The Brolucizumab Experience Thus Far: A Health Economics and Outcomes Research Analysis

Michael Ip[1], Thomas Albini[2], Marco Zarbin[3], Mathew MacCumber[4], Justin Yu[5], Guru Prasad B[5], Hersh Patel[5], Neetu Agashivala[5], Peter K. Kaiser[6]

[1]Doheny Eye Institute, Los Angeles, CA, USA; [2]Bascom Palmer Eye Institute, Miami, FL, USA; [3]Institute of Ophthalmology and Visual Science, Rutgers-New Jersey Medical School, Rutgers University, Newark, NJ, USA; [4]Rush University Medical Center, Chicago, Illinois; [5]Novartis Pharmaceuticals, East Hanover, NJ, USA; [6]Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA.

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Michael Ip: Consultant for Novartis, Genentech, Allergan, Regeneron, RegenexBio, Apellis, Aerie, Alimera, Amgen, Cell Lineage Therapeutics, Clearside, and OCCURX

Thomas Albini: Consultant for Adverum Biotechnologies, Allergan, Beaver Visitec, Applied Genetic Technologies Corporation, Clearside Biomedical, Inc., Eyepoint Pharmaceuticals, Inc., Genentech, Novartis, RegenexBio, and Valeant Pharmaceuticals

Marco Zarbin: Consultant for Novartis Pharma AG, Genentech/Roche, Iveric Bio, Perfuse Therapeutics, Selphagy, Iduna, and Frequency Therapeutics, Co-Founder of Nvasc

Mathew MacCumber: Consultant for Alimera Sciences, Allergan, Apellis, Genentech, Novartis Pharma AG, Regeneron, and Spark Therapeutics

Justin Yu: Employee of Novartis Pharmaceuticals Corporation

Guru Prasad B: Employee of Novartis Pharmaceuticals Corporation

Hersh Patel: Employee of Novartis Pharmaceuticals Corporation

Neetu Agashivala: Employee of Novartis Pharmaceuticals Corporation

Peter K. Kaiser: Consultant for Novartis, Allergan, Bayer, Regeneron, and Kanghong

Background

- Phase III trials have shown that brolucizumab-dbll is an effective treatment option in exudative (wet) AMD, with the potential to extend injection intervals, and that the majority of patients experience benefit without severe adverse events
- Brolucizumab was approved by the FDA in October 2019 for the treatment of wet AMD
- Currently, limited data exist regarding real-world characteristics and outcomes of patients with wet AMD who were treated with brolucizumab

AMD, age-related macular degeneration; FDA, Food and Drug Administration; IRIS, Intelligent Research in Sight.

