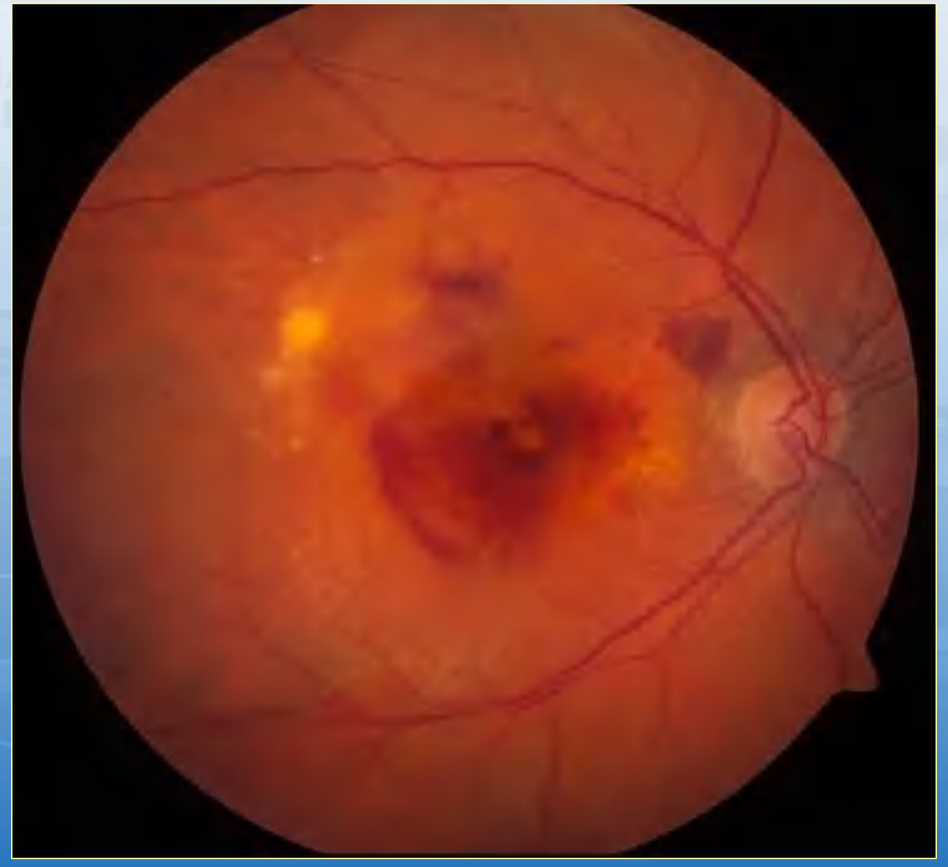
Advances in Macular Degeneration Treatments

Mark Barakat, MD

Neovascular (Wet) AMD



Neovascular (Wet) AMD

Current Anti-VEGF Options

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab
    - Off-Label Usage

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab
    - Off-Label Usage

The NEW ENGLAND JOURNAL of MEDICINE

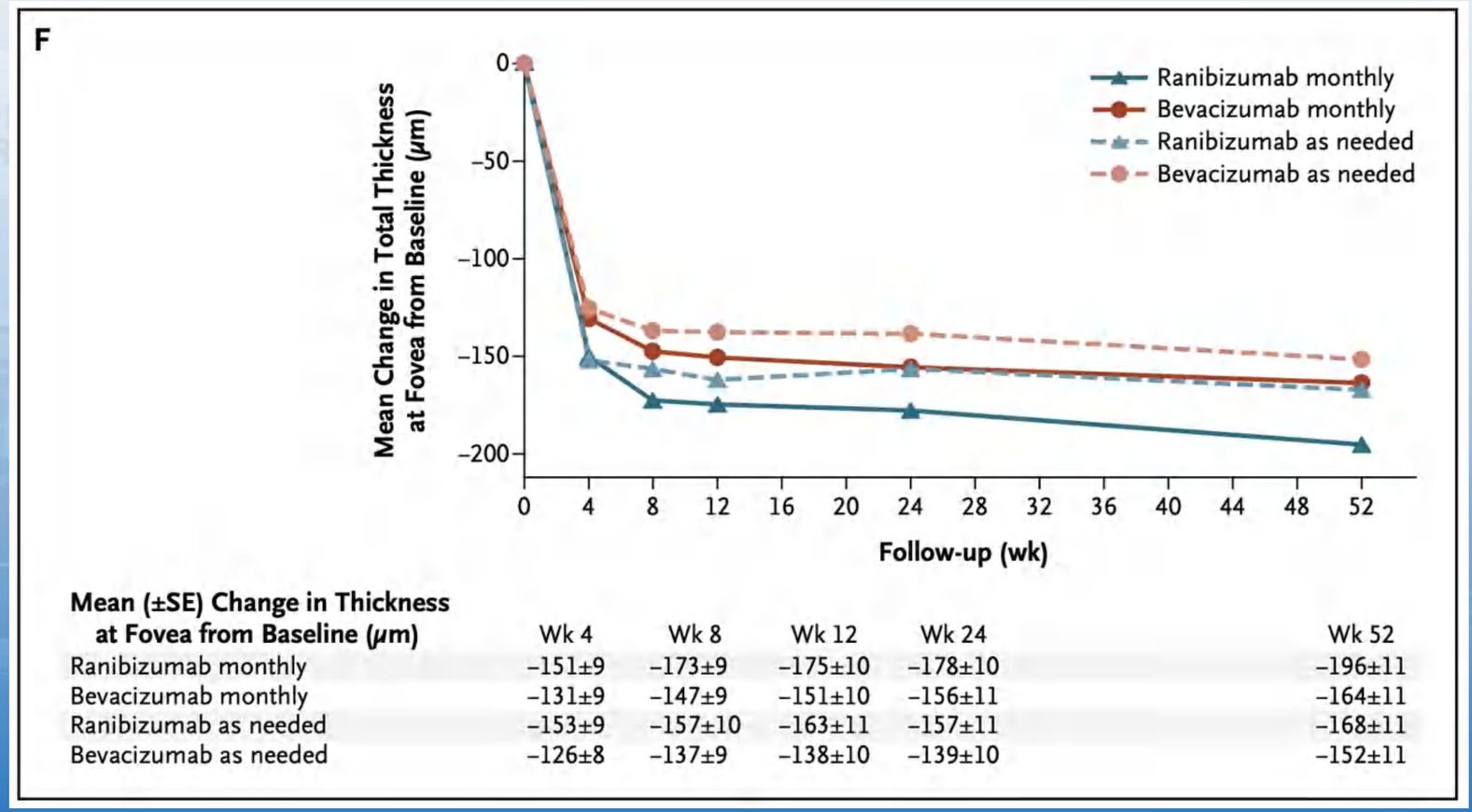
ESTABLISHED IN 1812 MAY 19, 2011 VOL. 364 NO. 20

Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration

The CATT Research Group*

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab
    - Off-Label Usage



Mean (±SE) Change in Thickness at Fovea from Baseline (μm)	Wk 4	Wk 8	Wk 12	Wk 24	Wk 52
Ranibizumab monthly	−151±9	−173±9	−175±10	−178±10	−196±11
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Bevacizumab as needed	−126±8	−137±9	−138±10	−139±10	−152±11

Neovascular (Wet) AMD

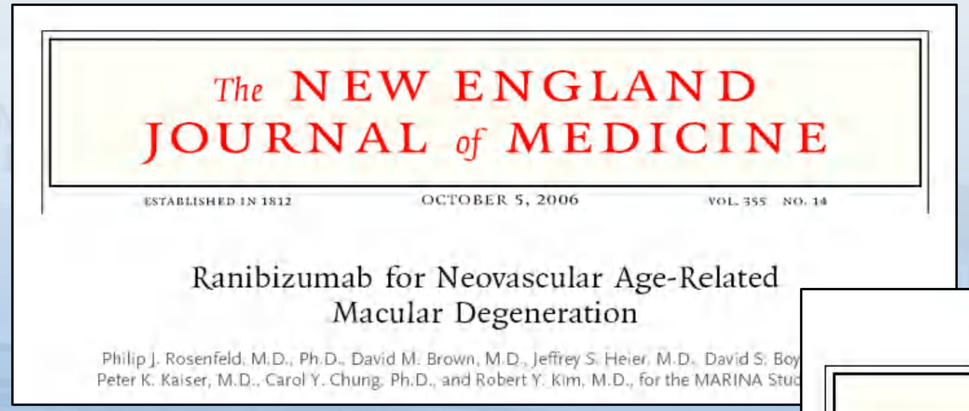
- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab

    - Off-Label Usage
  - Ranibizumab
    - Monthly Dosing

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab
    - Off-Label Usage

  - Ranibizumab
    - Monthly Dosing

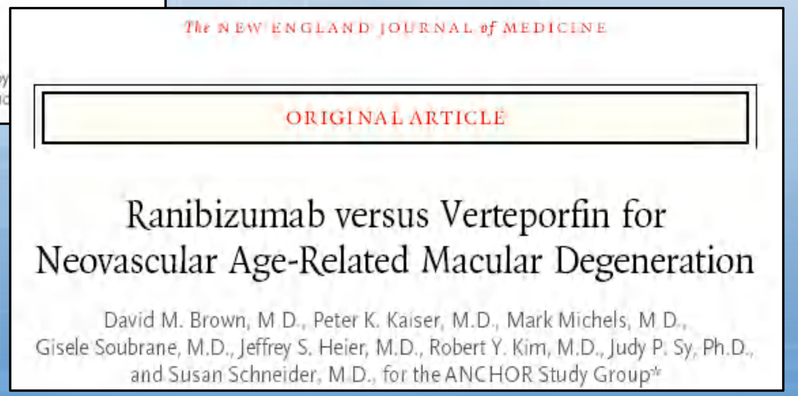


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 5, 2006 VOL. 355 NO. 14

Ranibizumab for Neovascular Age-Related Macular Degeneration

Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boy
Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D., for the MARINA Stud



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

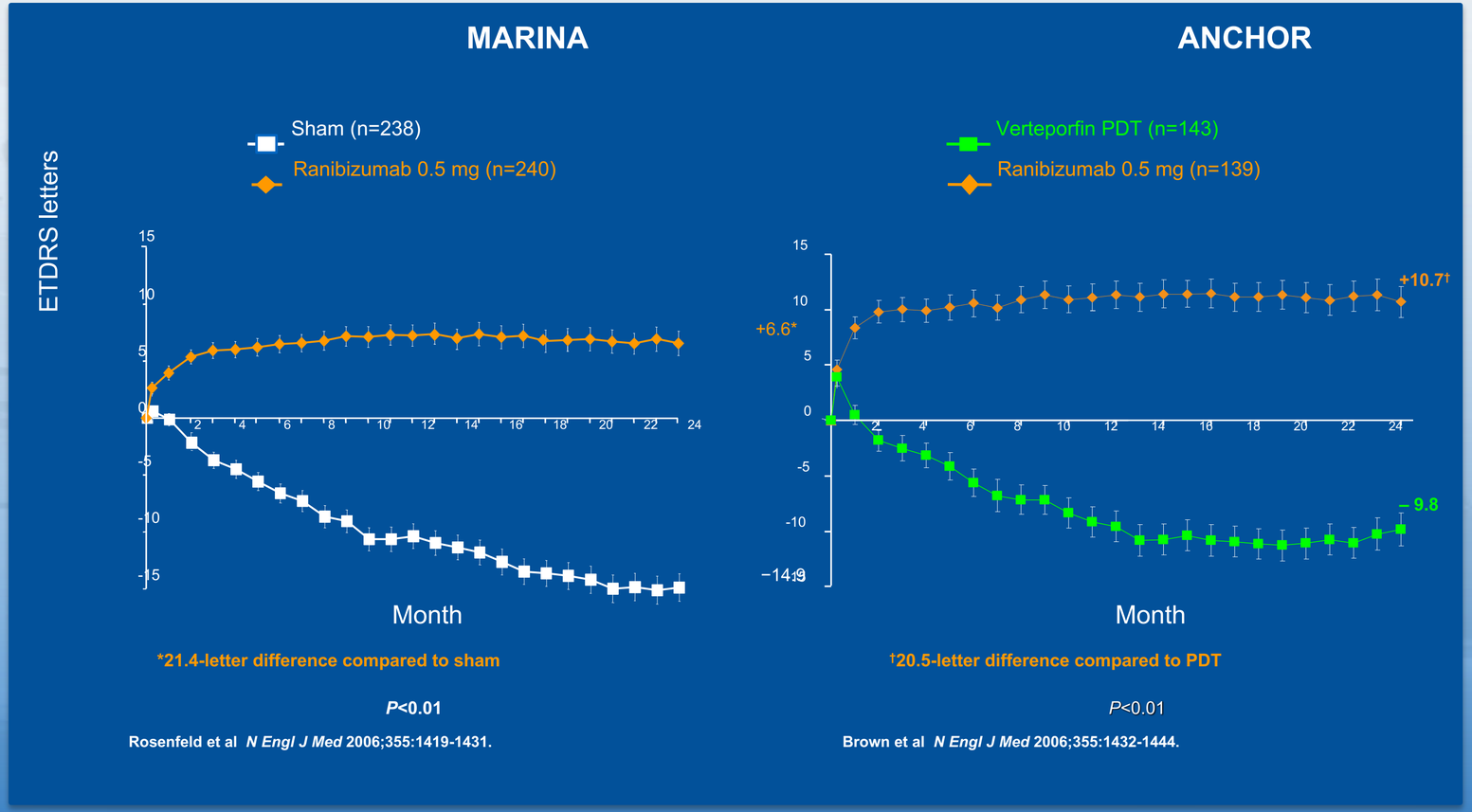
David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D., for the ANCHOR Study Group*

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab

    - Off-Label Usage
  - Ranibizumab

    - Monthly Dosing



Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:

  - Bevacizumab
    - Off-Label Usage

  - Ranibizumab
    - Monthly Dosing
  - Aflibercept
    - Bimonthly Dosing

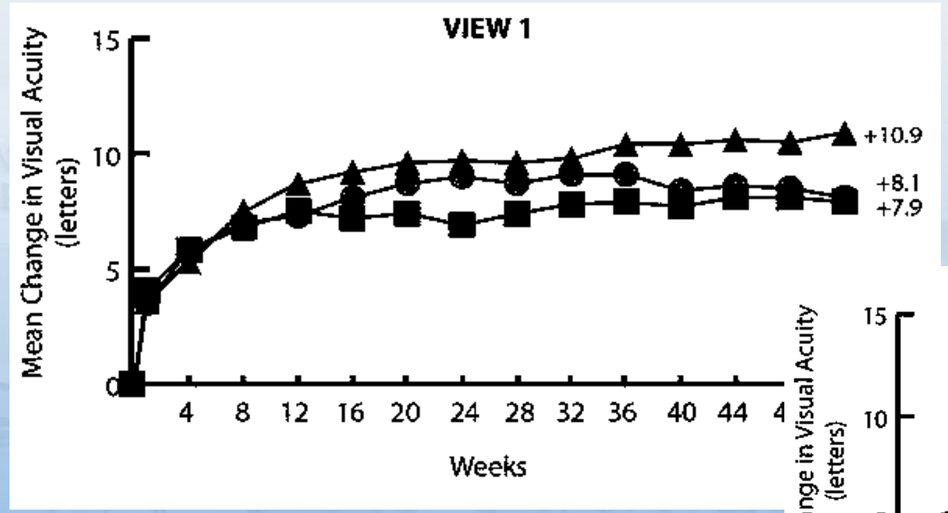
Neovascular (Wet) AMD

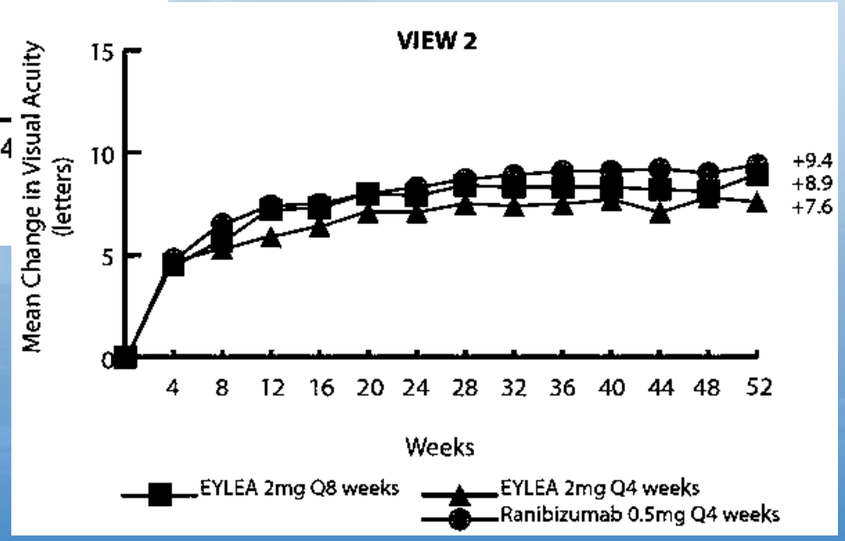
- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab

    - Off-Label Usage
  - Ranibizumab

    - Monthly Dosing
  - Aflibercept

    - Bimonthly Dosing





Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - 

Bevacizumab
    - Off-Label Usage
  - 
Ranibizumab
    - Monthly Dosing
  - 

Aflibercept
    - Bimonthly Dosing
  - Brolucizumab
    - 8- to 12-week Dosing

Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab

    - Off-Label Usage
  - Ranibizumab

    - Monthly Dosing
  - Aflibercept

    - Bimonthly Dosing
  - Brolucizumab

    - 8- to 12-week Dosing

Drug	bevacizumab	aflibercept	ranibizumab	brolucizumab
Format[1-5]	Full antibody (IgG1)	VEGFR1/2- Fc fusion protein	Fab fragment	Single-chain antibody fragment
Molecular structure				
Molecular weight[1-5]	≈ 149 kDa	97-115 kDa[a]	≈ 48 kDa	26 kDa
Clinical dose[2,3,5-7]	1.25 mg	2.00 mg	0.50 mg	6.00 mg
Equivalent molar dose	**0.4-0.5**	**1.0**	**0.5-0.6**	**11.2-13.3**

Neovascular (Wet) AMD

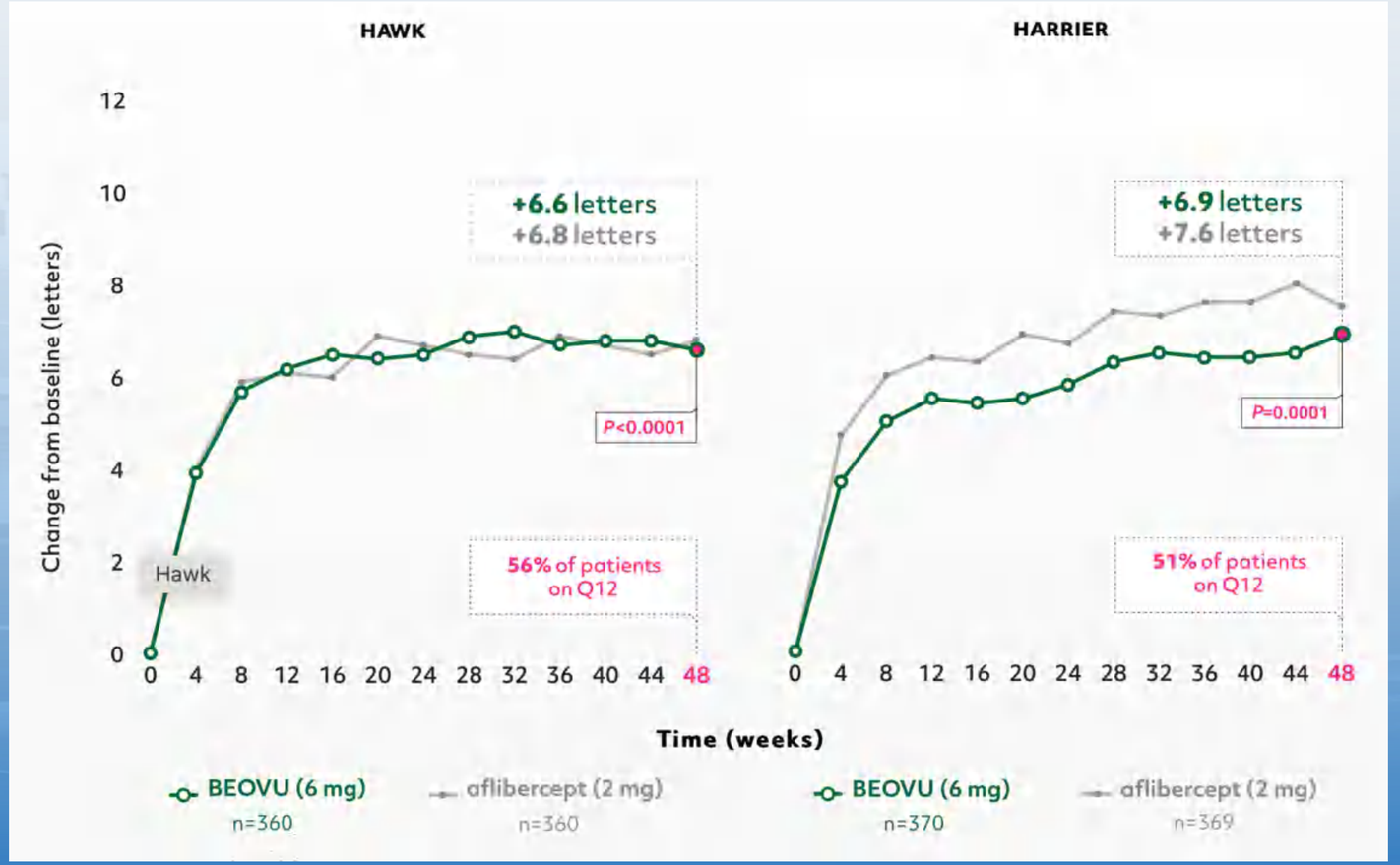
- Anti-Vascular Endothelial Growth Factor Treatments:
  - Bevacizumab

    - Off-Label Usage
  - Ranibizumab

    - Monthly Dosing
  - Aflibercept

    - Bimonthly Dosing
  - Brolucizumab

    - 8- to 12-week Dosing



Neovascular (Wet) AMD

- Anti-Vascular Endothelial Growth Factor Treatments:
  - 

Bevacizumab
    - Off-Label Usage
  - 
Ranibizumab
    - Monthly Dosing
  - 

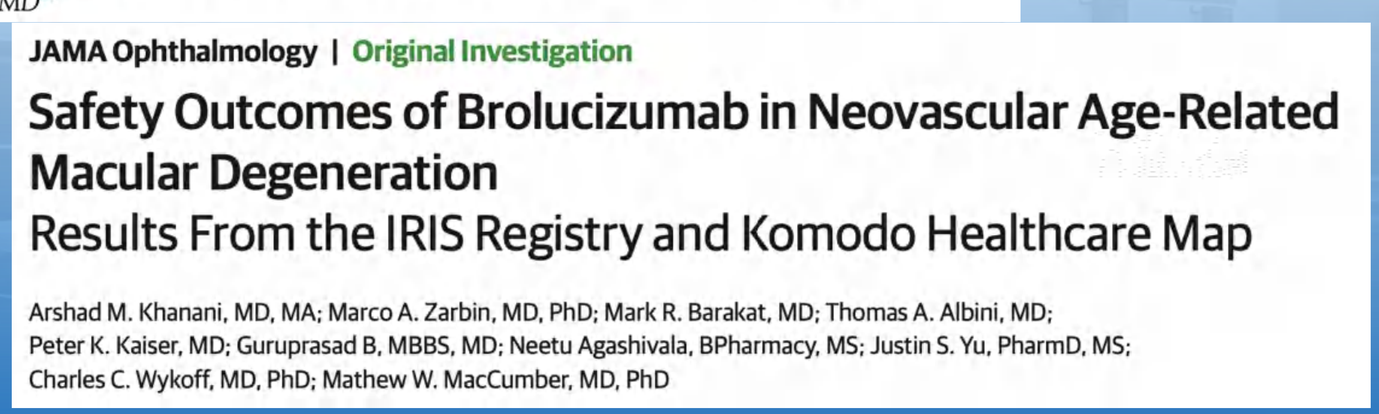
Aflibercept
    - Bimonthly Dosing
  - 

Brolucizumab
    - 8- to 12-week Dosing

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Retinal Vasculitis and Intraocular Inflammation after Intravitreal Injection of Brolucizumab

Caroline R. Baumal, MD,[1] Richard F. Spaide, MD,[2] Lejla Vajzovic, MD,[3] K. Bailey Freund, MD,[2,4] Scott D. Walter, MD,[5] Vishak John, MD,[6] Ryan Rich, MD,[7] Nauman Chaudhry, MD,[8] Rohit R. Lakhanpal, MD,[9] Patrick R. Oellers, MD,[10] Thellea K. Leveque, MD, MPH,[11] Bryan K. Rutledge, MD,[10] Mark Chittum, MD,[7] Tommaso Bacci, MD,[2] Ana Bety Enriquez, MD,[1] Newman J. Sund, MD, PhD,[9] Eric N.P. Subong, MD,[12] Thomas A. Albini, MD[13]



JAMA Ophthalmology | Original Investigation

Safety Outcomes of Brolucizumab in Neovascular Age-Related Macular Degeneration
Results From the IRIS Registry and Komodo Healthcare Map

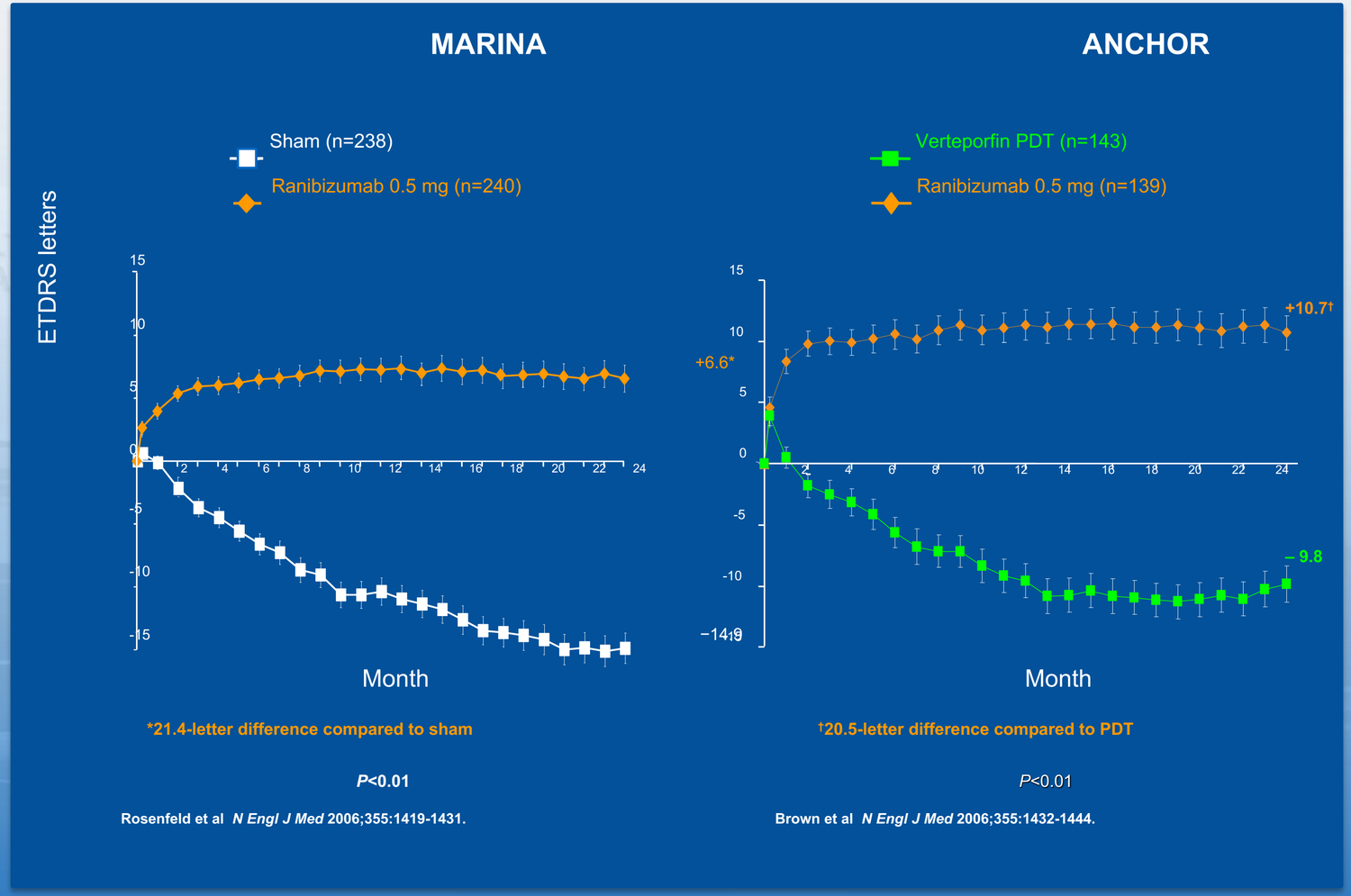
Arshad M. Khanani, MD, MA; Marco A. Zarbin, MD, PhD; Mark R. Barakat, MD; Thomas A. Albini, MD; Peter K. Kaiser, MD; Guruprasad B, MBBS, MD; Neetu Agashivala, BPharmacy, MS; Justin S. Yu, PharmD, MS; Charles C. Wykoff, MD, PhD; Mathew W. MacCumber, MD, PhD

Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
- Treat-and-Extend

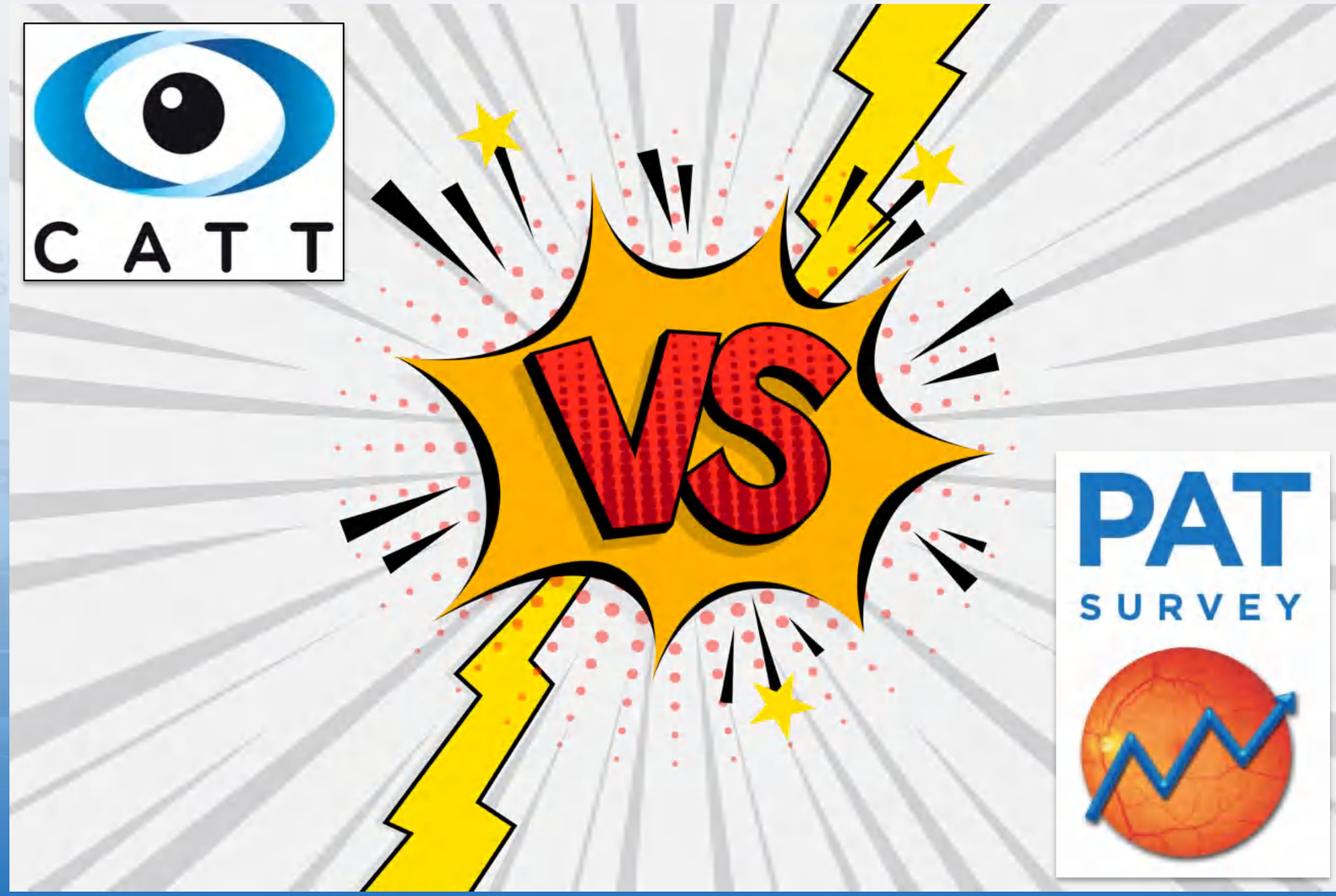
Dosing Strategies

- Standing Treatment
  - Typically Monthly or Bimonthly
  - Closest to Pivotal Clinical Trials



Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
- Treat-and-Extend

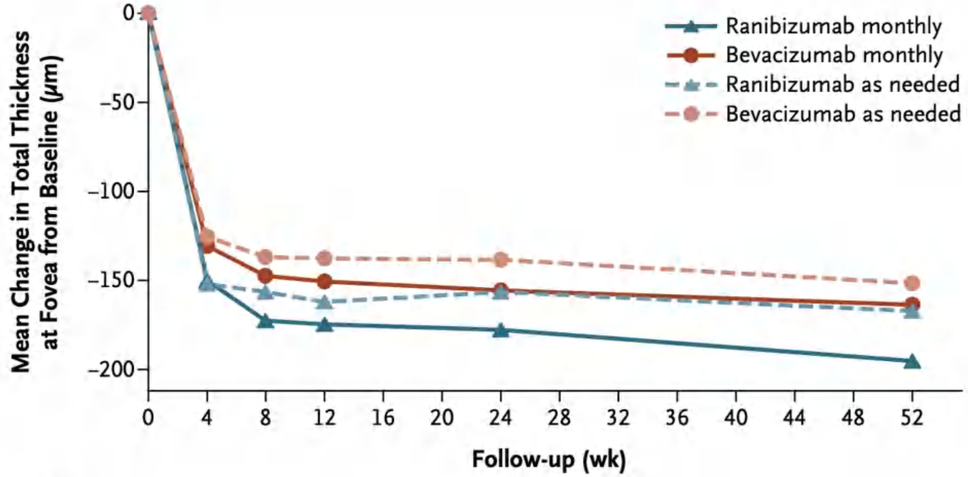


Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
  - As Needed
  - Skipping Treatment based on OCT imaging
  - CATT Trial

