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Extending Treatment Durability With Next-Generation Neovascular AMD Therapies

Enduring CME News Broadcast Video

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Extending Treatment Durability With Next-Generation Neovascular AMD Therapies

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SPECIAL REPORT

The State of Care for Patients With nAMD

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Twenty Years of Anti-VEGF Therapy for nAMD

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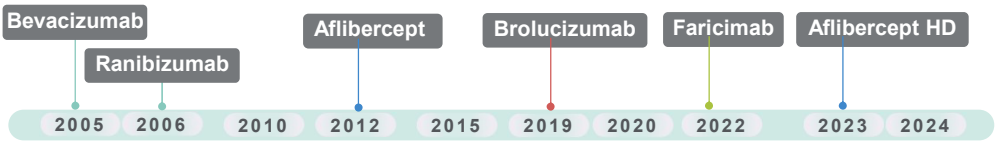

Treatment Approaches

Fixed • PRN • T&E

HD, high dose; nAMD, neovascular age-related macular degeneration; PRN, pro re nata; T&E, treat and extend; VEGF, vascular endothelial growth factor

Extending Treatment Durability With Next-Generation Neovascular AMD Therapies

Impact of Anti-VEGF Treatment and Patient Characteristics on Vision Outcomes in nAMD

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Up to 6-Y Analysis of the Academy IRIS Registry

- **Purpose: E**valuate anti-VEGF treatment patterns and influence of patient demographic and clinical characteristics on vision outcomes in nAMD
- **Design:** Retrospective, multicenter, noninterventional registry study with up to 6 y follow-up
- **Participants:** A cohort of 254,655 eyes (226,767 patients) with first anti-VEGF injection and at least 2 y follow-up; 160,423 eyes had VA data
- **Methods:** Anonymized patient data were collected in the United States through the IRIS Registry (Intelligent Research in Sight)
- **Outcomes:** Changes in VA from baseline; frequency of and gaps between intravitreal anti-VEGF injections; treatment discontinuations; switching anti-VEGF agents; influence of baseline clinical and demographic characteristics on VA

VA, visual acuity
Wykoff CC et al. *Ophthalmol Sci.* 2024;4:100421.

Use of Anti-VEGF Agents Demonstrates Value of More Durable Therapies (January 2013 to June 2020)

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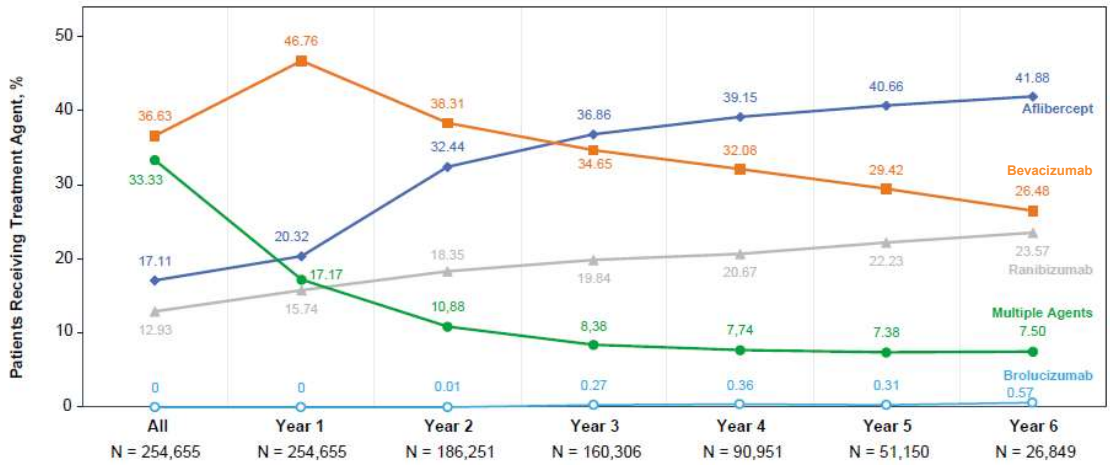
Relative Change in Proportions of Patients Receiving Different Treatment Agents at Each Time Point



The patients within each cohort changed over time. Data are not continuous.
Wykoff CC et al. *Ophthalmol Sci.* 2024;4:100421.

