantial heterogeneity in anti-VEGF treatment and extensive anti-VEGF treatment switching among patients with wet AMD in the US. Most patients with wet AMD initiating brolucizumab switched from a prior anti-VEGF agent, most commonly aflibercept. The widespread switching among patients with wet AMD to brolucizumab suggests that unmet needs persist. Future research will focus on longer follow-ups to fully assess brolucizumab effectiveness, safety, and treatment patterns in patients with wet AMD.

Date of Clinical Study Report

09 March 2021