CATT

F



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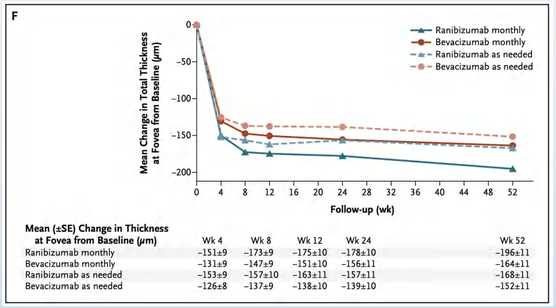
Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
  - As Needed
  - Skipping Treatment based on OCT imaging
  - CATT Trial

CATT



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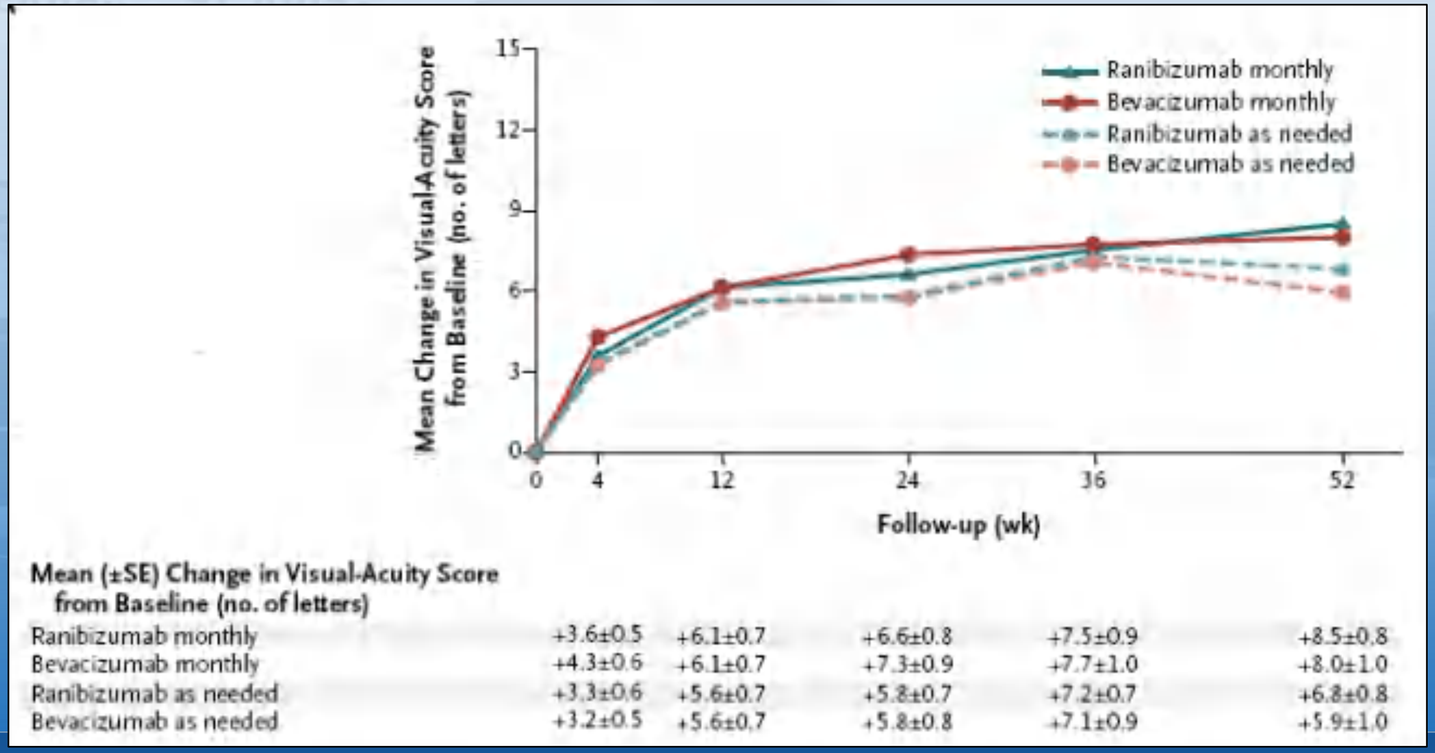
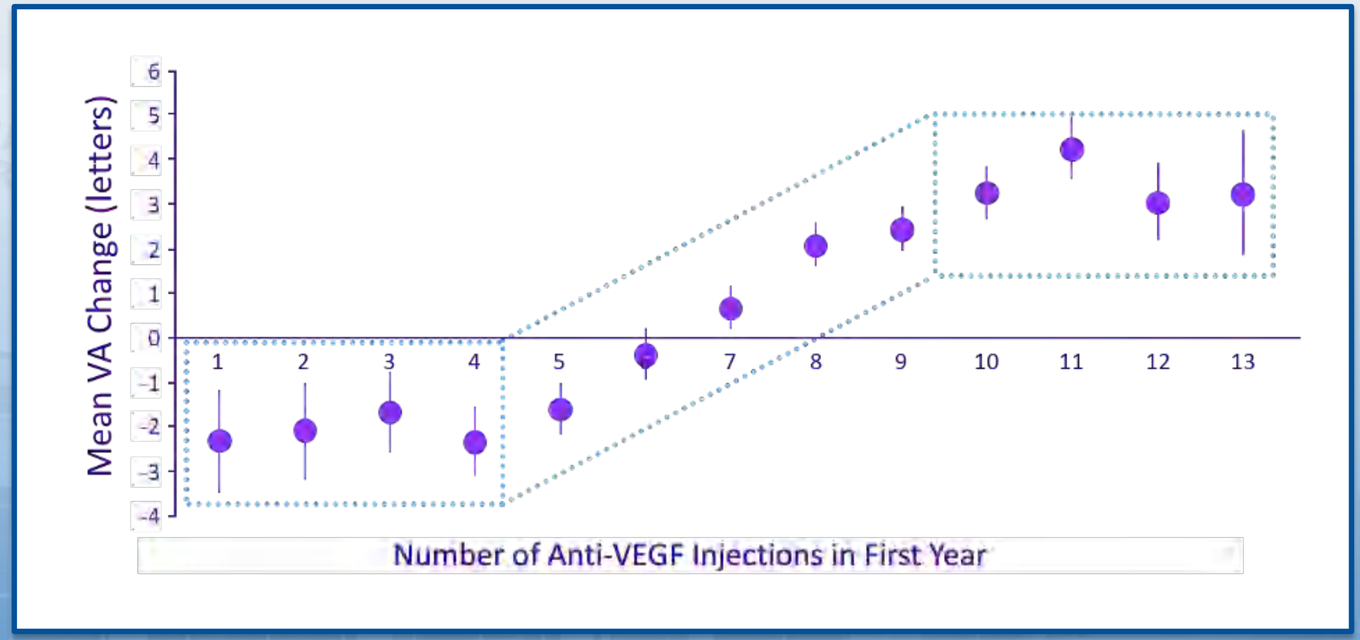


Mean (±SE) Change in Visual-Acuity Score from Baseline (no. of letters)					
Ranibizumab monthly	+3.6±0.5	+6.1±0.7	+6.6±0.8	+7.5±0.9	+8.5±0.8
Bevacizumab monthly	+4.3±0.6	+6.1±0.7	+7.3±0.9	+7.7±1.0	+8.0±1.0
Ranibizumab as needed	+3.3±0.6	+5.6±0.7	+5.8±0.7	+7.2±0.7	+6.8±0.8
Bevacizumab as needed	+3.2±0.5	+5.6±0.7	+5.8±0.8	+7.1±0.9	+5.9±1.0

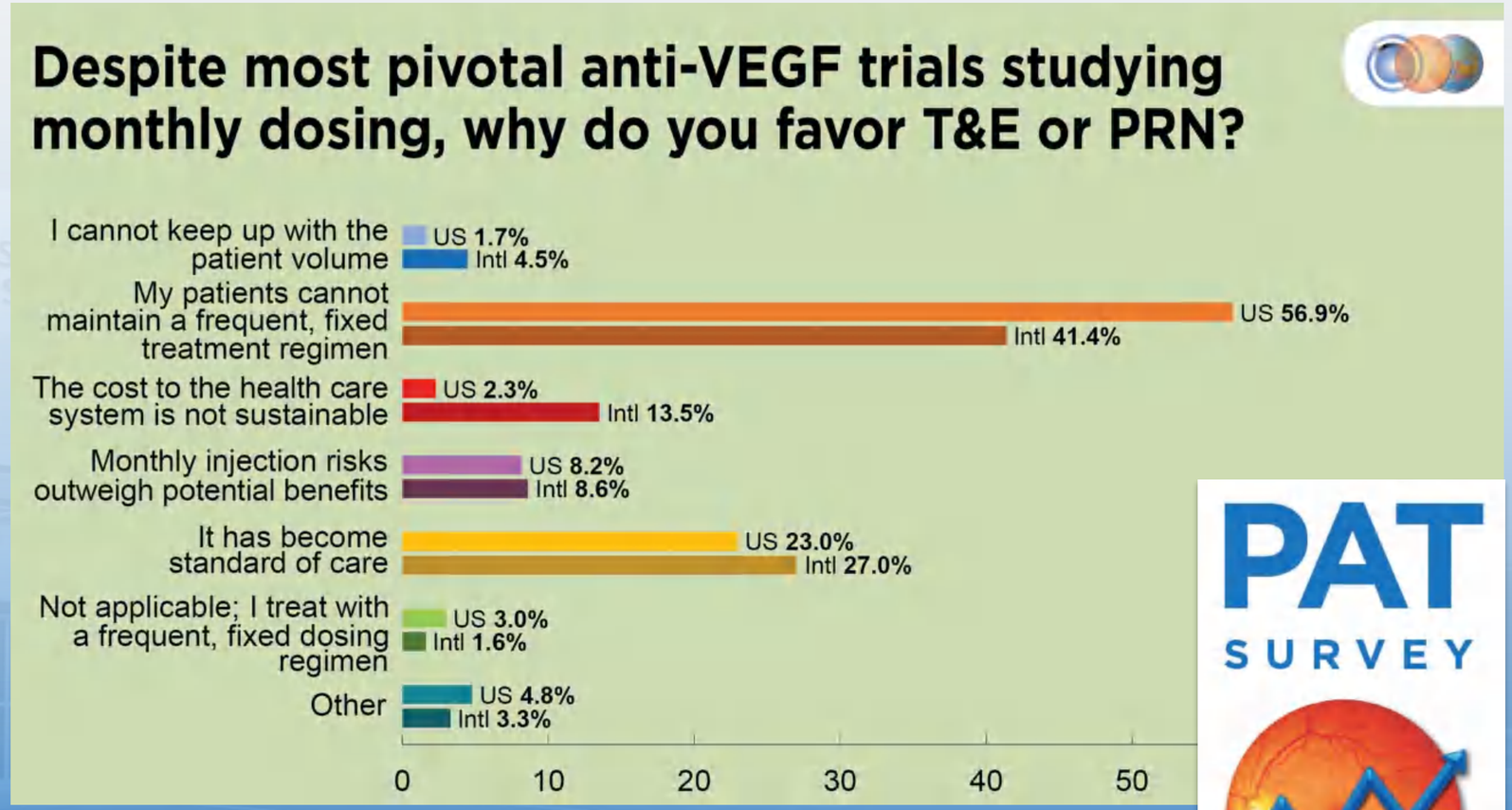
Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
  - As Needed
  - Skipping Treatment based on OCT imaging
  - CATT Trial
  - Real-life Data



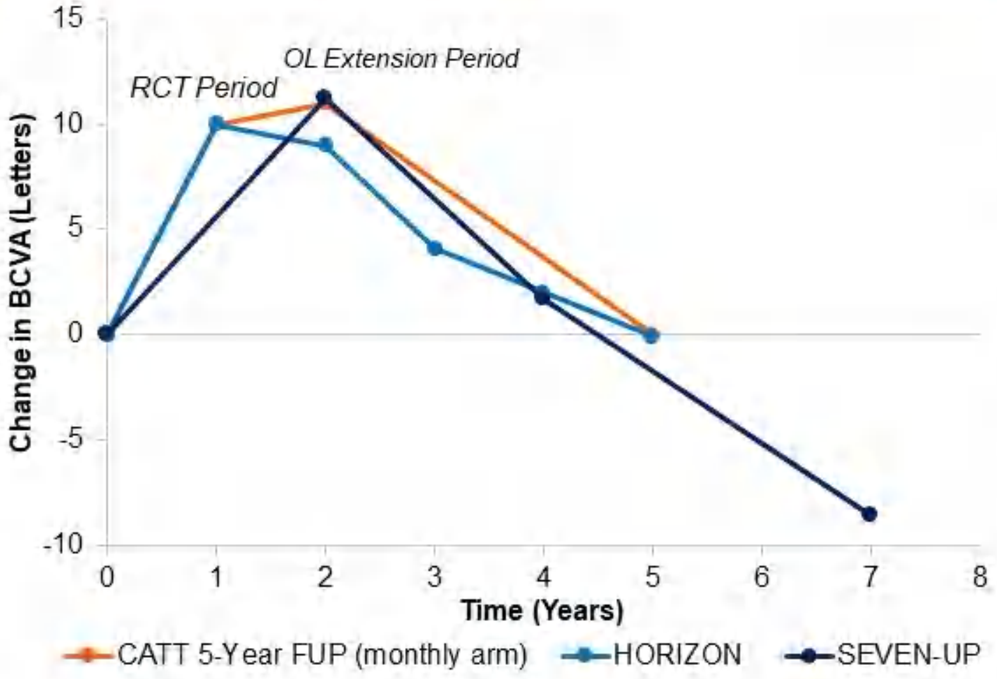
Dosing Strategies

- Standing Treatment
- Pro Re Nata (PRN)
- Treat-and-Extend
  - Extending Interval Between Treatments
  - Based on OCT-Guidance
  - Most Common Algorithm

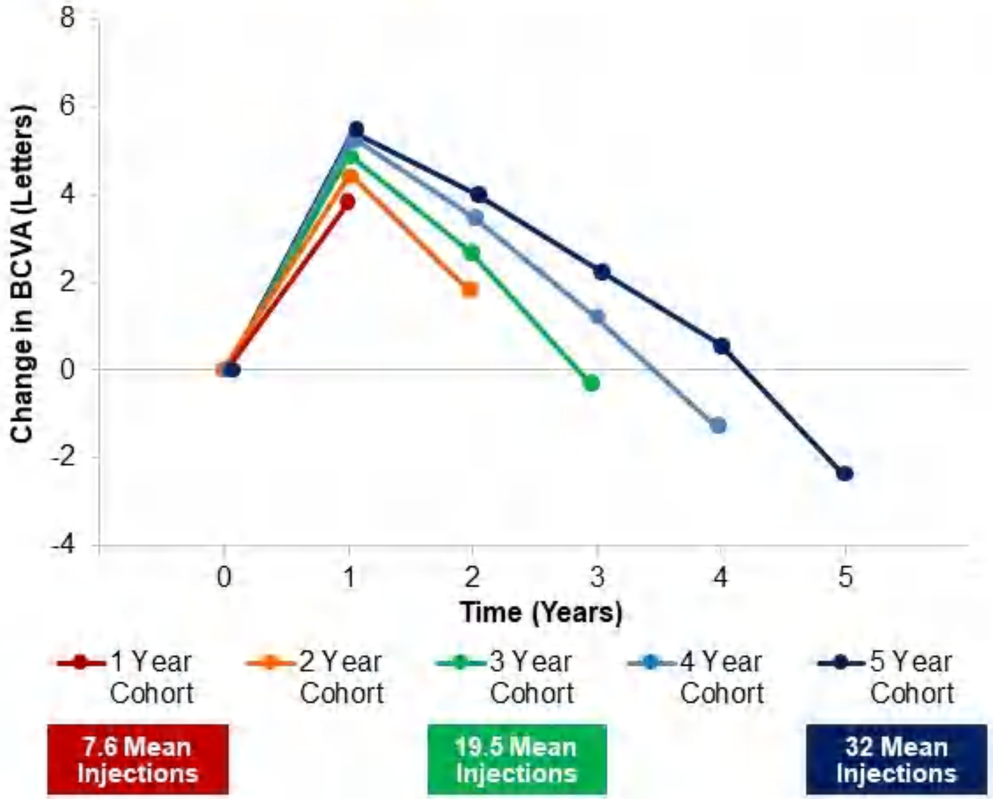


Even So, Vision Outcomes Decrease over Time

Mean VA Change after RCTs[1]



Mean VA Change in Real World Practice[2]



