Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Aflibercept, Bevacizumab, Ranibizumab

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

Protocol Number
CRTH258AUS19

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 (KOMODA Health)

Clinical Trial Phase
NA

Phase of Drug Development
NA

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

Study Completion Date: 11 December 2020

Reason for Termination
NA

Study Design/Methodology

In this cross-sectional study of patients with wet AMD who received ≥1 anti-VEGF injection (excluding brolucizumab), evidence was generated to describe the period prevalence of specific ocular AEs. The study was conducted using the Komodo Healthcare Map, and all results were based on the study period from 01/01/2018 to 12/31/2019.

Komodo Healthcare Map data from 01/01/2018 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: 01/01/2018 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 Komodo 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. ≥1 HCPCS code (J code) or NDC code for treatment with brolucizumab in 2019

Participant Flow

After applying the inclusion criteria, 324,930 patients and 408,995 corresponding eyes remained (master cohort).

Patient Attrition

Criteria	Number of Patients	Patients Remaining (%)	Number of Eyes	Eyes Remaining (%)
Patients with ≥1 HCPCS code (J code) or NDC for treatment with an anti-VEGF agent (including brolucizumab) in 2019 AND at least 1 wAMD claim in study period.	369,600		461,674	
Patients ≥18 years old on the index date* with ≥2 wet AMD-related office visits in 2019	326,653	88.38%	411,387	89.11%
Exclude patients treated with brolucizumab in 2019	324,930	87.91%	408,995	88.59%

*Index date=01/01/2019

Baseline Characteristics

Refer to Secondary Outcomes section for baseline characteristics.

Primary Outcome Results(s)

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

AE of Interest	Total AEs			Incident Events		
	Patient Eyes			Patient Eyes		
	Total (n)	AE Rate (%)	AEs per 10,000 injections	Total (n)	AE Rate (%)	AEs per 10,000 injections
Total	57835			57835		
No IOI, no endophthalmitis, no panuveitis, no RV, no RO ("controls")	55600	96.14%	1996.77	56847	98.29%	2041.55
Intraocular inflammation and/or endophthalmitis and/or panuveitis and/or RV and/or RO	2235	3.86%	80.27	988	1.71%	35.48
Retinal vasculitis (RV)	4	0.01%	0.14	0	0.00%	0.00
Retinal vascular occlusion (RO) (retinal artery occlusion [RAO] and/or retinal vein occlusion [RVO])	1190	2.06%	42.74	449	0.78%	16.12
Intraocular inflammation (IOI) - incl. Panuveitis	854	1.48%	30.67	425	0.73%	15.26
Anterior chamber inflammation events	407	0.70%	14.62	206	0.36%	7.40
Posterior segment inflammation events	481	0.83%	17.27	242	0.42%	8.69
Intraocular inflammation (IOI) - incl. Panuveitis, RV	855	1.48%	30.71	425	0.73%	15.26
Intraocular inflammation (IOI) - incl. Panuveitis, RV, Endophthalmitis	1088	1.88%	39.07	552	0.95%	19.82
Panuveitis	34	0.06%	1.22	12	0.02%	0.43
Endophthalmitis relevant to safety evaluation	274	0.47%	9.84	156	0.27%	5.60
Retinal artery occlusion	201	0.35%	7.22	96	0.17%	3.45
Branched RAO (BRAO)	73	0.13%	2.62	31	0.05%	1.11
Central RAO (CRAO)	37	0.06%	1.33	17	0.03%	0.61
Retinal vasculitis and/or RO (RAO and/or RVO)	1194	2.06%	42.88	449	0.78%	16.12
Any RVO	907	1.57%	32.57	317	0.55%	11.38
Branched RVO (BRVO)	622	1.08%	22.34	226	0.39%	8.12
Central RVO (CRVO)	317	0.55%	11.38	114	0.20%	4.09
Other RVO	36	0.06%	1.29	26	0.04%	0.93
Unspecified RO (RVO or RAO)	1190	2.06%	42.74	449	0.78%	16.12
Retinal vasculitis without RO (RAO and/or RVO)	4	0.01%	0.14	0	0.00%	0.00

*AEs that occurred in the post-index period in the absence of the same AE in the pre-index period.
Note 1: Events were counted only once per patient for patient-level analyses
Note 2: Events were counted only once per patient-eye for eye-level analyses

