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Taking Stock of Current and Emerging

Anti-VEGF Therapy Dosing Regimens for nAMD

Provided by
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This activity is supported by an independent medical education grant from Regeneron Pharmaceuticals, Inc.

Age-Related Macular Degeneration (AMD): A Growing Problem

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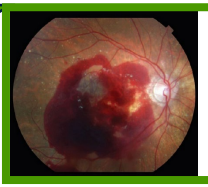
Most common cause of severe vision loss in developed countries and 3rd common cause of legal blindness worldwide

288 Million People forecast to be affected by AMD worldwide by 2040

>25% Proportion of patients with advanced AMD in one eye who will develop advanced AMD in the other eye within 10 years



Neovascular AMD (nAMD)

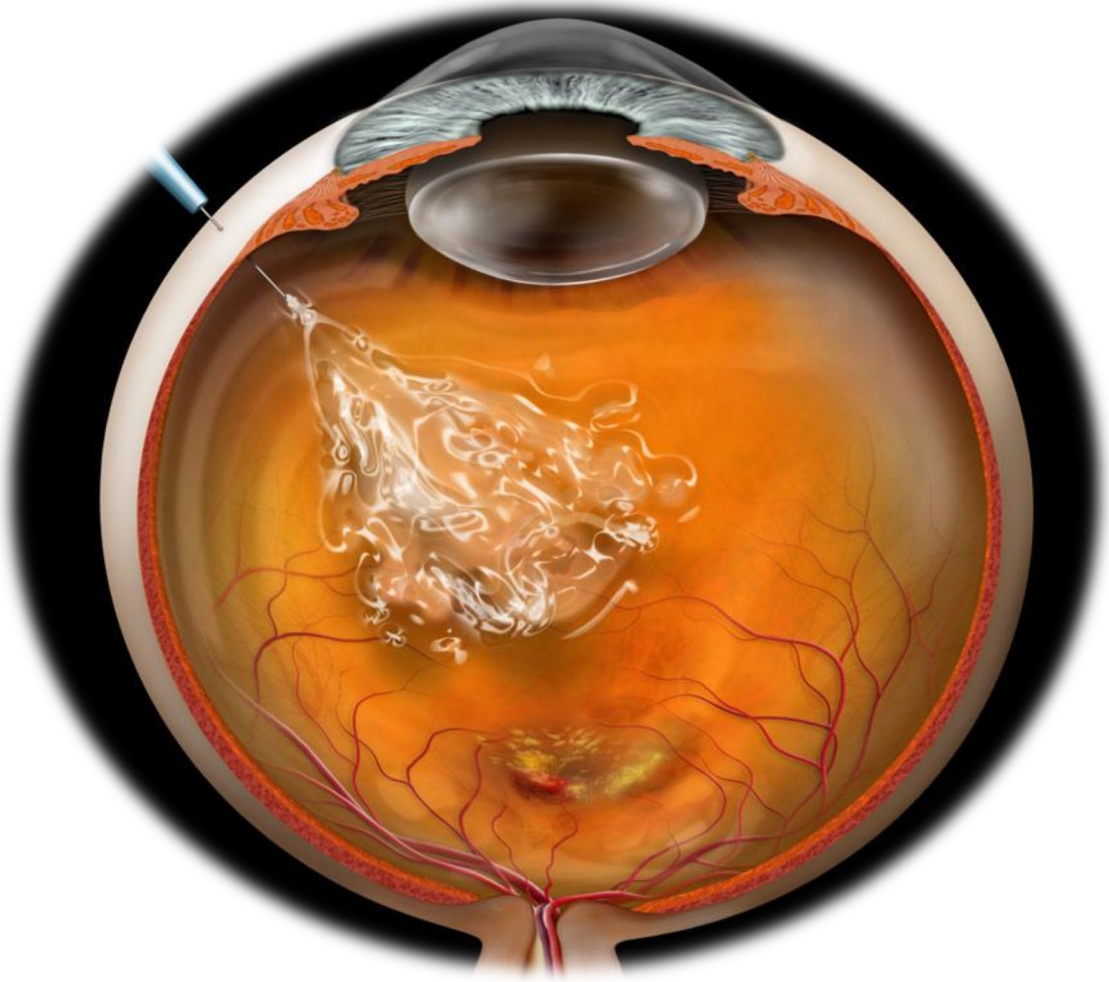
Accounts for 10–15% of AMD cases

Characterized by:
- Choroidal neovascularization (CNV)
- Fluid leakage
- Central vision loss

Dependent on angiogenesis mediated by the vascular endothelial growth factor (VEGF)

Mathenge W. *Community Eye Health*. 2014;27:49–50. Resnikoff S, et al. *Bull World Health Organ*. 2004;82:844–851. Khanna S, et al. *BMJ Open Ophthalmol.* 2019;4:e000398. Wong WL, et al. *Lancet Global Health.* 2014;2:e106–e116. Yonekawa Y, et al. *J Clin Med.* 2015;4:343-359. Rastoin O, et al. *Int J Mol Sci*. 2020;21:4627.

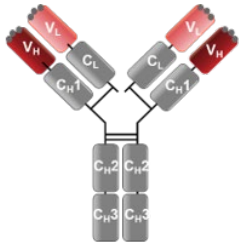
IVT Anti-VEGF Therapy for nAMD



- Intravitreal (IVT) anti-VEGF therapy is the current standard of care for patients with nAMD
- Pegaptanib was the first anti-VEGF therapy approved for the treatment of nAMD
- However, pegaptanib largely became obsolete since its approval in 2004, as more effective agents were studied/approved

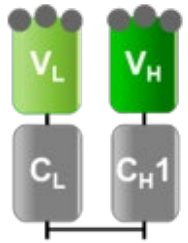
Anti-VEGF eye injection interactive - Stock eye images (jirehdesign.com) Kaiser SM, et al. *J Experiment Pharmacol.* 2021;13:905-912.

Conventional IVT Anti-VEGF Therapies for nAMD: Bevacizumab & Ranibizumab



Bevacizumab

- Full-length, humanized, recombinant monoclonal antibody against all isoforms of VEGFA
- Not FDA approved: off-label use began in 2005
- **Dosing:** 1.25 mg Q4W initially with PRN/T+E/fixed dosing thereafter



Ranibizumab

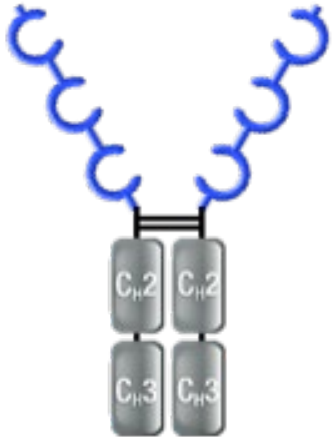
- Humanized, monoclonal antibody fragment that targets all isoforms of VEGFA
- FDA approved in 2006; improved vision compared to sham injection and photodynamic therapy in the MARINA and ANCHOR studies, respectively
- **Dosing:** 0.5 mg, Q4W initially with PRN/T+E/fixed dosing thereafter

Data has shown ranibizumab and bevacizumab produce similar gains in visual acuity