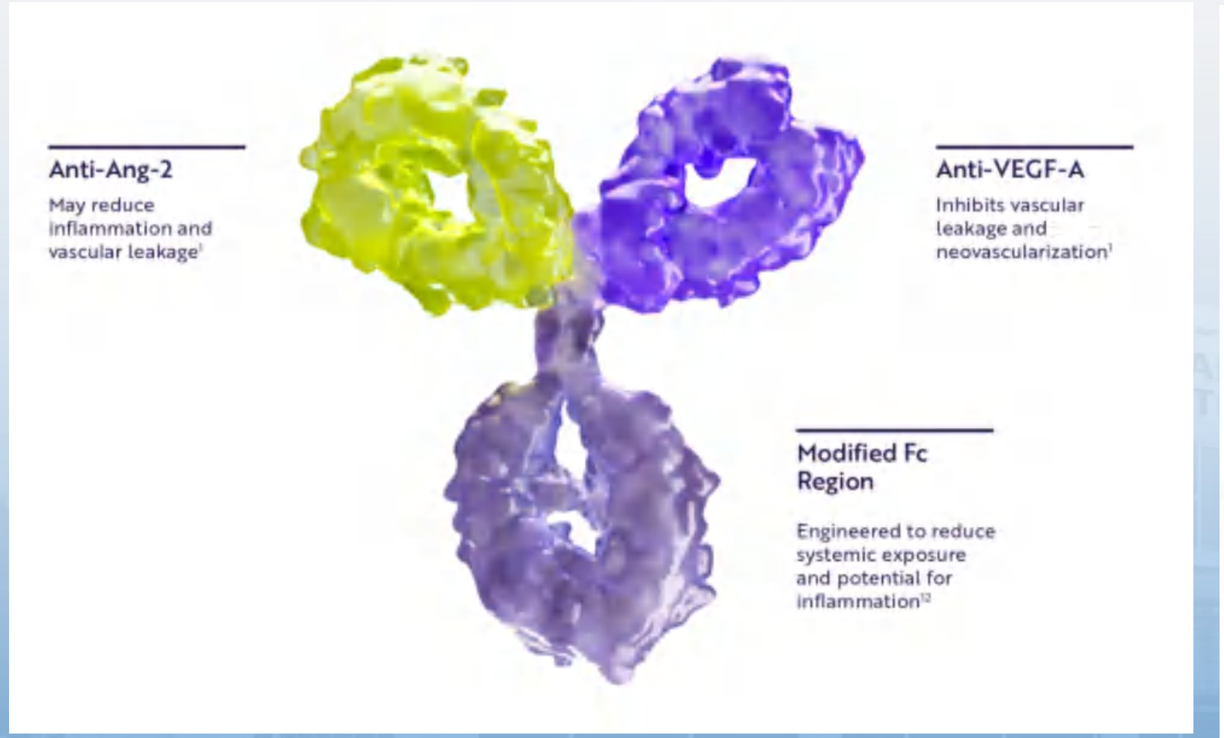
RCT: Randomized Controlled Trial; OL: Open-label.
[1]Singer, 2012 (HORIZON). Rofagha, 2013 (SEVEN-UP). Maguire, 2016 (CATT).
[2]Ciulla, T et al. *Ophthalmology Retina* vol. 6,9(2022): 796–806.

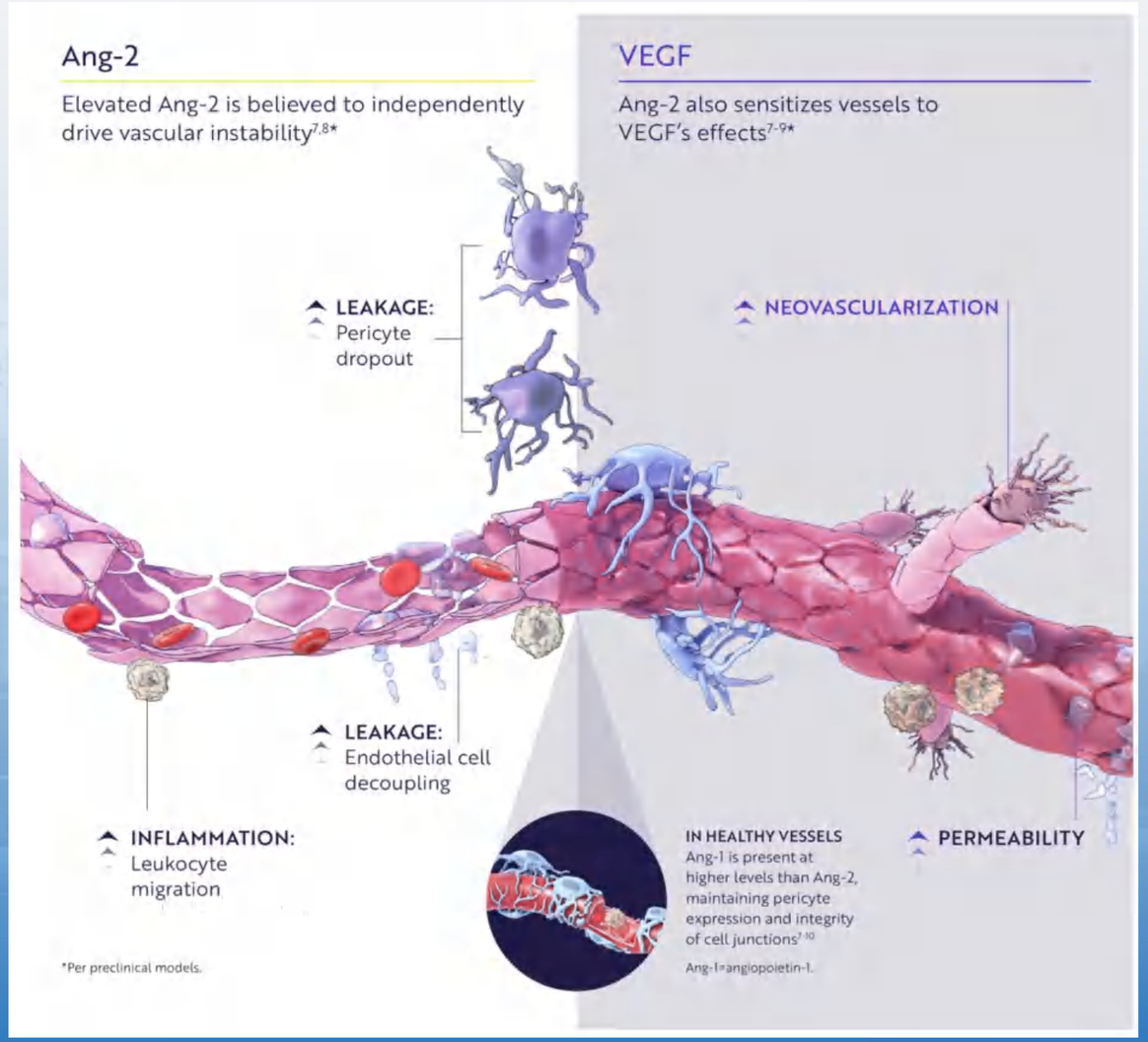
Campochiaro, AAO 2022

Agents Recently Approved

- Faricimab
- Port Delivery Device

Faricimab





https://www.vabysmo-hcp.com/how-it-works.html

Faricimab

Faricimab in Neovascular Age-Related Macular Degeneration: Year 2 Patient Case Profiles From the Phase 3 TENAYA/LUCERNE Trials

Shih-Jen Chen, MD[1]

Adrian H. C. Koh, MBBS, MMed (Ophth), FRCS (Ed), FAMS[2]; Balakumar Swaminathan, MSc[3]; Vaibhavi Patel, BPharm[4]; Philippe Margaron, PhD[5]; and Aachal Kotecha, PhD[4]

[1] Taipei Veterans General Hospital, National Yang Ming Chiao Tung University, Taipei, Taiwan
[2] Eye & Retina Surgeons, Camden Medical Centre, Singapore
[3] F. Hoffmann-La Roche Ltd., Mississauga, ON, Canada
[4] Roche Products Ltd, Welwyn Garden City, UK
[5] F. Hoffmann-La Roche Ltd., Basel, Switzerland

Presented at the 38th Asia-Pacific Academy of Ophthalmology Congress
Kuala Lumpur, Malaysia | 23–26 February 2023

TENAYA LUCERNE

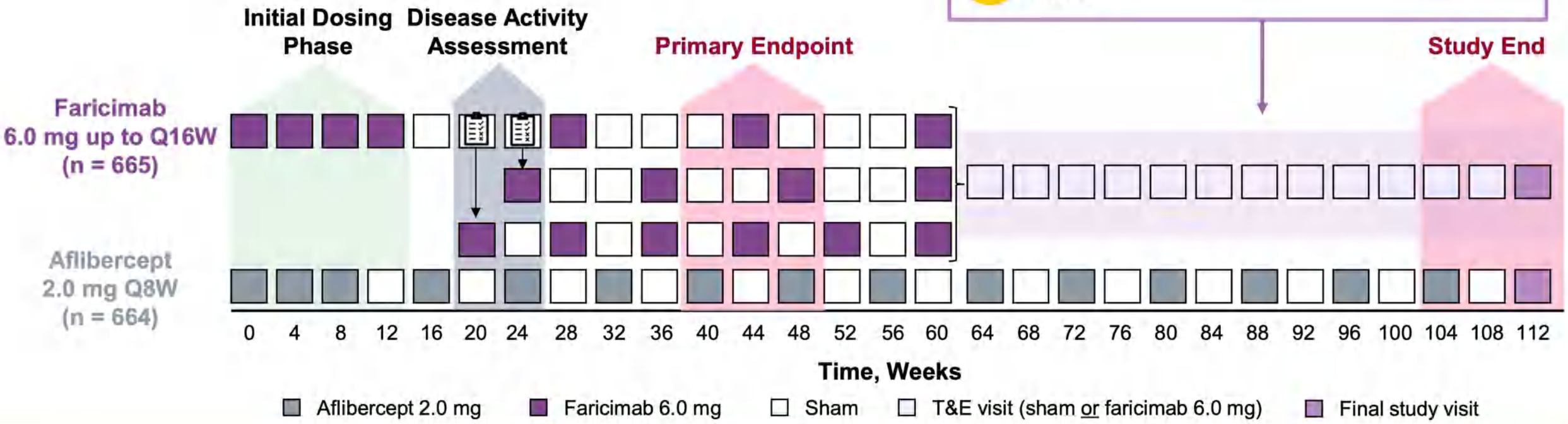
TENAYA and LUCERNE Trial Design

Faricimab nAMD Trials Use Disease Criteria Reflective of Clinical Practice

Disease activity assessment criteria
(at weeks 20 and 24) based on
CST OR BCVA OR new macular haemorrhage[a]

T&E Regimen (PTI per Protocol)

- Dosing **extended** (by 4 weeks, max Q16W) based on **CST AND BCVA AND macular haemorrhage[a]**
- Dosing **reduced** (by 4 or 8 weeks[b], min Q8W) based on **CST OR BCVA OR macular haemorrhage[a]**
- Dosing **maintained** if extension or reduction criteria not met



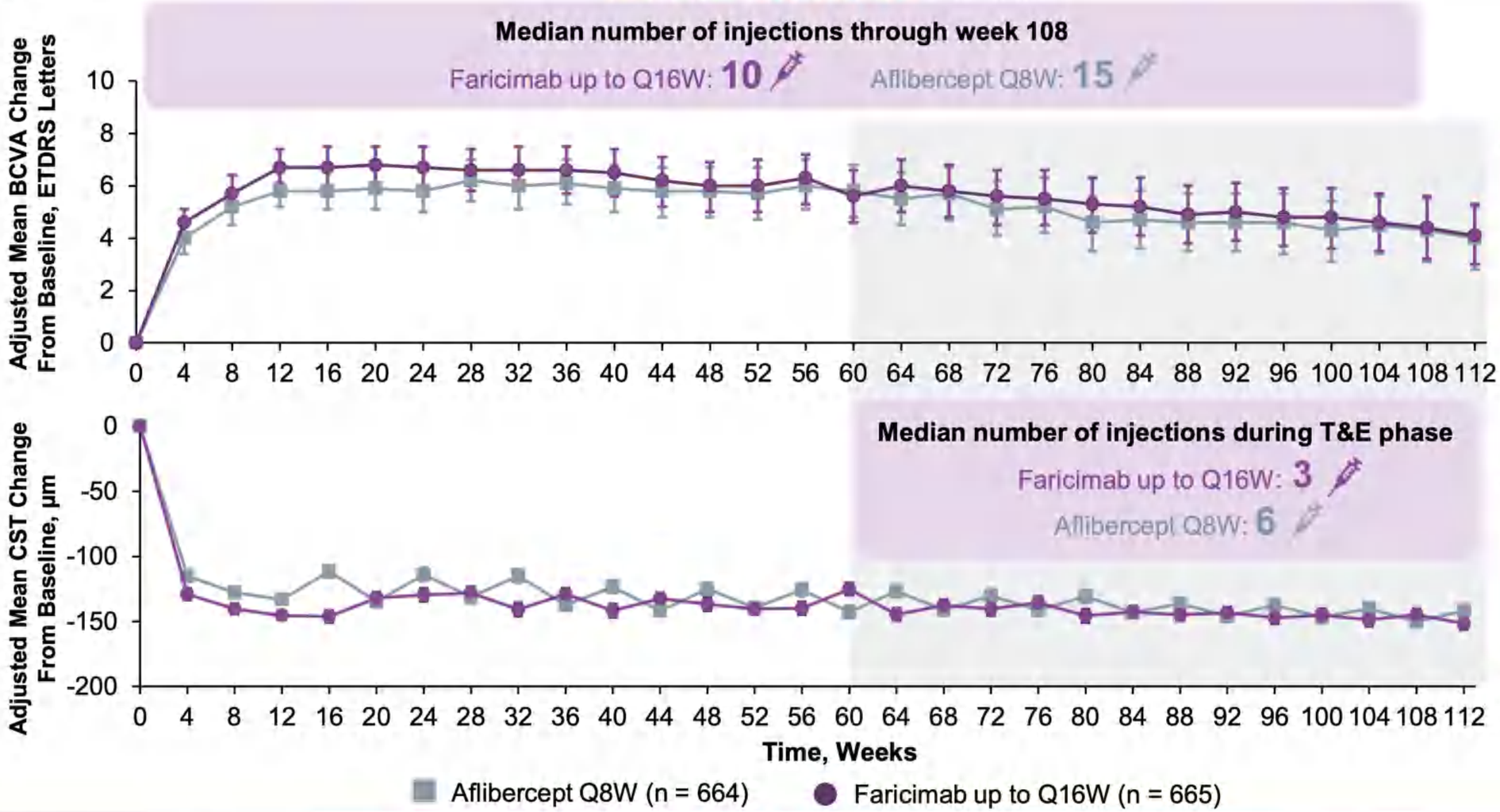
T&E regimen in TENAYA (NCT03823287) and LUCERNE (NCT03823300) uses different criteria than those used in the YOSEMITE and RHINE clinical trials. [a] Per the investigator. [b] if ≥ 2 of the reduction criteria were met or 1 criterion includes new macular haemorrhage, the interval was reduced to an 8-week interval. BCVA, best-corrected visual acuity; CST, central subfield thickness; max, maximum; min, minimum; nAMD, neovascular age-related macular degeneration; PTI, personalised treatment interval; Q8W, every 8 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

Over 2 Years, Patients in the Faricimab Arm Achieved Disease Control With Fewer Injections

ITT population

TENAYA/LUCERNE Pooled



Average of weeks 104–112[a]

+4.4 letters

+4.3 letters

Average of weeks 104–112[a]

−148.4 µm

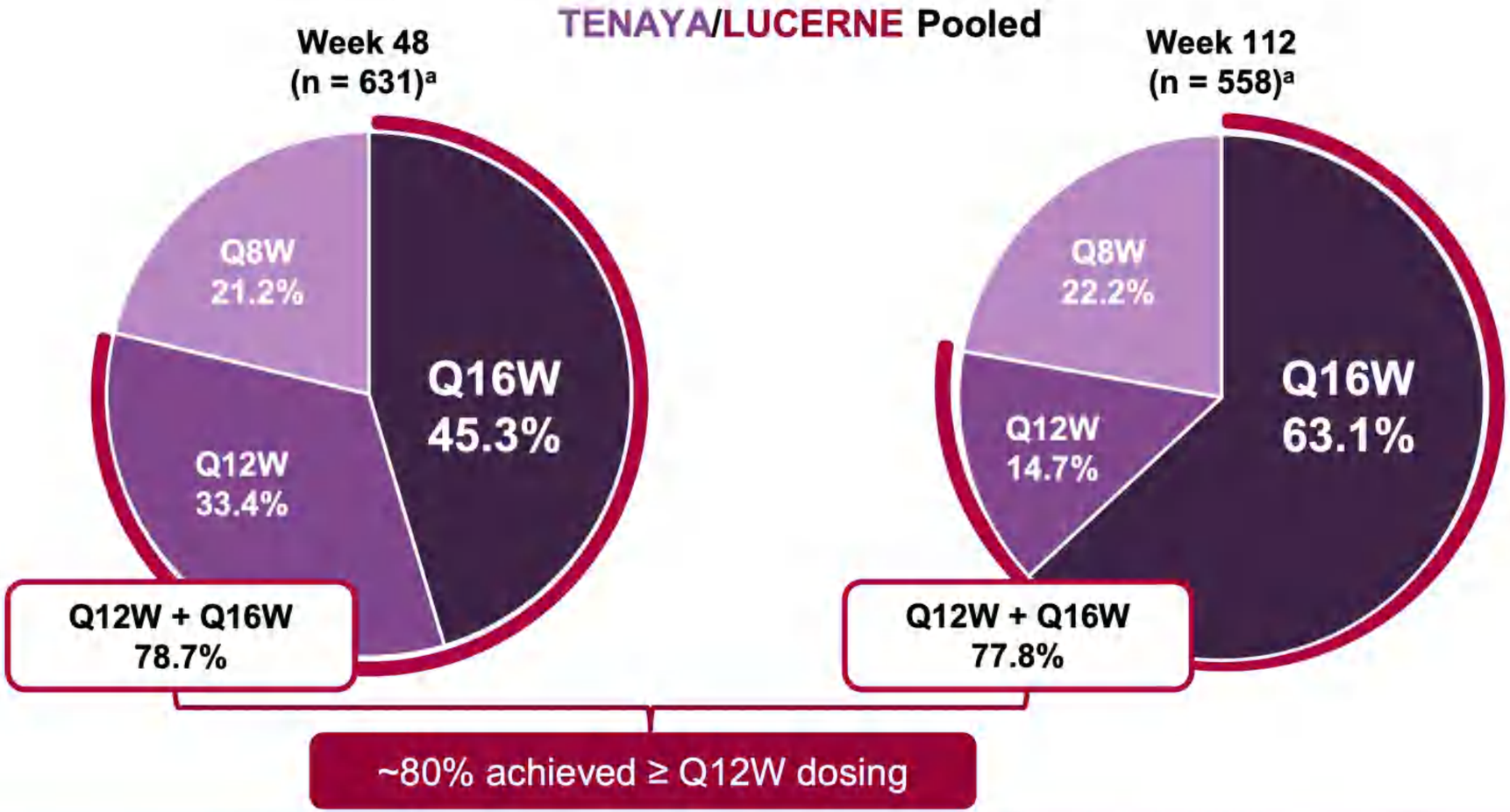
−144.0 µm

Results are based on a mixed model for repeated measures analysis in the ITT population. The median number of injections is based on the safety-evaluable population. 95% CIs are shown. CST is measured as ILM-RPE, as graded by central reading centre. [a] Adjusted mean change from baseline at 2 years, averaged over weeks 104, 108 and 112. T&E dosing regimen was delayed in some patients due to dose holds or missed visits.
BCVA, best-corrected visual acuity; CST, central subfield thickness; ILM, internal limiting membrane; ITT, intent-to-treat; Q8W, every 8 weeks; Q16W, every 16 weeks; RPE, retinal pigment epithelium ; T&E, treat-and-extend.

