Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Aflibercept, Bevacizumab, Ranibizumab

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

Protocol Number
CRTH258AUS20

Protocol Title
Real-world evaluation of prevalence of ocular adverse events in patients with neovascular (wet) age-related macular degeneration (AMD) who received anti-vascular endothelial growth factor (VEGF) agents (IRIS Registry)

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study Start Date: 15 July 2020

Study Completion Date: 20 November 2020

Reason for Termination
NA

Study Design/Methodology

This was a retrospective cohort study of eyes in adult patients with a diagnosis of wet AMD who were treated with anti-VEGF agents from 01/01/2019 to 12/31/2019.

IRIS Registry data from 01/01/2019 to 12/31/2019 for patients with a diagnosis of wet AMD who were treated with ≥1 anti-VEGF agent (excluding brolucizumab) were included.

• Identification period: Patients fulfilling the selection criteria during the period from 01/01/2019 to 12/31/2019 were identified

• Index date: 01/01/2019

• Study Period: 01/01/2019 to 12/31/2019

• Pre-index period: 01/01/2018 to 12/31/2018

• Post-index period: 01/01/2019 to 12/31/2019

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

To assess the period prevalence of IOI in patients with wet AMD who were treated with anti- VEGF agents (excluding brolucizumab) over a one-year period in 2019, further stratified by subgroup (defined as treatment-naive, continuing treatment, switchers).

Secondary objective(s)

1. To assess demographic characteristics of patients with wet AMD who were treated with anti-VEGF agents (excluding brolucizumab)

2. To assess anti-VEGF agent utilization in patients with wet AMD who were treated with anti-VEGF agents (excluding brolucizumab)
3. To assess the period prevalence of other ocular AEs in patients with wet AMD who were treated with anti-VEGF agents (excluding brolucizumab)

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

≥1 Aflibercept / Bevacizumab / Ranibizumab Intravitreal injection

Statistical Methods

All analyses were performed by Verana Health.

Descriptive statistics were tabulated for the baseline demographic and clinical characteristics and outcome variables for each of the cohorts. Python was used to run all planned analyses.

Continuous and categorical variables: 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 percentages, with missing data considered a separate category.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. ≥1 International Classification of Diseases, Clinical Modification-9/10 CM (ICD- 9/10) code for wet AMD in 2019

2. ≥1 Healthcare Common Procedure Coding System (HCPCS) code (J code) or National Drug Code (NDC) code for treatment with an anti-VEGF agent (excluding brolucizumab) in 2019

3. ≥18 years old in 2019

4. ≥2 wet AMD-related office visits in 2019

Exclusion criteria

1. Patient eyes that received >1 type of anti-VEGF treatment on the same date
2. Patient eyes that did not have laterality any time during 2018-2019
3. Treatment with brolucizumab during 2019

Participant Flow

Overall, 794,632 patients and 1,001,200 corresponding eyes with a diagnosis of wet AMD who were treated with an anti-VEGF agent (excluding brolucizumab) from 01/01/2019 to 12/31/2019 from the IRIS Registry were included in the study (Table 10-1). After applying the inclusion criteria, 331,541 patients (41.7%) and 399,029 corresponding eyes (39.9%) were left for analysis (master cohort).

Patient Attrition

Criteria	Number of Patients	Patients Remaining (%)	Number of Eyes	Eyes Remaining (%)
Patients with ≥1 HCPCS code (J code) for treatment with an anti-VEGF agent (excluding brolucizumab) in 2019	794,632		1,001,200	
Exclude patient eyes that received >1 type of anti-VEGF treatment on the same date	784,426	98.7%	982,006	98.1%
Exclude patient eyes that did not have laterality any time during 2018-2019	709,335	89.3%	885,269	88.4%
Patients ≥18 years old on the index date*	707,358	89.0%	882,769	88.2%
Patient eyes with ≥1 ICD-9/10-CM code for wet AMD in 2019*	357,125	44.9%	426,746	42.6%
Patients with ≥2 wet AMD-related office visits in 2019	331,864	41.8%	399,449	39.9%
Exclude patients treated with brolucizumab in 2019	331,541	41.7%	399,029	39.9%

AMD, age-realted macular degneration; CM, Clinical Modification; HCPCS, Healthcare Common Procedure Coding System; ICD, International Classfication of Diseases; VEGF, vascular endothelial growth factor.
*Index date=01/01/2019

Baseline Characteristics

Refer to Secondary Outcomes section for baseline characteristics.

