Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Brolucizumab

Trial Indication(s)

Age-related macular degeneration (AMD)

Protocol Number

CRTH258AUS15

Protocol Title

Real-world evaluation of brolucizumab for the treatment of neovascular (wet) age-related macular degeneration (AMD) (IRIS Study)

Clinical Trial Phase

NA

Phase of Drug Development

NA

Study Start/End Dates

Study Start Date: 03 June 2020

Study Completion Date: 15 December 2020

Reason for Termination

NA

Study Design/Methodology

This study was a retrospective cohort study of patients with wet AMD who received brolucizumab. Evidence was generated to describe their patient characteristics and clinical outcomes. The study was conducted using the IRIS Registry.

Setting and study population

IRIS Registry EHR data from 08-Oct-2016 to the date of most recent data from patients with wet AMD who initiated brolucizumab were analyzed in this study.

· Identification period of the index date (index period): The patients fulfilling the selection criteria were be identified during the period from 08-Oct-2019 to the date of most recent data (05-Jun-2020)

· Index date: Defined as the date of the earliest brolucizumab injection during the index period

· Study Period: The period from 08-Oct-2016 to the date of most recent data (05-Jun-2020)

· Pre-index period: The period 36 months prior to the index date

  ▪ Note: Data within 36 months prior to the index date was used to assess baseline characteristics.

· Post-index period: The period 180 days after the index date

· Follow-up: The longest duration of follow-up was 6 months. Patient eyes included in the studies have varying lengths of follow-up depending on when they initiated brolucizumab treatment and when the last visit was recorded in the respective databases.

The last follow-up date was defined as the date of the last recorded visit or day that the ophthalmology practice that administered the index brolucizumab injection contributed data to the IRIS Registry, whichever occurred later.

Centers

IRIS Registry

Objectives:

Primary objective(s)

To assess Intraocular Inflammation (IOI) events observed after starting treatment with brolucizumab

Secondary objective(s)

Secondary objectives of this study were to assess baseline demographic and clinical characteristics, and the incidence of specific ocular AEs among patients treated with brolucizumab

Other objective(s)

To assess the association between specific ocular AEs (any form of IOI [including RV] and/or RO, RV and/or RO) and baseline demographic and clinical characteristics among patients treated with brolucizumab

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

≥1 Brolucizumab Intravitreal injection

Statistical Methods

Descriptive statistics were tabulated for the baseline demographic and clinical characteristics and outcome variables. Analyses was performed at the patient level or patient eye level. 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 proportions, with missing data considered a separate category.

Multivariable analyses
Generalized estimating equations were used to assess the association between the specific AEs (any form of IOI [including RV] and/or RO, RV and/or RV) and baseline patient demographics and clinical characteristics. Independent variables were selected based on clinical and statistical significance. GEE models were fit and output estimated marginal means based on the models to derive probabilities.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. ≥1 Healthcare Common Procedure Coding System (HCPCS) code (J code) or EMR note for treatment with brolucizumab during the index period (date of earliest code or EMR note = index date)

Note: The date of brolucizumab injection was confirmed. Some patients are seen on one day, have the proposed treatment documented in an EMR note, but then treated on a later date.

2. ≥18 years old on the index date

3. ≥1 Current Procedural Terminology (CPT) code for intravitreal administration on the index date

4. ≥1 ICD-9/10 code for wet AMD in the 36 months prior to or on the index date

Note: Off-label use of brolucizumab is not expected given payer access restrictions in the US.

5. ≥1 follow-up visit after the index date

6. ≥1 VA assessment on the index date or within 365 days prior to the index date

Exclusion criteria
1. Use of brolucizumab prior to 08-Oct-2019 (e.g. clinical trials)

2. Unknown laterality of the index eye on the index date

Participant Flow Table

Patients with a diagnosis of wet AMD who were treated with brolucizumab from 08-Oct-2016 to 05-Jun-2020 were included from the IRIS Registry. The dataset included 14,126 eyes and 12,155 patients who received ≥1 brolucizumab injection between 08-Oct-2019 and 05-Jun-2020. After applying further inclusion and exclusion criteria, there were 13,603 eyes (11,801 patients) with ≥1 ICD-9/10-CM code for wet AMD in the 36 months prior to or on the index date. The following criteria were applied to derive the study population.

Criteria	Number of Patients	% of Patient Remaining	Number of Eyes	% of Eyes Remaining
≥1 brolucizumab injection between 2019/10/07 and 2020/06/05 with IVI CPT code on index date	12,155		14,126	
Patient ≥18 years old at index date	12,142	99.9%	14,106	99.9%
ICD-9/10 code for wet AMD in the 36 months prior to or on the index date	11,801	97.1%	13,603	96.3%
≥1 follow-up visit ophthalmology after the index date	11,541	94.9%	13,294	94.1%
≥1 VA assessment on the index date or within 365 days prior to the index date	9,951	81.9%	11,455	81.1%
No use of brolucizumab prior to 2019/10/07	9,950	81.9%	11,454	81.1%
Known laterality on index date	9,456	77.8%	10,654	75.4%

AMD, age-related macular degeneration; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD, International Classfication of Diseases; IVI, intravitreal injection; VA, visual acuity.

Baseline Characteristics

Refer to Secondary Outcomes section for baseline characteristics.

Primary Outcome Result(s)

In the brolucizumab-treated eyes from the IRIS Registry, approximately 2.39% of patient eyes had any forms of IOI (including RV) and/or RO and approximately 0.55% were reported to have RV and/or RO only. Other AE incidence rates in the total eyes were RV (0.16%), RO (0.42%), RAO (0.28%), IOI (1.56%), endophthalmitis (relevant to the safety evaluation, 0.24%), and panuveitis (0.30%). Observed events were identified using ICD codes and a causality link of events with brolucizumab injections cannot be confirmed.

AEs	Number of Events	Incidence Rate (%, n/ total eyes)
Any Form of IOI (Including RV) and/or RO	255	2.39%
RV and/or RO (RAO and/or RO)	59	0.55%
RV and RO (RAO and/or RVO)	3	0.03%
RV	17	0.16%
RO	45	0.42%
RAO	30	0.28%
IOI*	166	1.56%
Endophthalmitis Relevant to Safety Evaluation	26	0.24%
Panuveitis	32	0.30%

Secondary Outcome Result(s):

