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Evolving Strategies to Ease the Burden Related to the Treatment of nAMD

Case Reflections for Better Therapeutic Strategies

Provided by
RMEI Medical Education, LLC

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

Agenda

Case 1: Pitfalls of PRN Therapy

Eric Schneider, MD

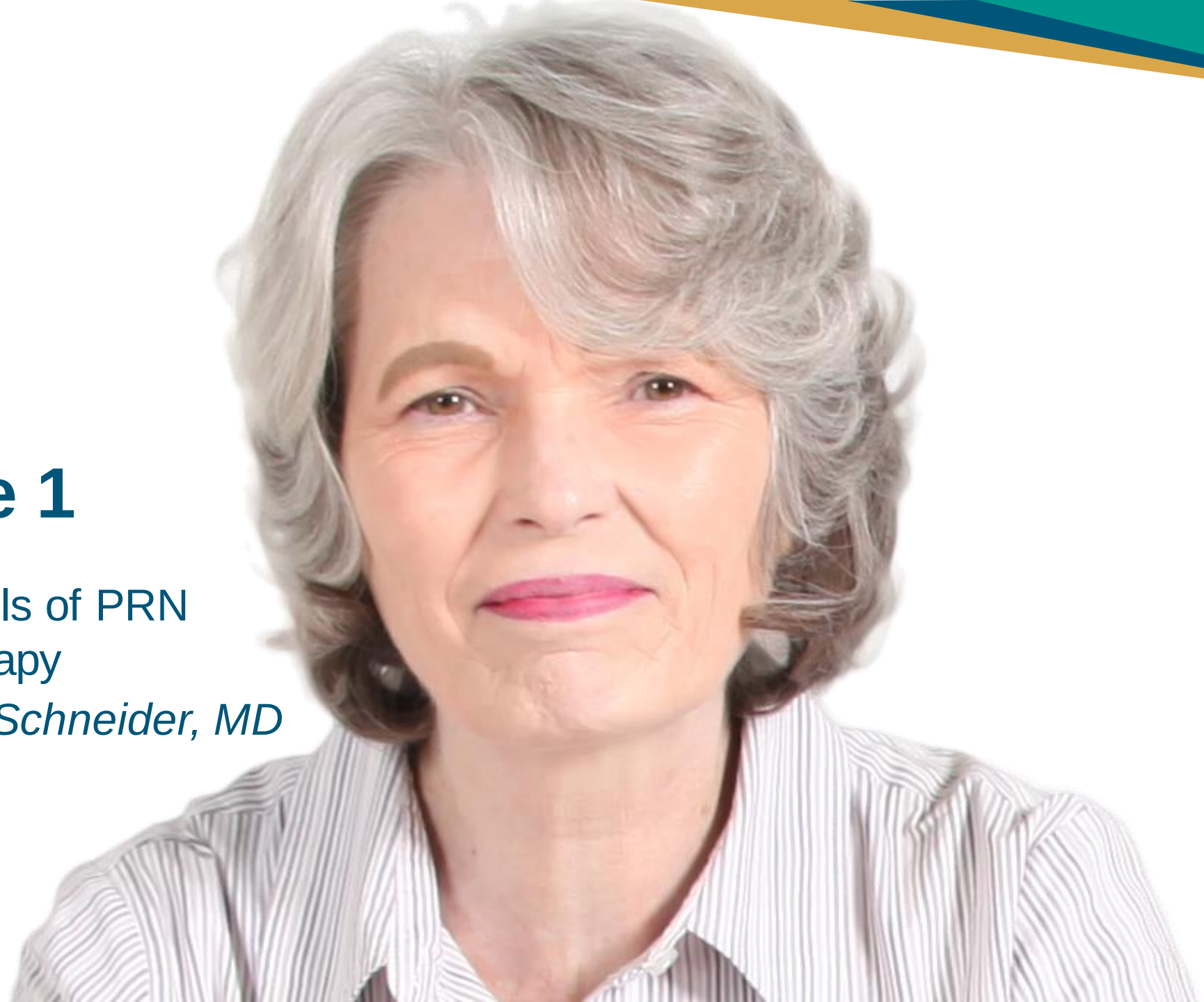
Case 2: Pitfalls in Patient Follow-up

David Brown, MD

PRN, physical rehabilitation network

Case 1

- Pitfalls of PRN Therapy
- *Eric Schneider, MD*



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“Susan”

Demographics
74-year-old
Female

Diagnosis
nAMD, right eye

Current Presentation

Self-referred for ongoing anti-VEGF treatment

- Previously treated at fixed 4-week interval by her previous doctor

Six months ago, she developed endophthalmitis

- Recovered BCVA following PPV/intravitreal antibiotics
- She is now very hesitant about receiving further injections.
- She agreed to resume injection therapy, but only with as needed (“PRN”) administration

