Absence of Safety Signal for Occlusive Retinal Vasculitis with Intravitreal Aflibercept Injection

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Disclosures

- Dr. Do is a consultant for Regeneron Pharmaceuticals, Inc., Genentech, Kodiak Sciences, Novartis, Santen, and Clearside, and has received research funding from Regeneron Pharmaceuticals, Inc. and Genentech
- De-identified electronic medical records of patients were used for this analysis. On this basis, IRB approval was not obtained
- This analysis was conducted by Regeneron Pharmaceuticals, Inc. (Tarrytown, New York, USA) and Bayer AG Pharmaceuticals (Berlin, Germany). The sponsors participated in the design and conduct of the study, analysis of the data, and preparation of this presentation

Background

- Majority of retinal artery occlusion (RAO) events are thromboembolic in origin and prevalent in patients with retinal vascular diseases and/or cardiovascular risk factors
- Co-occurrence of RAO or retinal vasculitis with intraocular inflammation (IOI), however, represents a distinct clinical entity
- Events of occlusive retinal vasculitis (ORV) and RAO in the context of IOI represent severe forms of inflammatory response and are considered sight-threatening conditions
- Information recently communicated to the retina community regarding the confirmed safety signal of retinal vasculitis and/or retinal vascular occlusion with brolucizumab resulting in substantial vision loss is of pertinent interest

Rate of Adverse Events of Interest With Brolucizumab in HAWK & HARRIER and During Post-Marketing Experience

Rates Over 2 Years in HAWK & HARRIER as Reported by the Safety Review Committee*

	Brolucizumab** (N = 1088)	Aflibercept (N = 729)
IOI, n (%)	50 (4.6%)	8 (1.1%)
IOI with retinal vasculitis, n (%)	36 (3.3%)	1 (0.1%)
IOI and retinal vasculitis with retinal vascular occlusion, n (%)	23 (2.1%)	1 (0.1%)

*https://www.asrs.org/members/login/4013?returnUrl=%2Fclinical%2Fclinical-updates%2F4013%2FMember-Update-Novartis-Appointed-Safety-Review-Committee-Reports-Initial-Broluci

**Brolucizumab 3 mg and 6 mg groups combined

Post-Marketing Rates (per 10,000 injections)*

	Brolucizumab
RAO, vasculitis, or severe vision loss	8.75
RAO (RAO, eye stroke, vascular occlusion, boxcarring gaps in vessels, occlusive arteriolitis)	1.96
Vasculitis (vasculitis, occlusive [retinal] vasculitis, retinal occlusive vasculitis)	3.21
Severe vision loss (endophthalmitis, uveitis, cataract, necrotizing retinitis, blindness, counting fingers, hand movement, visual acuity 20/100 or less)	3.92

*As of February 28, 2020; Accessed at https://www.brolucizumab.info/dist/files/beovu-postmarketing-adverse-events-feb-mar-2020.pdf on April 8, 2020