PRN: Pro Re Nata; T+E: treat-and-extend

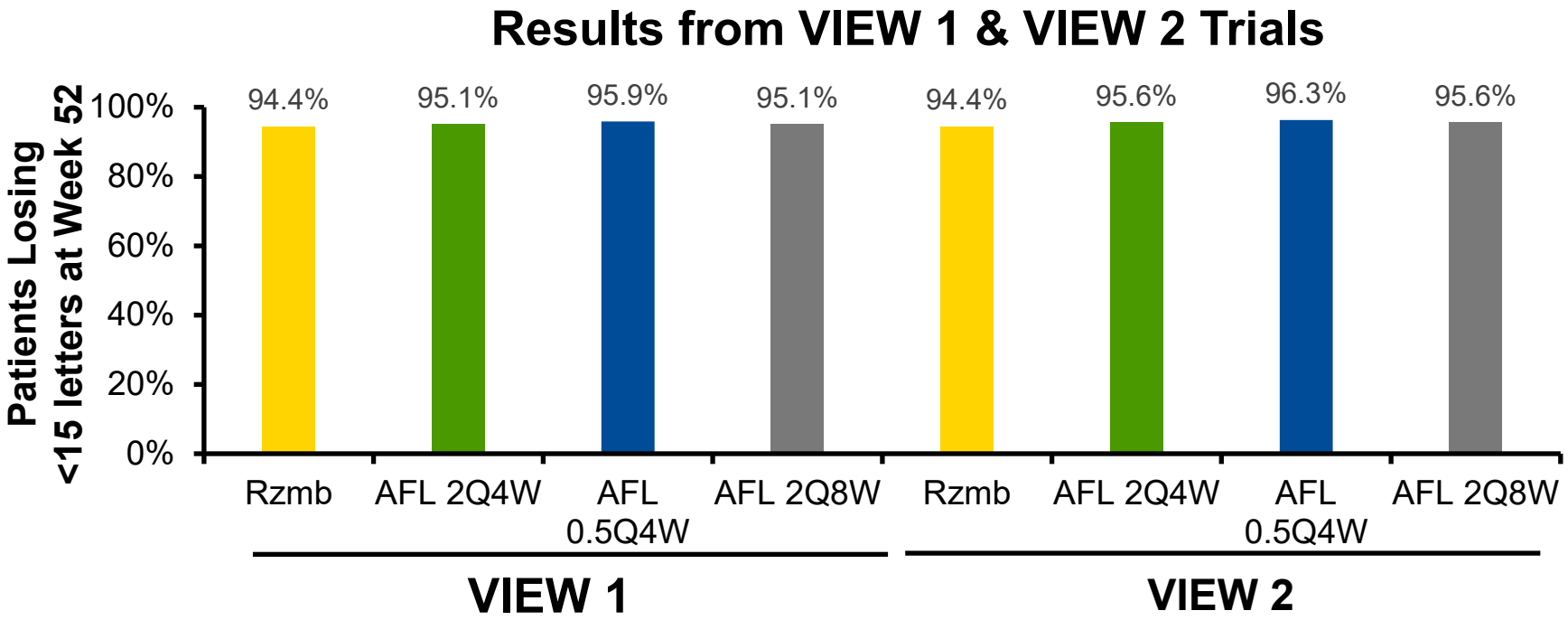
Kaiser SM, et al. *J Experiment Pharmacol.* 2021;13:905-912. Rosenfeld PJ, et al. *N Engl J Med*. 2006;355:1419-1431. Brown DM, et al. *N Engl J Med.* 2006;355:1432-1444. Martin DF, et al. *N Engl J Med.* 2011;364:1897-908. Martin DF, et al. *Ophthalmology* 2012;119:1388-1398. Martin DF, et al. *Ophthalmology.* 2020;127:S135-S145.

Conventional IVT Anti-VEGF Therapies for nAMD: Aflibercept



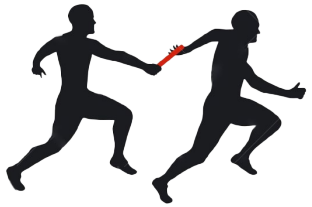
Aflibercept

- Recombinant fusion protein that targets VEGFA, VEGFB, & PGF
- FDA approved in 2011
- 2 mg Q4W first 3 doses, Q8W thereafter



- Prespecified integrated analysis of the 2 studies showed all aflibercept regimens were within 0.5 letters of the reference ranibizumab for mean change in BCVA
- All aflibercept regimens also produced similar improvements in anatomic measures
- Ocular & systemic AEs were similar across treatment groups

Kaiser SM, et al. *J Experiment Pharmacol.* 2021;13:905-912. Heier JS, et al. *Ophthalmology*. 2012;119:2537-2548.



Baton Pass: Challenge Question

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Which of the following statements about the role of IVT anti-VEGF therapies in the management of nAMD is *true*?

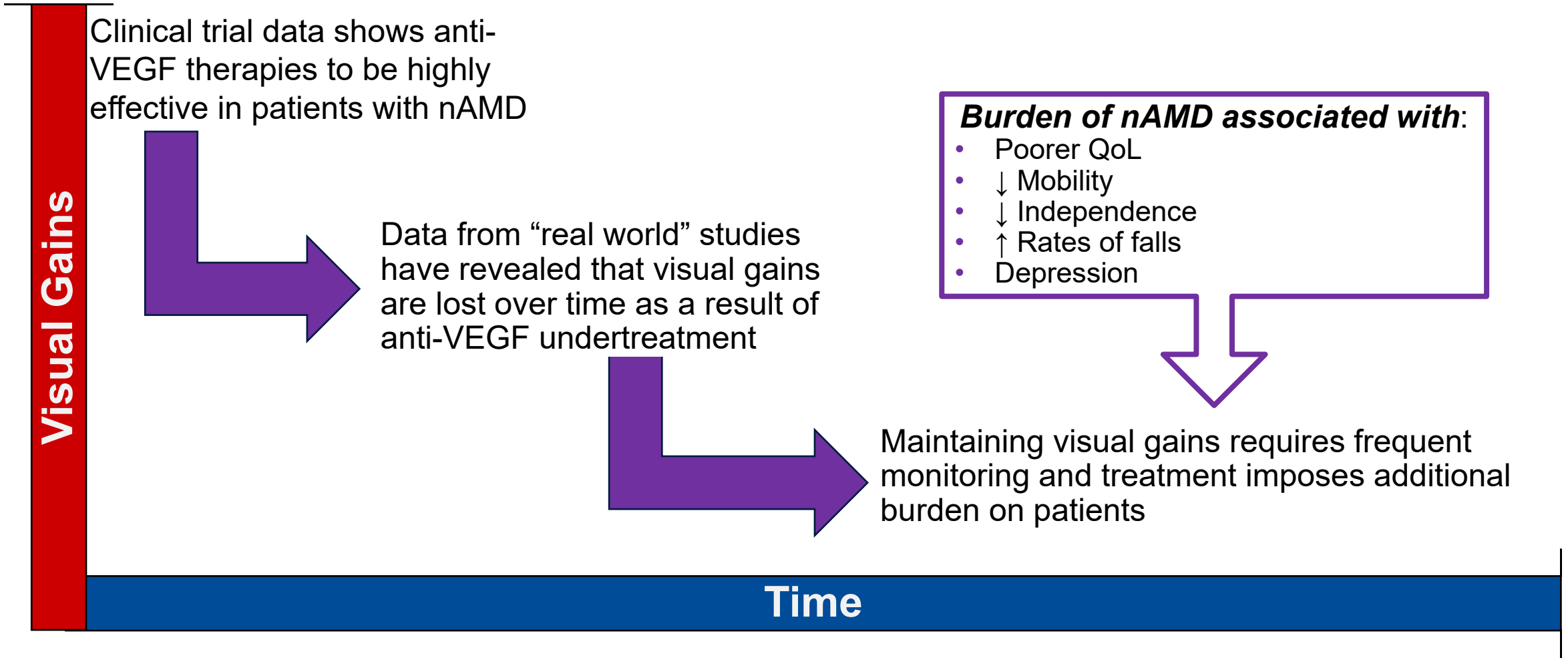
a. These therapies are typically reserved for second-line in patients who do not respond to photodynamic therapy

b. All of these therapies have limited efficacy because they only target a single isoform of VEGFA

c. Despite the approval and/or off-label use of other agents, pegaptinib has remained the standard of care since its approval in 2004

d. Available data has shown aflibercept, bevacizumab, and ranibizumab produce similar effects with respect to visual gains

Anti-VEGF Therapy Contributes to the Burden of nAMD



Guymer RH, Campbell TG. *Lancet.* 2023;401:1459-79. Chakravarthy U, et al. *Eye (London).* 2022;36:2232-33. Ciulla T, et al. *Ophthalmol Retina.* 2018;2:645:645-53.

Initial Steps Towards Alleviating the Burden of Anti-VEGF Therapy

Fewer treatments impose less burden on providers and patients, but does it translate into better outcomes?

Trials extending fixed dosing to longer intervals, and studies that tested PRN treatment regimens, have not been successful

T&E
Regimens

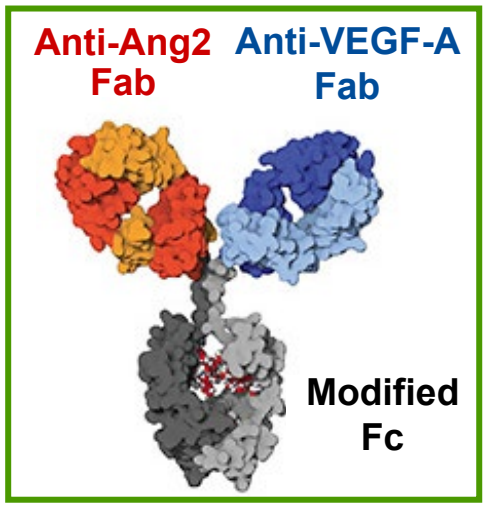
Meta-analysis: treat & extend regimen are as efficacious as fixed interval (Q4W or Q8W), with fewer visits & injections, but relies on clinicians' ability to identify ongoing disease activity that is likely to be responsive to treatment

Guymer RH, Campbell TG. *Lancet.* 2023;401:1459-1479. Chakravarthy U, et al. *Eye (London).* 2022;36:2232-2233. Fallico M, et al. *Eur J Ophthalmol.* 2021; 31: 2496–504.