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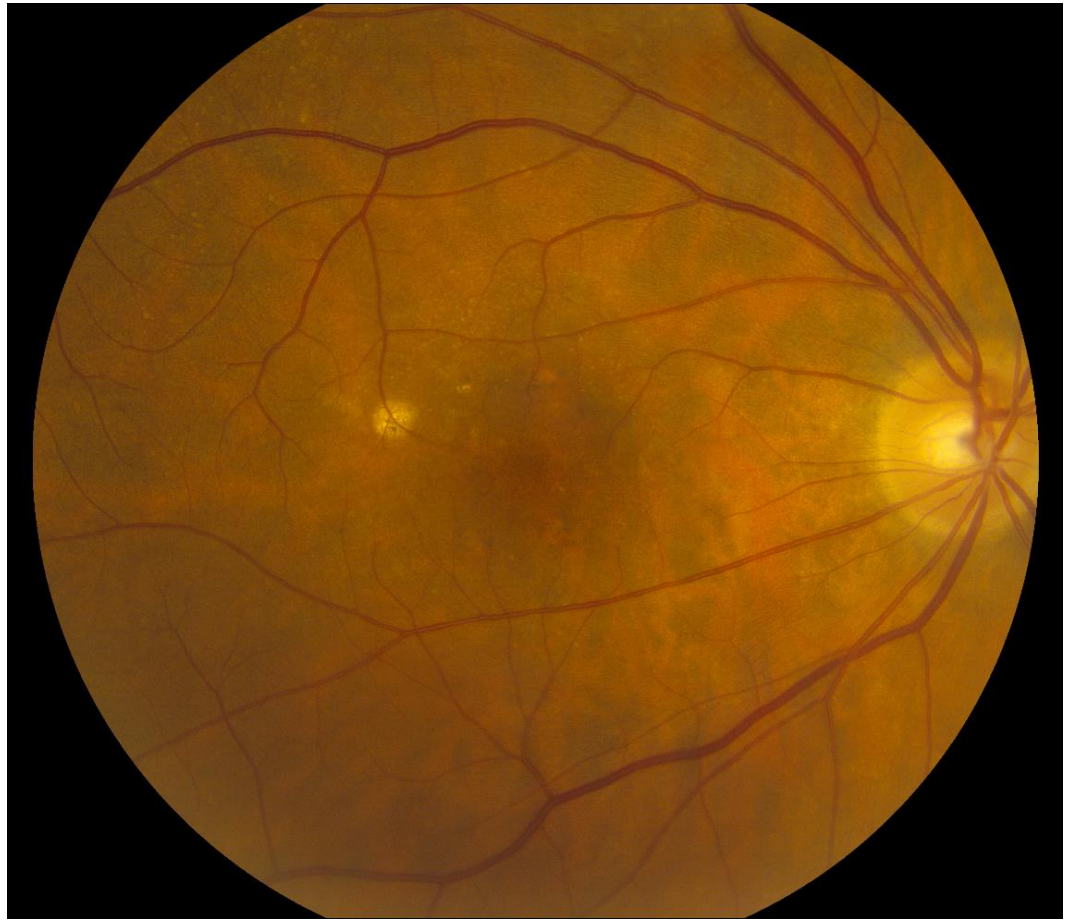
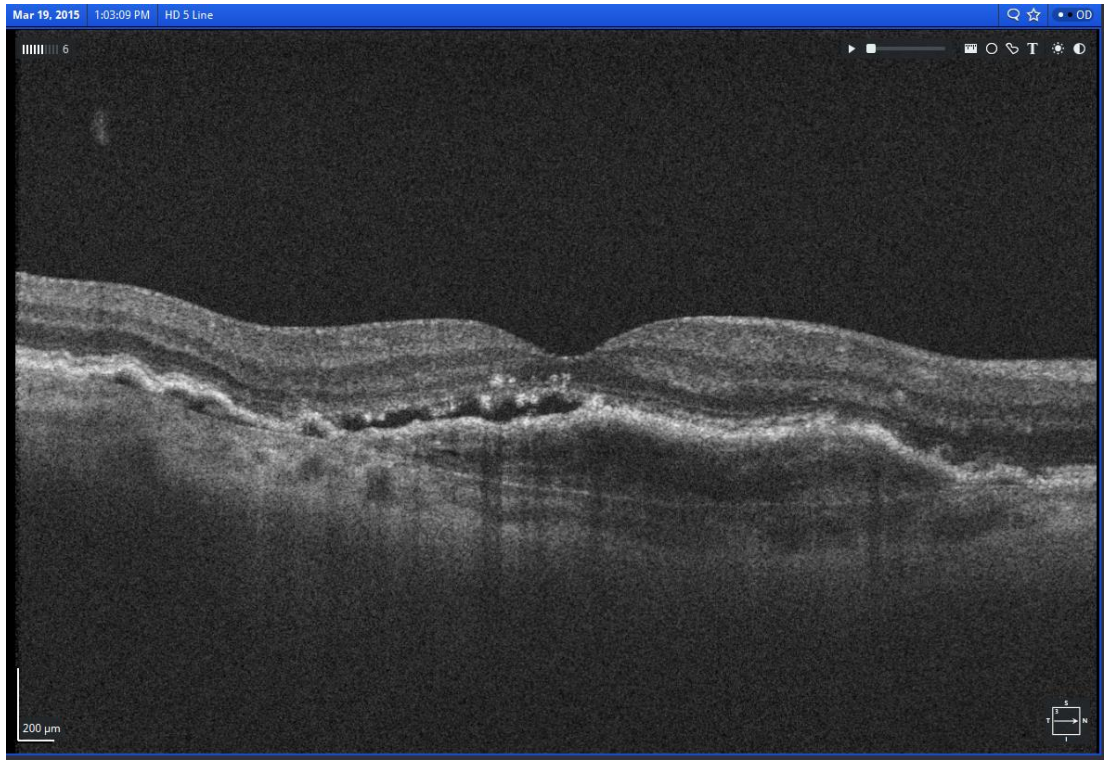
History: Initial Visit