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Visual Acuity at Baseline and Over Follow-Up Years

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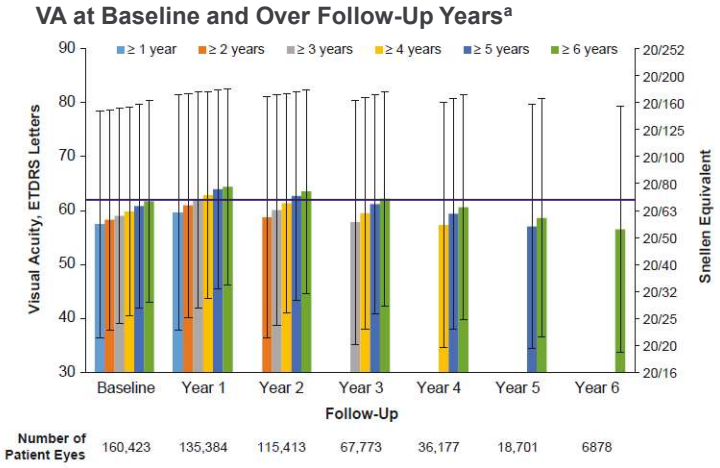

VA improvement at y 1 with net loss of VA by y 6

[a]The number of patients' eyes included in each follow-up y was not mutually exclusive (ie, patient eyes with 6 y follow-up were included in all previous follow-up years). Patient eyes must have had consecutive VA measurements. ETDRS, Early Treatment Diabetic Retinopathy Study

Wykoff CC et al. *Ophthalmol Sci.* 2024;4:100421.

Treatment Patterns in Overall Cohort for Patients With at Least 2 Y Follow-up: Number of Anti-VEGF Injections

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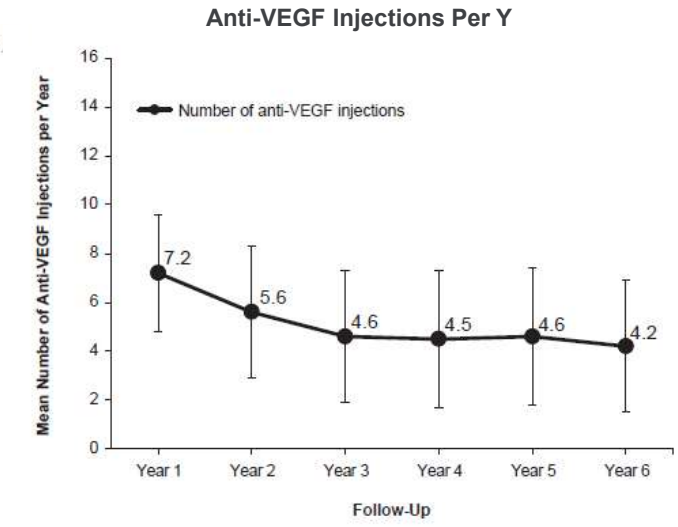

- Injection number decreased over time
- Relatively high rate of discontinuation
- VA cohort
  - Mean duration treatment, 148±83 wk
  - Treatment discontinuation 38.8% (62,188/160,423)

Wykoff CC et al. *Ophthalmol Sci.* 2024;4:100421.