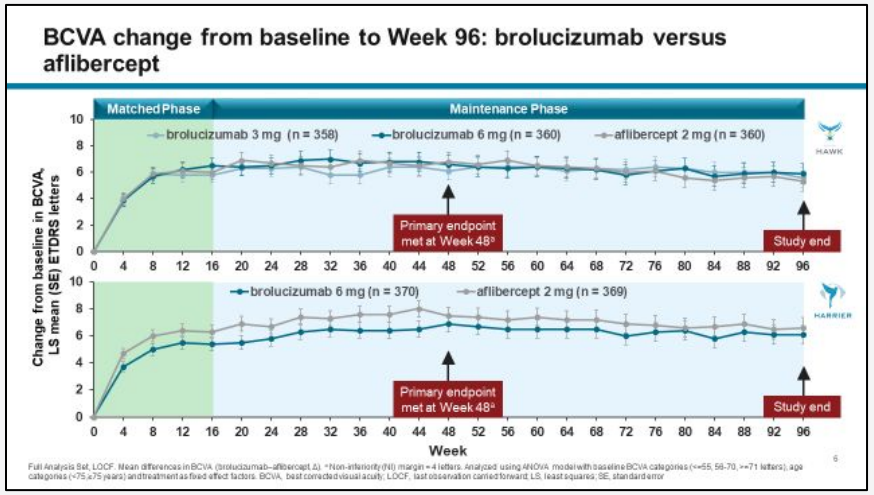
Objectives

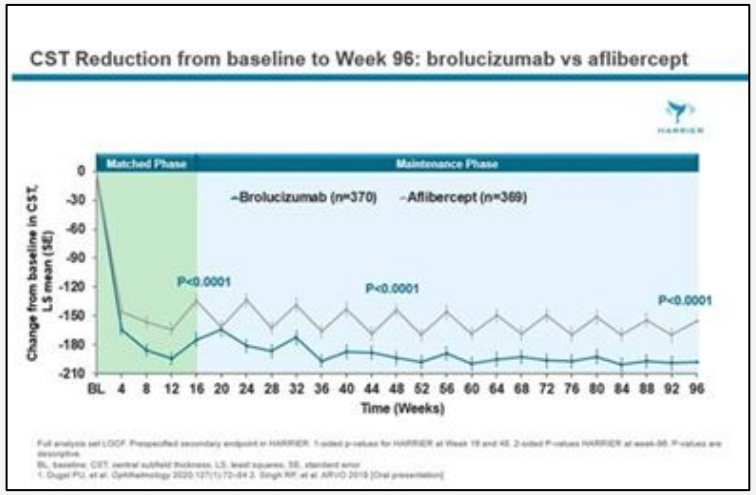
- The purpose of this analysis was to assess, using the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) (US data source), early safety of brolucizumab in patients with wet AMD
  - **Safety: Rate** and **risk stratification** of all forms of intraocular inflammation (including retinal vasculitis) and/or retinal vascular occlusion

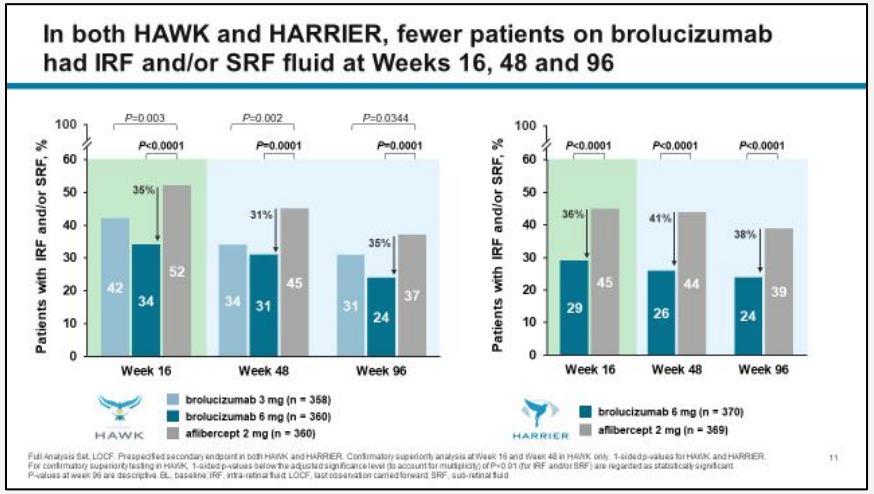
AMD, age-related macular degeneration; FDA, Food and Drug Administration; IRIS, Intelligent Research in Sight.

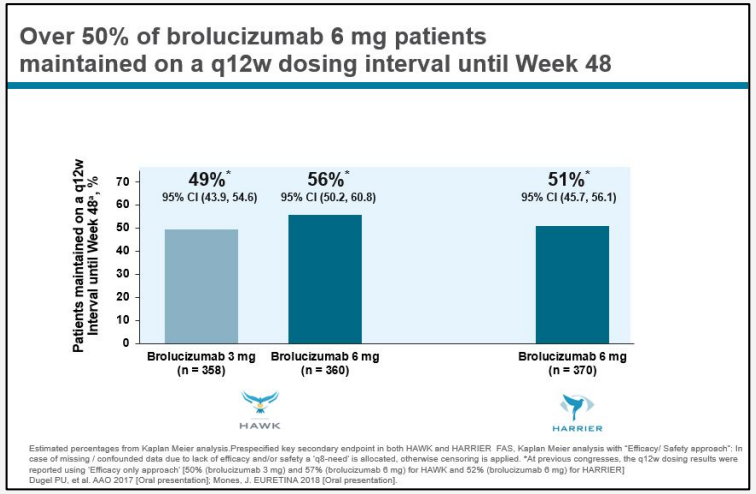
HAWK and HARRIER: Efficacy[1,2]