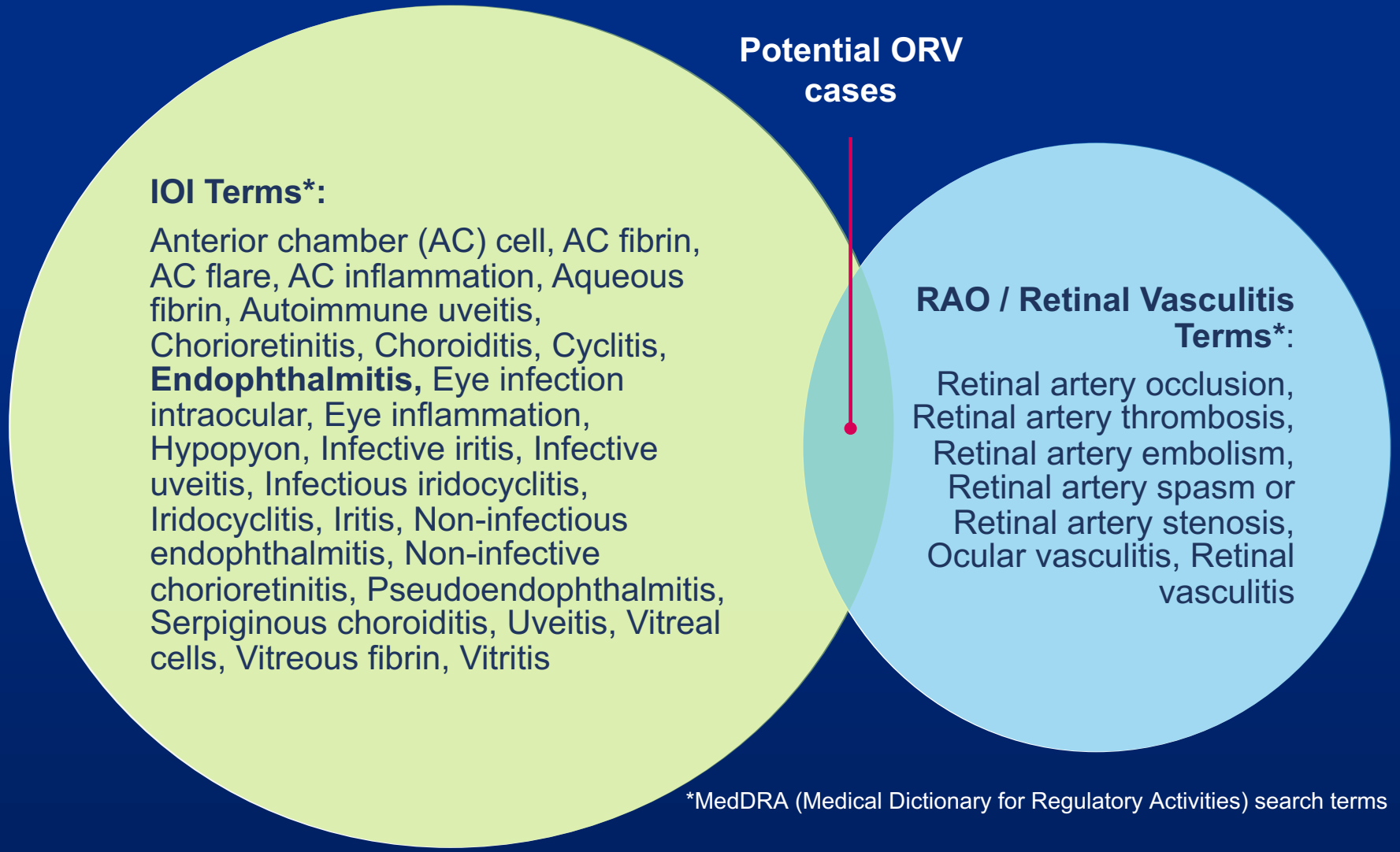
Estimated number of vials used post marketing was 56,000 for brolucizumab

Objective

- To identify reported events similar to reports of ORV with brolucizumab use including RAO or retinal vasculitis in the presence of IOI in the following aflibercept databases:
  - Phase 3 clinical trials database (2007-2019)
  - Post-marketing Global Safety Database (2011-2020)
- To evaluate post-marketing rates of the following events for aflibercept similar to event rates publicly disclosed for brolucizumab
  - RAO
  - Vasculitis
  - Severe vision loss

Search Methodology For ORV

- There is no single MedDRA Preferred Term for “ORV” as described in the ASRS update*
- To ascertain events similar in nature, the search methodology shown here was employed to Identify events based on concurrent IOI and RAO / retinal vasculitis terms
- Post-marketing experience cut-off date was March 31, 2020