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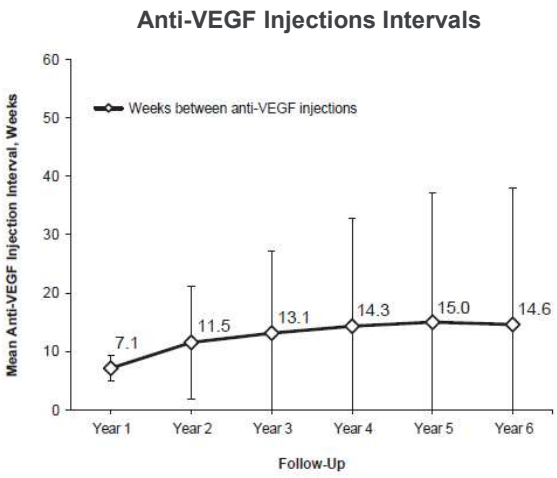
Treatment Patterns in Overall Cohort for Patients With at Least 2 Y Follow-up: Interval Between Injections



- Injection interval increased with time
- Majority of patients received 1 to 6 injections each y
- Injection frequency per y in patient eyes years 3 through 6 in overall cohort
  - 1 to 3 injections: 39% to 46%
  - 4 to 6 injections: 34.7% to 37.6%
  - 7 to 9 injections: 14.4% to 17.4%

Wykoff CC et al. *Ophthalmol Sci.* 2024;4:100421.

Conclusions

- After modest mean VA improvement with intravitreal anti-VEGF injections at y 1, patients netted a loss of VA by y 6
- Injection frequency decreased over time; this was paired with a relatively high rate of discontinuation
- Injection interval increased with time, with the majority of patients receiving 1 to 3 injections each y

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FROM THE FIELD

Challenges in Monitoring Treatment Response

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Reasons Why Real-World VA Outcomes Show Efficacy Gap Compared With Clinical Trials

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- Factors outside control of ophthalmologist
  - Age
  - Wider range of lesion type
  - Wider range of baseline characteristics
  - Less compliance with regular follow-up
  - Agent selection
    - Insurance-mandated bevacizumab as step therapy
- Factors ophthalmologists can control
  - Treatment paradigms
    - Fixed dosing
    - PRN
    - T&E
  - **Selection of disease activity criteria**

Polling Question 1

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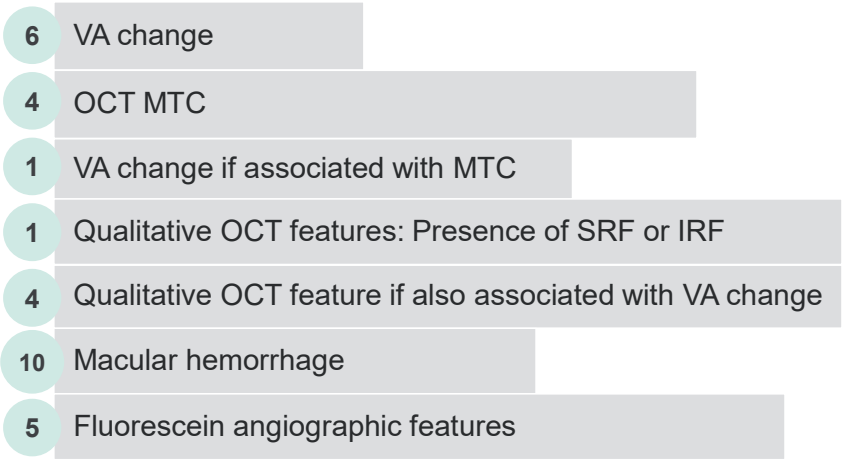
What disease activity measurement do you routinely use to evaluate treatment efficacy in patients with nAMD? (Select all that apply)

A. Visual acuity change
B. OCT MTC
C. Qualitative OCT features
D. Macular hemorrhage
E. Fluorescein angiographic features
F. OCT angiography

MTC, macular thickness change; OCT, optical coherence tomography

Different Disease Activity Criteria Used to Determine Dosing Intervals in 12 Randomized Clinical Trials



IRF, intraretinal fluid; SRF, subretinal fluid
Patel PJ et al. *Ophthalmol Ther.* 2023;12:2323-2346.