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

AE of Interest	Total AEs Patient Eyes			Incident Events Patient Eyes		
	Total (n)	AE Rate (%)	AEs per 10,000 injections	Total (n)	AE Rate (%)	AEs per 10,000 injections
Total	142664			142664		
No IOI, no endophthalmitis, no panuveitis, no RV, no RO ("controls")	136857	95.93%	1964.86	139761	97.97%	2006.55
Intraocular inflammation and/or endophthalmitis and/or panuveitis and/or RV and/or RO	5807	4.07%	83.37	2903	2.03%	41.68
Retinal vasculitis (RV)	18	0.01%	0.26	14	0.01%	0.20
Retinal vascular occlusion (RO) (retinal artery occlusion [RAO] and/or retinal vein occlusion [RVO])	2883	2.02%	41.39	1075	0.75%	15.43
Intraocular inflammation (IOI) - incl. Panuveitis	2441	1.71%	35.05	1431	1.00%	20.54
Anterior chamber inflammation events	1061	0.74%	15.23	650	0.46%	9.33
Posterior segment inflammation events	1463	1.03%	21.00	842	0.59%	12.09
Intraocular inflammation (IOI) - incl. Panuveitis, RV	2454	1.72%	35.23	1450	1.02%	20.82
Intraocular inflammation (IOI) - incl. Panuveitis, RV, Endophthalmitis	3054	2.14%	43.85	1886	1.32%	27.08
Panuveitis	88	0.06%	1.26	46	0.03%	0.66
Endophthalmitis relevant to safety evaluation	731	0.51%	10.49	536	0.38%	7.70
Retinal artery occlusion	488	0.34%	7.01	277	0.19%	3.98
Branched RAO (BRAO)	194	0.14%	2.79	110	0.08%	1.58
Central RAO (CRAO)	106	0.07%	1.52	71	0.05%	1.02
Retinal vasculitis and/or RO (RAO and/or RVO)	2901	2.03%	41.65	1089	0.76%	15.63
Any RVO	2198	1.54%	31.56	722	0.51%	10.37
Branched RVO (BRVO)	1347	0.94%	19.34	455	0.32%	6.53
Central RVO (CRVO)	928	0.65%	13.32	332	0.23%	4.77
Other RVO	78	0.05%	1.12	60	0.04%	0.86
Unspecified RO (RVO or RAO)	2883	2.02%	41.39	1075	0.75%	15.43
Retinal vasculitis without RO (RAO and/or RVO)	18	0.01%	0.26	14	0.01%	0.20

*AEs that occurred in the post-index period in the absence of the same AE in the pre-index period.
Note 1: Events were counted only once per patient for patient-level analyses
Note 2: Events were counted only once per patient-eye for eye-level analyses

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

AE of Interest	Total AEs			Incident Events		
	Patient Eyes			Patient Eyes		
	Total (n)	AE Rate (%)	AEs per 10,000 injections	Total (n)	AE Rate (%)	AEs per 10,000 injections
Total	166195			166195		
No IOI, no endophthalmitis, no panuveitis, no RV, no RO ("controls")	159896	96.21%	2317.85	162814	97.97%	2360.15
Intraocular inflammation and/or endophthalmitis and/or panuveitis and/or RV and/or RO	6299	3.79%	91.31	3381	2.03%	49.01
Retinal vasculitis (RV)	33	0.02%	0.48	21	0.01%	0.30
Retinal vascular occlusion (RO) (retinal artery occlusion [RAO] and/or retinal vein occlusion [RVO])	3834	2.31%	55.58	1744	1.05%	25.28
Intraocular inflammation (IOI) - incl. Panuveitis	2179	1.31%	31.59	1362	0.82%	19.74
Anterior chamber inflammation events	860	0.52%	12.47	574	0.35%	8.32
Posterior segment inflammation events	1387	0.83%	20.11	853	0.51%	12.37
Intraocular inflammation (IOI) - incl. Panuveitis, RV	2202	1.32%	31.92	1386	0.83%	20.09
Intraocular inflammation (IOI) - incl. Panuveitis, RV, Endophthalmitis	2600	1.56%	37.69	1704	1.03%	24.70
Panuveitis	75	0.05%	1.09	43	0.03%	0.62
Endophthalmitis relevant to safety evaluation	480	0.29%	6.96	387	0.23%	5.61
Retinal artery occlusion	620	0.37%	8.99	372	0.22%	5.39
Branched RAO (BRAO)	265	0.16%	3.84	150	0.09%	2.17
Central RAO (CRAO)	150	0.09%	2.17	105	0.06%	1.52
Retinal vasculitis and/or RO (RAO and/or RVO)	3860	2.32%	55.95	1760	1.06%	25.51
Any RVO	2924	1.76%	42.39	1234	0.74%	17.89
Branched RVO (BRVO)	1902	1.14%	27.57	827	0.50%	11.99
Central RVO (CRVO)	1136	0.68%	16.47	514	0.31%	7.45
Other RVO	142	0.09%	2.06	112	0.07%	1.62
Unspecified RO (RVO or RAO)	3834	2.31%	55.58	1744	1.05%	25.28
Retinal vasculitis without RO (RAO and/or RVO)	26	0.02%	0.38	16	0.01%	0.23

*AEs that occurred in the post-index period in the absence of the same AE in the pre-index period.
Note 1: Events were counted only once per patient for patient-level analyses
Note 2: Events were counted only once per patient-eye for eye-level analyses

Secondary Outcome Result(s):