Approved Newer Anti-VEGF Agents for nAMD: Moving Towards A Lower Treatment Burden

Brolucizumab

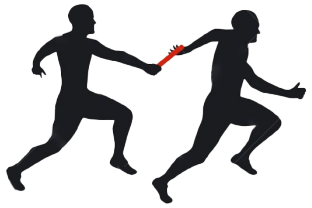
- Engineered by grafting complementary determining regions of a novel anti-VEGF-A antibody to a human single-chain variable fragment (scFv) scaffold
- FDA approved in 2019
- Dosing: 6 mg Q4W x3 then Q8W-Q12W thereafter



Faricimab

- Bispecific antibody composed of 2 heavy chains and 2 light chains
  - Arms bind to VEGF-A and angiopoietin-2 (Ang2)
- FDA approved in 2022
- 6 mg Q4W x4 then Q8W, Q12W, or Q16W thereafter

Nguyen QD, et al. *Ophthalmology*. 2020;127:963-976. Regula JT, et al. *EMBO Mol Med.* 2016;8(11):1265-1288.



Baton Pass: Challenge Question

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Which of the following statements about the burden of nAMD treatment is the most accurate?

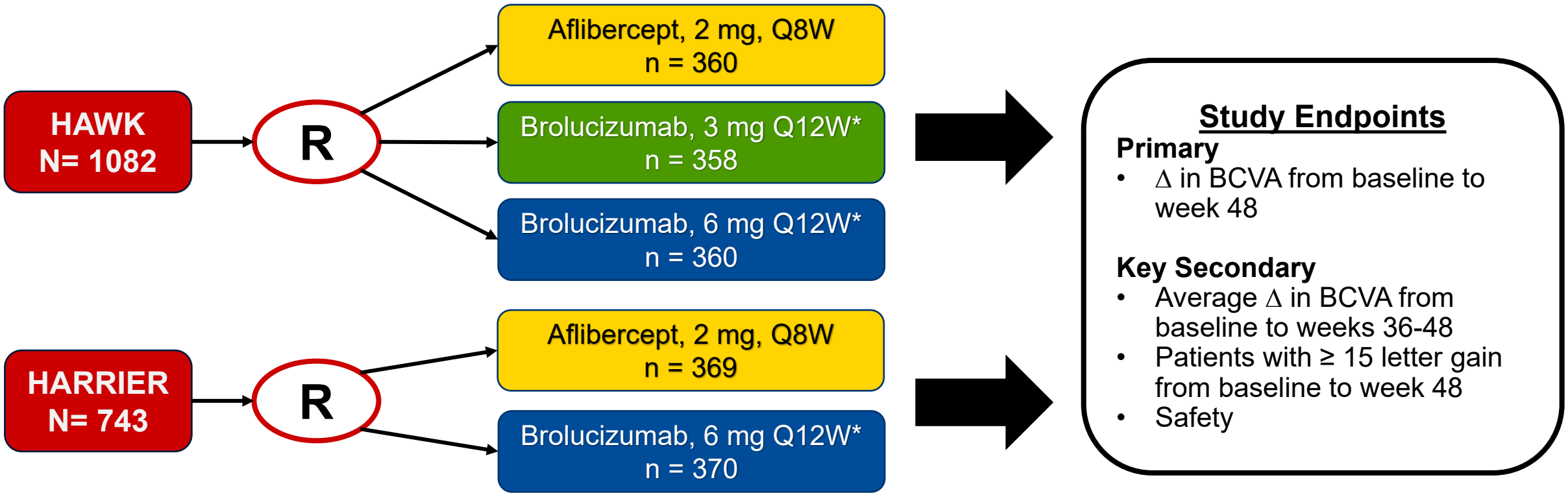
a. Pro re nata (PRN) regimens reduce the burden of treatment while maintaining visual gains in patients with nAMD

b. The burden of treatment can be alleviated by extending fixed dosing to longer intervals without compromising efficacy

c. Treat-and-extend regimens allow for fewer visits and injections at the expense of decreased efficacy

d. The general need for frequent treatment and monitoring to maintain visual gains adds to the burden of nAMD

HAWK & HARRIER: Randomized Phase 3, NI Trials of Brolucizumab for Treatment-Naïve nAMD



*Interval-adjusted to Q8W if disease activity was present
NI: non-inferiority
Dugel PU, et al. *Ophthalmology.* 2020;127:72-84.

HAWK & HARRIER: Results

Study Endpoint	HAWK			HARRIER	
	Aflibercept Q8W	Brolucizimab 3Q12W	Brolucizimab 6Q12W	Aflibercept Q8W	Brolucizimab 6Q12W
LS Mean Δ From Baseline in BCVA at Week 48	6.8	6.1	6.6	7.6	6.9
LS Mean Difference	-	-0.6 *P* <.001*	-0.2 *P* <.001*	-	-0.7 *P* <.001*
LS Mean Average Δ From Baseline in BCVA over Weeks 36-48	6.7	6.2	6.7	7.7	6.5
LS Mean Difference	-	-0.5; *P* <.001*	0.0; *P* <.001*	-	-1.2; *P* <.001*
Patients with ≥ 15 Letter Gain from Baseline to Week 48	25.4%	25.2%	33.6%	29.9%	29.3%
**1-sided test for non-inferiority at 4-letter margin*					

Dugel PU, et al. *Ophthalmology.* 2020;127:72-84.

Brolucizumab: Safety

Brolucizumab was generally well tolerated in HAWK & HARRIER with overall ocular and nonocular adverse event rates similar to those with aflibercept within each trial[1]

In the phase 3b MERLIN Trial, although visual acuity outcomes in previously treated participants with nAMD and persistent retinal fluid receiving brolucizumab 6 mg Q4W were noninferior to aflibercept 2 mg Q4W, incidences of IOI, including retinal vasculitis and retinal vascular occlusion, were higher in patients receiving brolucizumab, leading to study termination[2]

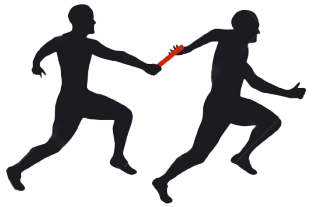
A post-hoc analysis conducted by the independent Safety Review Committee of HAWK/HARRIER found much higher rates of IOI/RV/RVO than were initially reported[3]

The results of a retrospective, real-world evidence analysis in nAMD patients suggest that patients with IOI and/or occlusion in the 12 months prior to the first brolucizumab injection had the highest observed rate of IOI and/or occlusion 6 months following their initial brolucizumab treatment[4]

The potential for ocular adverse events may preclude many healthcare providers from using brolucizumab in patients with nAMD

IOI: intraocular inflammation

1. Dugel PU, et al. *Ophthalmology.* 2020;127:72-84 2. Khanani AM, et al. *Ophthalmology.* 2022;129:974-985. 3. Fonollosa A, et al. *Arch Soc Oftalmol (Engl Ed).*2022 Jul 23;S2173-5794(22)00084-6. 4. Khanani AM, JAMA Ophthalmol. 2022;140:20-28.