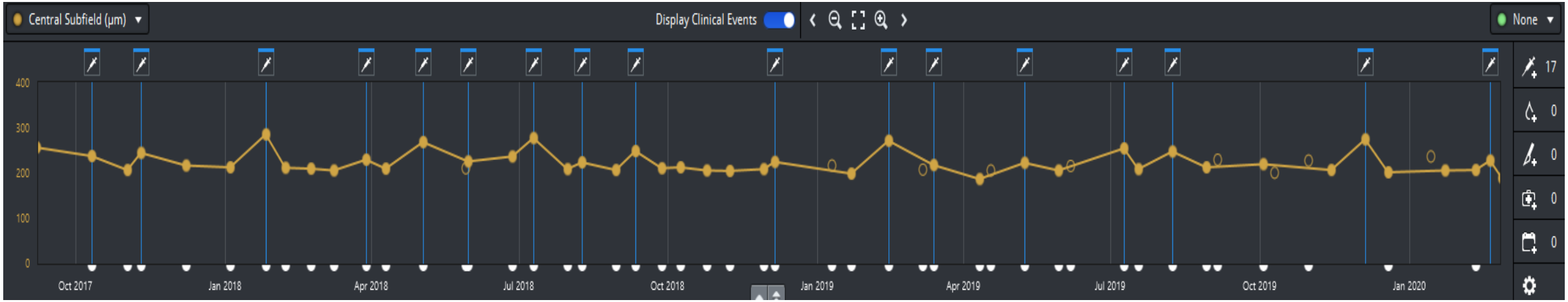




Treatment History

PRN Therapy → Fluid Fluctuations

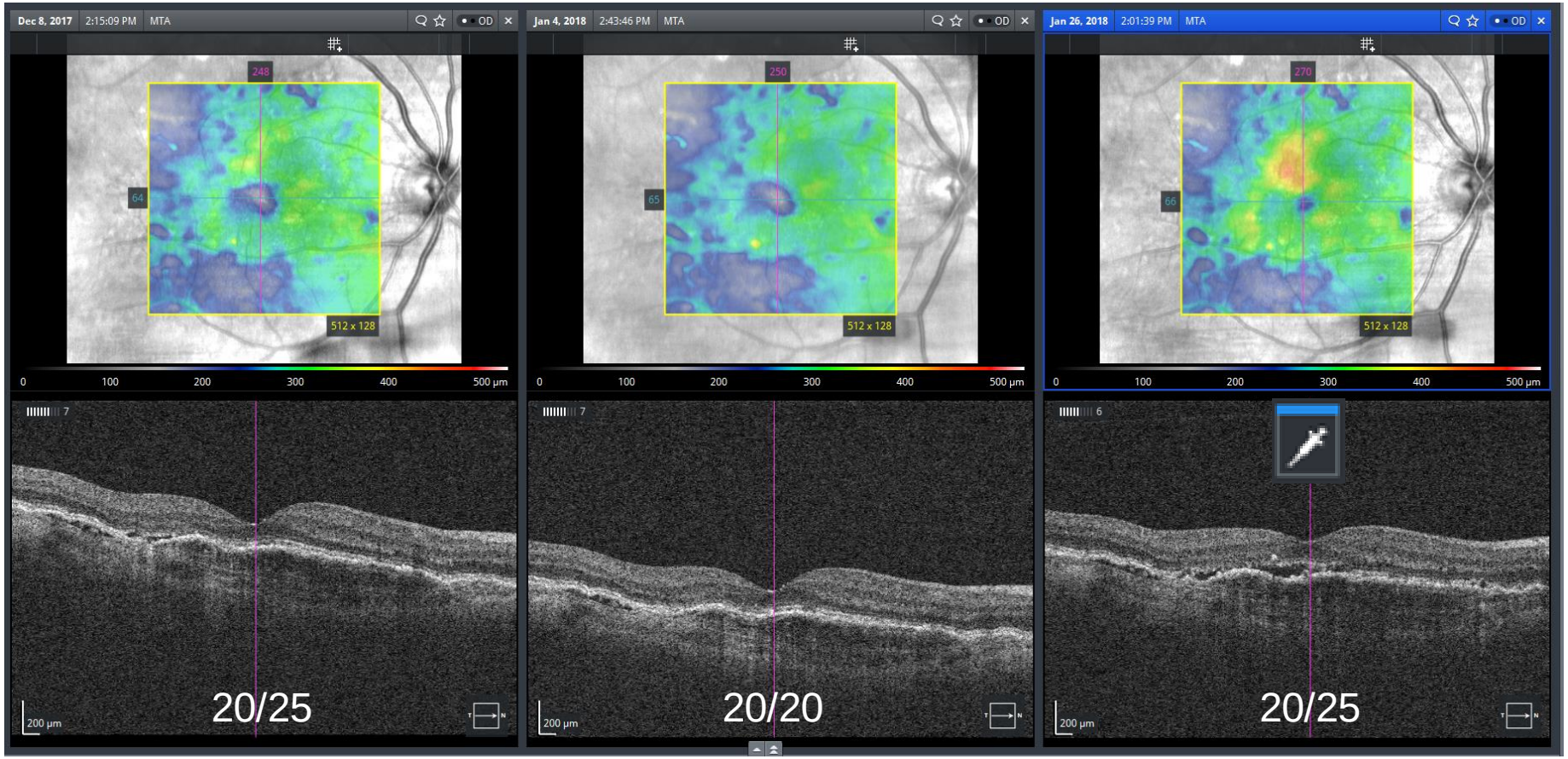
October 2017 – January 2020

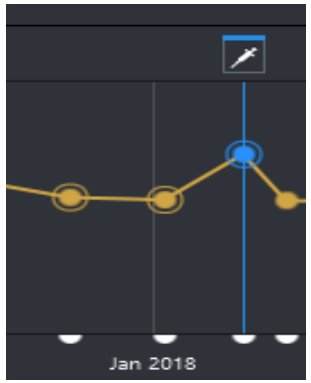


= Aflibercept injection

= Central field subfield thickness