Baseline Patient and Clinical Demographics

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Patient Demographics									
Age (Patient-level), n	9,456	9,238	241	58	17	29	26	92	109
Mean (SD)	80.77 (8.45)	80.83 (8.44)	78.67 (8.40)	80.10 (7.73)	77.94 (7.04)	80.76 (8.08)	76.19 (7.03)	78.83 (7.77)	78.41 (8.25)
Median	81.00	81.00	80.00	80.00	77.00	81.00	77.00	79.00	79.00
Years, n (%)									
18–49 years	16 (0.17)	16 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
50–64 years	270 (2.86)	260 (2.81)	11 (4.56)	1 (1.72)	0 (0.00)	1 (3.45)	1 (3.85)	3 (3.26)	4 (3.67)
65–74 years	1,898 (20.07)	1,831 (19.82)	69 (28.63)	17 (29.31)	8 (47.06)	7 (24.14)	10 (38.46)	25 (27.17)	33 (30.28)
75–84 years	3,963 (41.91)	3,878 (41.98)	98 (40.66)	23 (39.66)	6 (35.29)	11 (37.93)	12 (46.15)	43 (46.74)	44 (40.37)
85+ years	3,309 (34.99)	3,253 (35.21)	63 (26.14)	17 (29.31)	3 (17.65)	10 (34.48)	3 (11.54)	21 (22.83)	28 (25.69)
P-value			**<0.001**	**0.48**	**0.09**	**0.96**	**<0.001**	**0.71**	
Age (Eye-level), n	10,654	10,399	255	59	17	30	32	98	113
Mean (SD)	80.86 (8.39)	80.92 (8.38)	78.78 (8.32)	80.12 (7.66)	77.94 (7.04)	80.77 (7.94)	76.94 (7.50)	78.83 (7.77)	78.41 (8.25)
Median	81.00	81	80	80	77	81	77	79	79
Years, n (%)									
18–49 years	18 (0.17)	18 (0.17)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
50–64 years	294 (2.76)	283 (2.72)	11 (4.31)	1 (1.69)	0 (0.00)	1 (3.33)	1 (3.13)	3 (3.06)	4 (3.54)
65–74 years	2,096 (19.67)	2,024 (19.46)	72 (28.24)	17 (28.81)	8 (47.06)	7 (23.33)	12 (37.50)	26 (26.53)	33 (29.20)
75–84 years	4,490 (42.14)	4,385 (42.17)	105 (41.18)	24 (40.68)	6 (35.29)	12 (40.00)	14 (43.75)	46 (46.94)	47 (41.59)
85+ years	3,756 (35.25)	3,689 (35.47)	67 (26.27)	17 (28.81)	3 (17.65)	10 (33.33)	5 (15.63)	23 (23.47)	29 (25.66)
P-value			**<0.001**	**0.44**	**0.07**	**0.98**	**0.062**	-	
Gender (Patient-level), n (%)									
Female	5,402 (57.13)	5,241 (56.73)	176 (73.03)	46 (79.31)	15 (88.24)	19 (65.52)	23 (88.46)	62 (67.39)	84 (77.06)
Male	4,052 (42.85)	3,995 (43.25)	65 (26.97)	12 (20.69)	2 (11.76)	10 (34.48)	3 (11.54)	30 (32.61)	25 (22.94)
Not reported	2 (0.02)	2 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
P-value			**<0.001**	**0.003**	**0.03**	**0.63**	**0.005**	**0.13**	
Gender (Eye-level), n (%)									
Female	6,105 (57.30)	5,915 (56.88)	190 (74.51)	47 (79.66)	15 (88.24)	20 (66.67)	29 (90.63)	68 (69.39)	88 (77.88)
Male	4,547 (42.68)	4,482 (43.10)	65 (25.49)	12 (20.34)	2 (11.76)	10 (33.33)	3 (9.38)	30 (30.61)	25 (22.12)
Not reported	2 (0.02)	2 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
P-value			**<0.001**	**0.002**	**0.03**	**0.56**	**<0.001**	**0.16**	
Region (Patient-level), n (%)									
Midwest	2,168 (22.93)	2,120 (22.95)	50 (20.75)	11 (18.97)	3 (17.65)	7 (24.14)	4 (15.38)	21 (22.83)	20 (18.35)
Northeast	764 (8.08)	745 (8.06)	21 (8.71)	7 (12.07)	2 (11.76)	4 (13.79)	2 (7.69)	13 (14.13)	8 (7.34)
South	3,051 (32.27)	2,987 (32.33)	72 (29.88)	24 (41.38)	4 (23.53)	11 (37.93)	9 (34.62)	16 (17.39)	43 (39.45)
West	2,233 (23.61)	2,172 (23.51)	69 (28.63)	12 (20.69)	5 (29.41)	6 (20.69)	7 (26.92)	34 (36.96)	27 (24.77)
Unknown	1,240 (13.11)	1,214 (13.14)	29 (12.03)	4 (6.90)	3 (17.65)	1 (3.45)	4 (15.38)	8 (8.70)	11 (10.09)
P-value			**0.42**	**0.30**	**0.84**	**0.46**	**0.92**	**0.01**	
Insurance (Patient-level), n (%)									
Medicare	6,447 (68.18)	6,304 (68.24)	158 (65.56)	36 (62.07)	13 (76.47)	19 (65.52)	16 (61.54)	68 (73.91)	62 (56.88)
Medicare Advantage	754 (7.97)	730 (7.90)	27 (11.20)	7 (12.07)	3 (17.65)	3 (10.34)	5 (19.23)	11 (11.96)	13 (11.93)
Medicaid	45 (0.48)	45 (0.49)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Commercial	376 (3.98)	369 (3.99)	9 (3.73)	4 (6.90)	0 (0.00)	3 (10.34)	0 (0.00)	4 (4.35)	5 (4.59)
Government	46 (0.49)	45 (0.49)	1 (0.41)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)	1 (1.09)	0 (0.00)
Military	48 (0.51)	47 (0.51)	1 (0.41)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.92)
No insurance	2 (0.02)	2 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Miscellaneous	239 (2.53)	232 (2.51)	7 (2.90)	0 (0.00)	0 (0.00)	0 (0.00)	2 (7.69)	2 (2.17)	3 (2.75)
Unknown	1,499 (15.85)	1,464 (15.85)	38 (15.77)	11 (18.97)	1 (5.88)	4 (13.79)	2 (7.69)	6 (6.52)	25 (22.94)
P-value			**0.67**	**0.63**	**0.88**	**0.76**	**.08**	**0.91**	
Race (Patient-level), n (%)									
Asian	91 (0.96)	87 (0.94)	4 (1.66)	1 (1.72)	1 (5.88)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.83)
Black	60 (0.63)	60 (0.65)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
White	7,946 (84.03)	7,768 (84.09)	198 (82.16)	48 (82.76)	14 (82.35)	26 (89.66)	22 (84.62)	78 (84.78)	90 (82.57)
Other	31 (0.33)	30 (0.32)	1 (0.41)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.85)	1 (1.09)	0 (0.00)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Unknown	1,328 (14.04)	1,293 (14.00)	38 (15.77)	9 (15.52)	2 (11.76)	3 (10.34)	3 (11.54)	13 (14.13)	17 (15.60)
P-value			0.48	0.90	0.33	0.92	0.04	0.56	
Race (Eye-level), n (%)									
Asian	97 (0.91)	93 (0.89)	4 (1.57)	1 (1.69)	1 (5.88)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.83)
Black or African American	64 (0.60)	64 (0.62)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Caucasian	9,018 (84.64)	8,807 (84.69)	211 (82.75)	49 (83.05)	14 (82.35)	27 (90.00)	28 (87.50)	84 (91.30)	94 (86.24)
Other	32 (0.30)	31 (0.30)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.09)	0 (0.00)
Unknown	1,443 (13.54)	1,404 (13.50)	39 (15.29)	9 (15.25)	2 (11.76)	3 (10.00)	3 (9.38)	13 (14.13)	17 (15.60)
P-value			0.46	0.89	0.30	0.92	0.06	0.56	
Patient Clinical Characteristics									
Laterality of Wet AMD at Index Date, n (%)									
Unilateral	4,622 (48.88)	4,509 (48.81)	113 (46.89)	28 (48.28)	9 (52.94)	12 (41.38)	10 (38.46)	36 (39.13)	56 (51.38)
Bilateral	4,834 (51.12)	4,729 (51.19)	128 (53.11)	30 (51.72)	8 (47.06)	17 (58.62)	16 (61.54)	56 (60.87)	53 (48.62)
			0.56	0.94	0.73	0.42	0.29	0.08	
Laterality of AMD at Index Date, n (%)									
Unilateral	443 (4.68)	436 (4.72)	7 (2.90)	3 (5.17)	2 (11.76)	0 (0.00)	1 (3.85)	1 (1.09)	4 (3.67%)
Bilateral	9,013 (95.32)	8,802 (95.28)	234 (97.10)	55 (94.83)	15 (88.24)	29 (100.00)	25 (96.15)	91 (98.91)	105 (96.33%)
			0.70	0.70	0.70	0.70	0.70	0.70	
Eye Clinical Characteristic									
Time Since Wet AMD Diagnosis, n (%)	10,654	10,399	255	59	17	30	32	98	113
<6 months	1,066 (10.01)	1,041 (10.01)	25 (9.80)	10 (16.95)	1 (5.88)	4 (13.33)	5 (15.63)	8 (8.16)	13 (11.50%)
6 to <12 months	1,010 (9.48)	988 (9.50)	22 (8.63)	5 (8.47)	0 (0.00)	3 (10.00)	4 (12.50)	8 (8.16)	10 (8.85)
12 to <24 months	2,088 (19.60)	2,033 (19.55)	55 (21.57)	14 (23.73)	5 (29.41)	7 (23.33)	7 (21.88)	17 (17.35)	27 (23.89)
≥24 months	6,490 (60.92)	6,337 (60.94)	153 (60.00)	30 (50.85)	11 (64.71)	16 (53.33)	16 (50.00)	65 (66.33)	63 (55.75)
Mean (days)	760.18	760.23	758.07	698.32	886.06	706.47	655.69	799.69	726.99
SD	360.31	360.34	359.72	408.63	291.29	404.13	357.42	347.69	367.55