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Measures of Disease Activity: *Challenges in Real-World Practice*

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VA Change

- Measurements subject to measurement variability in clinical settings
- Lagging indicator of worsening nAMD compared with structural OCT imaging
- Ceiling effect in VA change
  - Eyes with worse baseline VA frequently demonstrate better VA gains

MTC

- Can be a time-consuming measurement, might not be routinely performed in clinical practice
- Some nAMD lesion components can affect detection of retinal pigment epithelium by automated segmentation algorithms
- Accurate, repeatable measurement of macular thickness is difficult
- Images need manual correction or verification of boundary detection

Patel PJ et al. *Ophthalmol Ther.* 2023;12:2323-2346.

Measures of Disease Activity: *Challenges in Real-World Practice*

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Structural OCT Imaging[1,2]

- Well established measure of disease activity
- Used to determine change in macular fluid
- Need to be aware that some biomarkers measured by OCT have robust evidence base, whereas other biomarkers have less evidence supporting their use
- Presence of IRF
  - Important to distinguish IRF associated with atrophy and tubulation from IRF associated with worsening nAMD

Macular Hemorrhage

- New macular hemorrhage secondary to nAMD is important marker of disease activity
- Can be measured by clinical examination, color fundus photography, OCT imaging

1. Patel PJ et al. *Ophthalmol Ther.* 2023;12:2323-2346. 2. Flaxel CJ et al. *Ophthalmology.* 2020;127(1):P1-P65.

Measures of Disease Activity: *Challenges in Real World Practice*

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Increase in Lesion Size

- Value of assessing increase in lesion size not a well established measure of disease activity
- Requires use of fundus fluorescein angiography
  - Not routinely used in clinical practice to assess treatment response
- OCT can be used to assess increase in lesion size
- Increase in PED height or lateral growth of PED
- OCT angiography might be a future approach to measuring lesion size change

PED, pigment epithelial detachment
Patel PJ et al. *Ophthalmol Ther.* 2023;12:2323-2346.

Measures of Disease Activity: Real-World Practice

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- VA change
- OCT MTC
- VA change if associated with MTC
- Qualitative OCT features: Presence of SRF or IRF
- Qualitative OCT feature if also associated with VA change
- Macular hemorrhage
- Fluorescein angiographic features

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FEATURE STORY

More Durable Anti-VEGF Therapies

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Changes in Molecular Properties Might Offer Improved Durability

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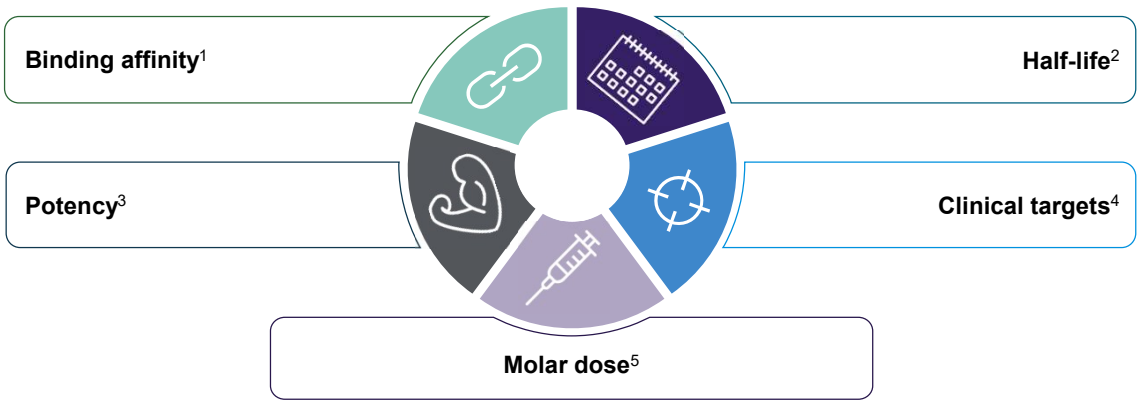

The relevance of these molecular properties on clinical outcomes has not been clinically proven.