PRN Therapy → Fluid Fluctuations





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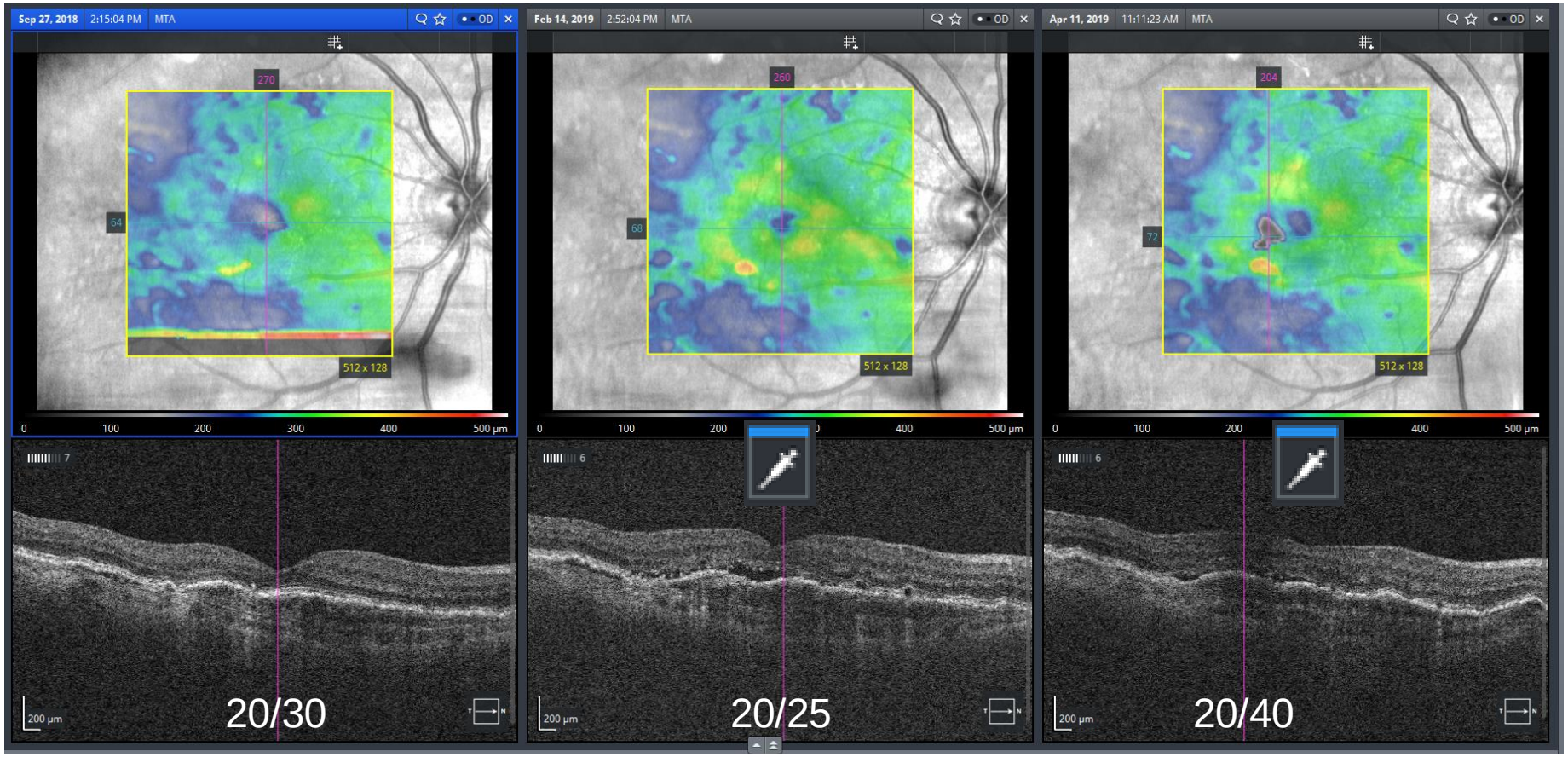
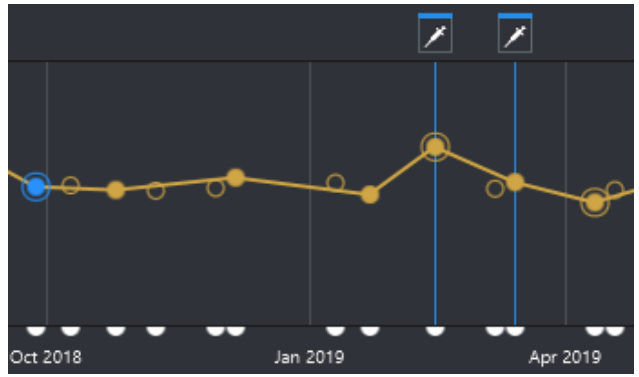
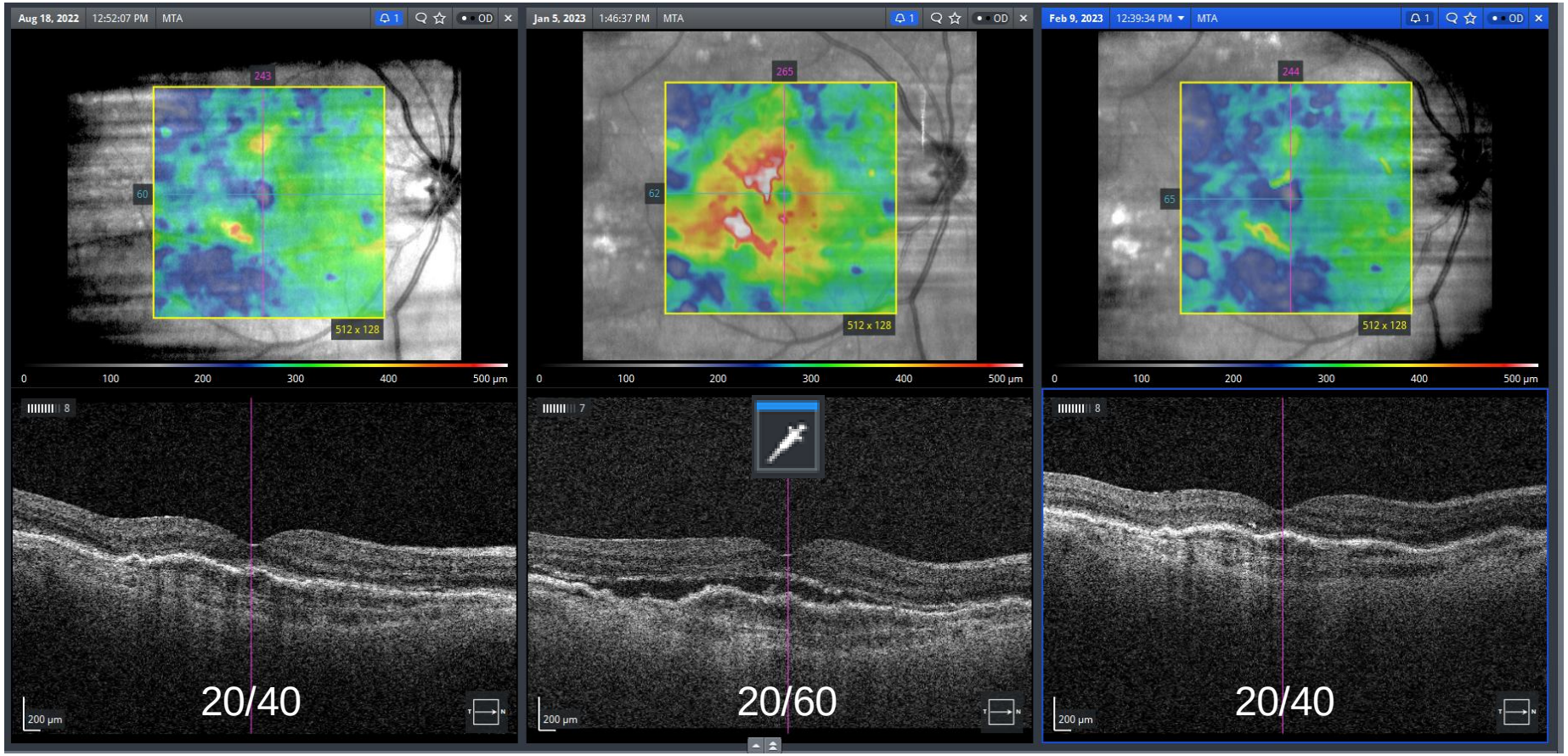
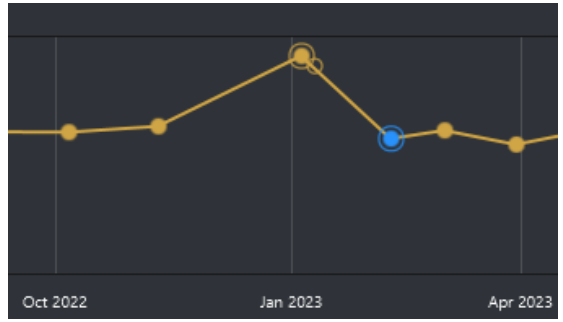
PRN Therapy → Fluid Fluctuations