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Median	948.00	949.00	904.00	738.00	1063.00	880.50	706.00	1019.00	833.00
P-value			**0.86**	**0.22**	**0.43**	**0.84**	**0.57**	**0.45**	
Time Since Any AMD Diagnosis									
<6 months	661 (6.20)	649 (6.24)	12 (4.71)	5 (8.47)	0 (0.00)	2 (6.67)	5 (15.63)	2 (2.04)	7 (6.19)
6 to <12 months	734 (6.89)	715 (6.88)	19 (7.45)	4 (6.78)	0 (0.00)	2 (6.67)	4 (12.50)	8 (8.16)	8 (7.08)
12 to <24 months	1,778 (16.69)	1,731 (16.65)	47 (18.43)	11 (18.64)	5 (29.41)	5 (16.67)	6 (18.75)	9 (9.18)	27 (23.89)
≥24 months	7,481 (70.22)	7,304 (70.24)	177 (69.41)	39 (66.10)	12 (70.59)	21 (70.00)	17 (53.13)	79 (80.61)	71 (62.83)
P-value			**0.67**	**0.86**	**0.27**	**1.00**	**0.06**	**0.01**	
Concomitant Disease / Procedure History									
Concurrent Eye Disease (within 180 days prior to index date), n (%)									
Cataracts	2,691 (25.26)	2,618 (25.18)	73 (28.63)	15 (25.42)	7 (41.18)	6 (20.00)	6 (18.75)	27 (27.55)	31 (27.43)
Posterior vitreous detachment	3,567 (33.48)	3,467 (33.34)	100 (39.22)	22 (37.29)	7 (41.18)	13 (43.33)	8 (25.00)	36 (36.73)	40 (35.40)
Puckering of macula	1,015 (9.53)	981 (9.43)	34 (13.33)	11 (18.64)	2 (11.76)	6 (20.00)	4 (12.50)	11 (11.22)	17 (15.04)
Macular hole	50 (0.47)	49 (0.47)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.13)	0 (0.00)	0 (0.00)
Vitreomacular traction	90 (0.84)	87 (0.84)	3 (1.18)	1 (1.69)	0 (0.00)	1 (3.33)	2 (6.25)	2 (2.04)	1 (0.88)
Glaucoma	1,800 (16.90)	1,744 (16.77)	56 (21.96)	11 (18.64)	3 (17.65)	6 (20.00)	9 (28.13)	26 (26.53)	21 (18.58)
Amblyopia	27 (0.25)	26 (0.25)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.88)
Papillitis	1 (0.01)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ischemic optic atrophy	9 (0.08)	8 (0.08)	1 (0.39)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.88)
Diabetic retinopathy	199 (1.87)	194 (1.87)	5 (1.96)	2 (3.39)	1 (5.88)	0 (0.00)	0 (0.00)	3 (3.06)	0 (0.00)
Diabetic macular edema	40 (0.38)	39 (0.38)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Hypertensive retinopathy	446 (4.19)	432 (4.15)	14 (5.49)	5 (8.47)	1 (5.88)	4 (13.33)	1 (3.13)	4 (4.08)	7 (6.19)
Pathologic myopia	47 (0.44)	44 (0.42)	3 (1.18)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.02)	1 (0.88)
RAO	43 (0.40)	36 (0.35)	7 (2.75)	6 (10.17)	0 (0.00)	6 (20.00)	0 (0.00)	4 (4.08)	1 (0.88)
RVO	93 (0.87)	82 (0.79)	11 (4.31)	10 (16.95)	0 (0.00)	1 (3.33)	0 (0.00)	7 (7.14)	4 (3.54)
RV	2 (0.02)	2 (0.02)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Vitritis	7 (0.07)	7 (0.07)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Endophthalmitis	62 (0.58)	56 (0.54)	6 (2.35)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	4 (4.08)	2 (1.77)
Uveitis	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Autoimmune diseases	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Choroidal neovascularization	278 (2.61)	273 (2.63)	5 (1.96)	1 (1.69)	0 (0.00)	1 (3.33)	0 (0.00)	0 (0.00)	4 (3.54)
IOI	346 (3.25)	309 (2.97)	37 (14.51)	18 (30.51)	0 (0.00)	8 (26.67)	0 (0.00)	20 (20.41)	10 (8.85)
Cataract Status, n (%)									
Phakic	5,602 (52.58)	5,475 (52.65)	127 (49.80)	35 (59.32)	10 (58.82)	18 (60.00)	11 (34.38)	59 (60.20)	52 (46.02)
Pseudophakic	5,040 (47.31)	4,914 (47.25)	127 (49.80)	24 (40.68)	7 (41.18)	12 (40.00)	20 (62.50)	39 (39.80)	60 (53.10)
Aphakic	12 (0.11)	10 (0.10)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.13)	0 (0.00)	1 (0.88%)
P-value			**0.24**	**0.55**	**0.84**	**0.69**	**<0.001**	**.005**	
Concomitant Ocular Medications, n (%)									
Corticosteroids	4,497 (42.21)	4,387 (42.19)	120 (47.06)	25 (42.37)	7 (41.18)	12 (40.00)	11 (34.38)	51 (52.04)	51 (45.13%)
Prednisone	207 (1.94)	203 (1.95)	5 (1.96)	2 (3.39)	2 (11.76)	0 (0.00)	0 (0.00)	3 (3.06)	1 (0.88%)
Prednisolone acetate	496 (4.66)	480 (4.62)	19 (7.45)	3 (5.08)	1 (5.88)	1 (3.33)	4 (12.50)	12 (12.24)	5 (4.42%)
Difluprednate	238 (2.23)	235 (2.26)	4 (1.57)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	2 (1.77%)
Biologics	682 (6.40)	672 (6.46)	10 (3.92)	1 (1.69)	0 (0.00)	1 (3.33)	1 (3.13)	5 (5.10)	3 (2.65%)
Cyclosporine	212 (1.99)	210 (2.02)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.04)	0 (0.00)
Methotrexate	50 (0.47)	48 (0.46)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Ganciclovir	4 (0.04)	3 (0.03)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Acyclovir	103 (0.97)	102 (0.98)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Trifluridine	3 (0.03)	3 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Rituxan	1 (0.01)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Ocular Surgeries or Procedures, n (%)									