The Phase III HAWK & HARRIER trials demonstrated that brolucizumab 6 mg provides robust visual gains and favorable anatomical outcomes with over 50% of patients on a q12w dosing interval after the initial loading dose until Week 48*









BCVA, best corrected visual acuity; CST, central subfield thickness; IRF, intraretinal fluid; q12w, every 12 weeks; SRF, subretinal fluid.
*BCVA outcomes were lower in patients with a q8w need; the primary endpoint was at Week 48, with treatment and follow-up until Week 96.

1. Dugel PU, et al. Ophthalmology 2020;127:72-84; 2. Dugel PU, et al. Ophthalmology 2020 doi: 10.1016/j.ophtha.2020.06.028. [Epub ahead of print];

HAWK and HARRIER: Ocular Safety Profile[1,2]

Data from Phase III clinical trials:	HAWK			HARRIER	
	Brolucizumab 3 mg (n = 358)	Brolucizumab 6 mg (n = 360)	Aflibercept 2 mg (n = 360)	Brolucizumab 6 mg (n = 370)	Aflibercept 2 mg (n = 369)
Patients with ≥1 ocular AE, n (%)*	218 (60.9)	220 (61.1)	201 (55.8)	174 (47.0)	176 (47.7)
Patients with ≥1 ocular serious AE, n (%)*	7 (2.0)	12 (3.3)	5 (1.4)	13 (3.5)	6 (1.6)
Ocular AEs of potential relevance to intravitreal anti-VEGF in HAWK and HARRIER#					
Intraocular inflammation, n (%)	17 (4.7)	21 (5.8)	2 (0.6)	11 (3.0)	4 (1.1)
Retinal artery occlusion,† n (%)	4 (1.1)	4 (1.1)	0 (0.0)	2 (0.5)	1 (0.3)
Endophthalmitis, n (%)	4 (1.1)	4 (1.1)	0 (0.0)	1 (0.3)	1 (0.3)
Visual outcomes					
Patients with ≥15 letter loss from baseline at Week 96,§ %	8.6%	8.1%	7.4%	7.1%	7.5%
Patients with ≥30 letter loss from baseline at Week 96, %	2.6%	2.0%	3.0%	2.3%	3.3%

AE, adverse event; Afl, aflibercept; Bro, brolucizumab.
*AE with a start date on or after the date of first study treatment administration were counted. A patient with multiple occurrences of an AE for a preferred term or system organ class was counted only once in each specific category. #Selected for clinician interest. A sample of these cases have been reviewed by the Safety Review Committee. †Includes the preferred terms retinal artery embolism, retinal artery thrombosis and retinal artery occlusion. §Full Analysis Set, last observation carried forward.

1. Dugel PU, et al. Ophthalmology 2020;127:72-84; 2. Dugel PU, et al. Ophthalmology 2020 doi: 10.1016/j.ophtha.2020.06.028. [Epub ahead of print]; 3. Beovu [US prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; Oct 2019. 4. Beovu [summary of product characteristics], Basel, Switzerland, Novartis Pharma AG. Sept 2020. 5. Brolucizumab.info.com. Medical Dictionary for Regulatory Activities Version 20.1 has been used for the reporting of adverse events. Safety Analysis Set, 96-week data.