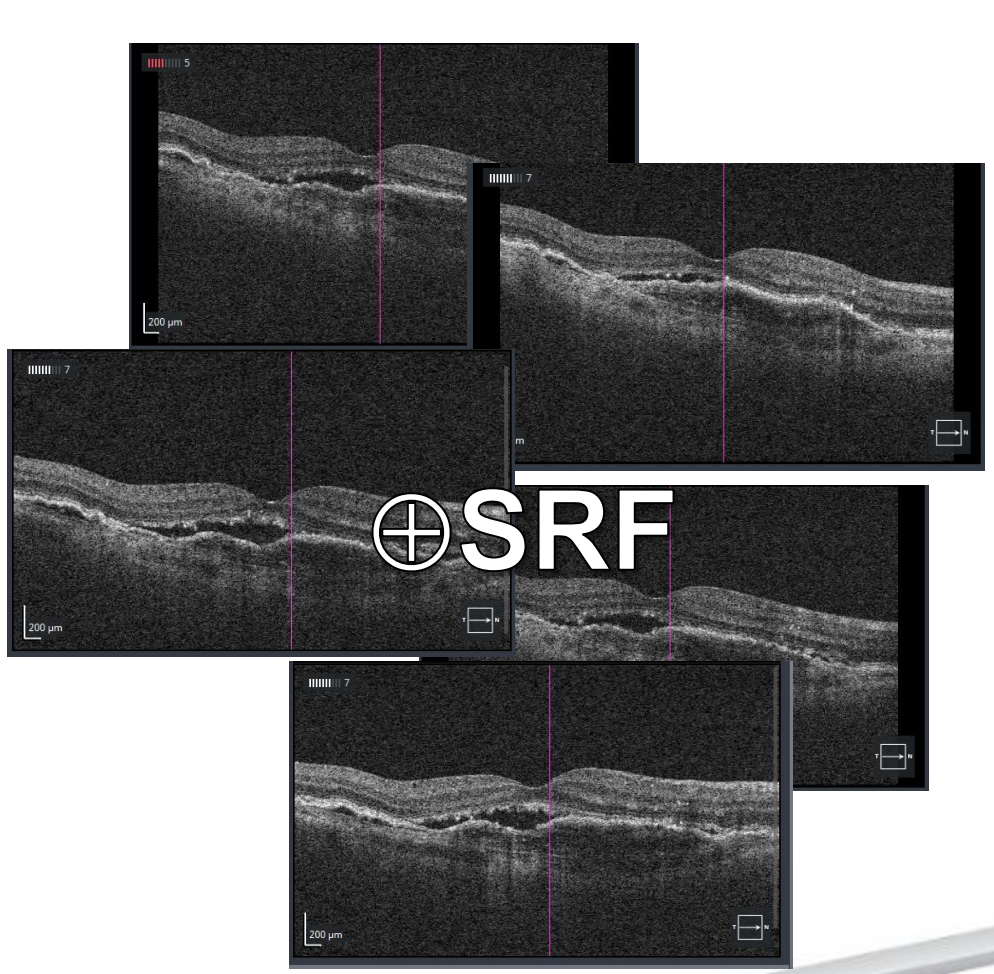


PRN Therapy → Fluid Fluctuations





PRN Therapy → Fluid Fluctuations



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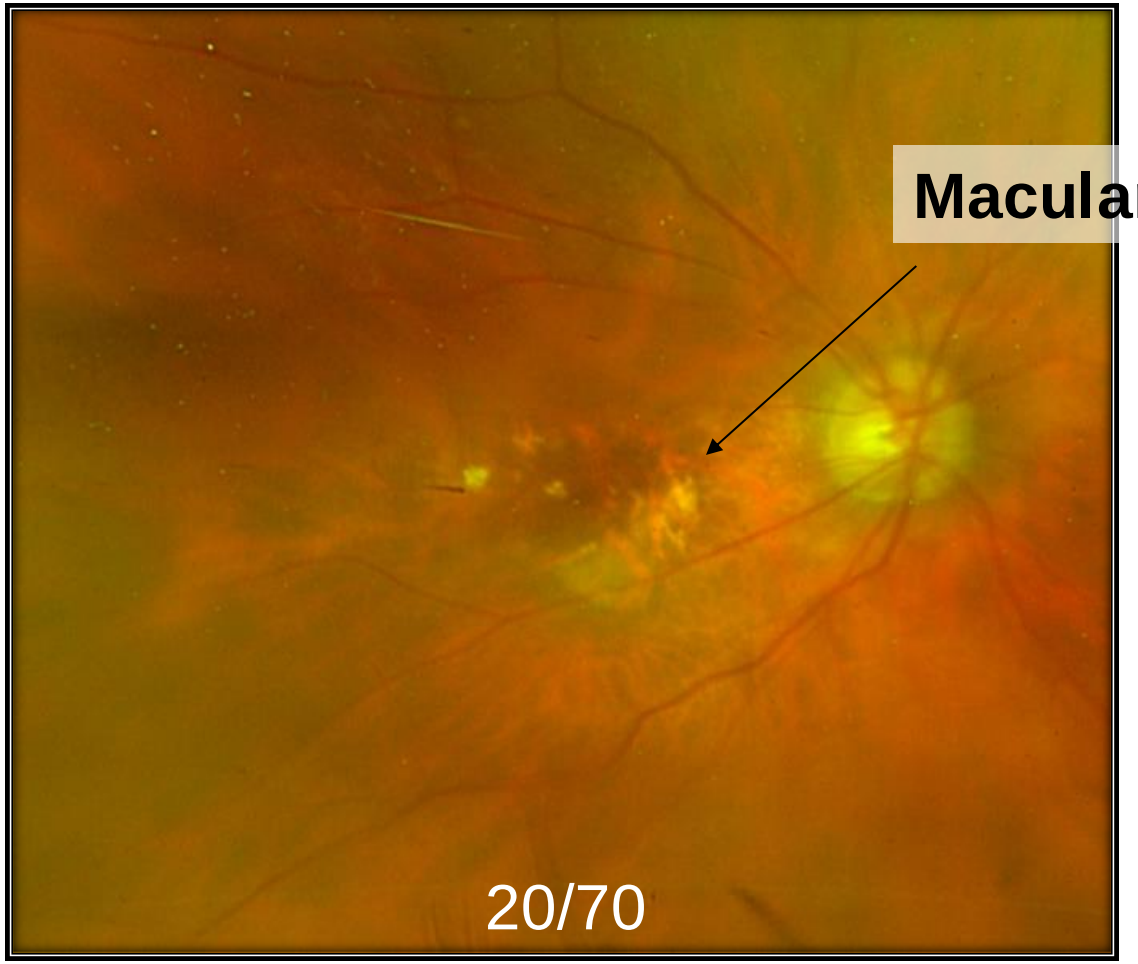
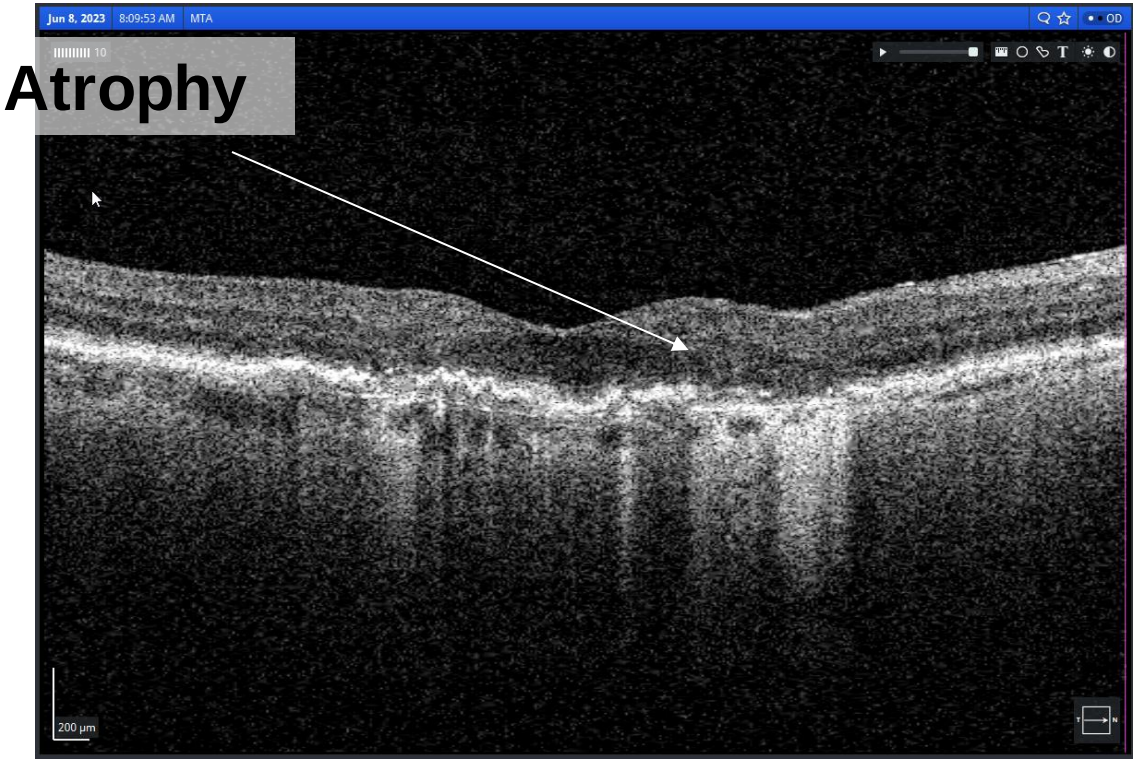
History: Most Recent Visit



Macular Atrophy



PRN Therapy: Consequences?

*Associations of **Variation** in Retinal Thickness with Visual Acuity and Anatomic Outcomes in Eyes with Neovascular Age-Related Macular Degeneration Lesions Treated with Anti-Vascular Endothelial Growth Factor Agents*

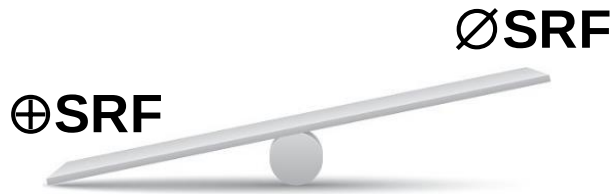
Evens RN, et al. *JAMA Ophthalmol.* 2020;138(10):1043-1051.

*Effect of Retinal Thickness **Variability** on Visual Outcomes and Fluid Persistence in Neovascular Age-Related Macular Degeneration, A post Hoc Analysis of the HAWK and HARRIER Studies*

Dugel PU, et al. *Retina*. 2022;42(3):511-518.

***Fluctuations** in Central Foveal Thickness and Association with Vision Outcomes with anti-VEGF Therapy for nAMD: HARBOR Post Hoc Analysis*

Sheth V, et al. *BMJ Open Ophthalmol*. 2022;7(1):e000957.



Greater Fluctuation/Variation in Macular Thickness

↓

Worse BCVA + More Macular Atrophy

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Reflection Point

Considering Susan's case, what would you have done differently?

A. Continued with fixed-dose administration
B. Implemented a treat-and-extend regimen
C. Monitored her more closely on a PRN regimen
D. Considered lower burden treatment options like high-dose therapy or implants

Dosing Strategies: Fixed and PRN

Fixed Dosing

Advantages

Consistent treatment
Predictable outcomes
Less frequent imaging

Disadvantages

Non-individualized
Over-treatment
High treatment burden
Higher cost

PRN

Advantages

Lower treatment burden
Cost effective
More personalized

Disadvantages

Fluid fluctuations
Allows for recurrent disease
Risk of irreversible tissue damage
Inconsistent response
Frequent monitoring

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Volkmann I, et al. *BMC Ophthalmol.* 2020;20(1):122.