Laser Therapy	102 (0.96)	97 (0.93)	5 (1.96)	2 (3.39)	0 (0.00)	1 (3.33)	0 (0.00)	1 (1.02)	2 (1.77)
Laser Coagulation	7 (0.07)	6 (0.06)	1 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Photodynamic Therapy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
IOP Lowering Surgery (e.g. Trabeculectomy, MIGS)	195 (1.83)	179 (1.72)	16 (6.27)	2 (3.39)	1 (5.88)	1 (3.33)	0 (0.00)	7 (7.14)	5 (4.42)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Cataract Surgery	125 (1.17)	118 (1.13)	7 (2.75)	1 (1.69)	1 (5.88)	0 (0.00)	1 (3.13)	0 (0.00)	6 (5.31)
Iridotomy	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Intraocular or Refractive Surgery (Almost All IOP & Cataract Surgeries)	304 (2.85)	283 (2.72)	21 (8.24)	2 (3.39)	1 (5.88)	1 (3.33)	1 (3.13)	7 (7.14)	10 (8.85)
Previous Penetrating Keratoplasty, Vitrectomy, or Ocular Radiation	58 (0.54)	46 (0.44)	12 (4.71)	1 (1.69)	1 (5.88)	1 (3.33)	0 (0.00)	7 (7.14)	1 (0.8)
Previous Panretinal Photocoagulation	112 (1.05)	107 (1.03)	5 (1.96)	2 (3.39)	0 (0.00)	1 (3.33)	0 (0.00)	1 (1.02)	2 (1.77)
Previous Submacular Surgery, Other Surgical Intervention or Laser Treatment for AMD	125 (1.17)	111 (1.07)	14 (5.49)	3 (5.08)	1 (5.88)	2 (6.67)	0 (0.00)	7 (7.14)	3 (2.65)
Prior IOI and/or Prior RO									
36 Months Prior to Brolucizumab Initiation, n (%)									
No History of Inflammation	10,065 (94.47)	9,852 (94.74)	213 (83.53)	40 (67.80)	17 (100.00)	21 (70.00)	31 (96.88)	76 (77.55)	101 (89.38)
History of Any Ocular Inflammation	589 (5.53)	547 (5.26)	42 (16.47)	19 (32.20)	0 (0.00)	9 (30.00)	1 (3.13)	22 (22.45)	12 (10.62)
History of Severe Ocular Inflammation	113 (1.06)	106 (1.02)	7 (2.75)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	5 (5.10)	2 (1.77)
History of Anterior Inflammation	165 (1.55)	155 (1.49)	10 (3.92)	1 (1.69)	0 (0.00)	1 (3.33)	0 (0.00)	5 (5.10)	2 (1.77)
History of Posterior Inflammation	140 (1.31)	132 (1.27)	8 (3.14)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.06)	3 (2.65)
History of IOI / endophthalmitis due to infections and other underlying disease	3 (0.03)	3 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
History of inflammation excluding RVO, n (%)	471 (4.42)	439 (4.22)	32 (12.55)	9 (15.25)	0 (0.00)	7 (23.33)	1 (3.13)	16 (16.33)	8 (7.08)
P-value			**<0.001**	**<0.001**	**0.33**	**<0.001**	**0.59**	**0.02**	
12 Months Prior to Brolucizumab Initiation, n (%)									
No History of Inflammation	10,241 (96.12)	10,023 (96.38)	218 (85.49)	41 (69.49)	17 (100.00)	22 (73.33)	32 (100.00)	78 (79.59)	103 (91.15)
History of Any Ocular Inflammation	413 (3.88)	376 (3.62)	37 (14.51)	18 (30.51)	0 (0.00)	8 (26.67)	0 (0.00)	20 (20.41)	10 (8.85)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthal-mitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthal-mitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an AE [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
History of Severe Ocular Inflammation	59 (0.55)	54 (0.52)	5 (1.96)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.06)	2 (1.77)
History of Anterior Inflammation	101 (0.95)	94 (0.90)	7 (2.75)	1 (1.69)	0 (0.00)	1 (3.33)	0 (0.00)	3 (3.06)	1 (0.88)
History of Posterior Inflammation	91 (0.85)	83 (0.80)	8 (3.14)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.06)	3 (2.65)
History of IOI / endophthalmitis due to infections and other underlying disease	3 (0.03)	3 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
History of inflammation excluding RVO, n (%)	318 (2.98)	290 (2.79)	28 (10.98)	9 (15.25)	0 (0.00)	7 (23.33)	0 (0.00)	14 (14.29)	7 (6.19)
P-value			**<0.001**	**<0.001**	**0.42**	**<0.001**	**0.27**	**0.02**	
6 Months Prior to Brolucizumab Initiation, n (%)									
No History of Inflammation	10,308 (96.75)	10,090 (97.03)	218 (85.49)	41 (69.49)	17 (100.00)	22 (73.33)	32 (100.00)	78 (79.59)	103 (91.15)
History of Any Ocular Inflammation	346 (3.25)	309 (2.97)	37 (14.51)	18 (30.51)	0 (0.00)	8 (26.67)	0 (0.00)	20 (20.41)	10 (8.85)
History of Severe Ocular Inflammation	46 (0.43)	41 (0.39)	5 (1.96)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.06)	2 (1.77)
History of Anterior Inflammation	82 (0.77)	75 (0.72)	7 (2.75)	1 (1.69)	0 (0.00)	1 (3.33)	0 (0.00)	3 (3.06)	1 (0.88)
History of Posterior Inflammation	77 (0.72)	69 (0.66)	8 (3.14)	1 (1.69)	0 (0.00)	0 (0.00)	0 (0.00)	3 (3.06)	3 (2.65)
History of IOI / endophthalmitis due to infections and other underlying disease	3 (0.03)	3 (0.03)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
History of inflammation excluding RVO, n (%)	263 (2.47)	235 (2.26)	28 (10.98)	9 (15.25)	0 (0.00)	7 (23.33)	0 (0.00)	14 (14.29)	7 (6.19)
P-value			**<0.001**	**<0.001**	**0.47**	**<0.001**	**0.32**	**0.02**	