Baton Pass: Challenge Question

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Which of the following statements best summarizes available data related to IVT brolucizumab for the treatment of nAMD?

a. Q8W brolucizumab is superior to Q8W aflibercept with respect to visual outcomes

b. Although noninferior to Q8W aflibercept in terms of efficacy when dosed ≤Q12W, the potential for ocular adverse events associated with brolucizumab may preclude its use in patients with nAMD

c. Q8W brolucizumab is inferior to Q4W ranibizumab with respect to anatomic outcomes

d. Although noninferior to Q4W ranibizumab in terms of efficacy when dosed ≤Q12W, the safety profile of brolucizumab is more advantageous in patients with nAMD

TENAYA & LUCERNE: Randomized Phase 3 Trials of Faricimab for Treatment-Naïve nAMD

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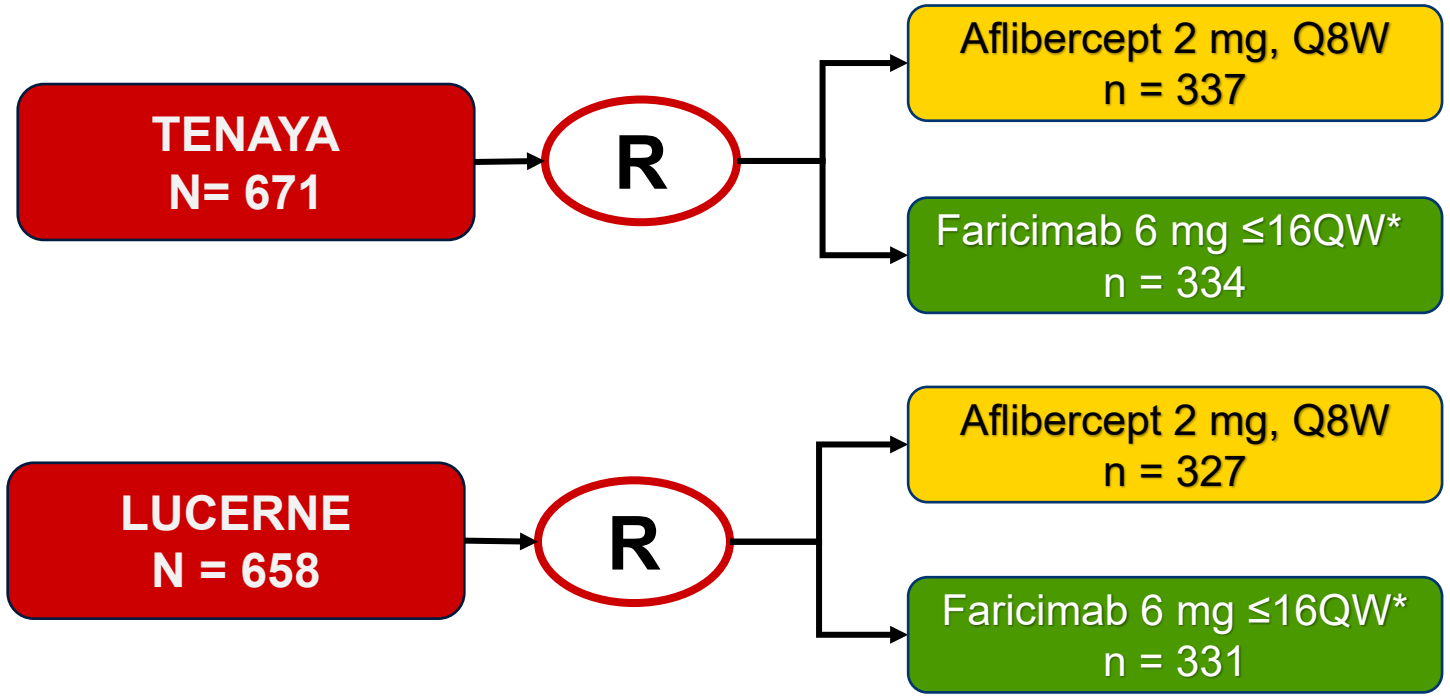
Phase 2 STAIRWAY Study showed faricimab dosing Q16W and Q12W resulted in maintenance of initial vision and anatomic improvements comparable with monthly ranibizumab at Week 52



Endpoints

Primary

- Δ in BCVA from baseline averaged over weeks 40, 44, and 48

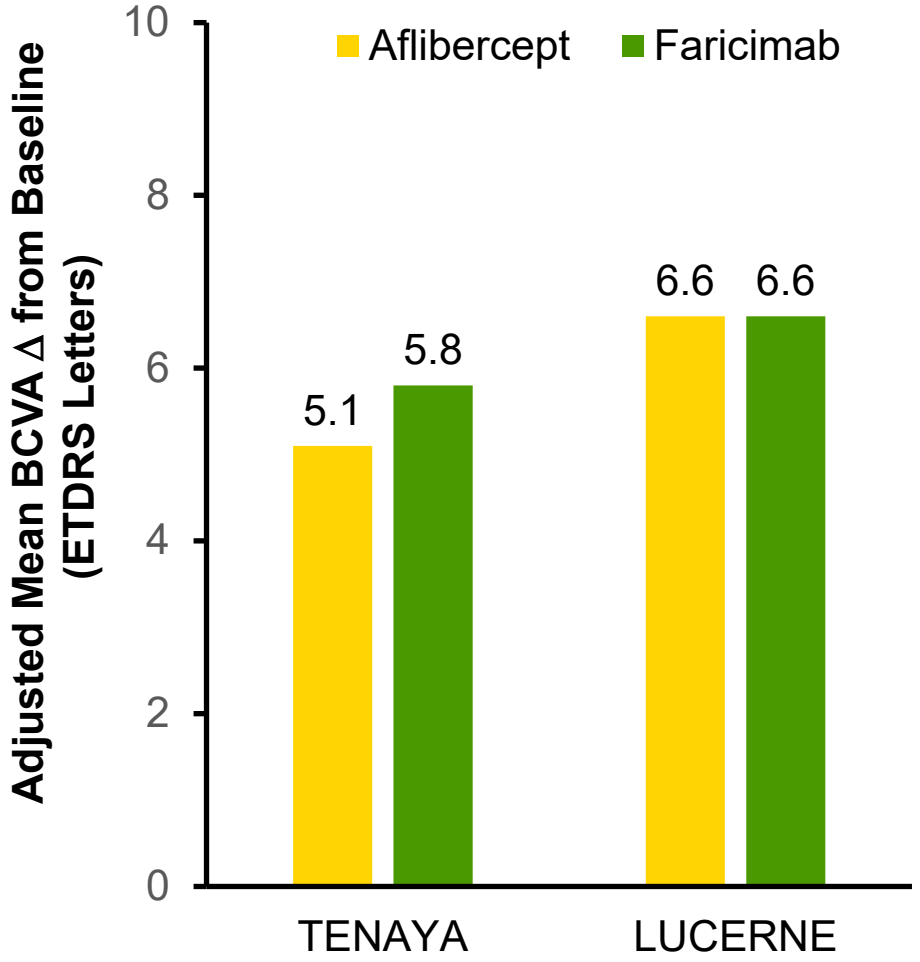
Key Secondary

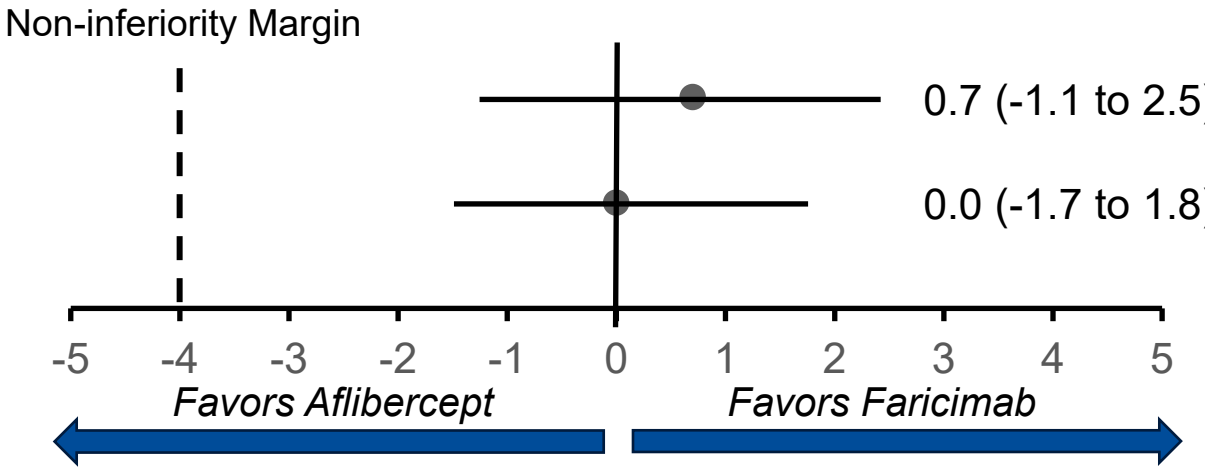
- Proportion of faricimab-treated patients on 16-week, 12-week, and 8-week schedules at week 48
- Safety