TENAYA LUCERNE

~80% of Faricimab-Treated Patients Achieved ≥ Q12W Dosing at the End of the Second Year

More patients achieved Q16W during the T&E phase from week 48 with a median of 3 injections



[a] Percentages are based on number of patients randomised to the faricimab arm who have not discontinued the study at that visit. Treatment interval at a given visit is defined as the treatment interval decision followed at that visit. Interval at week 112 is calculated using data recorded at week 108. [b] Weeks 60–112. Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

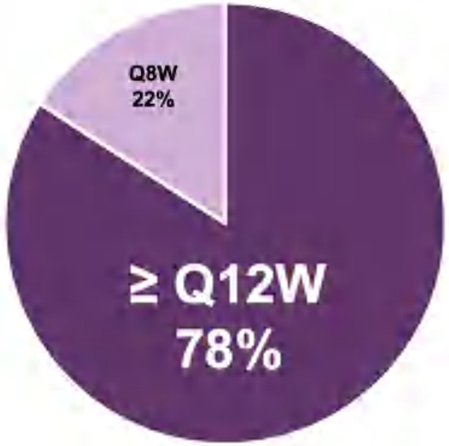
TENAYA LUCERNE

With the Protocol-Defined Disease Activity Criteria Based on VA or Anatomic Decline, 78% of Patients Were Assigned to ≥ Q12W Dosing

Individual Disease Activity Criteria (TENAYA and LUCERNE)

≥ 5-letter BCVA loss vs average BCVA[a]	OR	≥ 10-letter BCVA loss vs highest BCVA recorded[a]	OR	> 50-µm CST increase vs average CST[a]	OR	≥ 75-µm CST increase vs lowest CST recorded[b]	OR	New macular haemorrhage[c]
36 (29%)[d] patients		24 (20%)[d] patients		94 (76%)[d] patients		76 (62%)[d] patients		11 (9%)[d] patients

Week 20 Assessment



[a] Over the previous 2 scheduled visits. [b] At either of the previous 2 scheduled visits. [c] Per the investigator and attributable to nAMD. [d] Proportion based on the number of patients who had positive disease activity at week 20 (n = 123).
BCVA, best-corrected visual acuity; CST, central subfield thickness; nAMD, neovascular age-related macular degeneration; Q8W, every 8 weeks; Q12W, every 12 weeks; VA, visual acuity.

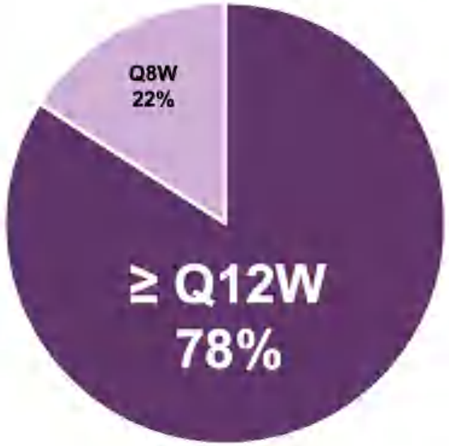
TENAYA LUCERNE

If Meeting Both Vision and Anatomical Criteria Was Required, 96% of Patients Would Have Been Assigned to ≥ Q12W Dosing

Individual Disease Activity Criteria (TENAYA and LUCERNE)

- **≥ 5-letter BCVA loss** vs average BCVA[a] — **36 (29%)[d] patients**
- OR
- **≥ 10-letter BCVA loss** vs highest BCVA recorded[a] — **24 (20%)[d] patients**
- OR
- **> 50-µm CST increase** vs average CST[a] — **94 (76%)[d] patients**
- OR
- **≥ 75-µm CST increase** vs lowest CST recorded[b] — **76 (62%)[d] patients**
- OR
- **New macular haemorrhage**[c] — **11 (9%)[d] patients**

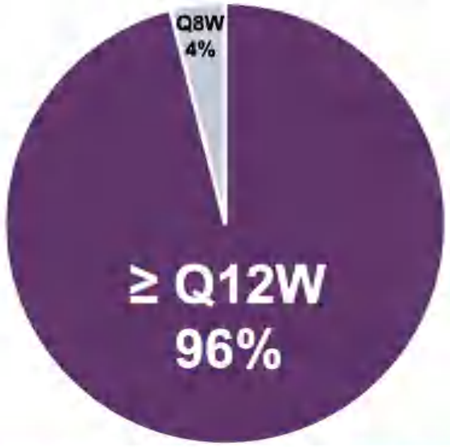
Week 20 Assessment



Alternative Combination Disease Activity Criteria

- **> 5-letter BCVA loss** vs week 16 BCVA
- **AND**
- **> 25-µm CST increase** vs week 16 or **new macular haemorrhage**

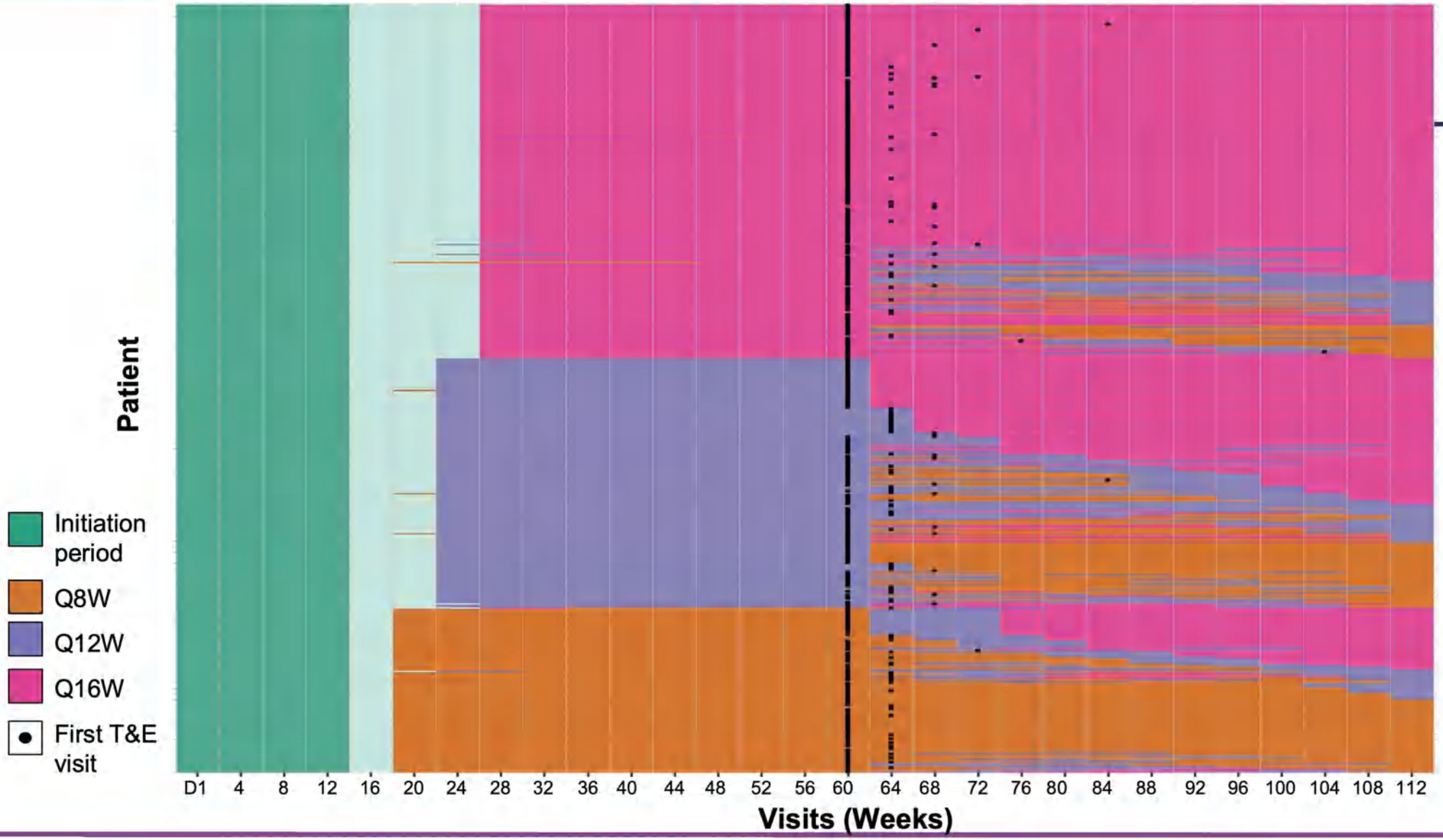
Week 20 Assessment



[a] Over the previous 2 scheduled visits. [b] At either of the previous 2 scheduled visits. [c] Per the investigator and attributable to nAMD. [d] Proportion is based on the number of patients who had positive disease activity at week 20 (n = 123).
This analysis is not intended as a cross-trial comparison and cannot predict whether faricimab-treated patients in TENAYA and LUCERNE would have achieved non-inferiority versus aflibercept 2.0 mg if the treatment regimen had been modified. BCVA, best-corrected visual acuity; CST, central subfield thickness; nAMD, neovascular age-related macular degeneration; Q8W, every 8 weeks; Q12W, every 12 weeks.

TENAYA LUCERNE

Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2

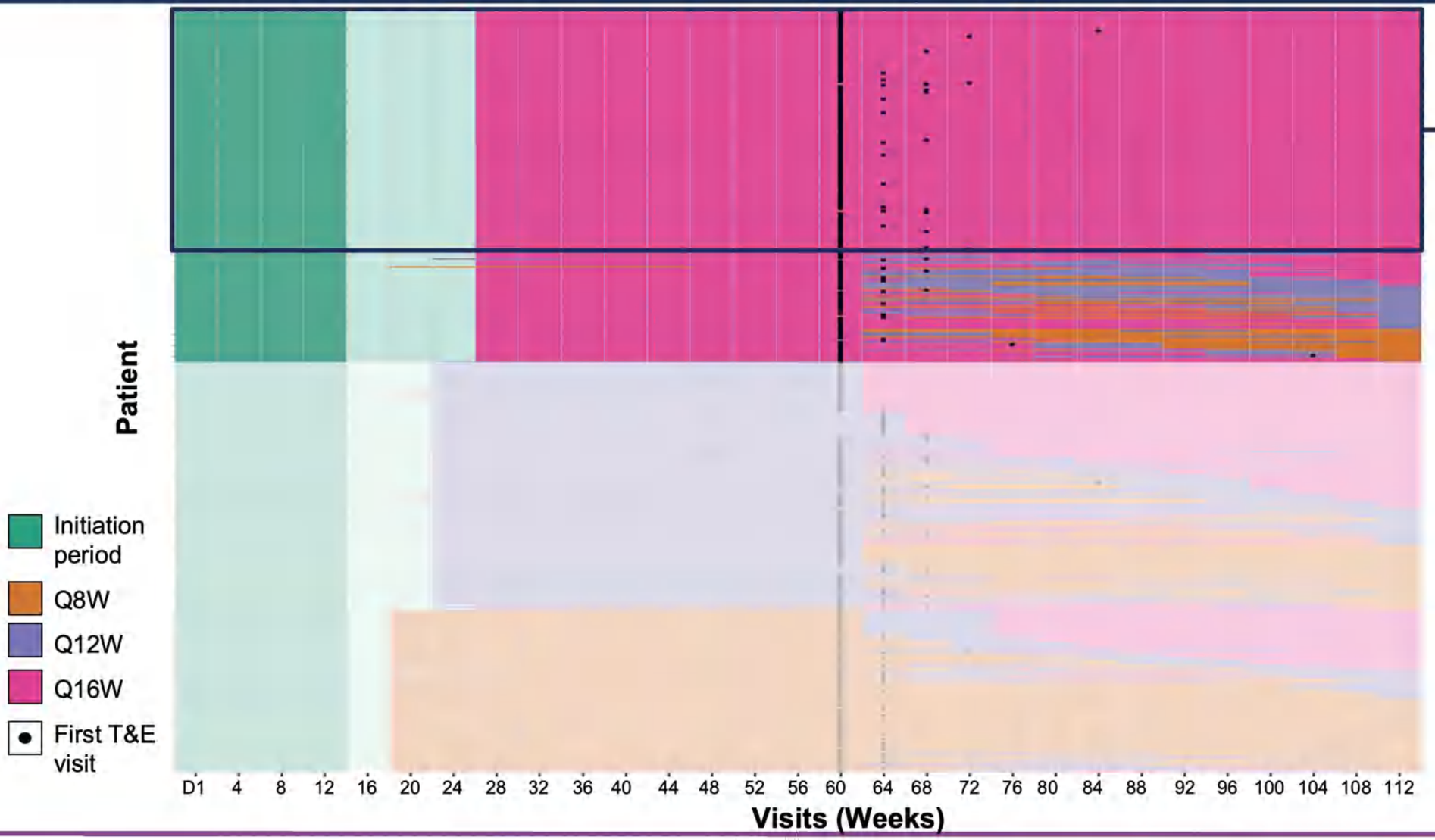


Each individual horizontal row represents a single patient over time

[a] Percent of total number of patients at week 48.
D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2