AE, Adverse event; IOI, intraocular inflammation; IOP, intraocular pressure; MIGS, Micro-Invasive Glaucoma Surgery; RAO, retinal artery occlusion; RO, retinal vascular occlusion; RV, retinal vasculitis; RVO, retinal vein occlusion; SD, standard deviation.

Overall, most (77.51%) patient eyes received unilateral treatment with brolucizumab. At the index date the median VA was 65.00 ETDRS letters and 86.58% of eyes had Snellen VA scores of 20/12-20/160. Retina specialists were the most common (86.76%) types of provider for the first brolucizumab injection. Only 968 (9.08%) of the eyes were treatment naïve. Most eyes (6,019, 56.50%) had received 1 prior anti-VEGF agent. The mean interval of time between a prior anti-VEGF and brolucizumab initiation was 86.18 (median 56.00) days.

Greater than 90% of patient eyes had switched from another anti-VEGF agent, with aflibercept being the most common immediate prior

anti-VEGF agent (73.92% of eyes). The mean (SD) duration of the last anti-VEGF treatment for any agent was 580.91 (361.38) days. The mean (SD) number of injections prior to the initiation of brolucizumab for any prior anti-VEGF agent was 11.75 (8.65). Similar trends were observed in the other cohorts.

Brolucizumab Treatment Characteristics & Baseline VA

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthalmitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthalmitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an Adverse Event [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Number of Injections of brolucizumab									
1	5,458	Provided in Table 10-5 and Table 10-7							
2	3,289								
3+	1,907								
Mean (SD) Duration of Follow-Up	92.97 (33.46)	92.74 (33.55)	102.69 (28.10)	112.20 (25.68)	-	-	-	-	-
Eye Treated with Brolucizumab, n (%)									
Right (OD)	5,564 (52.22)	5,425 (58.72)	139 (5768)	37 (63.79)	10 (58.82)	19 (65.52)	17 (65.38)	58 (63.04)	56 (51.38)
Left (OS)	5,090 (47.78)	4,974 (53.84)	116 (48.13)	22 (37.93)	7 (41.18)	11 (37.93)	15 (57.69)	40 (43.48)	57 (52.29)
Unilateral	8,258 (77.51)	8.077 (87.43)	227 (94.19)	57 (98.28)	17 (100.00)	28 (96.55)	20 (76.92)	86 (93.48)	105 (96.33)
Bilateral	2,396 (22.49)	2,322 (25.14)	28 (11.62)	2 (3.45)	0 (0.00)	2 (6.90)	12 (46.15)	12 (13.04)	8 (7.34)
P-value			**0.46**	**0.11**	**0.58**	**0.22**	**0.91**	**0.16**	
VA at Index Date (Snellen), n	10,654	10,399	255	59	17	30	32	98	113
ETDRS Mean (SD)	61.78 (18.67)	61.70 (18.71)	65.00 (16.43)	61.31 (19.98)	66.53 (13.2)	66.00 (18.51)	60.78 (19.04)	67.27 (13.98)	63.52 (18.24)
ETDRS Median	65.00	65.00	70.00	65.00	65.00	70.00	65.00	70.00	70.00
Snellen, n (%)									
20/10 or better	1 (0.01)	1 (0.01)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
20/12-20/20	597 (5.60)	576 (5.54)	21 (8.24)	5 (8.47)	2 (11.76)	3 (10.00)	1 (3.13)	10 (10.20)	8 (7.08)
20/12-20/20	4,445 (41.72)	4,325 (41.59)	120 (47.06)	24 (40.68)	6 (35.29)	16 (53.33)	12 (37.50)	46 (46.94)	54 (47.79)
20/50-20/160	4,183 (39.26)	4,094 (39.37)	89 (34.90)	18 (30.51)	8 (47.06)	7 (23.33)	15 (46.88)	34 (34.69)	41 (36.28)
20/200 or worse	1,428 (13.40)	1,403 (13.49)	25 (9.80)	12 (20.34)	1 (5.88)	4 (13.33)	4 (12.50)	8 (8.16%)	10 (8.85)
P-value			**0.0002**	**0.88**	**0.13**	**0.20**	**0.79**	**0.01**	
Provider Specialty at Date of First									

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthalmitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthalmitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an Adverse Event [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Brolucizumab Injection, n (%)									
Retina Specialist	8,204 (86.76)	8,017 (86.78)	206 (85.48)	51 (87.93)	15 (88.24)	26 (89.66)	24 (92.31)	75 (81.52)	96 (88.07)
General ophthalmologist	779 (8.24)	715 (8.17)	25 (10.37)	4 (6.90)	2 (11.76)	2 (6.90)	2 (7.69)	11 (11.96)	11 (10.09)
Non-Retina Specialist	424 (4.48)	418 (4.52)	9 (3.73)	2 (3.45)	0 (0.00)	1 (3.45)	0 (0.00)	5 (5.43)	2 (1.83)
Unknown	134 (1.42)	133 (1.44)	2 (0.83)	1 (1.72)	0 (0.00)	0 (0.00)	0 (0.00)	2 (2.17)	0 (0.00)
Prior Therapy									
Treatment-naïve Status of Patient Eyes Treated with Brolucizumab, n (%)									
Treatment-naïve	968 (9.09)	949 (9.13)	19 (7.45)	10 (16.95)	0 (0.00)	7 (23.33)	1 (3.13)	7 (7.14)	7 (6.19)
Prior-treated	9,686 (90.91)	9,450 (90.87)	236 (92.55)	49 (83.05)	17 (100.00)	23 (76.67)	31 (96.88)	91 (92.86)	106 (93.81)
P-value			0.35789	0.003787	**0.19139**	**0.000708**	**0.23878**	**0.78256**	
Number of Different Prior Anti-VEGF Agents, n (%)									
0	968 (9.09)	949 (9.13)	19 (7.45)	10 (16.95)	0 (0.00)	7 (23.33)	1 (3.13)	7 (7.14)	7 (6.19)
1	6,019 (56.50)	5,870 (56.45)	149 (58.43)	28 (47.46)	8 (47.06)	14 (46.67)	20 (62.50)	60 (61.22)	67 (59.29)
2	3,052 (28.65)	2,973 (28.59)	79 (30.98)	18 (30.51)	8 (47.06)	8 (26.67)	10 (31.25)	27 (27.55)	37 (32.74)
3+	615 (5.77)	607 (5.84)	8 (3.14)	3 (5.08)	1 (5.88)	1 (3.33)	1 (3.13)	4 (4.08)	2 (1.77)
P-value			**0.21**	**0.18**	**0.28**	**0.01**	**0.58**	**0.67**	
Interval of Time between Prior Anti-VEGF and Brolucizumab Initiation, n (%)									
Mean (SD), days	86.18 (117.11)	86.50 (117.59)	73.36 (95.47)	57.12 (36.01)	47.00 (18.12)	64.65 (46.00)	69.26 (97.75)	84.18 (111.28)	68.20 (91.90)
Median (Min–Max), days	56.00 (14.00-1,093.00)	56.00 (14.00-1,093.00)	49.00 (15.00-814.00)	50.00 (28.00-252.00)	42.00 (28.00-77.00)	56.00 (28.00-252.00)	42.00 (15.00-549.00)	55.00 (28.00-814.00)	42.00 (15.00-756.00)
IQR, days	1,079	1,079	799	224	49	224	534	786	741
<4 weeks	88 (0.83)	86 (0.83)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	1 (3.13)	0 (0.00)	1 (0.88)
4 - <6 weeks	3,024 (28.38)	2,945 (28.32)	79 (30.98)	16 (27.12)	8 (47.06)	6 (20.00)	12 (37.50)	24 (24.49)	41 (36.28)
6 - <8 weeks	1,642 (15.41)	1,589 (15.28)	53 (20.78)	9 (15.25)	2 (11.76)	4 (13.33)	8 (25.00)	20 (20.41)	26 (23.01)
8 – <12 weeks	2,229 (20.92)	2,172 (20.89%)	57 (22.35)	18 (30.51)	7 (41.18)	8 (26.67)	7 (21.88)	26 (26.53)	17 (15.04)
≥12 weeks	2,703 (25.37)	2,658 (25.56)	45 (17.65)	6 (10.17)	0 (0.00)	5 (16.67)	3 (9.38)	21 (21.43)	21 (18.58)
Treatment-naïve	968 (9.09)	949 (9.13)	19 (7.45)	10 (16.95)	0 (0.00)	7 (23.33)	1 (3.13)	7 (7.14)	7 (6.19)
P-value			**0.003**	**<0.0001**	**<0.0001**	**0.001**	**0.32**	**0.26**	
Prior VEGF Utilization by Product									