Primary Outcome Results(s)

Aflibercept Cohort: Specified AEs for Patients Treated with Anti-VEGF Therapies Between January 1, 2019 and December 31, 2019 in the IRIS Registry

AEs: Any Anti-VEGF	Aflibercept Cohort					
	Eye Level (n=155,929, 39%)					
	Total AEs (n)	Total AE Rate (%, n/Total Eyes)	Total AEs per 10,000 Injections (n= 764,076)	Incident Events* (n)	Incident Event Rate (%, n/Total Eyes)	Incident Events per 10,000 Injections (n=764,076)
No IOI, Endophthalmitis, Panuveitis, RV, or RO ("controls")	150,002			153,787		
All forms of IOI (including RV) and/or RO	5,927	3.8	78	2,142	1.4	28
IOI (including Panuveitis or RV)	2,409	1.5	32	997	0.6	13
IOI (including Panuveitis or RV or Endophthalmitis)	3,219	2.1	42	1,394	0.9	18
RV and/or RO	2,862	1.8	37	849	0.5	11
RV	26	0.02	0	10	0.006	0
RO	2,837	1.8	37	839	0.5	11
RAO (any)	622	0.4	8	208	0.1	3
BRAO	195	0.1	3	53	0.03	1
CRAO	98	0.06	1	46	0.03	1
IOI	2,308	1.5	30	971	0.6	13
Panuveitis	110	0.07	1	37	0.02	0
Endophthalmitis relevant to safety evaluation	950	0.60	12	496	0.3	6
All IOI events	2,392	1.5	31	992	0.6	13
Anterior chamber inflammation events	1,170	0.8	15	539	0.4	7

AEs: Any Anti-VEGF	Aflibercept Cohort					
	Eye Level (n=155,929, 39%)					
	Total AEs (n)	Total AE Rate (%, n/Total Eyes)	Total AEs per 10,000 Injections (n= 764,076)	Incident Events* (n)	Incident Event Rate (%, n/Total Eyes)	Incident Events per 10,000 Injections (n=764,076)
Posterior segment inflammation events	1,299	0.8	17	502	0.3	7
Any RVO	2,012	1.3	26	571	0.4	7
BRVO	1,392	0.9	18	384	0.2	5
CRVO	657	0.4	9	214	0.1	3
Unspecified RO	6	0.004	0	2	0.001	0
RV without RO	25	0.02	0	10	0.006	0

Bevacizumab Cohort: Specified AEs for Patients Treated with Anti-VEGF Therapies between January 1, 2019 and December 31, 2019 in the IRIS Registry

AEs: Any Anti-VEGF	Bevacizumab Cohort					
	Eye Level (n=125,572, 31%)					
	Total AEs (n)	Total AE Rate (%, n/Total Eyes)	Total AEs per 10,000 Injections (n=501,314)	Incident Events* (n)	Incident Event Rate (%, n/Total Eyes)	Incident Events per 10,000 Injections (n=501,314)
No IOI, Endophthalmitis, Panuveitis, RV, or RO ("controls")	121,629			124,018		
All forms of IOI (including RV) and/or RO	3,943	3.1	79	1,554	1.2	31
RV and/or RO	2,354	1.9	47	830	0.7	17
RV	18	0.01	0	8	0.006	0
RO	2,339	1.9	47	824	0.7	16
RAO (any)	477	0.4	10	181	0.1	4
BRAO	171	0.1	3	61	0.05	1
CRAO	91	0.07	2	51	0.04	1
IOI	1,337	1.1	27	583	0.5	12
IOI (including Panuveitis or RV)	1,392	1.1	18	601	0.5	8
IOI (including Panuveitis or RV or Endophthalmitis)	1,688	1.3	34	774	0.6	15
Panuveitis	57	0.05	1	18	0.01	0
Endophthalmitis relevant to safety evaluation	347	0.3	7	213	0.2	4
All IOI events	1,381	1.1	28	598	0.5	12
Anterior chamber inflammation events	600	0.5	12	276	0.2	6
Posterior segment inflammation events	820	0.7	16	340	0.3	7
Any RVO	1,617	1.3	32	566	0.5	11
BRVO	1,154	0.9	23	397	0.3	8
CRVO	489	0.4	10	186	0.1	4
Unspecified RO	21	0.02	0	9	0.007	0
RV without RO	15	0.01	0	6	0.005	0