*Based on protocol-defined disease activity assessments at weeks 20 & 24

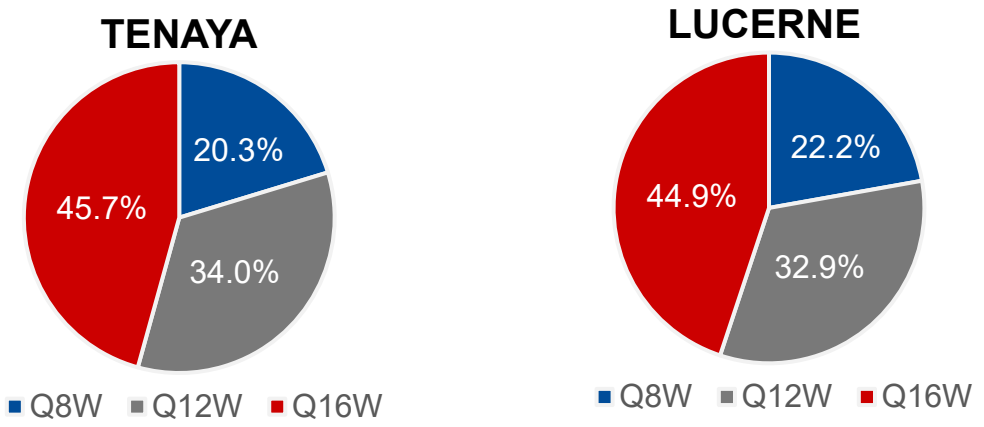
Heier JS, et al. *Lancet.* 2022;399:729-740. Khanani AM, et al. *JAMA Ophthalmol.* 2020;138(9):964-972.

TENAYA & LUCERNE: Results





Patients in Faricimab Group Who Completed Week 48 Treatment by Fixed-Dosing Interval

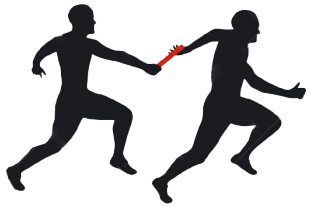


Heier JS, et al. *Lancet.* 2022;399:729-740.

TENAYA & LUCERNE: Additional Results

- Efficacy:
  - Treatment with faricimab dosed up to every 16 weeks resulted in CST reductions from baseline at all timepoints up to week 48, starting at 4 weeks after treatment initiation, and was comparable with aflibercept every 8 weeks
  - Adjusted mean changes in total CNV lesion area and total area of leakage from baseline with faricimab at week 48 were comparable with aflibercept
- Safety:
  - Overall, faricimab up to every 16 weeks was well tolerated; there was a low incidence of adverse events leading to study treatment discontinuation
  - The most common ocular adverse events were consistent with those expected in patients with nAMD receiving IVT; the incidence was comparable between treatment groups
  - Rates of IOI were low and comparable in both arms with no cases of retinal vasculitis or vascular occlusion noted in any arm
  - Non-ocular adverse events were generally similar, with no safety concerns, and occurred at similar rates in both treatment groups across both studies

Heier JS, et al. *Lancet.* 2022;399:729-740.



Finish Line: Challenge Question

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Which of the following statements best summarizes the results of the TENAYA and LUCERNE studies of faricimab in patients with nAMD?

a. When dosed ≤Q16W, faricimab is noninferior to Q8W aflibercept with respect to visual outcomes and has a similar safety profile.

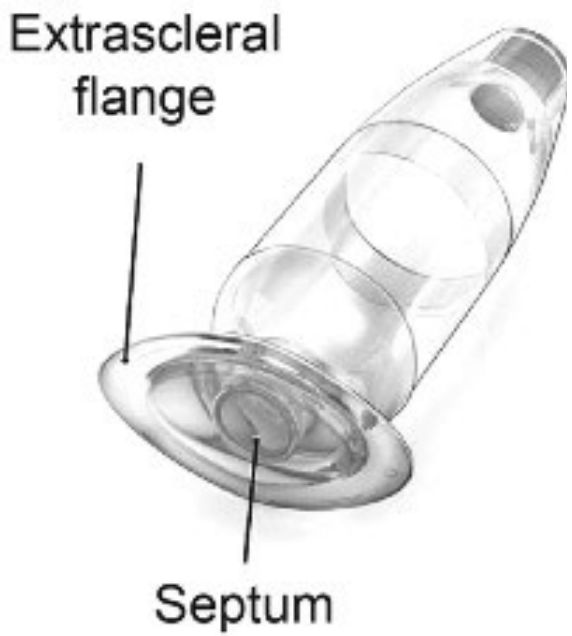
b. Although superior to Q8W aflibercept in terms of efficacy when dosed ≤Q16W, ocular adverse events are more frequent with faricimab.

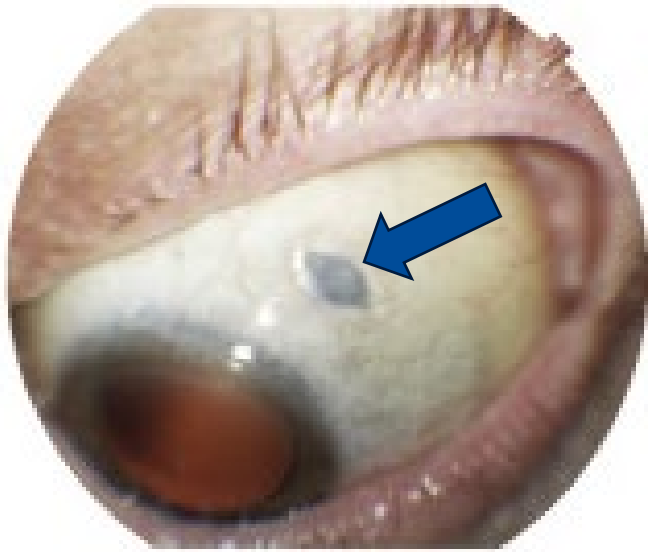
c. When dosed ≤Q16W, faricimab is inferior to Q8W aflibercept with respect to anatomic outcomes.

d. Although noninferior to Q4W ranibizumab in terms of efficacy when dosed ≤Q16W, the safety profile of faricimab is more favorable compared to the former agent.

Ranibizumab Port Delivery System (PDS)

Permanent, refillable implant that permits controlled continuous release of ranibizumab into the vitreous over time

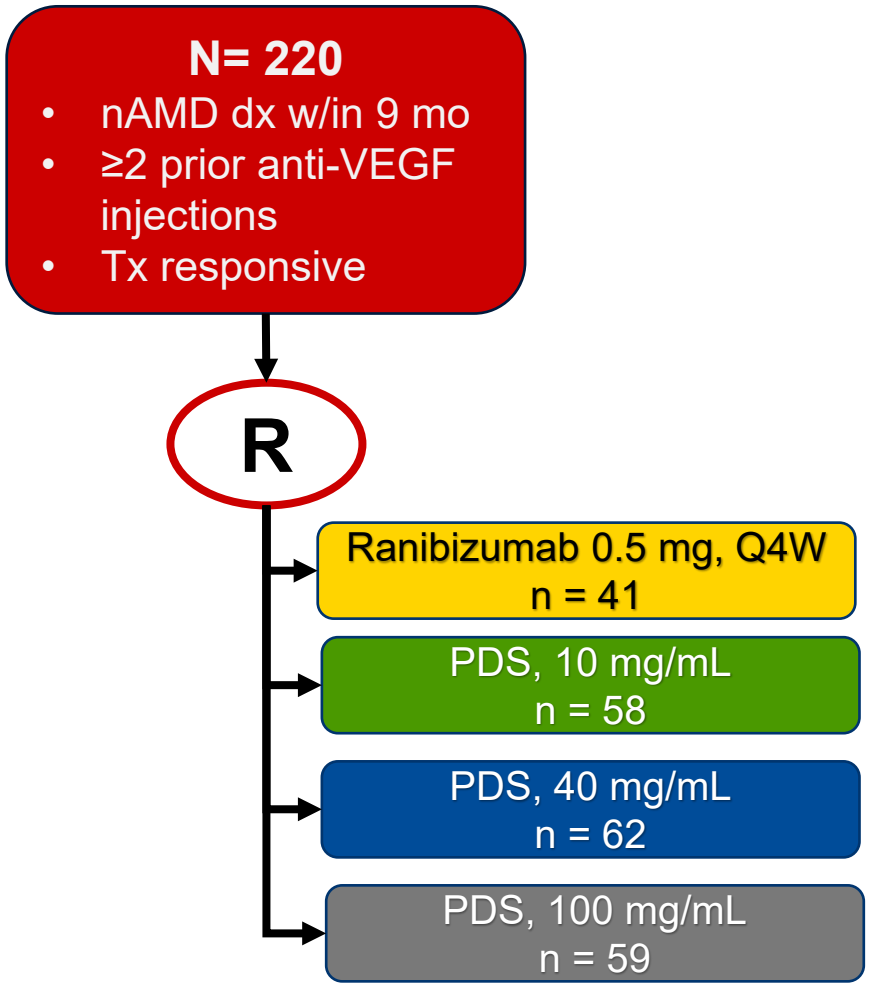




FDA approved in 2021

Campochiaro PA, et al. *Ophthalmology.* 2019;126:1141-1154. Holekamp NM, et al. *Ophthalmology* 2022;129:295-307.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761197s000lbl.pdf.