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthalmitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthalmitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an Adverse Event [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
Prior Treatment for Patient Eyes Treated with Brolucizumab, n (%)									
Bevacizumab	1,000 (9.39)	978 (9.40)	22 (8.63)	5 (8.47)	1 (5.88)	3 (10.00)	3 (9.38)	12 (12.24)	7 (6.19)
Aflibercept	7,160 (73.92)	6,975 (72.01)	185 (1.91)	43 (0.44)	15 (0.15)	20 (0.21)	23 (0.24)	72 (0.74)	86 (0.89)
Ranibizumab	1,478 (13.87)	1,451 (13.95)	27 (10.59)	1 (1.69)	1 (5.88)	0 (0.00)	5 (15.63)	6 (6.12)	13 (11.50)
Unknown	48 (0.45)	46 (0.44)	2 (0.78)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.02)	0 (0.00)
Treatment-naïve	968 (9.09)	949 (9.13)	19 (7.45)	10 (16.95)	0 (0.00)	7 (23.33)	1 (3.13)	7 (7.14)	7 (6.19)
P-value			**0.32**	**0.003**	**0.44**	**0.003**	**0.81**	**0.28**	
Duration of Last Anti-VEGF Treatment									
Any Agent, n (%)	9,686	9,450	236	49	17	23	31	91	106
Mean (SD)	580.91 (361.38)	580.33 (361.53)	604.27 (355.01)	568.18 (356.04)	587.94 (355.89)	594.09 (389.92)	499.45 (343.00)	647.60 (331.05)	567.60 (373.55)
Median	525.50	524.00	586.00	559.00	582.00	521.00	503.00	642.00	520.00
<6 months	1,689 (17.44)	1,652 (17.48)	37 (15.68)	10 (20.41)	4 (23.53)	4 (17.39)	6 (19.35)	7 (7.69)	23 (21.70)
6 to <12 months	1,799 (18.57)	1,764 (18.67)	35 (14.83%)	8 (16.33)	1 (5.88)	6 (26.09)	8 (25.81)	15 (16.48)	16 (15.09)
12 to <24 months	2,448 (25.27)	2,377 (25.15)	71 (30.08)	14 (28.57)	7 (41.18)	3 (13.04)	8 (25.81)	29 (31.87)	29 (27.36)
≥24 months	3,750 (38.72)	3,657 (38.70)	93 (39.41)	17 (34.69)	5 (29.41)	10 (43.48)	9 (29.03)	40 (43.96)	38 (35.85)
P-value			**0.31**	**0.81**	**0.93**	**0.87**	**0.19**	**0.11**	
Bevacizumab, n (%)	1,000	978	22	5	1	3	3	12	7
Mean (SD)	477.06 (357.73)	479.17 (357.74)	383.32 (352.70)	344.40 (428.19)	28.00 (-)	528.33 (488.04)	509.33 (334.86)	557.92 (385.13)	128.86 (81.22)
Median	378.00	385.00	248.50	109.00	28.00	521.00	317.00	409.50	138.00
<6 months	298 (29.80)	290 (29.65)	8 (36.36)	3 (60.00)	1 (100.00)	1 (33.33)	0 (0.00)	2 (16.67)	5 (71.43)
6 to <12 months	181 (18.10)	175 (17.89)	6 (27.27)	0 (0.00)	0 (0.00)	0 (0.00)	2 (66.67)	3 (25.00)	2 (28.57)
12 to <24 months	229 (22.90)	226 (23.11)	3 (13.64)	1 (20.00)	0 (0.00)	1 (33.33)	0 (0.00)	2 (16.67)	0 (0.00)
≥24 months	292 (29.20)	287 (29.35)	5 (22.73)	1 (20.00)	0 (0.00)	1 (33.33)	1 (33.33)	5 (41.67%)	0 (0.00)
P-value			**0.21**	**0.48**	**<0.0001**	**0.86**	**0.88**	**0.0002**	
Aflibercept, n (%)	7,160	6,975	185	43	15	20	23	72	86
Mean (SD)	612.48 (358.75)	611.95 (359.15)	632.23 (343.62)	583.98 (341.45)	597.27 (331.15)	603.95 (387.54)	557.78 (349.22)	666.13 (330.77)	615.26 (361.45)
Median	581.00	580.00	607.00	582.00	582.00	496.50	559.00	649.50	586.00
<6 months	1,030 (14.39)	1,008 (14.45)	22 (11.89)	7 (16.28)	3 (20.00)	3 (15.00)	4 (17.39)	5 (6.94)	13 (15.12)
6 to <12 months	1,309 (18.28)	1,282 (18.38)	27 (14.59)	8 (18.60)	1 (6.67)	6 (30.00)	4 (17.39)	11 (15.28)	13 (15.12)
12 to <24 months	1,804 (25.20)	1,745 (25.02)	59 (31.89)	13 (30.23)	7 (46.67)	2 (10.00)	7 (30.43)	23 (31.94)	26 (30.23)
≥24 months	3,017 (42.14)	2,940 (42.15)	77 (41.62)	15 (34.88)	4 (26.67)	9 (45.00)	8 (34.78)	33 (45.83)	34 (39.53)
P-value			**0.43**	**0.59**	**0.86**	**0.93**	**0.46**	**0.36**	
Ranibizumab, n (%)	1,478	1,451	27	1	1	0	5	6	13
Mean (SD)	511.40 (349.26)	509.39 (348.55)	619.56 (377.07)	1,008.00 (-)	1,008.00 (-)	0 (0-0)	225.20 (204.62)	635.67 (247.90)	488.62 (396.12)
Median	433.00	429.00	646.00	1,008.00	1,008.00	0.00	182.00	644.00	534.00
<6 months	324 (21.92)	318 (21.92)	6 (22.22)	0 (0.00)	0 (0.00)	0 (0.00)	2 (40.00)	0 (0.00)	5 (38.46)
6 to <12 months	304 (20.57)	302 (20.81)	2 (7.41)	0 (0.00)	0 (0.00)	0 (0.00)	2 (40.00)	1 (16.67)	1 (7.69)