Post-Approval: Ocular Safety Profile

Label updates have been approved by several health authorities, including the FDA and the EU: “retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of brolucizumab”[1,2]

Novartis initiated its own internal review of these post-marketing safety case reports, including the establishment of an external Safety Review Committee (SRC) to provide an independent, unmasked post-hoc review of these cases

The SRC and Novartis assessment confirmed a safety signal of rare adverse events termed as “retinal vasculitis” and/or “retinal vascular occlusion” that may result in severe vision loss. Typically, these events occurred in the presence of intraocular inflammation (IOI)

Based on an unmasked post-hoc review, the SRC reported[3]:

- Overall incidence of IOIs of any form of **4.6% (50/1088)**
  - Overall incidence of signs of retinal vasculitis of **3.3% (36/1088)**
  - Overall incidence of concomitant signs of RV and RO of **2.1% (23/1088)**
- Overall incidence of IOI of any form associated with losing 15 or more letters at the last visit / end of the study was 0.7% (8/1088)

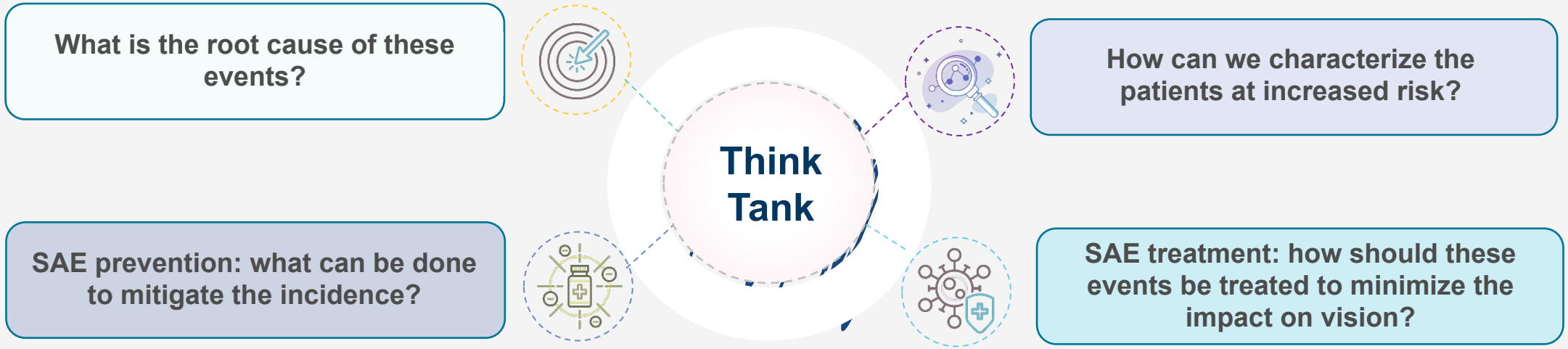
If active intraocular inflammation is present, you must not perform an intraocular injection with brolucizumab and should treat the intraocular inflammation according to medical practice[4]

IOI, intraocular inflammation; SRC, Safety Review Committee; RV, retinal vasculitis; RO, retinal vascular occlusion.

1. Beovu [US prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; Oct 2019. 2. Beovu [summary of product characteristics], Basel, Switzerland, Novartis Pharma AG. Sept 2020. 3. Member Update: Novartis-Appointed Safety Review Committee Reports Initial Brolucizumab Findings. American Society of Retina Specialists. June 4, 2020. 4. Beovu (brolucizumab) Global Safety Information for Healthcare Professionals. https://www.brolucizumab.info/. Accessed October 16, 2020.

Brolucizumab Coalition

- The Coalition, a fully dedicated multi-disciplinary internal team, has been established to collaborate with top global experts to investigate four key questions regarding adverse events associated with brolucizumab:



- A **crowdsourcing initiative** has just been launched to incorporate broad perspectives from external scientific and entrepreneurial communities into Coalition activities, with an emphasis on injecting fresh thoughts and ideas

Current Study Design

Retrospective analysis of real-world patients who received brolucizumab for wet AMD

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Electronic Health Records

600,000+ Patients with wet AMD

12,000+ Patients on Brolucizumab

- Includes **VA**
- Ability to search for **free text**
- No **holistic view** of patients (incomplete data on systemic comorbidities and medications)
- **Events** based on ICD codes: causality link of events with brolucizumab injection can not be confirmed