1. Papadopoulos N et al. *Angiogenesis.* 2012;15:171-185. **2.** Hallare J, Gerriets V. Half Life. June 20, 2023. Accessed March 8, 2024. https://pubmed.ncbi.nlm.nih.gov/32119385/.
3. Neubig RR et al. *Pharmacol Rev.* 2003;55:597-606. **4.** Marino M, Jet al. Pharmacodynamics. Jan 29, 2023. Accessed March 8, 2024. https://pubmed.ncbi.nlm.nih.gov/29939568/.
5. Wright DFB et al. *Br J Clin Pharmacol* 2011;71:815-823.

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Brolucizumab Clinical Trial Treatment Paradigm HAWK/HARRIER

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- **Methods:** After 3 monthly loading doses (3 mg or 6 mg), patients received intravitreal brolucizumab (3 mg or 6 mg) q12w dosing, adjusting downward to q8w dosing if disease activity was present at predefined DAA visits
- **Main Outcome Measures:** Mean BCVA change from baseline, proportion of patients on q12w regimen
- **Disease Activity Assessments:** BCVA, CST status, IRF status, clinical judgment

BCVA, best-corrected VA; CST, central subfield thickness; DAA, disease activity assessment; q8w, every 8 wk; q12w, every 12 wk
Dugel PU et al. *Ophthalmology*. 2021;128:89-99.

Brolucizumab Efficacy, Safety, Durability at 96 Wk HAWK/HARRIER

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- **Efficacy**
  - BCVA change
    - HAWK +5.9 (6 mg) and +5.6 (3 mg) letters
    - HARRIER +6.1 (6 mg) letters
  - CST
    - HAWK -174.8 um (6 mg)
    - HARRIER -197.7 um (6 mg)
- **Durability**
  - At 92 wk (last DAA), a 45.4% (HAWK) and 38.6% (HARRIER) probability was observed for brolucizumab 6 mg with patients maintaining q12w treatment regimen
- **Safety**

AE, % (n)	Brolucizumab n=1088
Any IOI	4.6 (50)
Retinal vasculitis	3.3 (36)
Retinal vasculitis with vascular occlusion	2.1 (23)
Retinal vasculitis and ≥3-line vision loss	22 (8/36)
Retinal vasculitis and ≥6-line vision loss	14 (5/36)

AE, adverse event; IOI, intraocular inflammation
Dugel PU et al. *Ophthalmology*. 2021;128:89-99.

Faricimab Clinical Trial Treatment Paradigm TENAYA/LUCERNE

- **Year 1:** After 4 monthly 6 mg loading doses, faricimab 6 mg up to q16w based on DAA at wks 20 and 24
- Active disease at wk 20 continued fixed q8w to wk 60
- Active disease at wk 24 continued fixed q12w to wk 60
- No active disease at wks 20 and 24 received faricimab at wk 28 and continued a 16-wk regimen up to wk 60
- **Year 2:** Active dose of faricimab at wk 60, treated according to PTI
- In PTI regimen, based on DAA at study drug dosing visits, dosing intervals can be
  - Extended in 4-wk increments or
  - Reduced in 4-wk or 8-wk increments to a minimum of
    - q8w or
    - A maximum of q16w or
    - Maintained

PTI, personalized treatment interval; q16w, every 16 wk
Heier JS et al. *Lancet*. 2022;399:729-740.

Faricimab Clinical Trial Treatment Paradigm Y 1 TENAYA/LUCERNE

- **Main outcome measures:** Mean BCVA change from baseline averaged over wk 40, 44, 48
- **Disease activity assessments:** BCVA, CST status, macular hemorrhage, clinical judgment

Khanani AM et al. *Ophthalmol Sci*. 2021;1:100076. Heier JS et al. *Lancet*. 2022;399:729-740.