Dosing Strategies: Treat and Extend

Best of Both

TE combines aspects of both with continuous regimen with a “PRN” or variable interval approach that avoids the disadvantages of each method[1]

Benefits

Individualized TE regimens have been shown to:[1]

- Increase persistence on therapy
- Achieve VA gains nearly comparable to clinical trials

Machine Learning

Machine learning has been shown to predict treatment demand and personalize the TE interval.[2]

1. Volkmann I, et al. *BMC Ophthalmol.* 2020;20(1):122.
2. Gallardo M, et al. *Ophthalmol Retina.* 2021;5(7):604-624.

TE versus Alternative Regimens

Systemic Review and Meta-Analysis

Aim: To compare the efficacy and treatment burden of TE versus fixed and PRN dosing for nAMD

VA Improvement

- Similar with TE and fixed dosing at 1 and 2 years
- TE was significantly better than PRN dosing at 1* and 2 years†
- Fewer ranibizumab injections were administered in the TE arm at 1‡ and 2 years§ versus fixed dosing

Conclusions

- TE preserves VA similar to fixed dosing, but with less injections at years 1 and 2
- TE achieved better VA outcomes than PRN
- TE was associated with more injections than PRN

*MD: 3.95 letters, *P*<.0001; †MD 4.08 letters, *P*<.001; ‡MD -2.42 injections, *P*<.0001; §MD -6.06 injections, *P*<.00001

Rosenberg D, et al. *Eye (Long).* 2023;37(1):6-16.

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Case 2

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“Joe”

Demographics
72-year-old
Male

Diagnosis
nAMD x 3 years

Current Presentation

- Started treatment with ranibizumab 0.05 mL IVT q4w
- Saw significant improvement on OCT and VA testing
- Persisted with treatment for 12 months after which he retired and expressed he had travel plans but felt restricted by his monthly treatment
- Doing very well on therapy, his interval was gradually extended over time to Q10W

“Joe”

Demographics

72-year-old
Male

Diagnosis

nAMD x 3 years

Current Presentation

- 8 months into his TE regimen, Joe was lost to follow-up for 4 months
- He returns today complaining of difficulty reading, driving, and recognizing faces
- Testing showed a decline in VA and increased fluid accumulation and new blood vessel growth on OCT

Reflection Point

Considering Joe's case, what would you have done differently?

A. Switched him to PRN dosing
B. Switched him to an implantable treatment option
C. Switched him to high-dose, extended interval therapy
D. Switched him to an agent with a longer dosing interval
E. Advised him to coordinate his travel around his treatment schedule

High-Dose (HD) Aflibercept (Approved)

Phase 2 CANDELA Investigating Aflibercept: 8 mg vs 2 mg[1,2,3]

Randomized, single-masked, open-label, non-inferiority trial

Endpoints

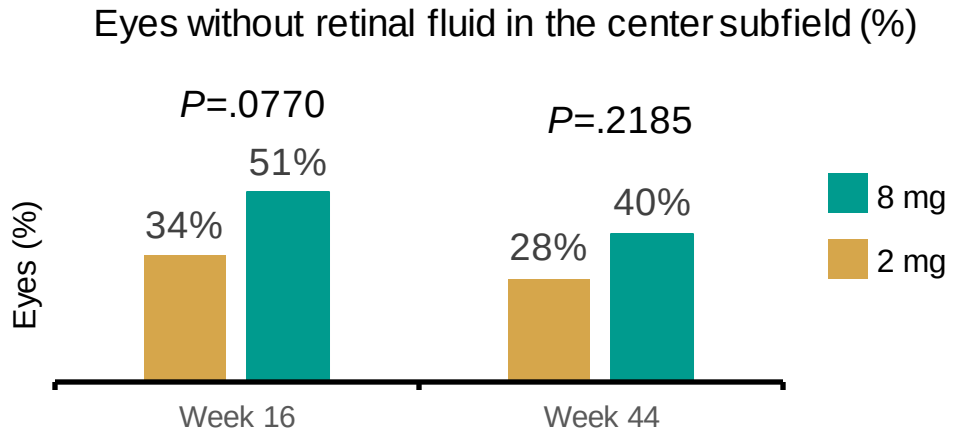
Safety

Efficacy: Eyes without retinal fluid in the center subfield at Week 16 (%)

Population

nAMD
Treatment naïve
Age ≥50 years
BCVA: 78 to 24 letters

Results: HD Regimens Non-inferior to Standard



HD Aflibercept May Improve Outcomes, Reduce Treatment Burden in Suboptimal Responders[4]

Retrospective Analysis (N=318 eyes of 288 adults)

Endpoints

Visual Acuity
OCT Outcomes
Injection Burden

Population

Suboptimal responders (with nAMD or DME) to standard dose aflibercept

Results

Efficacy

Mean BCVA improved significantly with AMT, maintained with IAE*

Central subfield thickness decreased significantly

Mean injection intervals increased or remained stable

Safety

No new safety signals

*Injection interval: AMT: ≤35 days, IAE: >36 days.

1. Brown DM. *IVOS.* 2022;1345-F0179; 2. Goren Fein J. ARVO 2023. Abstract 2180-C0133; 3. Wykoff CC, et al. *JAMA Ophthalmol*. 2023 Aug 3. [Online ahead of print]; 4. Neilsen JS, et al. *J Vitreoretin Dis*. 2023;7(2):116-124.

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High-Dose (HD) Aflibercept (Approved)

Phase 3 PULSAR Trial Investigating Aflibercept 2 mg q8 versus HDq12, HDq16

Randomized, double blind, active-controlled trial, non-inferiority trial

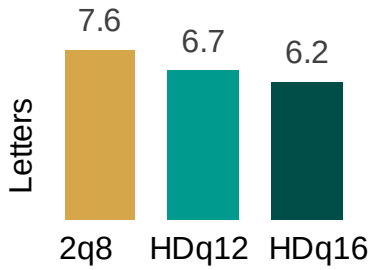
1

Primary
Change in BCVA from baseline (Week 48)

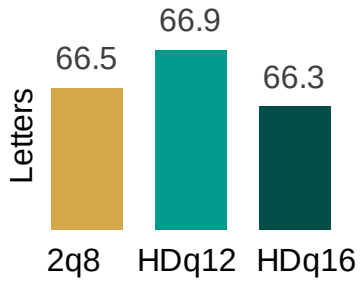
2

Secondary
Patients without fluid in central subfield (Week 16)
Additional efficacy measures, safety, and PROs

Mean Observed BCVA Improvement

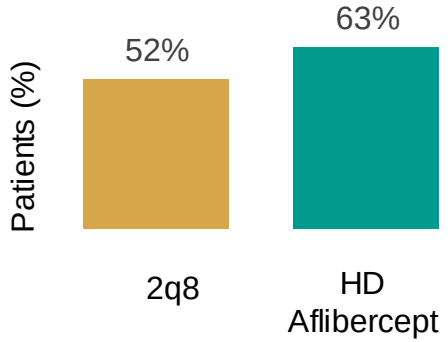


Mean Observed BCVA at Week 48



HDq12 vs 2q8: Δ -0.97, *P*=.0009
HDq16 vs 2q8: Δ -1.14, *P*=.0011

Patients without fluid in central subfield (Week 16)