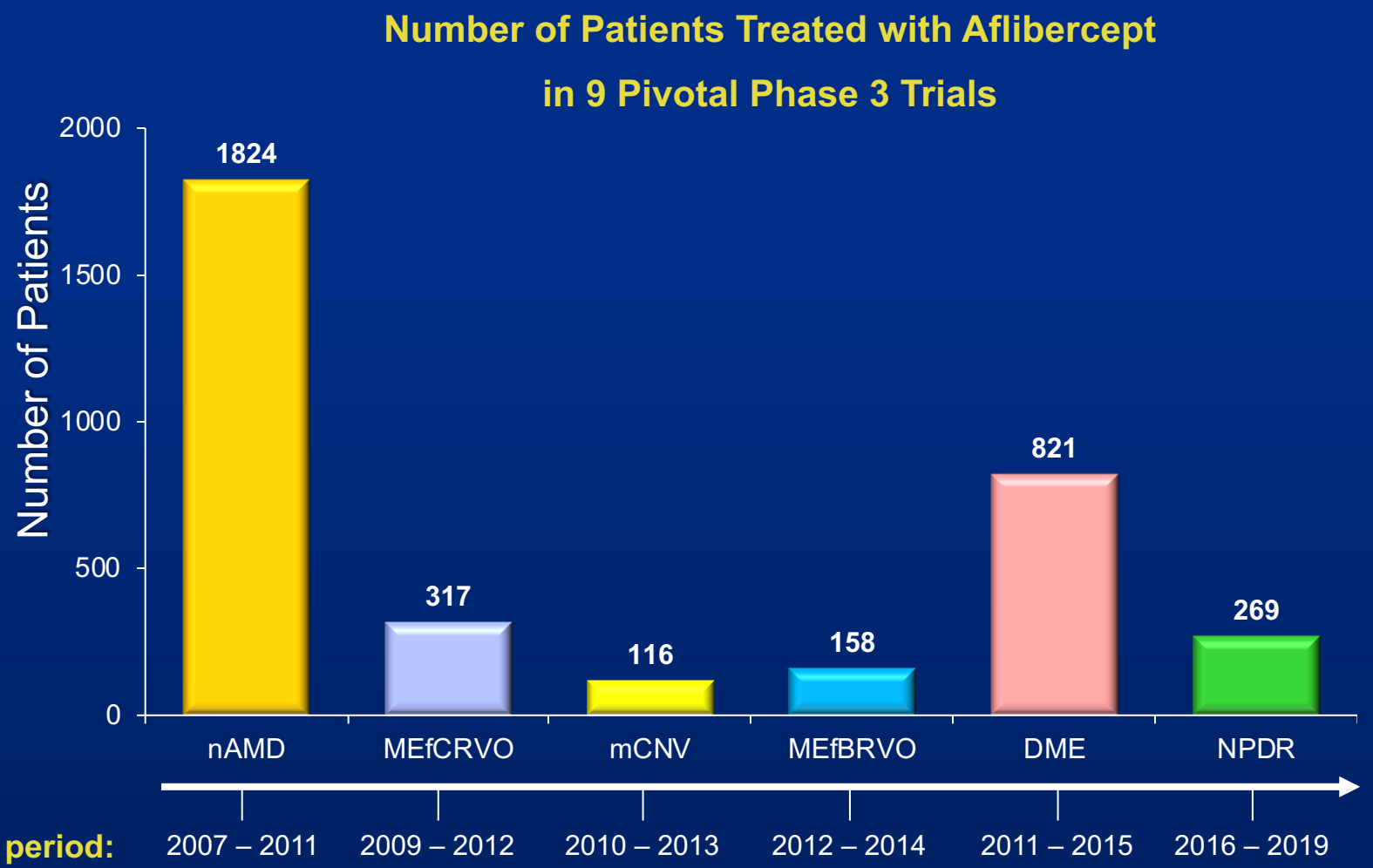


*MedDRA (Medical Dictionary for Regulatory Activities) search terms

*https://www.asrs.org/members/login/960?returnUrl=%2Fclinical%2Fclinical-updates%2F960%2Fbeovu-update-for-asrs-members

Review of Aflibercept Phase 3 Clinical Trial Database

- There were no reports of concurrent IOI with RAO or ORV in an aflibercept-treated eye across nine pivotal phase 3 clinical trials of aflibercept including >3000 patients



Review of Aflibercept Post-Marketing Global Safety Database

- Aflibercept Global Safety Database represents experience with over 34 million doses sold worldwide since 2011