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Faricimab Efficacy, Safety, Durability at 48 Weeks TENAYA/LUCERNE

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- **Efficacy**
  - BCVA change
    - TENAYA +5.8 letters
    - LUCERNE +6.6 letters
- **Safety**

AEs Through Study End, Patients With ≥1 AE, No. (%)	TENAYA/LUCERNE Pooled	
	Faricimab up to q16w (n=644)	Aflibercept 2 mg q8w (n=662)
IOI events	20 (3.0)	15 (2.3)
Endophthalmitis events	3 (0.5)	2 (0.3)
Retinal vasculitis events	0	0
Retinal occlusive events	0	0

- **Durability**

Proportion of patients in the faricimab group who completed wk 48 treatment on q8w, q12w, q16w fixed-dosing intervals

TENAYA (n=315)
- q8w 20.3% (n=64)
- q12w 34.0% (n=107)
- q16w 45.7% (n=144)
- ≥q12w 79.7%

LUCERNE
- q8w 22.2% (n=70)
- q12w 32.9% (n=104)
- q16w 44.9% (n=142)
- ≥q12w 77.8%

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

Aflibercept 8 mg Clinical Trial Treatment Paradigm PULSAR

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- **Methods:** After 3 monthly loading doses, aflibercept q8w (2 mg) or q16w (8 mg) dosing adjusting to q20w or q24w if DRMs were met at predefined DAA visits
- **Main outcome measures:** BCVA change from baseline
- **DAAs:** BCVA, CST status

DRM Criteria for Interval Shortening Ys 1 and 2
- BCVA loss compared with wk 12, increase in CST compared with wk 12, new onset foveal neovascularization, or foveal hemorrhage

DRM Criteria for Interval Extension Y 2
- No BCVA loss compared with wk 12, no fluid at CST compared with wk 12, no new-onset foveal neovascularization or foveal hemorrhage

If DRM Criteria Met Intervals Shortened at:
- **Wks 16 and 20:** 8q12 and 8q16 dosing shortened to q8w
- **Wk 24:** 8q16 dosing shortened to q12w
- **Wks 32 and 44 for 8q12 and wk 40 for 8q16:** Intervals shortened by 4 wk
- **Week 52 onward:** 8q12 and 8q16 dosing intervals shortened in 4-wk intervals (to a minimum of q8w)

If DRM Criteria Met Intervals Extend at:
- **Wk 52 onward:** 8q12 and 8q16 dosing intervals extended by 4-wk intervals. 8q16 can be extended to q20w and q24w

8q12,8 mg every 12 weeks; 8q16, 8 mg every 16 weeks; DRM, dosing regimen modification; q20w, every 20 wk; q24w, every 24 wk
Korobelnik J-F et al. Presented at: AAO 2023. 11/3/23-11/6/23; San Francisco, CA.

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Aflibercept 8 mg Efficacy and Durability at 96 Wk PULSAR

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- **Efficacy**
  - BCVA change from baseline
    - +6.6 (2q8)
    - +5.6 (8q12)
    - +5.5 (8q16)

- **Durability**

Proportion of patients in aflibercept HD group who completed wk 96 treatment on 8-wk,12-wk, 16-wk, 20-wk, or 24-wk fixed-dosing intervals

All aflibercept 8mg

- q8w: 12% (n=70)
- q12w: 17% (n=99)
- q16w: 24% (n=140)
- q20w: 19% (n=111)
- q24w: 28% (n=163)

- ≥q12w 88%
- ≥q16w 71%
- ≥q20w 47%

2q8,2 mg every 8 weeks; q20w, every 20 weeks; q24w, every 24 weeks
Korobelnik J-F et al. Presented at: AAO 2023. 11/3-23-11/6/23; San Francisco, CA.

Aflibercept 8 mg Safety PULSAR

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Most Frequent Ocular AEs Through Wk 48[1]	Aflibercept 2 mg q8w (n=336)	Aflibercept 8 mg q12w (n=335)	Aflibercept 8 mg q16w (n=338)	Aflibercept 8 mg pooled (n=673)
Any ocular TEAE, %	38.7	38.5	37.6	38.0
Cataract, %	3.0	3.6	3.6	3.6
SRF, %	3.3	3.0	1.5	2.2
IOP increased, %	2.1	3.3	2.7	3.0
VA reduced, %	6.0	3.6	5.3	4.5
Retinal hemorrhage, %	4.2	3.3	3.0	3.1
Vitreous floaters, %	3.3	1.2	3.6	2.4