LADDER: Phase 2 Study of Ranibizumab PDS for nAMD

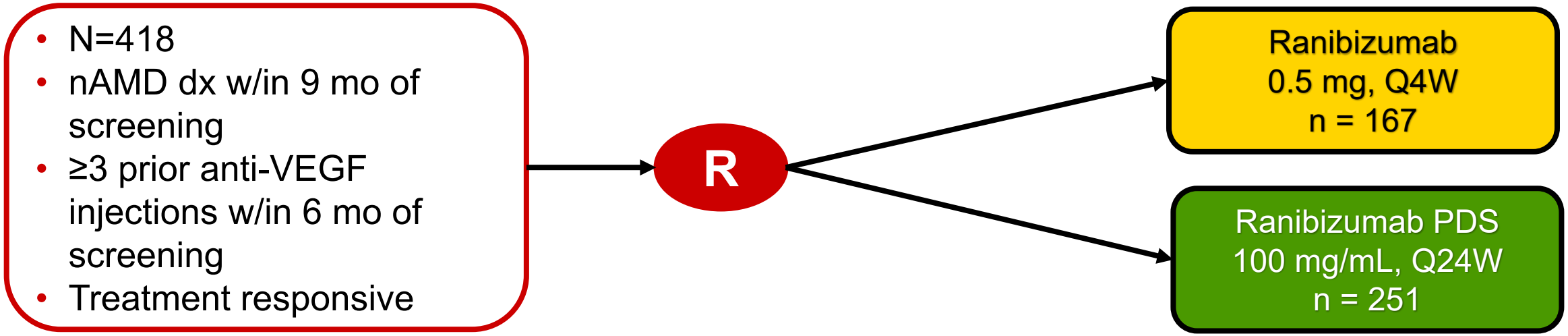


Study Endpoint	Rbzb 0.5 mg	PDS 10	PDS 40	PDS 100
Mean Δ From Baseline in BCVA at 9 mo (ETDRS Letters)	3.9	-3.2	-0.5	5.0
Mean Δ From Baseline in CFT at 9 mo (ILM-PRE), μm	-6.3	54.4	-0.5	-1.7
Mean Δ From Baseline in CFT at 9 mo (ILM-Bruch's), μm	-29.3	57.4	22.0	11.1
Patients Not Receiving Any Refill Through mo 6	-	63.5%	71.3%	79.8%

- As expected given the surgical nature of the study, more ocular AEs were observed in the PDS arms than in the monthly intravitreal ranibizumab 0.5-mg injection arm, particularly during the perioperative period
- No ocular serious AEs were reported in the monthly intravitreal ranibizumab 0.5-mg injection treatment arm
- Ocular serious AEs were reported in 8.9% PDS-treated patients; the most frequent was vitreous hemorrhage, occurring in 3.9% in the overall PDS-treated population

Campochiaro PA, et al. *Ophthalmology.* 2019;126:1141-1154.

ARCHWAY: Phase 3 Open-Label Study of Ranibizumab PDS for nAMD

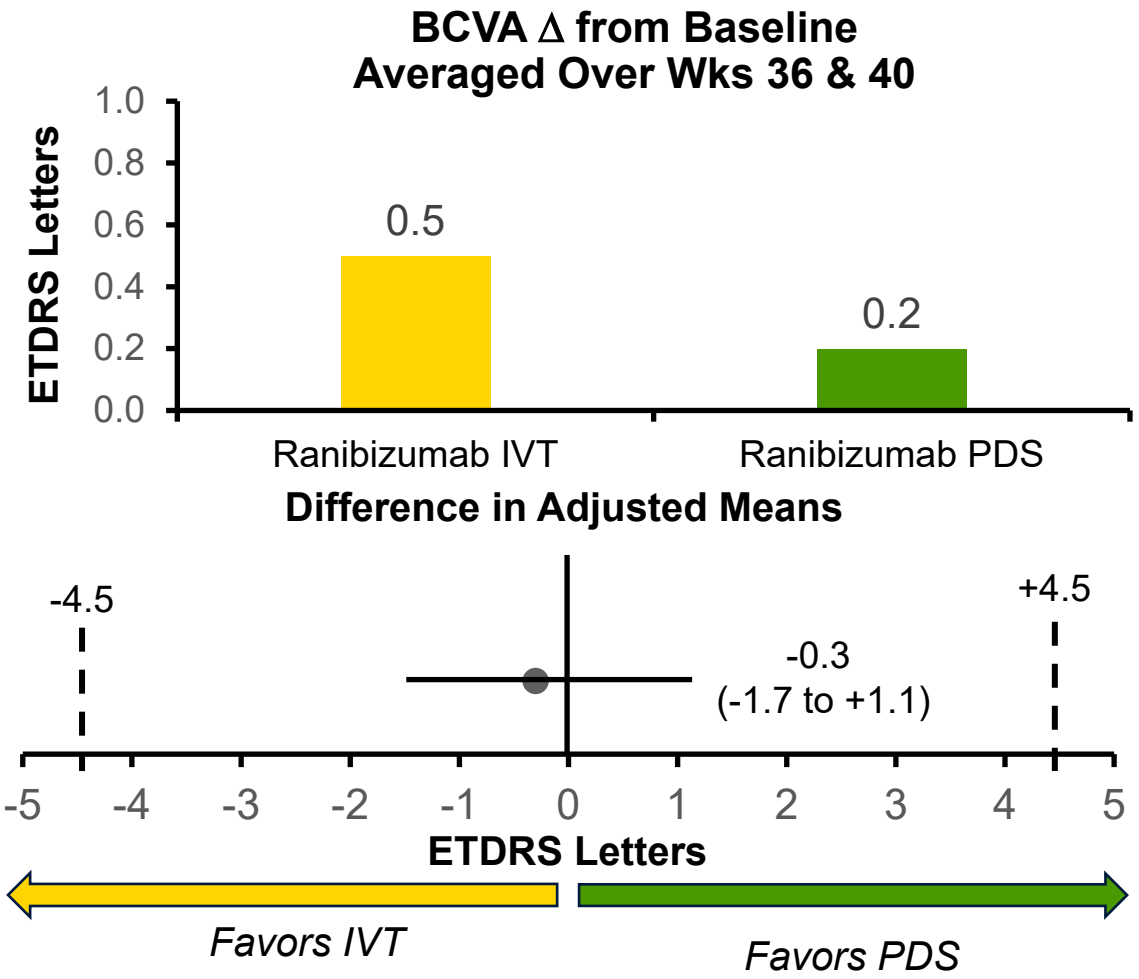


Primary Endpoint

Change from baseline in BCVA score at the average of weeks 36 and 40

Holekamp NM, et al. *Ophthalmology* 2022;129:295-307.

ARCHWAY: Study Results

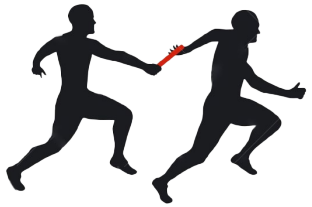


Endpoint	Rani IVT	Rani PDS
Adjust Mean CPT Δ from Baseline, mm	2.6	5.4
Ocular AEs of Special Interest		
-Vitreous Hemorrhage	2.4%	5.2%
-Endophthalmitis	0%	1.6%
-Retinal Detachment	0%	0.8%
-Conjunctival Erosion	0%	2.4%
-Conjunctival Retraction	0%	2.0%

Most ocular adverse events in the PDS arm occurred within 1 month of implantation.

In late 2022, the ocular implant, insertion tool assembly, (including the drug vial & initial fill needle) for ranibizumab PDS were voluntarily recalled due to septum dislodgement; this did not include the refill vial and needle.