Selection Criteria

Patients initiating **brolucizumab** between **10/08/2019** and **06/05/2020** (date of earliest injection = index date)

- **Wet AMD** diagnosis ≤36 months pre-index
- **≥18 years old** on index date
- **Intravitreal administration** claim on index date
- **Visual Acuity** assessment ≤365 days pre-index

Patients **excluded** included those with:

- Unknown **laterality**

Varied length of **follow-up post index date (up to 6 months)** per data availability

Limitations: No access to patient charts, Observed events based on ICD codes only, Follow-up of up to 6 months only

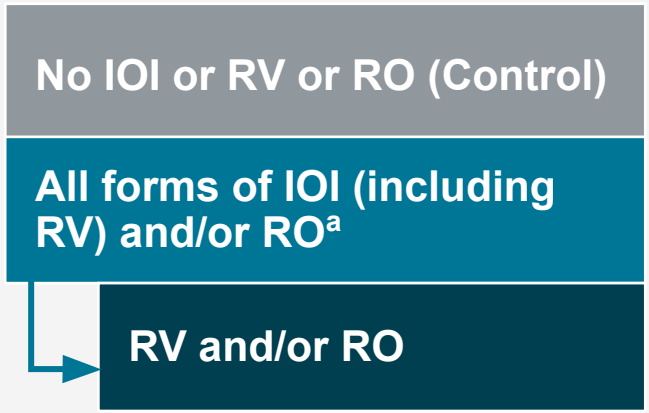
AMD, age related macular degeneration; ICD, International Classification of Diseases; VA, visual acuity.

Baseline Patient Characteristics (Overall Cohort)

Characteristics	Patient Eyes (N = 10,654)
Age (years), mean ± SD	80.9 ± 8.4
Female, n (%)	6,105 (57.3%)
Laterality of brolucizumab treatment at index date[a], Unilateral, n (%)	8,258 (77.5%)
Time since diagnosis of wet AMD, days, mean ± SD	760 ± 360
VA (approximate ETDRS[b]) letter score (mean ± SD)	61.8 ± 18.7
Prior treatment status, Switchers, n (%)	**9,686 (90.9%)**
≥2 prior anti-VEGFs, n (%)[b]	3,667 (37.9%)
Immediate prior anti-VEGF, n (%)	
Aflibercept	**7,160 (73.9%)**
Bevacizumab	1,000 (10.3%)
Ranibizumab	1,478 (15.3%)
Duration of follow-up, days, median	97

AMD, age related macular degeneration; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation; VA, visual acuity; VEGF, vascular endothelial growth factor.
[a.] Date of earliest injection = index date; [b] Approximation based on Snellen measurements; [c.] Sample size of switch patients used as denominator.

Overall Incidence Rates of All Forms of Intraocular Inflammation (Including Retinal Vasculitis) and/or Retinal Vascular Occlusion[a] Up to 6 Months After the First Brolucizumab Injection