Most Frequent Ocular AEs Through Wk 48[2]	Aflibercept 2 mg q8w[a]	Aflibercept 8 mg pooled[a]
Patients with ≥1 IOI AE, %	2.1	1.3

[a]Any ocular TEAE in the study eye
Aflibercept 8 mg is approved for use in the United States but not outside of the United States.
No cases of endophthalmitis, retinal vasculitis, or occlusive retinitis were reported in either trial through wk 96.
TEAE, treatment-emergent AE
1. Korobelnik J-F. Presented at: ARVO 2023. 4/23/23-4/27/23; New Orleans, LA. 2. Regeneron Pharmaceuticals Inc. 8/10/23. Accessed 3/8/24. https://investor.regeneron.com/news-releases/news-release-details/two-year-pulsar-trial-results-aflibercept-8-mg-demonstrate

Polling Question 2

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Are you starting new patients with a diagnosis of nAMD on one of the more durable therapies?

A. Yes, all my new patients are started on brolucizumab, faricimab, or aflibercept.

B. Yes, some of my new patients are started on brolucizumab, faricimab, or aflibercept.

C. Sometimes; many of my patients are required to start with bevacizumab due to insurance requirements.

D. No, I still need to see more clinical data supporting the use of these new agents.

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PANEL DISCUSSION

Approaches to Dosing Intervals to Achieve the Fewest Doses for Best Vision Outcomes

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Polling Question 3

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What is the greatest challenge to translating effective therapies in clinical trials to effective therapies in clinical practice? (Select one)

A. Patients' anatomic and visual response to injections
B. Clinician and patient treatment preferences
C. Agent options
D. Wide variability in clinical practice treatment patterns
E. Potentially conflicting expert opinions and evidence
F. Need to chronically treat patients for therapy to be effective
G. Insurance reimbursement

Clinical Practice Treatment Patterns and Dosing Intervals

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Treatment Pattern	Dosing Interval
• Fixed dosing • PRN • T&E	• Follow dosing interval methodology as established in clinical trial for a given agent • Start with clinical trial dosing strategy but change based on clinical experience

Wykoff CC et al. Ophthalmol Sci. 2024;4:100421

Polling Question 4

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What approach do you use when considering brolucizumab, faricimab, or aflibercept HD for your patients with nAMD? (Select one)

A. Follow dosing interval methodology as established in clinical trial for a given agent.

B. Start with clinical trial dosing strategy but change based on clinical experience and patient.

C. I have not used these agents.

Selecting Anti-VEGF Agents in Clinical Practice: Dosing Intervals

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Brolucizumab[1]
q12w

Wk
1
2
3
4
5
6
7
8
9
10
11
12

Faricimab[2]
q16w

Wk	
1	9
2	10
3	11
4	12
5	13
6	14
7	15
8	16
9	
10	
11	
12	

Aflibercept HD[3]
q16w

Wk		
1	9	21
2	10	22
3	11	23
4	12	24
5	13	
6	14	
7	15	
8	16	
9	17	
10	18	
11	19	
12	20	

1. Dugel PU et al. *Ophthalmology*. 2021;128:89-99. 2. Heier JS et al. *Lancet*. 2022;399:729-740. 3. Korobelnik J-F et al. Presented at: AAO 2023. 11/3/23-11/6/23; San Francisco, CA.

Extending Treatment Durability With Next-Generation Neovascular AMD Therapies

Summary

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- Bevacizumab
- Ranibizumab
- Brolicizumab
- Aflibercept
- Faricimab
- Aflibercept HD

Multiple Anti-VEGF Therapies Options Available for nAMD

- Brolucizumab q12w
- Faricimab q16w
- Aflibercept HD q16-q24w

More Durable Anti-VEGF Agents With Treatment Intervals to q24w

- T&E supports personalized treatment approach

Selection of Disease Activity Criteria and Treatment Approach Important for Outcomes

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Thank You!

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