Ranibizumab Cohort: Specified AEs for Patients Treated with Anti-VEGF Therapies between January 1, 2019 and December 31, 2019 in the IRIS Registry

AEs: Any Anti-VEGF	Ranibizumab Cohort					
	Eye Level (n=81,495, 20%)					
	Total AEs (n)	Total AE Rate (%, n/Total Eyes)	Total AEs per 10,000 Injections (n=408,967)	Incident Events* (n)	Incident Event Rate (%, n/Total Eyes)	Incident Events per 10,000 Injections (n=408,967)
No IOI, Endophthalmitis, Panuveitis, RV, or RO ("controls")	78,860			80,674		
All forms of IOI (including RV) and/or RO	2,635	3.2	64	821	1.0	20
IOI (including Panuveitis or RV)	954	1.2	12	329	0.4	4
IOI (including Panuveitis or RV or Endophthalmitis)	1,309	1.6	32	460	0.6	11
RV and/or RO	1,382	1.7	34	389	0.5	10
RV	17	0.02	0	3	0.004	0
RO	1,366	1.7	33	386	0.5	9
RAO (any)	318	0.4	8	100	0.1	2
BRAO	121	0.2	3	38	0.05	1
CRAO	40	0.05	1	18	0.02	0
IOI	901	1.1	22	319	0.4	8
Panuveitis	52	0.06	1	12	0.02	0
Endophthalmitis relevant to safety evaluation	421	0.5	10	174	0.2	4
All IOI events	944	1.2	23	326	0.4	8
Anterior chamber inflammation events	516	0.6	13	175	0.2	4
Posterior segment inflammation events	459	0.6	11	164	0.2	4
Any RVO	944	1.2	23	252	0.3	6
BRVO	694	0.9	17	173	0.2	4
CRVO	259	0.3	6	90	0.1	2
Unspecified RO	7	0.009	0	3	0.004	0
RV without RO	16	0.02	0	3	0.004	0

AE, adverse event; BRAO, branch retinal artery occlusion; BRVO, branch retinal vein occlusion; CRAO, central retinal artery occlusion; CRVO, central retinal vein occlusion; RVO; IOI, intraocular inflammation; IRIS, Intelligent Research in Sight; RAO, retinal artery occlusion; RO, retinal vascular occlusion; RVO, retinal vein occluaion; RV, retinal vasculitis; VEGF, vascular endothelial growth factor.
*AEs that occurred in the post-index period in the absence of the same AE in the pre-index period.
Note 1: Measured at the patient level and patient-eye level in the study year (2019)
Note 2: Events were counted only once per patient for patient-level analyses
Note 3: Events were counted only once per patient-eye for eye-level analyses
Note 4: Unspecified eyes were included to define AE
Note 5: For patient-level analyses, AE's were matched at eye level (e.g. study eye=OD and if AE reported in OS, it was not counted as an AE)
Note 7: IOI defined as anything in the IOI component in the protocol (no panuveitis).
Note 8: All IOI events defined as IOI components in the protocol and/or panuveitis

Secondary Outcome Result(s):

Demographic characteristics in patients with wet AMD who were treated with anti-VEGF agents (excluding brolucizumab)

Anti-VEGF Treatment Cohorts: Patient-level Demographic and Clinical Characteristics