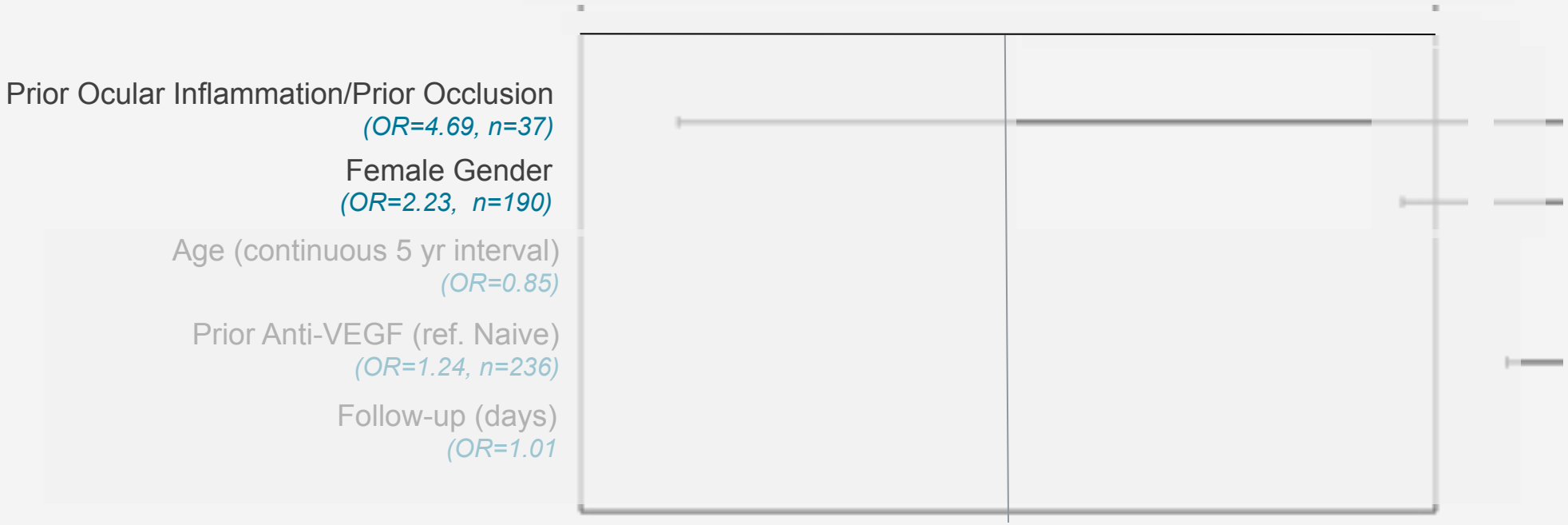


Events by Patient Eyes Treated with Brolucizumab	N = 10,654
No IOI or RV or RO (Control)	10,399 (97.61%)
All forms of IOI (including RV) and/or RO[a]	255 (2.39%)
RV and/or RO	59 (0.54%)

Observed events were identified using ICD diagnostic codes as real-world practice and not prospectively collected

IOI, Intraocular Inflammation; RO, Retinal vascular occlusion inclusive of RVO and RAO; RV, Retinal Vasculitis; RVO, Retinal vein occlusion; RAO, Retinal arterial occlusion.
[a]Represents IOI or Endophthalmitis or Panuveitis or RV or RO. Does not include infectious type of IOI or Endophthalmitis
In patient Eyes with up to 6 months of follow-up

Identification of Potential Risk Factors at Baseline on Incidence of an IOI and/or RO[a] Based on a Multivariate Model