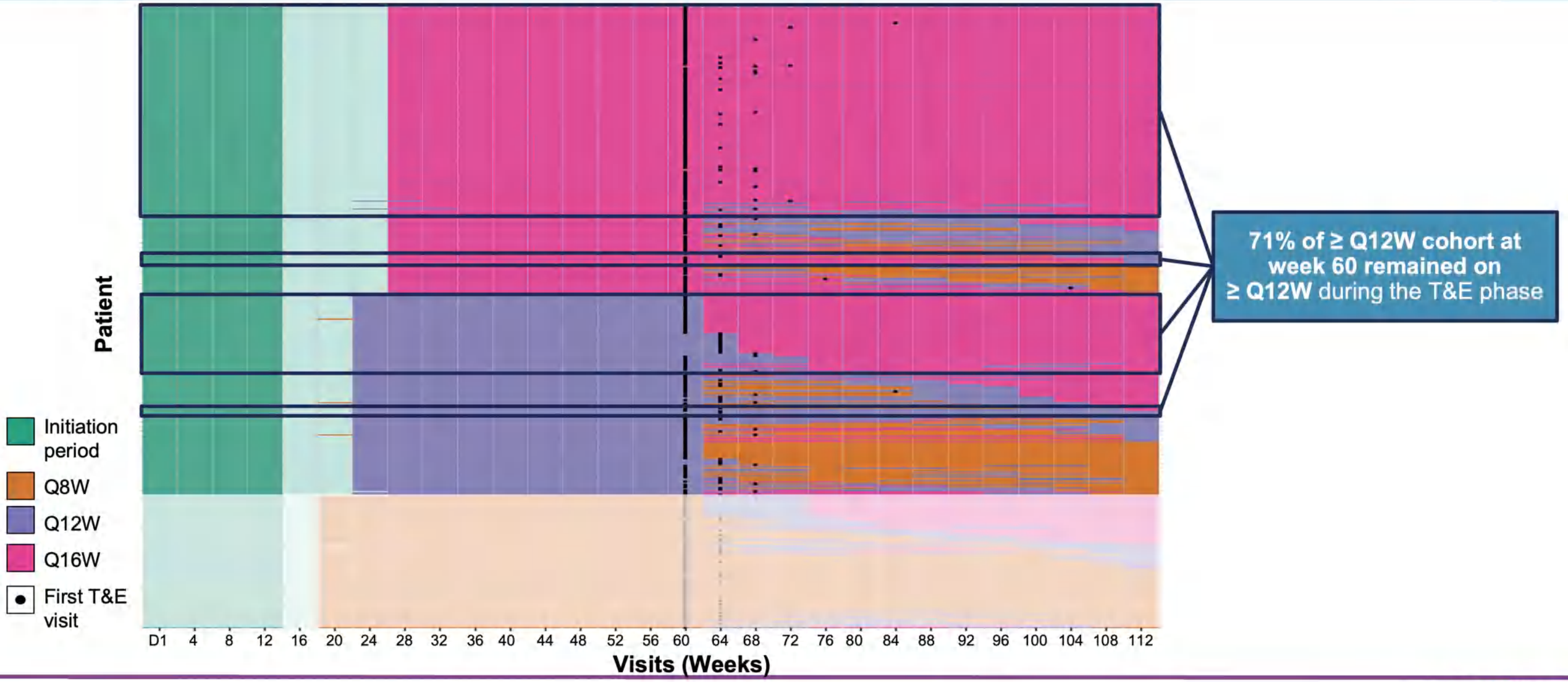


69% of Q16W cohort at week 60 remained on Q16W during the T&E phase

D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

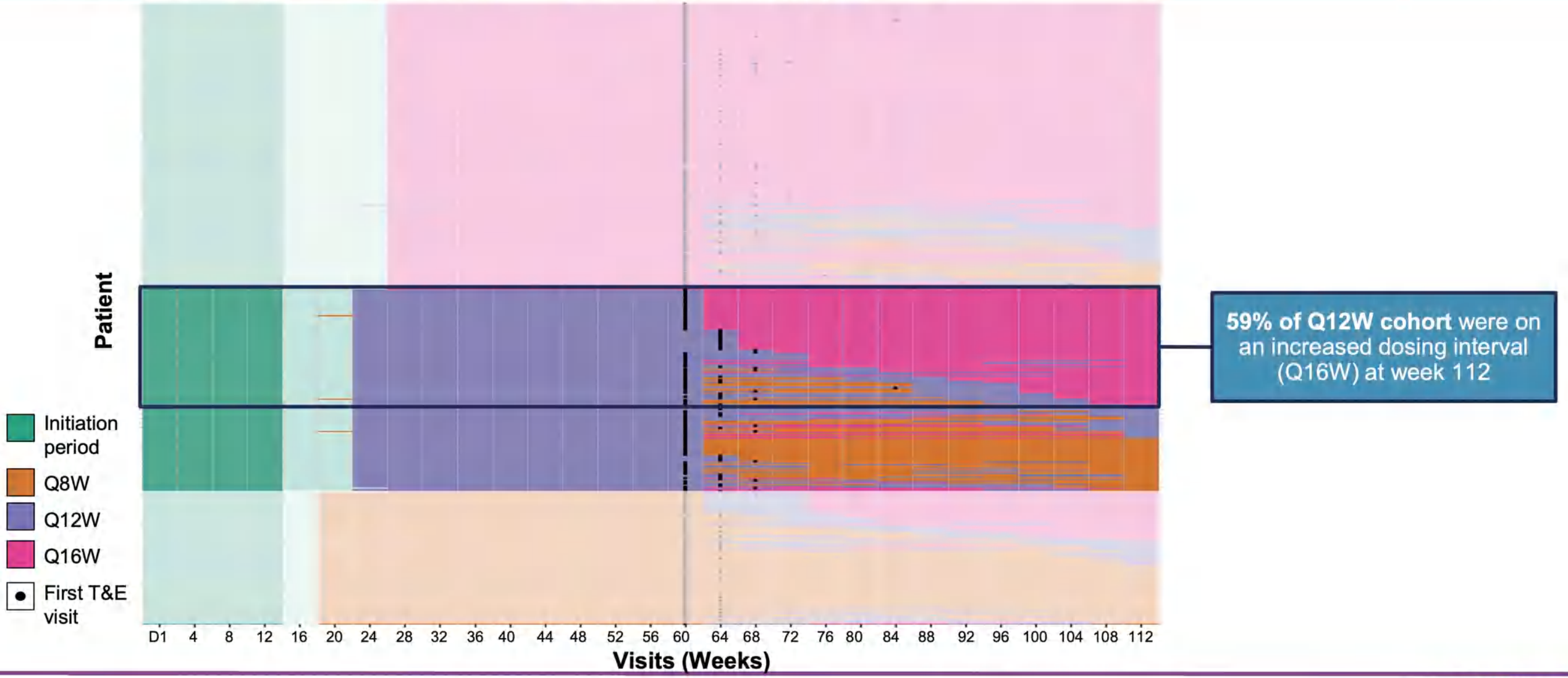
Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2



D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

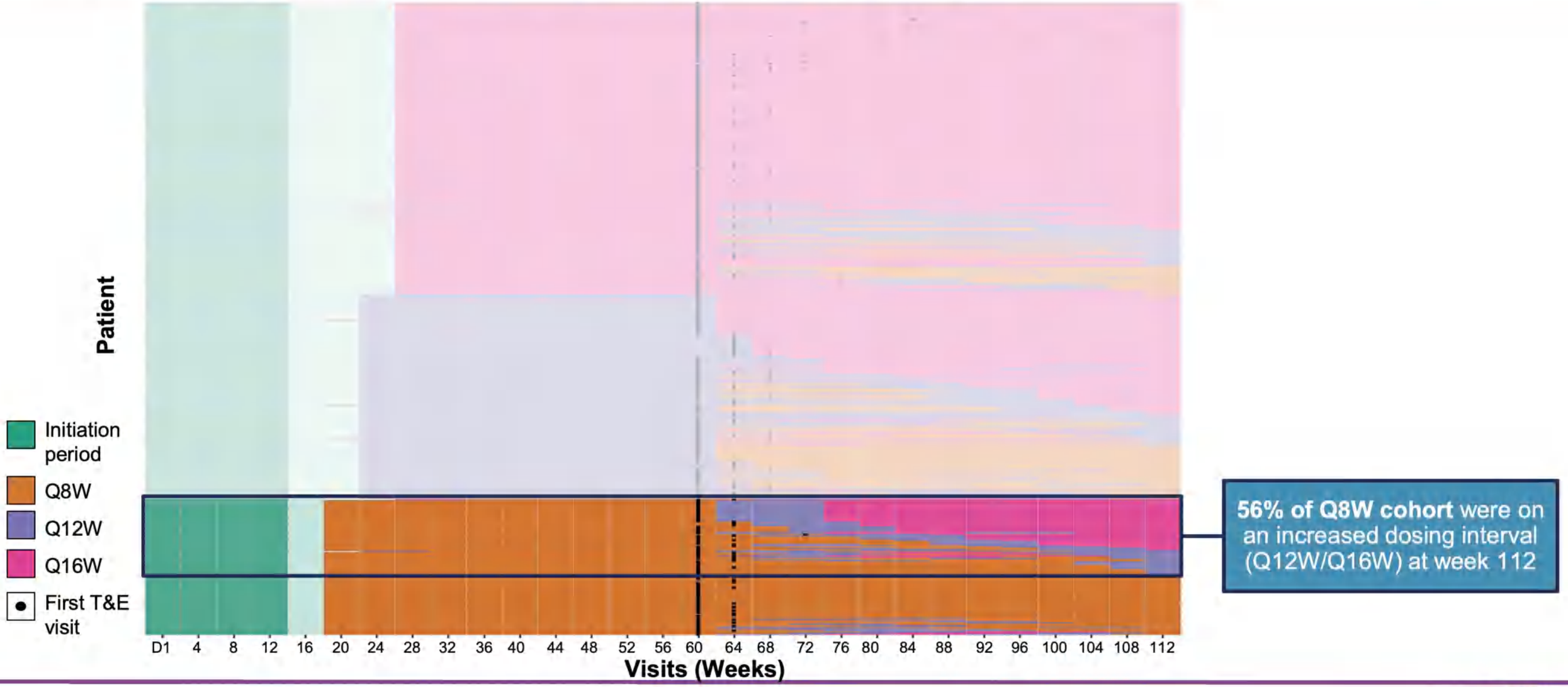
Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2



D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

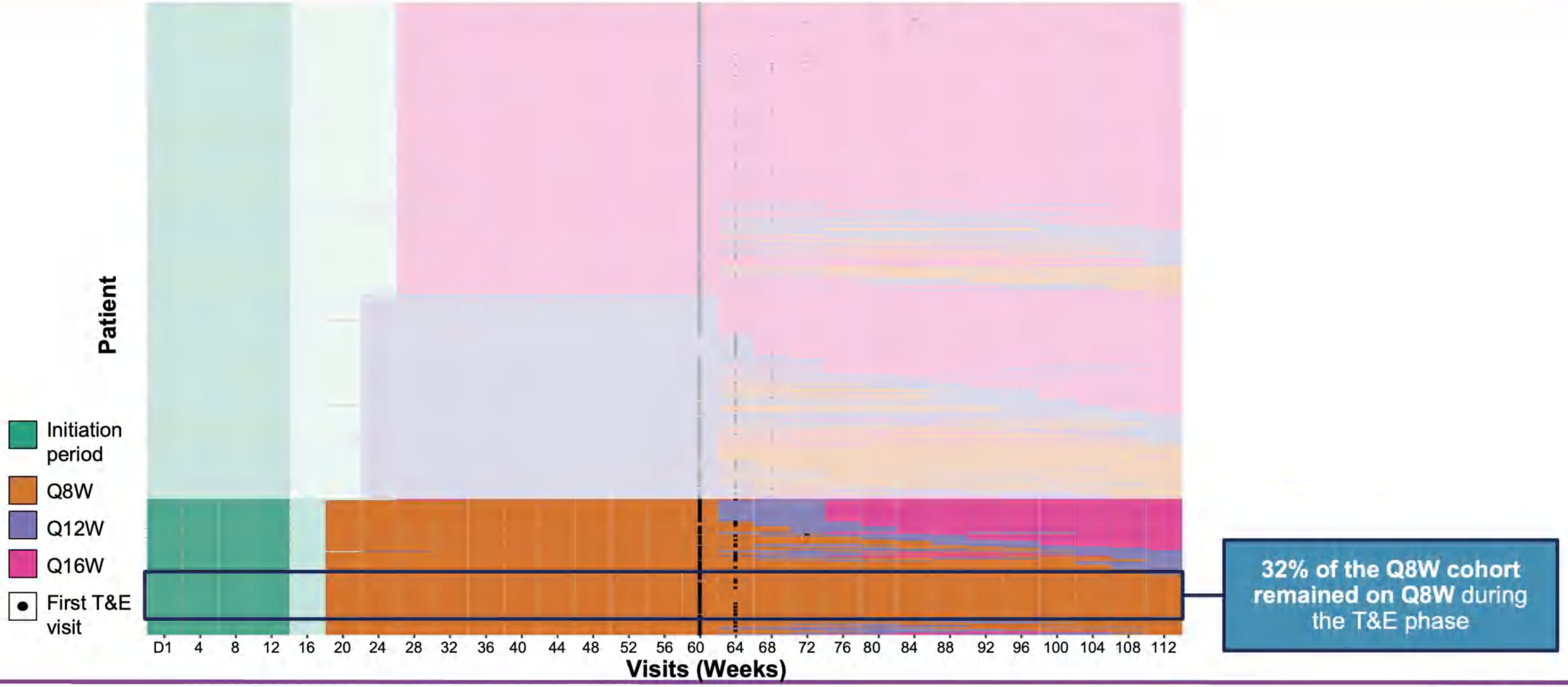
Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2



D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

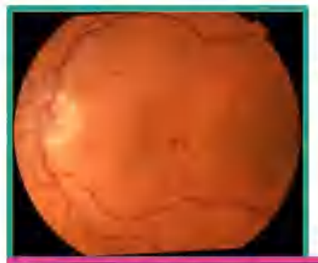
Most Patients Who Achieved Q12W or Q16W Dosing at Year 1 Maintained Extended Dosing Through Year 2



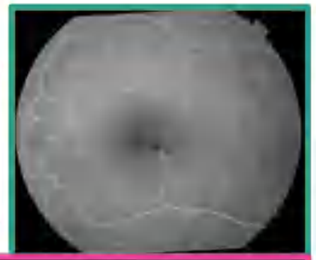
[a] Percentages of the total number of patients at week 48.
D, day; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

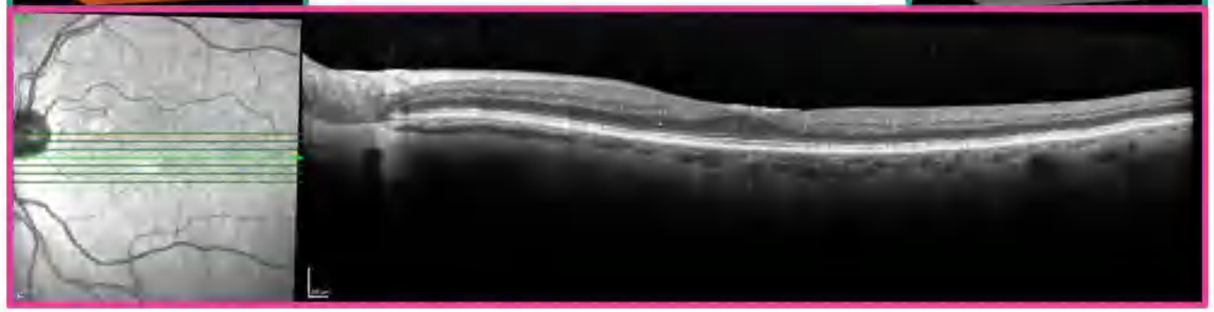
TENAYA LUCERNE

Patient Case 1: Q16W Dosing Throughout Study

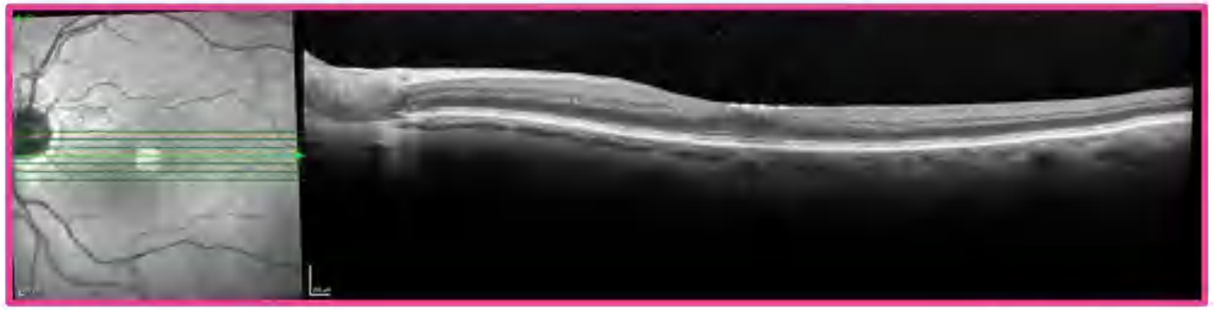


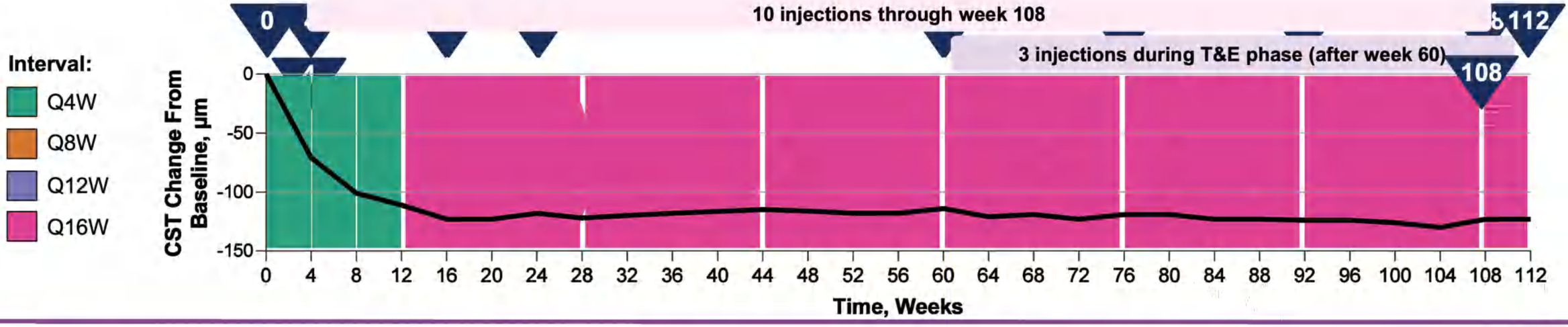
Week 108:
BCVA 84 ETDRS letters
CST 293 µm