	Master Cohort (All Brolucizumab-treated Patients)	Cohort 1X (Control: No IOI or Endophthalmitis or Panuveitis or RV or RO)	Cohort 2X (IOI or Endophthalmitis (Related to Safety) or Panuveitis or RV or RO)	Cohort 3X (Patients with RV and/or RO [RAO and/or RO])	Cohort 4X (Patients with RV)	Cohort 5X (Patients with RAO)	Cohort 6X (Patients with Panuveitis)	Cohort 7 (Patients with at least Moderate Vision Loss following an Adverse Event [Cohort 2 with 3+ lines of Vision Loss])	Cohort 8 (Patients without at least Moderate Vision Loss [3+ lines] following an AE)
12 to <24 months	412 (27.88)	404 (27.84)	8 (29.63)	0 (0.00)	0 (0.00)	0 (0.00)	1 (20.00)	3 (50.00)	3 (23.08)
≥24 months	438 (29.63)	427 (29.43)	11 (40.74)	1 (100.00)	1 (100.00)	0 (0.00)	0 (0.00)	2 (33.33)	4 (30.77)
P-value			**0.13**	**<0.0001**	**<0.0001**	0 (0.00)	**0.0002**	**0.34**	
Mean Number Injections Prior to Initiation of Brolucizumab by Prior Anti-VEGF Agents									
Any Agent, n (%)	9,686	9,450	236	49	17	23	31	91	106
Mean (SD)	11.75 (8.65)	11.72 (8.64)	12.86 (8.97)	12.33 (9.04)	14.35 (8.75)	12.70 (10.08)	10.97 (8.53)	13.57 (8.78)	12.32 (9.45)
Median	10.00	10.00	11.00	10.00	15.00	10.00	8.00	12.00	10.00
<6 months	2,956 (30.52)	2,892 (30.60)	64 (27.12)	15 (30.61)	3 (17.65)	8 (34.78)	10 (32.26)	16 (17.58)	37 (34.91)
6 to <12 months	2,537 (26.19)	2,478 (26.22)	59 (25.00)	10 (20.41)	3 (17.65)	4 (17.39)	10 (32.26)	29 (31.87)	21 (19.81)
12 to <24 months	3,056 (31.55)	2,976 (31.49)	80 (33.90)	18 (36.73)	9 (52.94)	7 (30.43)	7 (22.58)	31 (34.07)	33 (31.13)
≥24 months	1,137 (11.74)	1,104 (11.68)	33 (13.98)	6 (12.24)	2 (11.76)	4 (17.39)	4 (12.90)	15 (16.48)	15 (14.15)
Bevacizumab, n (%)	1,000	978	22	5	1	3	3	12	7
Mean (SD)	8.09 (7.09)	8.09 (7.10)	7.77 (6.61)	6.40 (6.62)	1.00 (-)	9.33 (7.37)	10.67 (4.51)	10.67 (7.45)	3.14 (1.68)
Median	6.00	6.00	5.00	3.00	1.00	12.00	11.00	11.00	3.00
<6 months	494 (49.40)	482 (49.28)	12 (54.55)	3 (60.00)	1 (100.00%)	1 (33.33)	0 (0.00)	3 (25.00)	7 (100.00)
6 to <12 months	244 (24.40)	240 (24.54)	4 (18.18)	0 (0.00)	0 (0.00)	0 (0.00)	2 (66.67)	4 (33.33)	0 (0.00)
12 to <24 months	219 (21.90)	214 (21.88)	5 (22.73)	2 (40.00)	0 (0.00)	2 (66.67)	1 (33.33)	4 (33.33)	0 (0.00)
≥24 months	43 (4.30)	42 (4.29)	1 (4.55)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (8.33)	0 (0.00)
P-value			**0.82**	**0.57**	**<0.0001**	**0.77**	**0.32**	**0.0004**	
Aflibercept, n (%)	7,160	6,975	185	43	15	20	23	72	86
Mean (SD)	12.63 (8.75)	12.61 (8.75)	13.32 (8.70)	13.12 (9.17)	15.67 (8.36)	13.20 (10.48)	12.57 (9.07)	14.07 (8.88)	13.07 (9.00)
Median	11.00	11.00	11.00	13.00	16.00	8.00	9.00	12.50	11.00
<6 months	1,867 (26.08)	1,826 (26.18)	41 (22.16)	12 (27.91)	2 (13.33)	7 (35.00)	6 (26.09)	11 (15.28)	23 (26.74)
6 to <12 months	1,897 (26.49)	1,845 (26.45)	52 (28.11)	9 (20.93)	2 (13.33)	4 (20.00)	7 (30.43)	24 (33.33)	21 (24.42)
12 to <24 months	2,419 (33.78)	2,353 (33.73)	66 (35.68)	16 (37.21)	9 (60.00)	5 (25.00)	6 (26.09)	24 (33.33)	30 (34.88)
≥24 months	977 (13.65)	951 (13.63)	26 (14.05)	6 (13.95)	2 (13.33)	4 (20.00)	4 (17.39)	13 (18.06)	12 (13.95)
P-value			**0.28**	**0.72**	**0.16**	**0.80**	**0.98**	**0.48**	
Ranibizumab, n (%)	1,478	1,451	27	1	1	0	5	6	13
Mean (SD)	10.23 (8.16)	10.15 (8.08)	14.67 (10.96)	8.00 (-)	8.00 (-)	0 (0)	3.80 (1.92)	15.33 (9.56)	12.31 (12.37)
Median	8.00	8.00	15.00	8.00	8.00	0.00	3.00	15.50	4.00
<6 months	553 (37.42)	544 (37.49)	9 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)	4 (80.00)	1 (16.67)	7 (53.85)
6 to <12 months	393 (26.59)	390 (26.88)	3 (11.11)	1 (100.00)	1 (100.00)	0 (0.00)	1 (20.00)	1 (16.67)	0 (0.00)
12 to <24 months	417 (28.21)	408 (28.12)	9 (33.33)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	3 (50.00)	3 (23.08)
≥24 months	115 (7.78)	109 (7.51)	6 (22.22)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (16.67)	3 (23.08)
P-value			**0.003**	**<0.0001**	**<0.0001**	**NA**	**<0.0001**	**0.57**	

ETDRS, Early Treatment Diabetic Retinopathy Study; IOI, intraocular inflammation; IOP, intraocular pressure; OD, right eye; OS, left eye; RAO, retinal artery occlusion; RO, retinal vascular occlusion; RV, retinal vasculitis; RVO, retinal vein occlusion; SD, standard deviation.