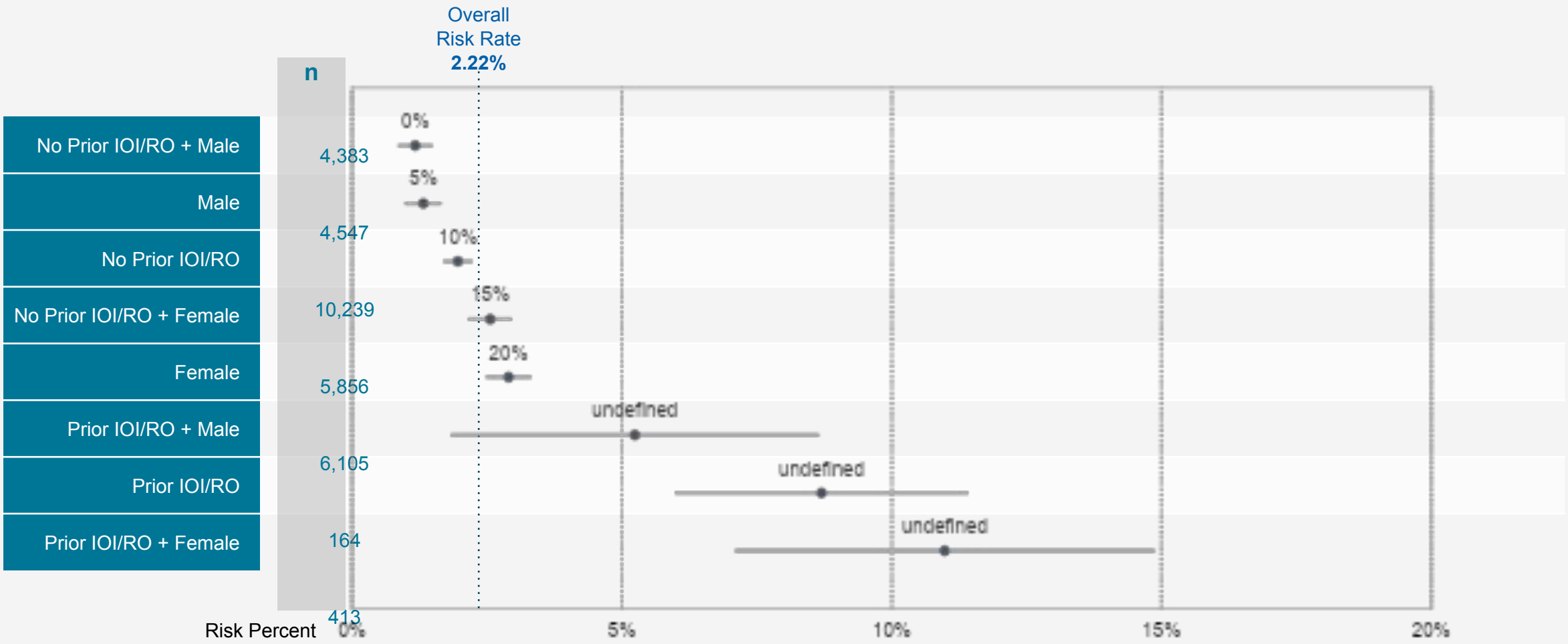
Adjusted risk of any IOI and/or RO was 2.22%
Similar results were seen in subgroup of RV and/or RO (adjusted risk = 0.46%)

Prior Ocular Inflammation/Occlusion = History of IOI or RV or RO or panuveitis or endophthalmitis in the past 12 months; Follow up days variable was used to adjust for varying length of follow up; Graphs are plotted to logarithmic scale; OR >1 indicates increased risk of AE of interest and OR<1 indicates a decreased risk of AE of interest

[a]Represents IOI or Endophthalmitis or Panuveitis or RV or RO; n=255, 2.39%
AE, adverse event; IOI, intraocular inflammation; OR, odds ratio; RO, retinal vascular occlusion inclusive of retinal vein occlusion and retinal arterial occlusion; RV, retinal vasculitis.
In patient eyes with up to 6 months of follow-up