Week 112:
BCVA 79 ETDRS letters
CST 293 µm



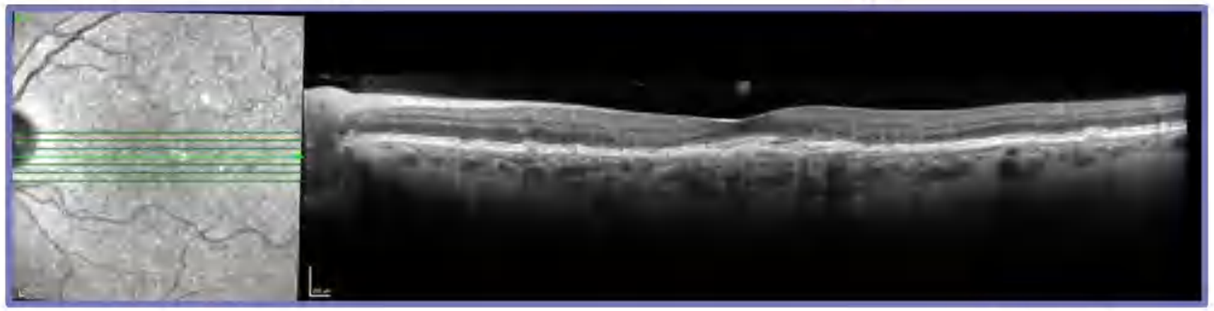


CST is measured as ILM-BM, as graded by a central reading centre. No serious ocular adverse drug reactions were observed/reported in the treated eye.
BCVA, best-corrected visual acuity; BM, Bruch's membrane; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

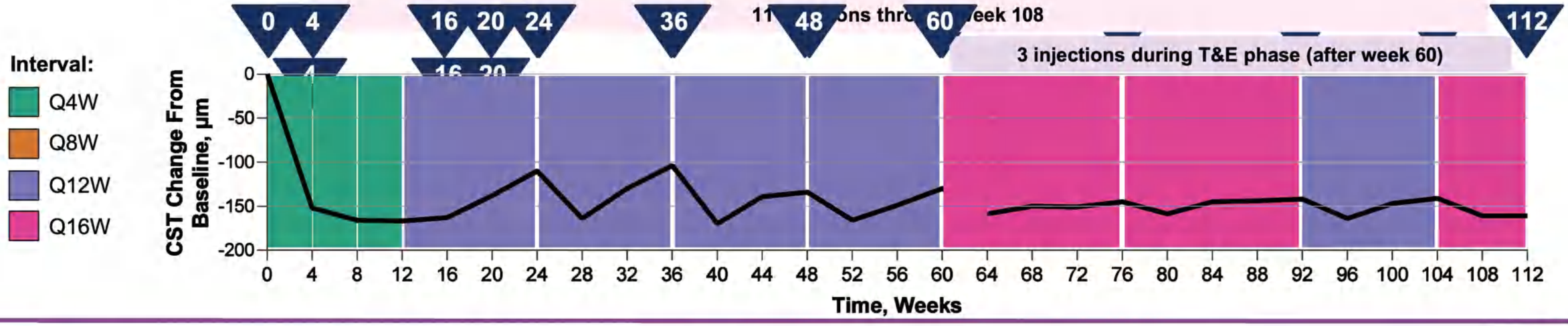
TENAYA LUCERNE

Patient Case 2: Q12W Dosing, Extended to Q16W

Week 48:
BCVA 72 ETDRS letters
CST 291 µm



Week 60:
BCVA 78 ETDRS letters
CST 295 µm



CST is measured as ILM-BM, as graded by a central reading centre. No serious ocular adverse drug reactions were observed/reported in the treated eye.
BCVA, best-corrected visual acuity; BM, Bruch's membrane; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; ILM, internal limiting membrane; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

Faricimab Was Well Tolerated With an Acceptable Safety Profile Through Year 2

AEs Through Study End, Patients With ≥ 1 AE, n (%)[a]	TENAYA/LUCERNE Pooled	
	Faricimab Up to Q16W n = 664	Aflibercept Q8W n = 662
Ocular AEs[b]	358 (53.9%)	345 (52.1%)
Serious ocular AEs[b]	29 (4.4%)	29 (4.4%)
Ocular AEs of special interest[c]	40 (6.0%)	43 (6.5%)
Intraocular inflammation events[d]	20 (3.0%)	15 (2.3%)
Uveitis	4 (0.6%)	3 (0.5%)
Iritis	8 (1.2%)	3 (0.5%)
Iridocyclitis	2 (0.3%)	1 (0.2%)
Vitritis	4 (0.6%)	1 (0.2%)
Post-procedural inflammation	0	5 (0.8%)
Chorioretinitis	1 (0.2%)	0
Keratic precipitates	2 (0.3%)	0
Non-infectious endophthalmitis	0	1 (0.2%)
Anterior chamber flare	0	1 (0.2%)
Endophthalmitis events	3 (0.5%)	2 (0.3%)
Retinal vasculitis events	0	0
Retinal occlusive events		
Retinal vein occlusion	0	0
Retinal artery occlusion	0	0
Retinal artery embolism	1 (0.2%)[f]	0
Serious non-ocular AEs	138 (20.8%)	162 (24.5%)
APTC events[e]	22 (3.3%)	20 (3.0%)

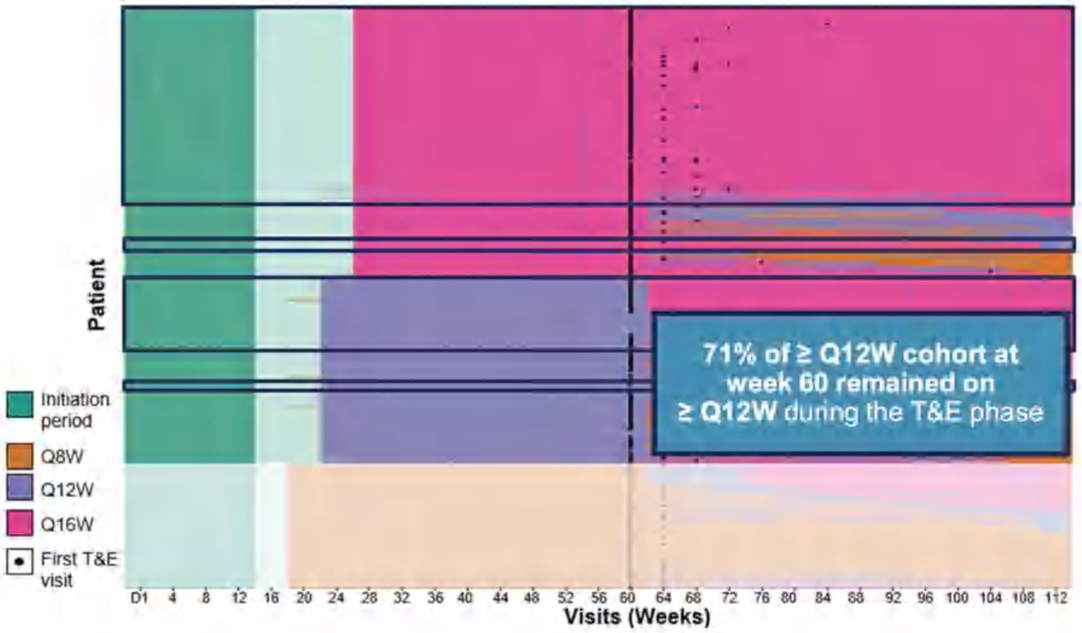
[a] Results are presented for the pooled safety-evaluable populations. Percentages are based on n values in the column headings; multiple occurrences of the same AE in an individual are counted only once. [b] Ocular AEs in the study eye only are presented. [c] Ocular AEs of special interest were defined as events associated with severe intraocular inflammation, events requiring surgical or medical intervention to prevent permanent loss of sight or events associated with BCVA loss of ≥ 30 letters for > 1 hour. [d] Excluding endophthalmitis. [e] APTC events were adjudicated by an external independent committee; all other events were investigator reported. [f] Hollenhorst plaque that was reported at the end of year 1 and was not treatment related as per the investigator.
AE, adverse event; APTC, Antiplatelet Trialists' Collaboration; BCVA, best-corrected visual acuity; Q8W, every 8 weeks; Q16W, every 16 weeks.

TENAYA LUCERNE

Personalised T&E-Based Faricimab Dosing Controls Anatomic Outcomes and Maintains Vision Through 2 Years

TENAYA/LUCERNE treatment criteria were designed to **reflect real-world clinical practice** as close as possible

During the T&E period, the **majority of patients** were able to either **maintain or extend their treatment**



Durability up to Q16W at year 2 with faricimab

≥ Q12W Dosing

Q16W Dosing

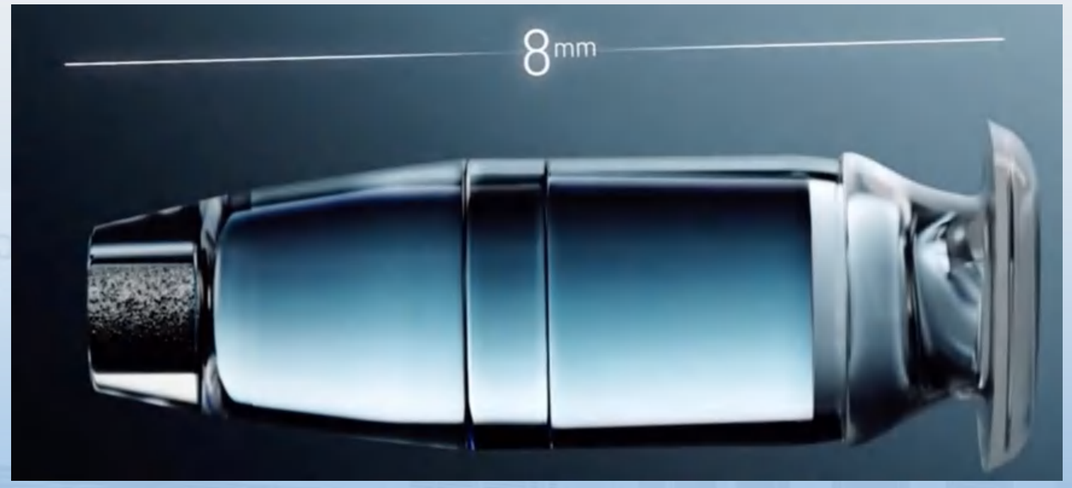
Resulting in **fewer injections with faricimab** vs aflibercept

Faricimab: 10 **Aflibercept: 15**

Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; T&E, treat-and-extend.

TENAYA LUCERNE

Port Delivery Device



Ranibizumab 100mg/ml

Port Delivery Device

Portal Extension Trial of the Port Delivery System With Ranibizumab (PDS): Three-Year Follow-Up From the Phase 3 Archway Trial

De-Kuang Hwang, MD, PhD[1]; Carl D. Regillo, MD, FACS[2]; Steven Blotner, MS[3]; Melina Cavichini Cordeiro, MD, MS[3]; Philip Jaycock, MD[4]; and Shamika Gune, MD[3]

[1] Department of Ophthalmology, Taipei Veterans General Hospital, Taipei City, Taiwan
[2] Wills Eye Hospital, Thomas Jefferson University, Mid Atlantic Retina, Philadelphia, PA, USA
[3] Genentech, Inc., South San Francisco, CA, USA
[4] Roche Products Ltd., Welwyn Garden City, UK

Presented at the 38th Asia-Pacific Academy of Ophthalmology Congress
Kuala Lumpur, Malaysia | 23–26 February 2023

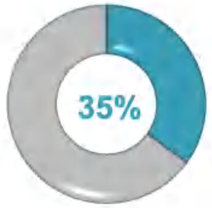
Visual Acuity Decreases Due to Fewer Intravitreal Injections and Patients Lost to Follow-up

Current anti-VEGF injections place significant burden on patients and caregivers[1,2]

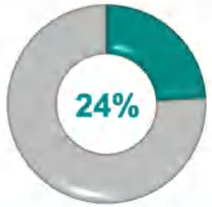
Most common reasons for patients discontinuing intravitreal injections[1]:

1. 

Distance from home to the hospital

2. 

Dissatisfied with injection benefit

3. 

Burden of follow-up visits

Other factors include[1,2]:

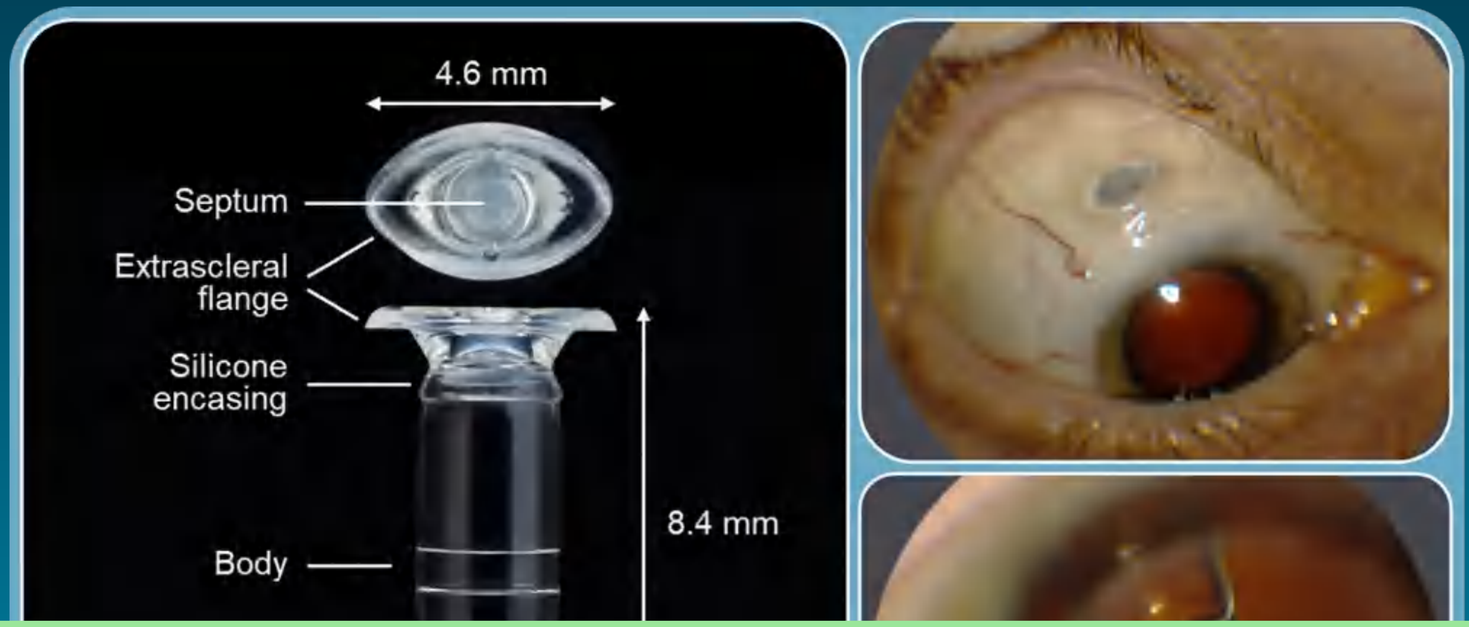
- Patient anxiety (reported in 56% of patients)
  - 39% fear going blind from injections/fear of the needle causing damage to the eye
  - 37% fear the treatment will not work
- Patients not being able to stick to the treatment plan

1. Boulanger-Scemama E et al. *J Fr Ophthalmol*. 2015;38:620-627. 2. Senra H et al. *Am J Ophthalmology*. 2017;177:213-224.
VEGF, vascular endothelial growth factor.

The Port Delivery System With Ranibizumab (PDS)

Continuous intravitreal delivery of a customized formulation of ranibizumab

The PDS was approved by the FDA in October 2021 as a drug-device combination with 2 refills per year for maintenance of vision and retinal anatomy in patients with nAMD[1,a]



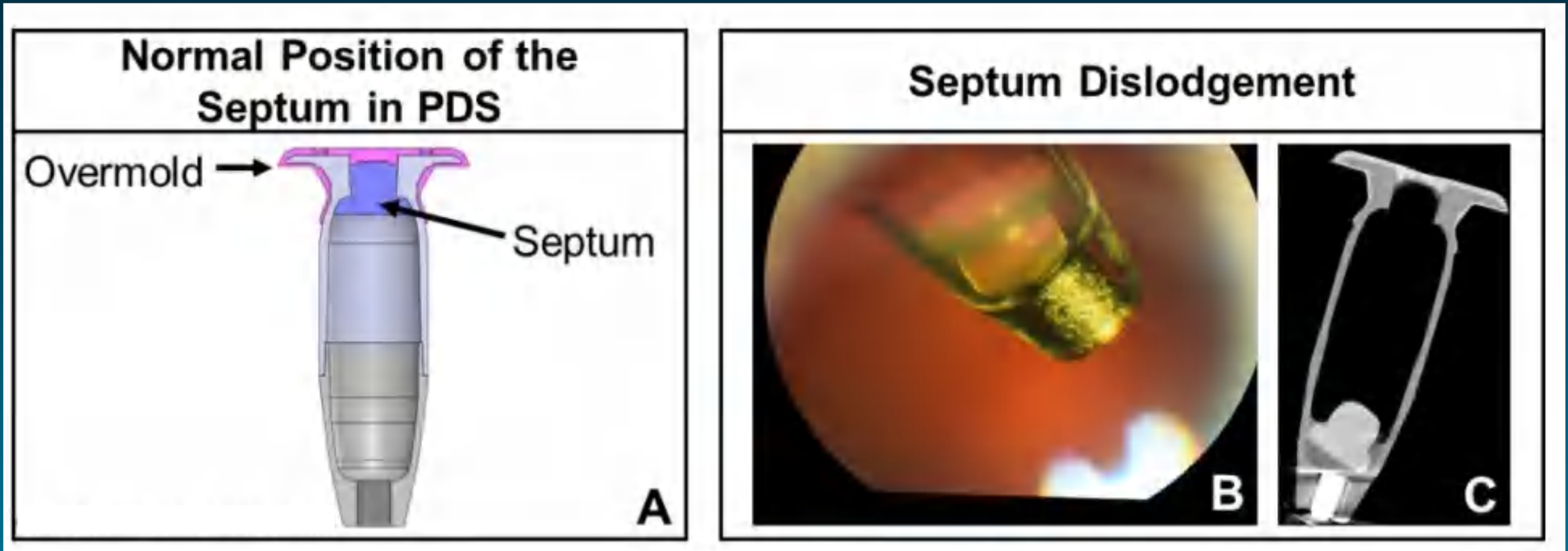
In October 2022 Roche/Genentech initiated a voluntary recall of the PDS ocular implant, insertion tool assembly, drug vial, and initial fill needle in the United States and paused new implantations, including in ongoing global clinical trials.