Holekamp NM, et al. *Ophthalmology* 2022;129:295-307.
US DHCP Voluntary recall of the ranibizumab ocular implant Oct 18th V2. http://bitly.ws/KKzq



Baton Pass: Challenge Question

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According to available clinical trial data, at which of the following dosages and intervals was the ranibizumab port delivery system shown to be noninferior to IVT ranibizumab Q4W?

a. 10 mg/mL, Q24W
b. 40 mg/mL, Q24W
c. 100 mg/mL, Q24W
d. 200 mg/mL, Q24W

Aflibercept 8 mg: A Recently Approved High Dose, Extended Interval Formulation for nAMD

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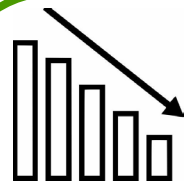
Rationale

Preclinical Studies

Experiments conducted in the DL-AAA rabbit model of chronic retinal vascular leak have shown the 8 mg equivalent dose of aflibercept resulted in prolonged efficacy compared to the 2 mg equivalent dose

PK Studies



Like most anti-VEGF agents, aflibercept has a linear PK curve; 8 mg should provide two half-lives more duration

Clinical Data

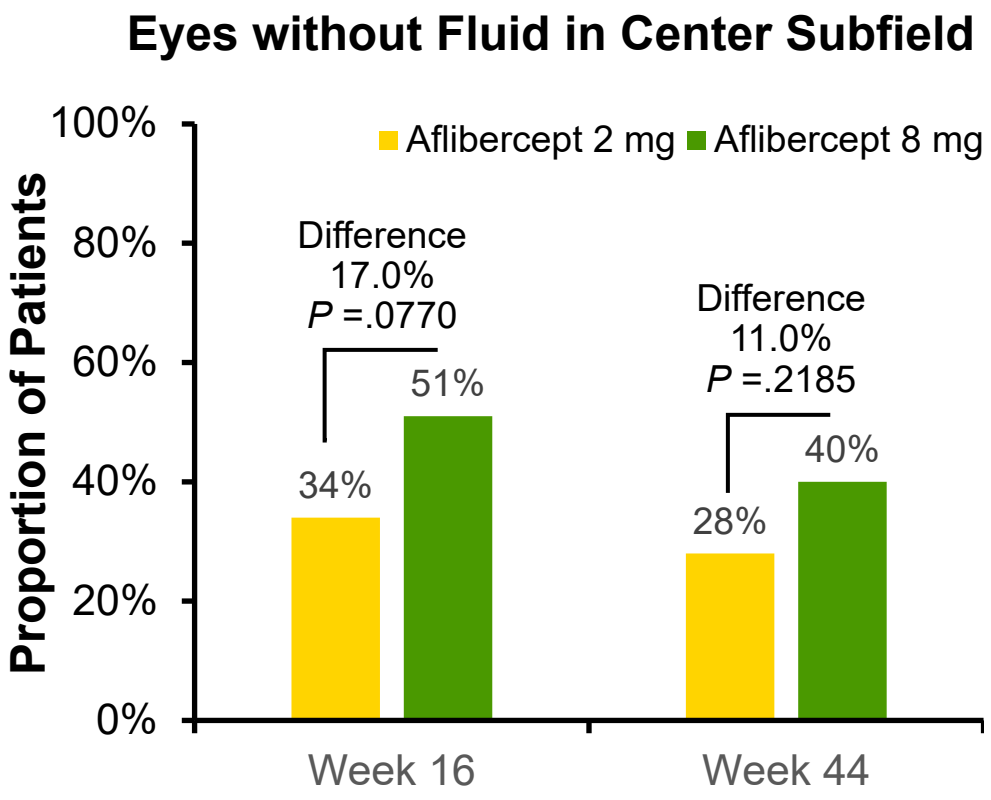
Data from treat & extend studies (ARIES and ALTAIR), and a post-hoc analysis of the VIEW trials have indicated that ~50% of patients are effectively treated with ~Q12W dosing of aflibercept 2 mg

FDA approved in August 2023

Brown DM. *Invest Ophthalmol. Vis Sci*. 2022;63:1345 (F0179). Do D, et al. *Retina.* 2020;40:643-647. Mitchell PW, et al. *Retina.* 2021;41:1911-1920. Ohji M, et al. *Adv Ther.* 2020;37:1173-1187. Khurana RN, et al. *Am J Ophthalmol.* 2019;200:161-168. FDA approves aflibercept injection 8mg for treatment of wet AMD, DME, DR (ophthalmologytimes.com)

CANDELA: Phase 2 Study of 8 mg Aflibercept for nAMD

- 106 treatment-naïve patients (≥50 years old) with nAMD were randomized 1:1 to receive 3 monthly doses of either 2 mg or 8 mg aflibercept followed by doses at Week 20 and 32



Endpoint	Aflibercept 2 mg	Aflibercept 8 mg
Eyes without Fluid in Macula at Week 44	15%	32% *P* =.0395 vs 2 mg
Eyes without IRF, SRF or Sub-RPE Fluid at Week 44	11%	25%
Mean Δ in CRT Baseline through Week 44	-137 μm	-159 μm
> 239 μm Reduction in CRT at Week 44	20%	27%
Mean Δ in BCVA Baseline through Week 44	5.1	7.9
≥ 15 Letter Gain at Week 44	14%	33%
Achieved BCVA ≥ 20/40 at Week 44	49%	61%
Achieved BCVA ≥ 20/20 at Week 44	2%	10%

Brown DM. *Invest Ophthalmol. Vis Sci*. 2022;63:1345-F0179. Goren Fein J. ARVO 2023. Abstract 2180-C0133.

PULSAR: Phase 3 Study of Aflibercept 8 mg for Treatment-naïve nAMD

Clinical SPRINTS℠

Multi-center, randomized, double-blind study

- **Aflibercept 2 mg** — 3 monthly injections → Q8W — n = 336
- **Aflibercept 8 mg** — 3 monthly injections → Q12W — n = 335
- **Aflibercept 8 mg** — 3 monthly injections → Q16W — n = 338

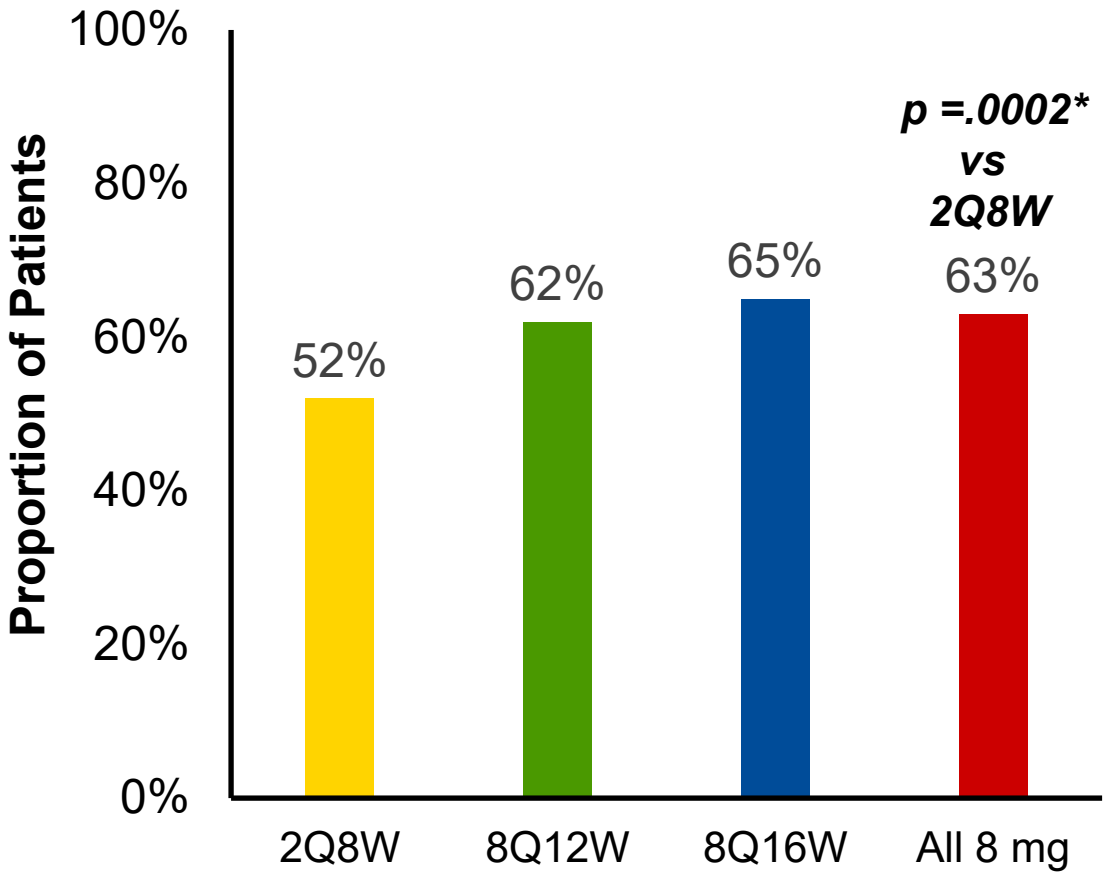
Study Endpoint	Aflibercept 2Q8W	Aflibercept 8Q12W	Aflibercept 8Q16W
Absolute BCVA at Wk 48 (ETDRS Letters)	66.5	66.9	66.3
Δ From Baseline in BCVA at Wk 48 (ETDRS Letters)	+7.6	+6.7	+6.2
LS Mean Δ From Baseline in BCVA at Wk 48 (MMRM)	7.0	6.1 -0.97 vs 2q8 p = 0.0009*	5.9 -1.14 vs 2q8 p =0.0011*