Patient-level Characteristics	Patient/Patient Eyes Treated With			
	Aflibercept (n=126,362)	Ranibizumab (n=66,621)	Bevacizumab (n=106,217)	≥2 Different Anti-VEGFs (n=32,341)
Demographic Characteristics				
Age (years), mean (SD)	81.6 (8.8)	82.7 (8.8)	81.6 (9.4)	80.2 (9.4)
Age (years), median	82.0	84.0	83.0	81.0
Age (years), n (%)				
18-49	274 (0.2)	150 (0.2)	450 (0.4)	134 (0.4)
50-64	4,157 (3.3)	1,866 (2.8)	4,505 (4.2)	1,651 (5.1)
65-74	21,139 (16.7)	9,556 (14.3)	17,382 (16.4)	6,457 (20.0)
75-84	49,468 (39.2)	24,452 (36.7)	39,324 (37.0)	12,723 (39.3)
85+	51,324 (40.6)	30,597 (45.9)	45,556 (42.0)	11,376 (35.2)
Sex, n (%)				
Female	77,033 (60.1)	42,745 (64.2)	66,890 (63.0)	19,692 (60.9)
Male	49,264 (39.0)	23,856 (35.8)	39,256 (37.0)	12,628 (39.1)
Not reported	65 (0.05)	20 (0.03)	71 (0.07)	21 (0.06)
Geographic region, n (%)				
Midwest	28,638 (22.7)	8,934 (13.4)	21,670 (20.4)	5,068 (15.7)
Northeast	15,925 (12.6)	9,888 (14.8)	11,049 (10.4)	3,377 (10.4)
South	39,961 (31.6)	25,551 (38.4)	36,179 (34.1)	12,111 (37.5)
West	21,942 (17.4)	9,764 (14.7)	20,326 (19.1)	6,261 (19.4)
Unknown	19,896 (15.8)	12,484 (18.7)	16,993 (16.0)	5,524 (17.1)
Type of insurance, n (%)				
Medicare	52,347 (41.4)	28,415 (42.7)	34,871 (32.8)	11,231 (34.7)
Medicare Advantage	30,163 (24.0)	15,973 (24.0)	25,050 (23.6)	7,359 (22.8)
Medicaid	898 (0.7)	397 (0.6)	1,410 (1.3)	357 (1.1)
Commercial	17,230 (13.6)	7,596 (11.4)	13,697 (12.9)	4,344 (13.4)
Government	965 (0.8)	510 (0.8)	661 (0.6)	244 (0.8)
Military	1,202 (1.0)	532 (0.8)	803 (0.8)	272 (0.8)
No insurance	267 (0.2)	30 (0.05)	173 (0.2)	63 (0.2)
Miscellaneous	4,520 (3.6)	1,492 (2.2)	1,704 (1.6)	838 (2.6)
Unknown	18,770 (14.9)	11,676 (17.5)	27,848 (26.2)	7,633 (23.6)
Race, n (%)				

Patient-level Characteristics	Patient/Patient Eyes Treated With			
	Aflibercept (n=126,362)	Ranibizumab (n=66,621)	Bevacizumab (n=106,217)	≥2 Different Anti-VEGFs (n=32,341)
Asian	1,450 (1.2)	593 (0.9)	1,868 (1.8)	495 (1.5)
Black or African American	1,122 (0.9)	635 (1.0)	1,469 (1.4)	418 (1.3)
Caucasian	104,047 (82.3)	55,561 (83.4)	80,834 (76.1)	25,732 (79.6)
Other	453 (0.4)	169 (0.3)	486 (0.5)	106 (0.3)
Unknown	19,290 (15.3)	9,663 (14.5)	21,560 (20.3)	5,590 (17.3)
Patient Clinical Characteristics				
Provider specialty at date of first anti-VEGF injection, n (%)				
Retina specialist	109,776 (86.9)	61,097 (91.7)	92,296 (86.9)	28,474 (88.0)
General ophthalmologist	11,490 (9.1)	3,832 (5.8)	10,236 (9.6)	2,921 (9.0)
Non-retina specialist	3,596 (2.9)	1,485 (2.2)	2,774 (2.6)	889 (2.8)
Unknown	1,500 (1.2)	207 (0.3)	911 (0.9)	57 (0.2)
Laterality of wet AMD on the index date,* n (%)				
Unilateral	62,540 (49.5)	36,018 (54.1)	63,183 (59.5)	19,855 (61.4)
Bilateral	63,822 (50.5)	30,603 (45.9)	43,034 (40.5)	12,486 (38.6)