Observed Risk Rate of IOI and/or RO[a] on Identified Risk Factors at Baseline

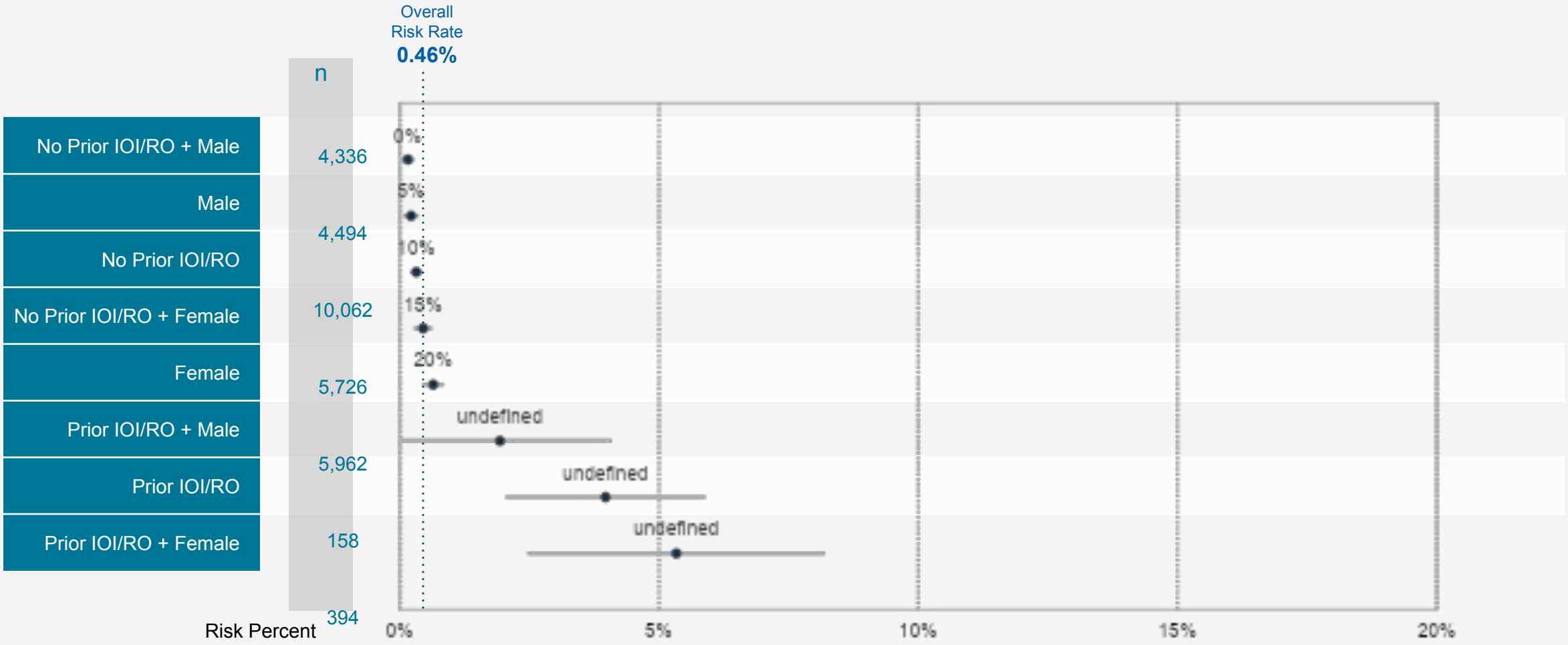
Observed Risk Rate Increased in Patients With Prior IOI and/or Prior RO



IOI, Intraocular Inflammation; RO, Retinal vascular occlusion inclusive of RVO and RAO; RV, Retinal Vasculitis.
[a.]Represents IOI or Endophthalmitis or Panuveitis or RV or RO;
Based on 12 month history data; In patients with up to 6 months of follow-up
Estimates for risk (95% CIs) were adjusted for age, prior anti-VEGF treatment and length of follow-up

Observed Risk Rate of RV and/or RO on Identified Risk Factors at Baseline

Observed Risk Rate Increased in Patients With Prior IOI and/or Prior RO



IOI, Intraocular Inflammation; RO, Retinal vascular occlusion inclusive of RVO and RAO; RV, Retinal Vasculitis.
Based on 12 month history data; In patient eyes with up to 6 months of follow-up
Estimates for risk (95% CIs) were adjusted for age, prior anti-VEGF treatment and length of follow up

Conclusions

- Phase III trials have shown that brolucizumab is an effective treatment option in wet AMD, with the potential to extend injection intervals; the majority of patients experience benefit without severe adverse events
- In the IRIS Registry, the majority of patients with wet AMD who initiated brolucizumab switched from a prior anti-VEGF agent (>70% aflibercept), suggesting unmet needs continue to exist for wet AMD patients on current anti-VEGF therapies
- Overall incidence among patient eyes post brolucizumab treatment in IRIS Registry:
  - All forms of IOI (including RV) and/or RO was observed at 2.39%
  - RV and/or RO was observed at 0.54%
- Intraocular inflammation and/or occlusion in the 12 months prior to the first brolucizumab injection was the highest observed risk for an event of IOI and/or RO or an event of RV and/or RO among patient eyes in the 6 months post first brolucizumab treatment
- Further analyses of the IRIS Registry are ongoing. Based on the limitations, future studies using additional data sources will also be considered to compare the findings of this study

AMD, age-related macular degeneration; FDA, Food and Drug Administration; IRIS, Intelligent Research in Sight.