Safety: No new safety signals

Results suggest HD regimens are non-inferior to standard

2q8 N=167; HDq12 N=326; HDq16 N=163

Lanzetta P, et al. AAO 2022. NCT04423718

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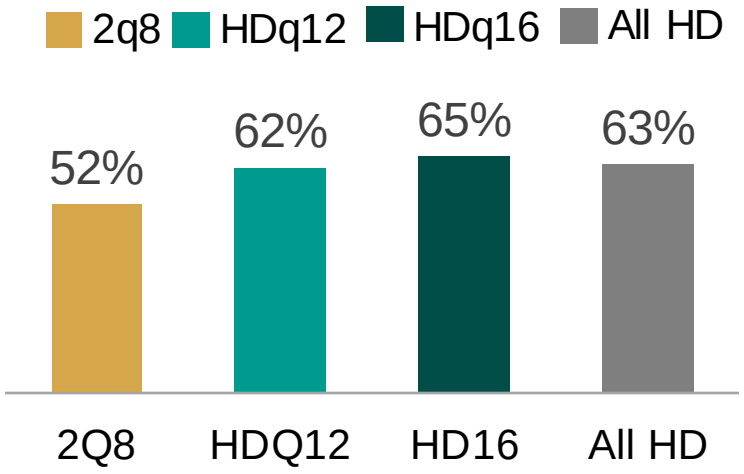
High-Dose (HD) Aflibercept (Approved)

Phase 3 PULSAR Trial Investigating Aflibercept 2 mg q8 (2q8) versus HDq12, HDq16

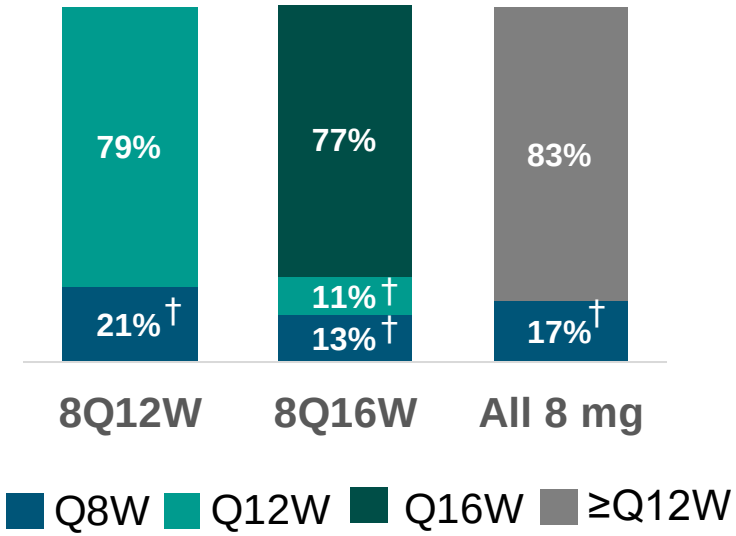
Randomized, double blind, active-controlled, non-inferiority trial

Patients Without Retinal Fluid in Center Subfield at Week 16



All HD vs 2Q8: *P=.0002, demonstrating superior drying*

Proportion of Patients Maintaining HDq12 and HDq16 Through Week 48



By 96-Weeks:

88% Were on a ≥12-week interval

Maintained a ≥12-week interval **78%**

71% Met criteria for even longer dosing intervals:

- 47% ≥20-week intervals
- 28% ≥24-week intervals

HD=8 mg

NCT04423718. †*Interval shortened based on DRM assessments at some point through Week 48*

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

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Ranibizumab Refillable Implant PDS (Approved*)

Phase 2 Ladder Clinical Trial: End of Study Results[1]

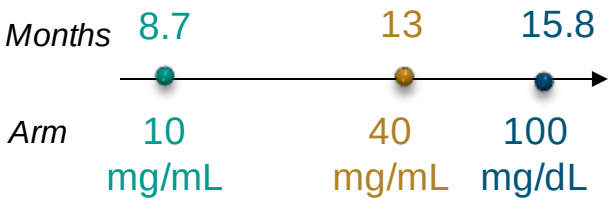
Randomized, double blind, active-controlled trial

Population: Patients with nAMD who previously received and responded to ≥2 anti-VEGF injections

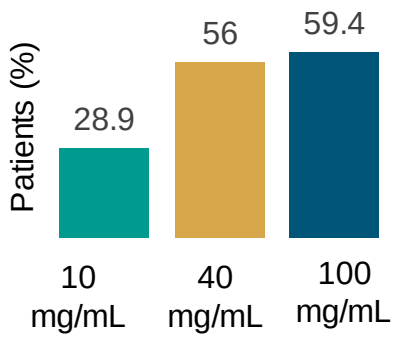
Treatment Arms: 10 mg/mL PDS, 40 mg/mL PDS, 100 mg/mL PDS, 0.5 mg/mL monthly intravitreal injections (control). PDS arms received **refills as needed** (PRN).

1 Primary Endpoint

Time to First Implant Refill



Patients Not Receiving any Refill for ≥12 Months



2 Secondary Endpoints

BCVA Improvement (Month 22, ETDRS):

Mean Central Foveal Thickness (CTF) Change from Baseline

At month 22, adjusted mean CFT change from baseline was similar between the 100 mg/mL and active control groups.

End-of-study results reinforce outcomes observed earlier at 9 months[2]

PDS: Port Delivery System. ***Voluntarily recalled*** due to septum dislodgement. Current patients may continue with refills, but no new devices can be implanted. 1. Khanani AM, et al. *Ophthalmol Retina.* 2021;5(8):775-787; 2.Campochiaro PA, et al. *Ophthalmol.* 2019;126(8):1141-1154.

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Ranibizumab Refillable Implant PDS (Approved*)

Phase 3 Archway Trial: 2-Year Results

Open-label, randomized, visual acuity assessor-masked noninferiority and equivalence trial

Population: Patients (N=415) with nAMD who were previously treated and responded to anti-VEGF injections

Treatment Arms: 100 mg/mL ranibizumab PDS with **fixed 24-week refills** (q24w), 0.5 mg/mL intravitreal ranibizumab injections q4w

1 Primary Endpoint

Change in BCVA (ETDRS letters) score§

Weeks Averaged	Difference in Adjusted Means	(95%CI)	
44 and 48	-0.2	-1.8	+1.3
60 and 64	0.4	-1.4	+2.1
88 and 92	-0.5	-2.5	+1.3

2 Secondary Endpoints

Change in BCVA score over time and *change in CPT from baseline* were generally the same between the 2 treatment arms.

***Voluntarily recalled**. §Noninferiority margin, –3.9 ETDRS letters; PDS: Port Delivery System

1. Holekamp NM, et al. *Ophthalmol.* 2022;129(3):295-307.
2. Regillo C, et al. *Ophthalmol.* 2023;130(7):735-747.

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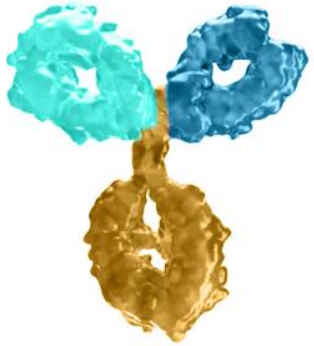
Faricimab (Approved)

Bispecific antibody targeting Ang-2 and VEGF-A

Reduces AH Ang-2 and VEGF-A levels, with Ang-2 suppression maintained through 16 weeks after dosing[1]

Anti-Ang-2



Anti-VEGF-A

Approved Dosing

1- to 4-month intervals*

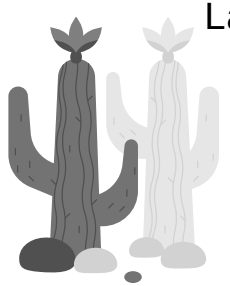
TENAYA and LUCERNE trials (total N=1329)

Faricimab was non-inferior to aflibercept 2Q8[2]

Faricimab meaningfully extended the treatment interval with sustained efficacy[2]

By 2-years, ~80% of patients achieved ≥Q12W dosing[3]

Faricimab resulted in greater CST reduction from baseline[4†]



Larger proportion of patients achieving absence of **SRF** and **IRF** on faricimab[4†]

Patients with baseline SRF and IRF, absence of SRF and IRF was achieved **faster** with faricimab and with **fewer** injections[4†]

AH: Aqueous humor; CST: Central subfield thickness; IRF: Intraretinal fluid; SRF: Subretinal fluid. *Depending on patient response and evaluation, †vs. aflibercept 2q8;

1. Muni RH, et al. ASRS. July 28-Aug 1, 2023. Paper Presentation; 2. Heier JS, et al. *Lancet*. 2022;399(10326):729-740; 3. Zarbin M, et al. ASRS. July 29, 2023. Paper Presentation; 4. London NJ, et al. Paper presentation at: ASRS Annual Meeting; 28 July – 1 August 2023.