**1-sided test for non-inferiority at 4-letter margin*

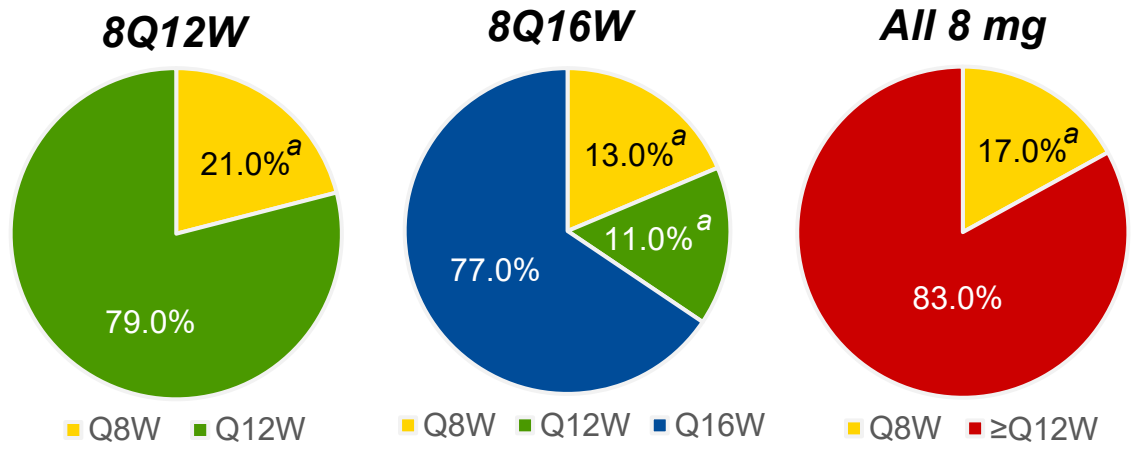
Spitzer MS, et al. ARVO 2023. Abstract 461.

PULSAR: Additional Results

Patients Without Retinal Fluid in Center Subfield at Week 16



Proportion of Patients Maintaining Q12W & Q16W Through Week 48



The two-year data from PULSAR trial are expected in the third quarter 2023.

**1-sided superiority test*

[a]Interval shortened based on DRM assessments at some point through Week 48

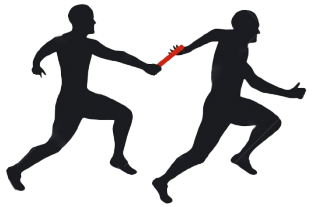
Spitzer MS, et al. ARVO 2023. Abstract 461.

Pooled Safety Analysis of Aflibercept 8 mg

Safety of aflibercept 8 mg and 2 mg were integrated through Week 44 across the CANDELA, and Week 48 in the PULSAR trial in nAMD (as well as PHOTON study in DME)

Adverse Events	Aflibercept 2 mg (n = 556)	Aflibercept 8 mg (n = 1217)
Ocular TEAEs	35.3%	35.2%
Reduced Visual Acuity	4.5%	2.9%
Vitreous Floaters	2.7%	3.0%
Cataract	2.2%	3.0%
Conjunctival Hemorrhage	2.3%	3.0%
Retinal Hemorrhage	3.1%	2.3%
Ocular Hypertension	0.4%	0.8%
Increased IOP	2.3%	2.3%
Intraocular Inflammation	0.5%	0.8%
Retinal Detachment	0%	0.4%
Vitreous Hemorrhage	0%	0.2%

Schneider E. ARVO 2023. Abstract 3724-C0501.



Baton Pass: Challenge Question

Clinical SPRINTS℠

Which of the following statements regarding the results of the PULSAR study, which compared standard IVT aflibercept (2 mg, Q8W) to high-dose, extended interval IVT aflibercept in patients with nAMD, is <u>true</u>?

a. 8 mg aflibercept Q12W-Q16W is superior to standard aflibercept in terms of visual outcomes
b. 8 mg aflibercept Q12W-Q16W is non-inferior to standard aflibercept in terms of visual outcomes
c. The incidence of ocular adverse effects is significantly higher with 8 mg aflibercept Q12W-Q16W compared to standard aflibercept
d. The incidence of ocular adverse effects is significantly lower with 8 mg aflibercept Q12W-Q16W compared to standard aflibercept

Emerging or Attempted Therapies for nAMD

Agent	Design	Status
Conbercept	Fusion protein designed to bind VEGF-A, VEGF-B and PlGF	Phase 3 PANDA-1 and PANDA-2 trials for nAMD were terminated in 2021 on the basis that the primary endpoint, conbercept non-inferiority compared with aflibercept, was not met
OPT-302	“Trap” molecule that binds to VEGF-C and VEGF-D	OPT-302 is recruiting for Phase III trials with and without either ranibizumab (ShORe) or aflibercept (COAST)
KSI-301	Antibody biopolymer conjugate that binds to all VEGF-A isoforms	• Phase 2b/3 DAZZLE trial did not meet its primary endpoint of non-inferiority in BCVA to aflibercept • Phase 3 DAYLIGHT study comparing KSI-301 to aflibercept recently completed

Khachigan LM, et al. *J Transl Med.* 2023;21:13. cliniclatrials.gov NCT03577899. clinicaltrials.gov NCT03630952. clinicaltrials.gov NCT04757610. clinicaltrials.gov NCT04757636. KSI-301 for wet AMD fails to meet primary endpoint in phase 2b/3 trial (healio.com) clinicaltrials,gov NCT04964089.

Emerging Gene Therapies for the Treatment of nAMD

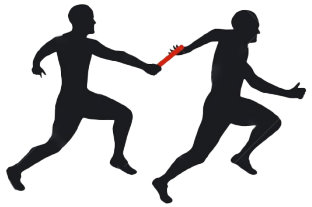
ADVM-022

- AAV7m8 gene therapy delivering aflibercept
- Phase 1 OPTIC Study Showed:
  - ADVM-022 was generally well tolerated
  - A single IVT injection of ADVM-022 resulted in sustained therapeutic aflibercept expression through at least 3 years
  - An extension study will follow-up with subjects out to 5 years

RGX-314

- AAV8 gene therapy delivering anti-VEGF Fab
- Interim conclusions drawn from phase 1/2a results were that RGX-314 was well tolerated by all patients and that the treatment provided a long-term, durable treatment effect seen with the 3 highest doses
- ASCENT and ATMOSPHERE studies are currently enrolling patients

Regillo C, et al. Retina Society Annual Meeting 2022. Oral Presentation. PDS and RGX-314: Two new surgical procedures for the treatment of wet AMD (ophthalmologytimes.com). Clinicaltrils.gov NCT05407636. clinicaltrials.gov NCT04704921.



Finish Line: Challenge Question

Clinical SPRINTS℠

Which of the following novel therapies under investigation for the treatment of nAMD is a “Trap” molecule that binds VEGF-C and VEGF-D?

a. ADVM-022
b. KSI-301
c. OPT-302
d. RGX-314

Summary

- nAMD is a major cause of visual impairment and blindness with increasing prevalence
- Since their first use as IVT drugs with nAMD patients more than 15 years ago, anti-VEGF therapies have transformed the treatment of this disease
- However, there is a need for longer-acting agents to reduce injection frequency, treatment burden; several strategies have either been approved in recent years or are in the later stages of clinical development
- Other potential therapeutic modalities, such as gene therapy, continue to be investigated