Other Relevant Findings

Association between specific ocular AEs (any form of IOI [including RV] and/or RO, RV and/or RO)

Identification of potential risk factors at baseline on incidence of any form of IOI (including RV) and/or RO[a] based on a multivariable model

RISK FACTORS	ODDS RATIO (OR)	P Values
Prior IOI (including RV) and/or RO (12 months prior to the first brolucizumab injection)	OR: 4.69 [95% CI: 3.24, 6.79]	<0.001
Female gender	OR 2.23 [95% CI: 1.67, 2.96]	<0.001
Age (Continuous 5 year interval)	OR: 0.85 [95% CI: 0.80, 0.91]	<0.001
Prior anti-VEGF treatment status (ref. Naive)	OR: 1.24 [95% CI: 0.77, 1.98]	0.38
Follow-up (Days)	OR 1.01 [95% CI: 1.01, 1.01]	<0.001

OR > 1 indicates increased risk of AE of interest and OR < 1 indicates a decreased risk of IOI and/or RO

Identification of potential risk factors at baseline on incidence of any RV and/or RO[a] based on a multivariable model

RISK FACTORS	ODDS RATIO (OR)	P Values
Prior IOI (including RV) and/or RO (12 months prior to the first brolucizumab injection)	OR: 12.53 [95% CI: 7.06, 22.25]	<0.001
Female gender	OR 2.89 [95% CI: 1.52, 5.50]	<0.001
Age (Continuous 5 year interval)	OR: 0.91 [95% CI: 0.80, 1.02]	0.10
Prior anti-VEGF treatment status (ref. Naive)	OR: 0.51 [95% CI: 0.26, 1.02]	0.06
Follow-up (Days)	OR 1.15 [95% CI: 1.09, 1.22]	<0.001

OR >1 indicates increased risk of AE of interest and OR<1 indicates a decreased risk of RV and/or RO

Estimation of incidence for any form of IOI (including RV) and/or RO based on identified risk factors at baseline

RISK FACTORS	NUMBER OF AVAILABLE PATIENT EYES	Estimated Incidence Rate
Overall	10,652	2.22%
No Prior IO/RO + Male	4,383	1.17% [95% CI: 0.85%, 1.49%]
Male	4,547	1.32% [95% CI: 0.98%, 1.65%]
No Prior IO/RO	10,239	1.96% [95% CI: 1.69%, 2.23%]
No Prior IO/RO + Female	5,856	2.56% [95% CI: 2.15%, 2.96%]
Female	6,105	2.90% [95% CI: 2.48%, 3.32%]
Prior IO/RO + Male	164	5.24% [95% CI: 1.83%, 8.65%]
Prior IO/RO	413	8.70% [95% CI: 5.98%, 11.42%]
Prior IO/RO + Female	249	10.98% [95% CI: 7.10%, 14.87%]

Estimation of RV and/or RO based on identified risk factors at baseline

RISK FACTORS	NUMBER OF AVAILABLE PATIENT EYES	ESTIMATED INCIDENCE RATE
Overall	10,458	0.46%
No Prior IO/RO + Male	4,336	1.16% [95% CI: 0.04%, 0.27%]
Male	4,494	0.22% [95% CI: 0.08%, 0.36%]
No Prior IO/RO	10,062	0.32% [95% CI: 0.21%, 0.44%]
No Prior IO/RO + Female	5,726	0.45% [95% CI: 0.28%, 0.63%]
Female	5,962	0.65% [95% CI: 0.44%, 0.85%]
Prior IO/RO + Male	158	1.93% [95% CI: 0.00%, 4.08%]
Prior IO/RO	394	3.97% [95% CI: 2.04%, 5.90%]
Prior IO/RO + Female	236	5.33% [95% CI: 2.47%, 8.20%]

Safety Results

Refer to primary outcome results (Overall incidence rates of any form of IOI (including RV) and/or RO[a] up to 6 months after the first brolucizumab injection)

Limitations

There are certain limitations with these types of retrospective analyses using data collected from routine clinical practice. Although these analyses were pre-specified, they were non-interventional and retrospective as opposed to a clinical trial in which data are collected prospectively. Limitations of these analyses include lack of access to patient charts or imaging, the use of ICD codes to identify observed events, and a median follow-up of only 3 months. Codes can only constitute a proxy for the event of interest and the severity remains unknown, thus, in the absence of charts or imaging a causality link of events with brolucizumab treatment cannot be confirmed. Other risk factors and confounders are not available in the dataset. The combination of the low number of events and the absence of robust discriminatory risk factors that can clearly distinguish patients with the risk factor from those without means that the risk factors identified in these analyses cannot be used as a predictor for the occurrence of IOI and/or RO in routine clinical practice. It is unknown whether not initiating brolucizumab treatment in patients with prior IOI (including RV) and/or RO in the past 12 months would reduce the incidence of AEs of interest observed following exposure to brolucizumab.

It was noted that there may have been a truncation bias introduced in these analyses due to the potential for the end of the index period and the end of the study period to coincide for some patients. This coincidence could reduce the follow-up window for observation of AEs if brolucizumab treatment was initiated later in the index period. Moreover, early 2020 coincided with the first wave of COVID-19 cases in the US, which led to decreased clinic attendance of AMD patients for follow-up anti-VEGF injections.22-24 AE estimates could be subject to bias as a result of patient failure to attend follow-up appointments before the end of the study period. In defining the boundary conditions of the analysis, we attempted to balance providing enough time for patient follow-up and obtaining early insights into the prevalence of AEs following brolucizumab injection.

Conclusion:

In conclusion, data from the IRIS registry provided early insights into the safety of patients with wet AMD who initiated brolucizumab. The incidence rate for any form of IOI and/or RO was approximately 2.4%.

Patients with IOI and/or RO in the 12 months prior to the first brolucizumab injection had the highest estimated incidence rate for an event of any form of IOI (including RV) and/or RO among patient eyes in the 6 months post first brolucizumab treatment. Similar findings were observed for the sub-group of patient eyes with RV and/or RO. However, considering the design and limitations of these analyses and the available data, this association is not predictive of the risk of occurrence of AEs of interest in patients with prior IOI (including RV) and/or RO treated with brolucizumab, and a causal link between this association and brolucizumab is unknown.

Additional studies are needed with longer follow-up intervals to assess the long-term safety of brolucizumab treatment and further analyses of the IRIS Registry may be warranted. These results represent early findings from routine clinical practice that explore potential risk factors for inflammation-related AEs that may occur following treatment with brolucizumab.

Date of Clinical Study Report

05 February 2021