AMD, age-related macular degeneration; n, number; %, percentage; SD, standard deviation.
Note 1: If a patient was in multiple groups as of the index date (e.g. continued treatment from prior year and then switched, naive and then switched), continuing treatment > naïve > switch hierarchy was used.
Note 2: If a patient was in multiple anti-VEGF agent groups, multiple > mono hierarchy was used.
Note 3: Patient level analyses were conducted for these subgroups. At any given point, one of the patient eyes can be on a different treatment than the other eye.

*Index date=01/01/2019

Anti-VEGF Treatment Cohorts: Eye-level Demographic and Clinical Characteristics

Eye-level Characteristics	Patient/Patient Eyes Treated With			
	Aflibercept (n=155,929)	Ranibizumab (n=81,495)	Bevacizumab (n=125,572)	≥2 Different Anti-VEFGFs (n=36,033)
Demographic Characteristics				
Age (years), mean (SD)	81.8 (8.7)	82.8 (8.7)	81.8 (9.3)	80.3 (9.3)
Age (years), median	83.0	84.0	83.0	81.0
Age (years), n (%)				
18-49	319 (0.2)	164 (0.2)	493 (0.4)	146 (0.4)
50-64	4,811 (3.1)	2,170 (2.7)	5,017 (4.0)	1,788 (5.0)
65-74	25,328 (16.2)	11,286 (13.9)	20,033 (15.6)	7,074 (19.6)
75-84	61,222 (39.3)	29,873 (36.7)	46,606 (37.1)	14,186 (39.4)
85+	64,249 (41.2)	38,002 (46.6)	53,423 (42.5)	12,839 (35.6)
Sex, n (%)				
Female	95,996 (61.6)	52,889 (64.9)	79,805 (63.6)	22,054 (61.2)
Male	59,853 (38.4)	28,580 (35.1)	45,684 (36.4)	13,956 (38.7)
Not reported	80 (0.05)	26 (0.03)	83 (0.07)	23 (0.06)
Geographic region, n (%)				
Midwest	34,173 (21.9)	10,347 ()12.7)	25,022 (19.9)	5,269 (14.6)
Northeast	20,072 (12.9)	12,392 (15.2)	13,197 (10.5)	3,832 (10.6)
South	49,471 (31.7)	31,378 (38.5)	42,377 (33.8)	13,627 (37.8)
West	27,379 (17.6)	11,874 (14.6)	24,527 (19.5)	7,079 (19.7)
Unknown	24,834 (15.9)	15,504 (19.0)	20,449 (16.3)	6,226 (17.3)
Type of insurance, n (%)				
Medicare	64,903 (41.6)	34,996 (42.9)	41,822 (33.3)	12,509 (34.7)
Medicare Advantage	37,448 (24.0)	19,777 (24.3)	30,.63 (23.9)	8,335 (23.1)
Medicaid	1,099 (0.7)	484 (0.6)	1,671 (1.3)	402 (1.1)
Commercial	21,458 (13.8)	9,411 (11.6)	16,178 (12.9)	4,876 (13.5)
Government	1,150 (0.7)	629 (0.8)	783 (0.6)	274 (0.8)
Military	1,489 (1.0)	674 (0.8)	957 (0.8)	321 (0.9)
No insurance	328 (0.2)	36 (0.04)	215 (0.2)	71 (0.2)
Miscellaneous	5,696 (3.7)	1,856 (2.3)	2,043 (1.6)	964 (2.7)
Unknown	22,358 (14.3)	13,632 (16.7)	31,840 (25.4)	8,281 (23.0)
Race, n (%)				
Asian	1,702 (1.1)	680 (0.8)	2,114 (1.7)	534 (1.5)
Black or African American	1,329 (0.9)	725 (0.9)	1,654 (1.3)	453 (1.3)
Caucasian	128,948 (82.7)	68,218 (83.7)	96,021 (76.5)	28,739 (79.8)
Other	555 (0.4)	209 (0.3)	572 (0.5)	114 (0.3)
Unknown	23,395 (15.0)	11,663 (14.3)	25,211 (20.1)	6,193 (17.2)
Patient Clinical Characteristics				
Provider specialty at date of first anti-VEGF injection, n (%)				
Retina specialist	134,826 (86.5)	74,702 (91.7)	108,911 (86.7)	31,721 (88.0)
General ophthalmologist	14,384 (9.2)	4,751 (5.8)	12,203 (9.7)	3,251 (9.0)
Non-Retina specialist	4,525 (2.9)	1,771 (2.2)	3,277 (2.6)	1,002 (2.8)
Unknown	2,194 (1.4)	271 (0.3)	1,181 (0.9)	59 (0.2)
Eye treated with an anti-VEGF, n (%)				
Right (OD)	81,185 (52.1)	41,778 (51.3)	64,465 (51.3)	18,708 (51.9)
Left (OS)	74,744 (47.9)	39,717 (48.7)	61,107 (48.7)	17,325 (48.1)
Number of anti-VEGF Injections in 2019, n	764,076	408,967	501,314	236,759
Number of anti-VEGF Injections in 2019, mean (SD)	4.9 (2.8)	5.0 (2.7)	4.0 (2.4)	6.6 (2.6)