	Rate*
IOI concurrent with RAO	<1 / 8,500,000 injections (4 cases, all associated with endophthalmitis)
IOI concurrent with retinal vasculitis	<1 / 17,000,000 injections (2 cases, all associated with endophthalmitis)

*Cut-off date of March 31, 2020

- As of March 31, 2020, IOI with RAO or retinal vasculitis has been reported at a rate of approximately 1 out of every 6 million injections (0.00002%), and all such cases were associated with endophthalmitis

Summary of Cases of IOI Concurrent with RAO

Case	Indication	Age (years)	Gender	Duration on aflibercept	Summary
1	nAMD	86	Male	3 years	Endophthalmitis and central RAO one day after last injection
2	nAMD	70	Male	6 years	Endophthalmitis and central RAO, with unclear timing relative to one another, following aflibercept & expired steroid injections
3	DME	77	Female	11 doses	Culture negative endophthalmitis 5 days after last injection with possibly concurrent RAO
4	nAMD	86	Female	6 years	Endophthalmitis with central RAO 3 days after last injection

As of cut-off date of March 31, 2020

Summary of Cases of IOI Concurrent With Retinal Vasculitis

Case	Indication	Age (years)	Gender	Duration on aflibercept	Summary
1	Unspecified	Unknown	Female	2 doses	Culture positive staph endophthalmitis and retinal vasculitis without occlusion 3 days after the second injection
2	nAMD	88	Male	1 dose	Culture-negative endophthalmitis with hemorrhagic occlusive vasculitis 2 days after the first injection

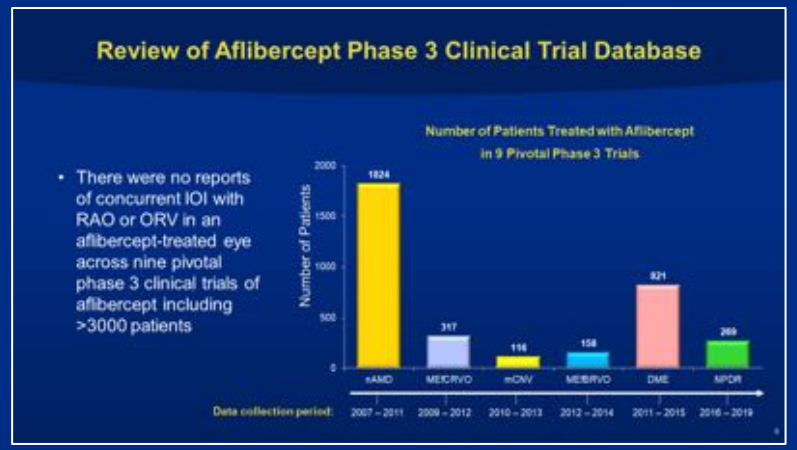
As of cut-off date of March 31, 2020

Post-Marketing Rates of Adverse Events of Interest With Aflibercept

	Rate (per 10,000 injections)
	Aflibercept As of March 16, 2020
RAO, vasculitis, or severe vision loss	0.9
RAO (RAO, retinal artery stenosis, retinal artery spasm, retinal artery thrombosis, retinal artery embolism, retinal vascular occlusion, vascular occlusion)*	0.03
Vasculitis (retinal vasculitis, ocular vasculitis, vasculitis, urticarial vasculitis)*	0.002
Severe vision loss (blindness; blindness: traumatic, unilateral, transient, congenital/cortical; VA reduced, VA reduced transient)*	0.9

*MedDRA terms
Estimated number of vials used post marketing was approximately 33,000,000 for aflibercept

Conclusions



- A review of the aflibercept clinical and post-marketing Global Safety Databases indicates that the new safety event associated with brolucizumab is not a safety concern with aflibercept
  - Cases with aflibercept were qualitatively different than those described with brolucizumab
- The new safety event seen with brolucizumab has not previously been described for any other anti-VEGF agent
- These findings provide evidence that IOI concurrent with RAO and/or ORV is not a general anti-VEGF class effect