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FDA Approved Dosing Regimens

	Aflibercept 2 mg	Aflibercept 8 mg	Faricimab 6 mg	Ranibizumab 0.5 mg	Ranibizumab PDS[§] *Voluntarily recalled**
Q4W	Q4W for the first 3 doses	Q4W for the first 3 doses[†]	Q4W for the first 4 doses	Recommended regimen	
Q8W	An option after 3 initial Q4W doses[§]	An option after 3 initial Q4W doses[‡]	An option based on VA and OCT evaluation[§]		
Q12W	An option after 1 year of effective therapy, but *less effective*[§]	An option after 3 initial Q4W doses[‡]	An option based on VA and OCT evaluation[§]	An option after 4 Q4W doses, but *less effective*[§]	
Q16W		An option after 3 initial Q4W doses[‡]	An option based on VA and OCT evaluation[§]		
Q24W					Option after response to 2 injections of an anti-VEGF medication

*Recall was due to septum dislodgement. Recall does not affect the 100 mg/mL vial for refill-exchange solution, refill needles, and explant tools. Existing patients can continue with refills. For more on the recall: Sharma A, et al. *Int J Retina Vitreous.* 2023;9(1):6.

[§]Patients may require supplemental injections based on individual evaluations. Assess patients regularly. [†]Interval is ±7 days. [‡]Interval is ±1 week.

Aflibercept [prescribing information. https://tinyurl.com/2p8tt7ay; Ranibizumab [prescribing information]. https://tinyurl.com/3k9n62x7; Ranibizumab PDS [prescribing information]. https://tinyurl.com/3j9ncub3; Faricimab [prescribing information]. https://tinyurl.com/32yztcmd.

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Adverse Events

Key Adverse Events Related to Anti-VEGF Therapy and Intravitreal Injections[1,2,3,4]

- Endophthalmitis
- Retinal detachments
- Increased IO pressure within 60 mins of injection
- Arterial thromboembolic events
  - Nonfatal stroke
  - Nonfatal myocardial infarction
  - Vascular death
- Conjunctival hemorrhage
- Eye pain
- Cataract
- Vitreous detachment
- Vitreous floaters

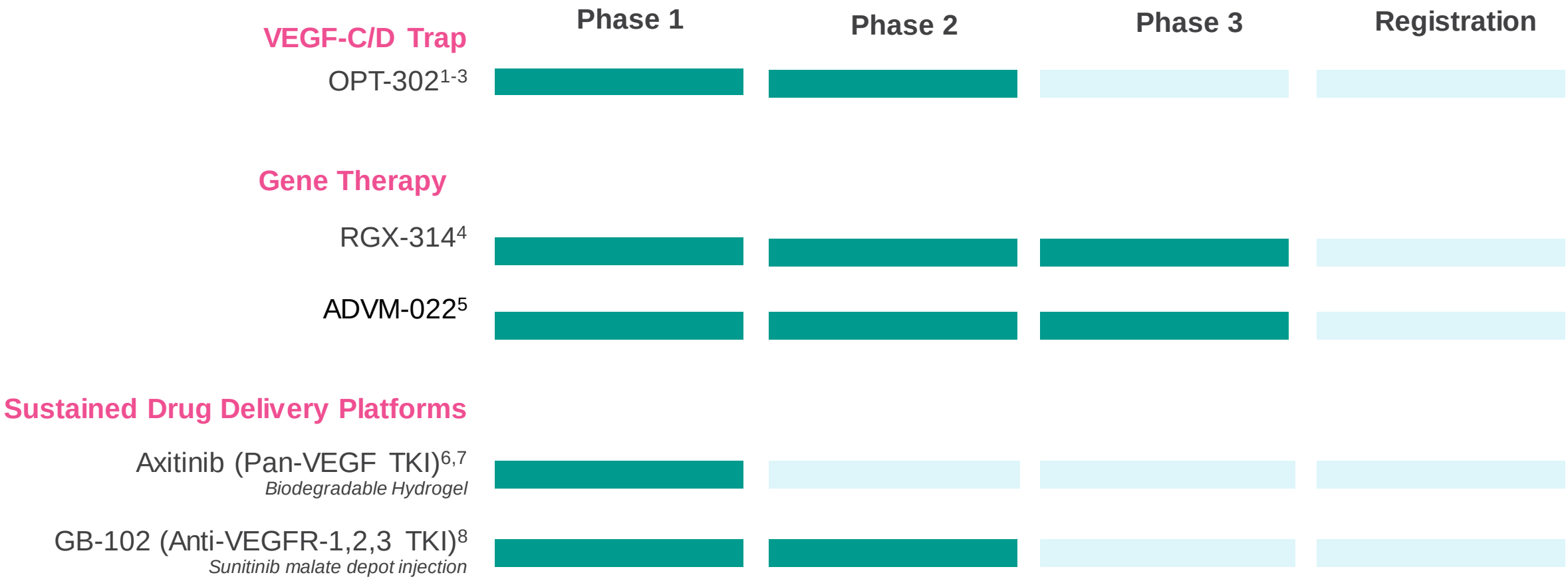
Key Adverse Events Related to PDS Implantation and Refill Procedures[5,6]

Conjunctival retraction
Conjunctival erosion
Endophthalmitis
Implant dislocation
Conjunctival blebs or conjunctival filtering bleb leaks
Wound leaks
Hypotony
Choroidal detachment
Vitreous hemorrhage
Rhegmatogenous retinal detachment
Cataract
Septum dislodgement

AEs were well understood, manageable, and did not prevent achievement of optimal outcomes in most cases

1. Schneider E. ARVO 2023. Abstract 3724-C0501; 2. Ranibizumab [prescribing information]. https://tinyurl.com/3k9n62x7;
3. Faricimab [prescribing information]. https://tinyurl.com/393vmcnk; 4. Aflibercept [prescribing information]. https://tinyurl.com/5dca267z;
5. Awh CC, et al. *Ophthalmol Retina.* 2022;6(11):1028-1043; 6. Sharma A, et al. *Int J Retina Vitreous.* 2023;9(1):6.

Emerging Agents



1. Dugel PU, et al. *Ophthalmol Retina.* 2020;4(3):250-263; 2. Jackson TL, et al. *Ophthalmol*. 2023;130(6):588-597; 3. NCT03345082; 4. NCT04514653, NCT04704921; 5. NCT03748784, NCT05536973, NCT04645212; 6. Ciulla T, Kansara V. The Macula Society. Feb 19-22, 2020. San Diego, CA; 7. NCT03630315; 8. NCT03953079, NCT03249740.

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Thank you!

Please remember to fill out the post-test and evaluation to receive CME credit.