Patient level Demographic and Clinical Characteristics

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

Patient-Level Characteristics	aVEGF Treatment in 2019			
	Aflibercept	Bevacizumab	Ranibizumab	Multiple
TOTAL, n (%)	112125 (100)	137608 (100)	45601 (100)	36395 (100)
Age (years), n (%)				
<50	274 (0.24)	657 (0.48)	124 (0.27)	137 (0.38)
50-64	3976 (3.55)	5820 (4.23)	1448 (3.18)	1803 (4.95)
65-74	18375 (16.39)	22141 (16.09)	6360 (13.95)	7089 (19.48)
75-84	42956 (38.31)	50836 (36.94)	16633 (36.48)	14544 (39.96)
85+	46544 (41.51)	58154 (42.26)	21036 (46.13)	12822 (35.23)
Age (years), Mean	80.67	80.5	81.36	79.48
Age (years), SD	7.69	8.19	7.56	8.21
Age (years), Median	83	83	84	81
Patient Gender, n (%)				
M	44124 (39.35)	51285 (37.27)	16681 (36.58)	14544 (39.96)
F	67985 (60.63)	86294 (62.71)	28913 (63.4)	21842 (60.01)
U	16 (0.01)	29 (0.02)	7 (0.02)	9 (0.02)
Geographic region, n (%)				

West	15760 (14.06)	31448 (22.85)	5964 (13.08)	6545 (17.98)
Northeast	26228 (23.39)	22785 (16.56)	9950 (21.82)	6222 (17.1)
Midwest	31146 (27.78)	39635 (28.8)	10582 (23.21)	8972 (24.65)
South	36756 (32.78)	40776 (29.63)	18210 (39.93)	13876 (38.13)
Unknown	2235 (1.99)	2964 (2.15)	895 (1.96)	780 (2.14)
Type of insurance, n (%)				
Private	22826 (20.36)	39680 (28.84)	9023 (19.79)	8994 (24.71)
Medicare	75108 (66.99)	72669 (52.81)	30843 (67.64)	21794 (59.88)
Medicare Advantage	10393 (9.27)	18473 (13.42)	4236 (9.29)	4154 (11.41)
Medicaid	3619 (3.23)	6514 (4.73)	1451 (3.18)	1398 (3.84)
Other / Unknown	179 (0.16)	272 (0.2)	48 (0.11)	55 (0.15)
Laterality of wet AMD on the index date,* n (%)				
Bilateral	55910 (49.86)	57384 (41.7)	22016 (48.28)	17003 (46.72)
Unilateral	56046 (49.99)	79830 (58.01)	23523 (51.58)	19345 (53.15)
Unspecified	169 (0.15)	394 (0.29)	62 (0.14)	47 (0.13)
Provider specialty at date of first anti-VEGF injection, per eye, n (%) - specialties with <150 eyes omitted				
Ophthalmology	102704 (91.6)	129026 (93.76)	42447 (93.08)	34265 (94.15)
Internal Medicine	1024 (0.91)	1306 (0.95)	376 (0.82)	360 (0.99)
General Practice	329 (0.29)	492 (0.36)	63 (0.14)	78 (0.21)
Hospitalist	89 (0.08)	82 (0.06)	16 (0.04)	26 (0.07)
Family Practice	77 (0.07)	82 (0.06)	21 (0.05)	25 (0.07)
Optometrist	53 (0.05)	64 (0.05)	9 (0.02)	14 (0.04)
First Eye Treated with aVEGF in 2019 (per patient)				
Left	46810 (41.75)	60415 (43.9)	19287 (42.3)	15645 (42.99)
Right	48488 (43.24)	62317 (45.29)	19453 (42.66)	15941 (43.8)
Bilateral	16827 (15.01)	14876 (10.81)	6861 (15.05)	4809 (13.21)

AMD, age-related macular degeneration; n, number; %, percentage; SD, standard deviation.
Note 1: Continuing treatment is defined as last aVEGF in 2018 = first aVEGF in 2019; naïve is defined as no aVEGF in 2018; switch is defined as last aVEGF in 2018 != first aVEGF in 2019
*Index date=01/01/2019

Anti-VEGF Treatment Cohorts: Eye-level aVEGF Utilization

Eye-Level Characteristics	aVEGF Treatment in 2019			
	Aflibercept	Bevacizumab	Ranibizumab	Multiple
Total # Patient Eyes	142664	166195	57835	42285
Total # Injections (2019)	696523	689847	278450	278155
Mean # Injections Per Eye	4.88	4.15	4.81	6.58
SD # Injections Per Eye	2.92	2.74	2.95	2.99
Median # Injections Per Eye	4	4	4	6

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 KOMODA Health)

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 KOMODA Health)

Conclusion:

In conclusion, data from the Komodo Healthcare Map provides insights into the safety of patients with wet AMD who were administered intravitreal anti-VEGF(excluding brolucizumab) during 2019 . The period prevalence of IOI as an incident AE (excluding events before the index date) was 1.3% at the patient level and 1.2% at the eye level. IOI was reported more frequently as an incident AE among eyes treated with aflibercept (1.3%) than ranibizumab or bevacizumab, which had comparable incidences of IOI (1.0%).

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

26 July 2021