Eye-level Characteristics	Patient/Patient Eyes Treated With			
	Aflibercept (n=155,929)	Ranibizumab (n=81,495)	Bevacizumab (n=125,572)	≥2 Different Anti-VEFGFs (n=36,033)
Number of anti-VEGF Injections in 2019, median	5	5	4	6

AMD, age-related macular degeneration; n, number; OD, oculus dexter; OS, oculus sinister; %, percentage; SD, standard deviation; VEGF, vascular endothelial growth factor.
Note 1: Eye level analyses were conducted for these subgroups. At any given point, one of the patient eyes can be on a different treatment than the other eye.

The period prevalence of other ocular AEs in patients with wet AMD who were treated with anti-VEGF agents (excluding brolucizumab) over a one-year period

Refer to Primary Outcomes section (Table: AEs for Patients Treated with Anti-VEGF Therapies Between January 1, 2019 and December 31, 2019 in the IRIS Registry)

Other relevant findings

None

Safety Results

Refer to Primary Outcomes section (Table: AEs for Patients Treated with Anti-VEGF Therapies Between January 1, 2019 and December 31, 2019 in the IRIS Registry)

Conclusion:

In conclusion, data from the IRIS Registry provide insights into the safety of patients with wet AMD who were administered intravitreal anti-VEGF agents (excluding brolucizumab) during 2019. The period prevalence of IOI as an incident AE (excluding events before the index date) was 0.9% at the patient level and 0.8% at the eye level. IOI was reported more frequently as an incident AE among eyes in the treatment-naïve (1.0%) and switchers (1.2%) cohorts than the continuing-treatment cohort (0.7%), and more frequently among eyes treated with aflibercept (0.9%) than ranibizumab or bevacizumab, which had comparable incidences of IOI6 (0.6%).

Additional studies with alternate study designs (i.e. incident vs prevalent patient populations) and longer follow-up intervals as well as further analyses of the IRIS Registry may be warranted to assess the long-term safety of other anti-VEGF treatments. These current findings represent key, early real-world findings for inflammation-related AEs that may occur while on treatment with anti-VEGF agents and ultimately may help guide clinicians in their decision-making regarding anti-VEGF therapy for wet AMD.

Date of Clinical Study Report

29 June 2021