Refill-exchange procedures can continue in eligible patients who already have an implant.

The voluntary recall is based on recent testing of the commercial supply of PDS implants where results showed that some implants did not perform to manufactures standards.

[a] The FI ctions of ranib

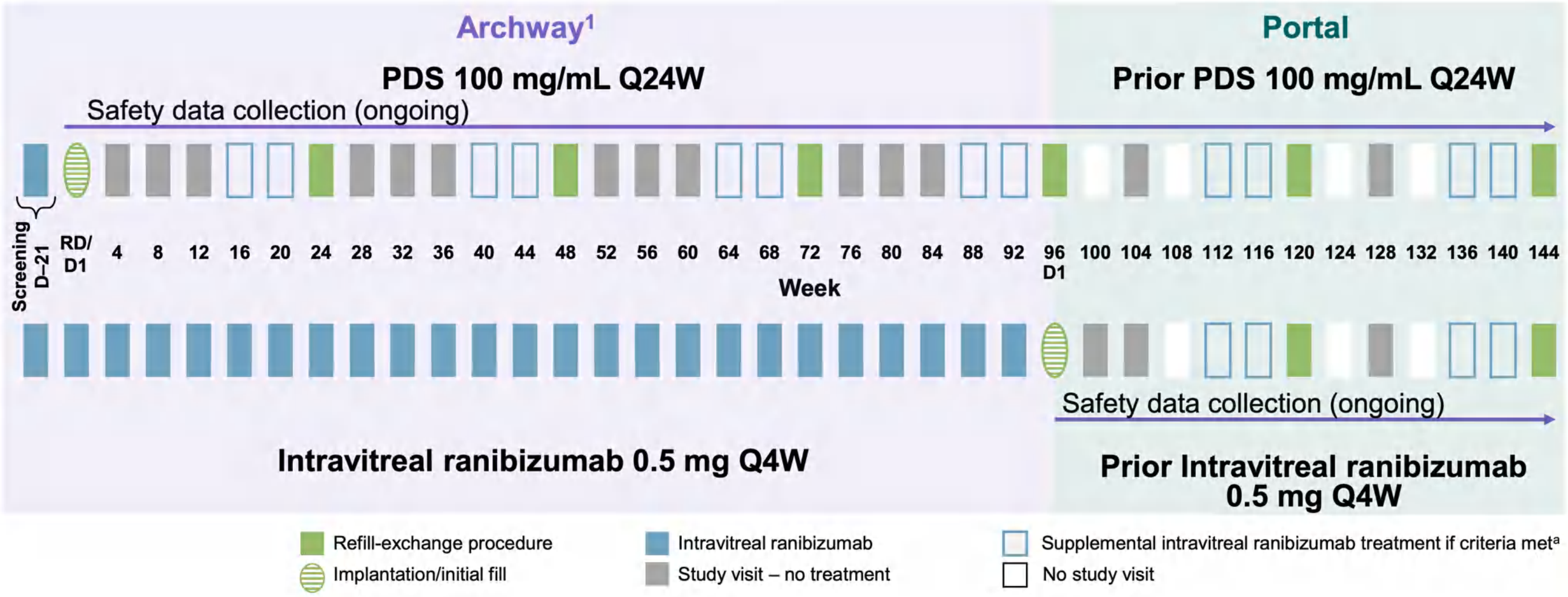
1. Ranibizumab injection. Package insert. Genentech, Inc.; 2022. Wykoff CC et al. Presented at: Angiogenesis, Exudation, and Degeneration Meeting; February 11-12, 2022; Virtual. Holekamp NM et al; Archway Investigators. Ophthalmology. 2022;129(3):295-307.



Visual representation of the normal position of the septum in the PDS (A) compared to septum dislodgement (B and C). Photo shows an example of a septum dislodged into the implant (B) and a micro computer tomography cross-sectional image of the implant dislodged septum (C)

Kitchens J. Presented at: Vail Vitrectomy Meeting 2022; March 12-15, 2022; Vail, CO.
Dear Health Care Provider Letter. October 2022. https://www.gene.com/download/pdf/Susvimo_DHCP_Important_Prescribing_Information_2022-10-18.pdf

Designed to Evaluate the Safety and Efficacy of Continuous Drug Delivery with PDS Q24W

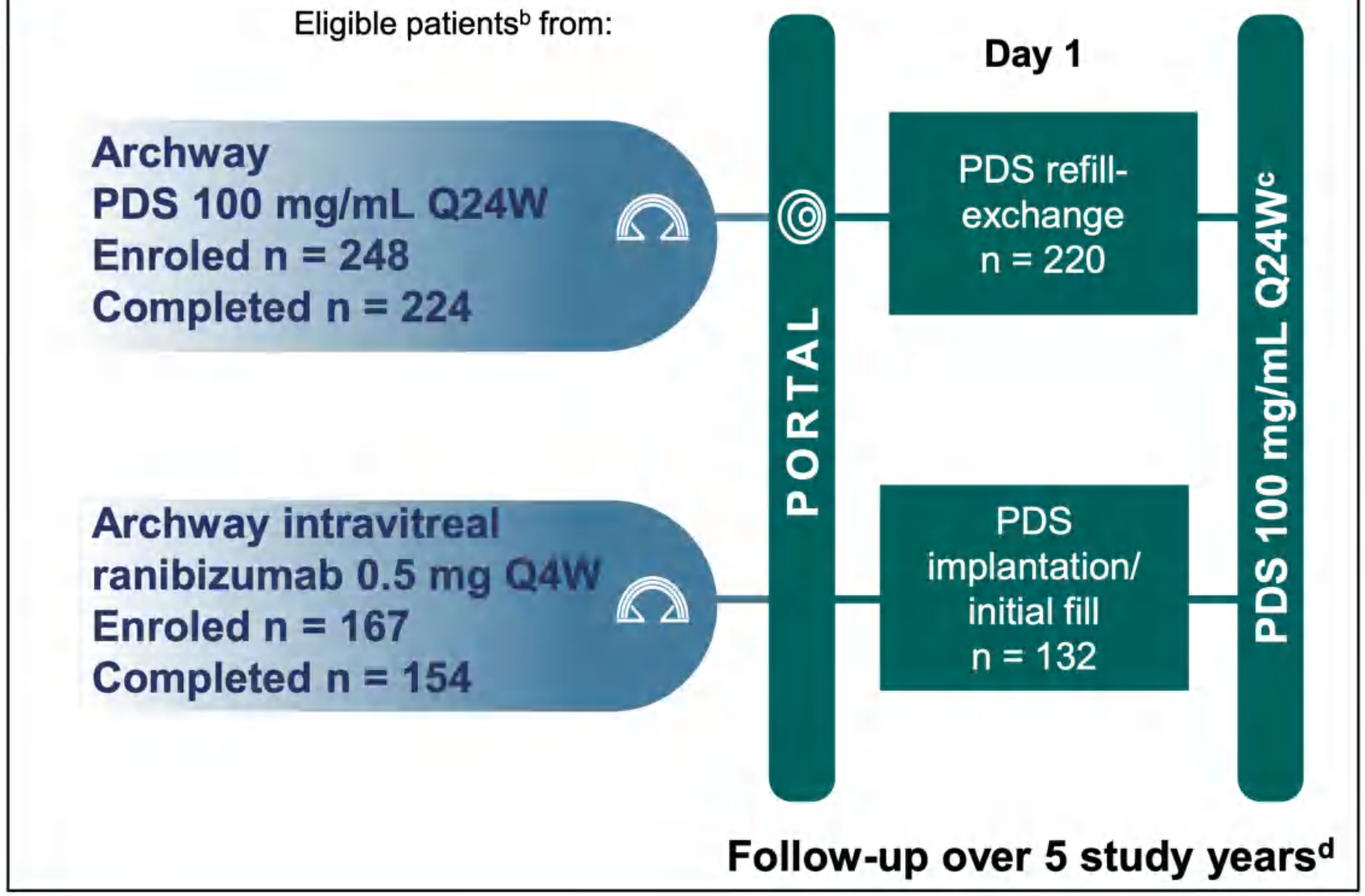


Archway, NCT03677934; Portal, NCT03683251. [a] Eligible for supplemental intravitreal ranibizumab treatment with open-label intravitreal ranibizumab at weeks 16 and 20 (after implant insertion) and at weeks 40, 44, 64, 68, 88, 92, 112, 116, 136 and 140 if any of the following 3 criteria were met: decrease of ≥ 15 letters from the best-recorded BCVA in the study OR increase of ≥ 150 µm in CST on SD-OCT from the lowest CST measurement in the study OR increase of ≥ 100 µm in CST on SD-OCT from the lowest CST measurement in the study associated with a decrease of ≥ 10 letters from the best-recorded BCVA during the study. 1. Holekamp NM et al; Archway Investigators. *Ophthalmology*. 2022;129(3):295-307. BCVA, best-corrected visual acuity; CST, central subfield thickness; D, day; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks; RD, randomization; SD-OCT, spectral-domain optical coherence tomography.

Archway Cohorts of the Portal Extension Study[a]

Portal Is Designed to Evaluate the Long-term Safety and Tolerability of the PDS for nAMD

Portal Study Design



Archway Cohorts in Portal (July 2022 Data Cut)

Prior PDS 100 mg/mL Q24W:
Received implant at Archway baseline after a mean 5 prior injections received before Archway

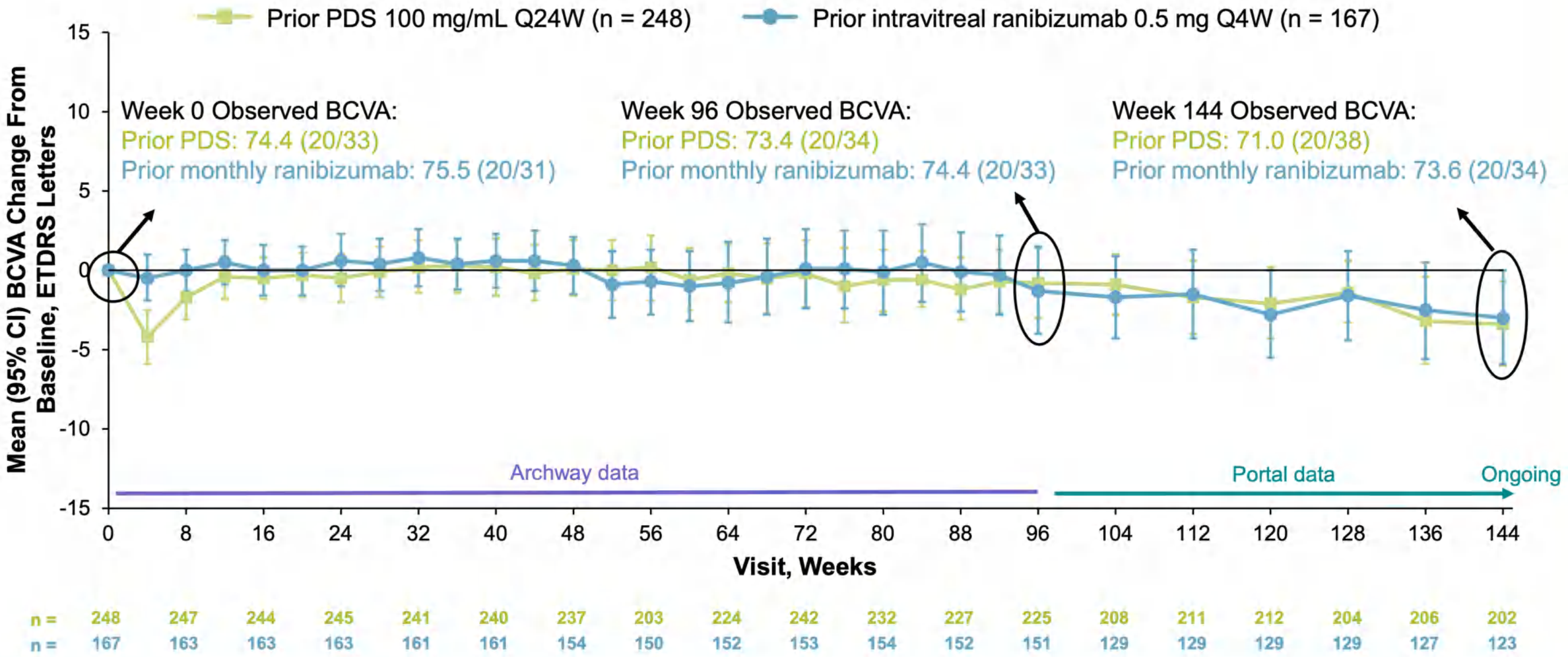
Mean (range) Follow-up Time:
160.44 (2.0–200.3) weeks

Prior intravitreal ranibizumab 0.5 mg Q4W:
Received implant at Portal baseline after a mean 23 prior injections received during Archway

Mean (range) Follow-up Time
77.49 (31.7–97.6) weeks

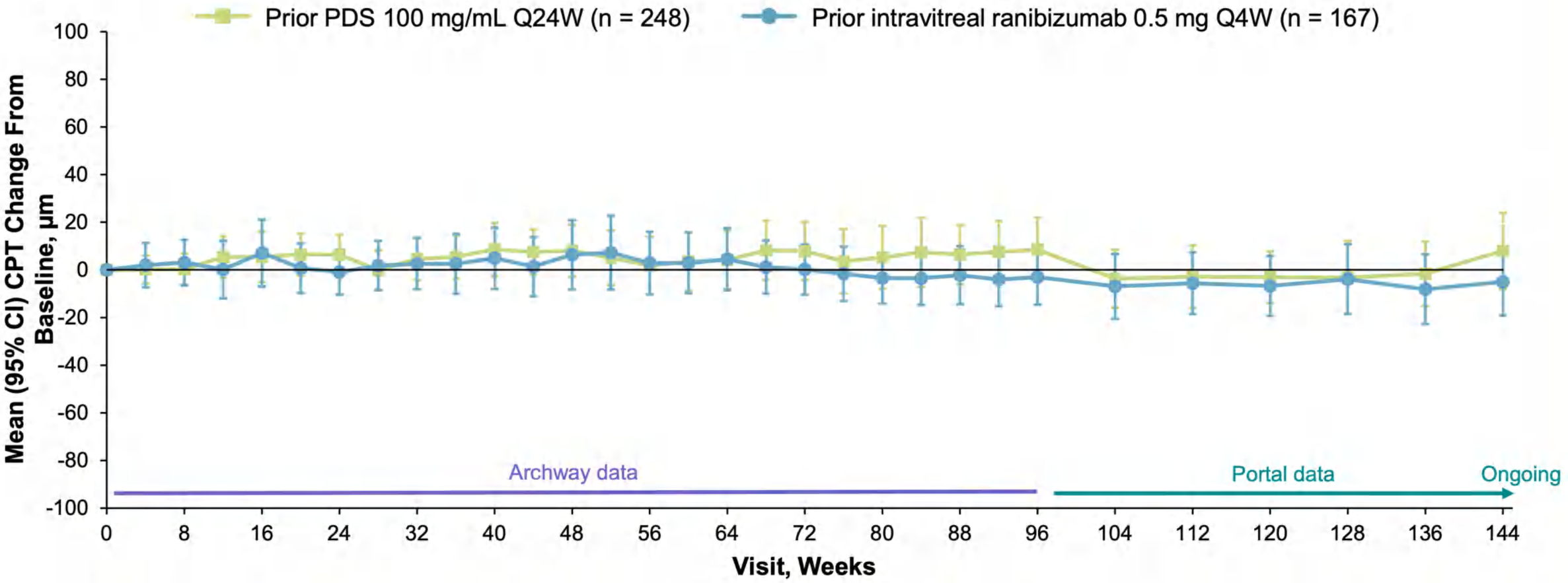
Archway, NCT03677934; Portal, NCT03683251. [a] Previous enrolment in and completion of Archway, without early treatment or study discontinuation in either trial. [b] The Portal trial also enrols patients from the Ladder (NCT02510794) and Velodrome trials (NCT04657289), but these patients are not included in the current analyses. [c] Patients may be eligible for supplemental treatment with intravitreal ranibizumab at weeks 16, 40, 64, 88, 112 and 136. If deemed clinically necessary per investigator's discretion, additional unscheduled visits to assess eligibility for supplemental treatment may be added 4 weeks (± 7 days) after each of the visits listed. [d] Study year = 48 weeks, based on 12 months comprising 4 weeks.
nAMD, neovascular age-related macular degeneration; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

PDS Q24W Maintained Vision Through Week 144



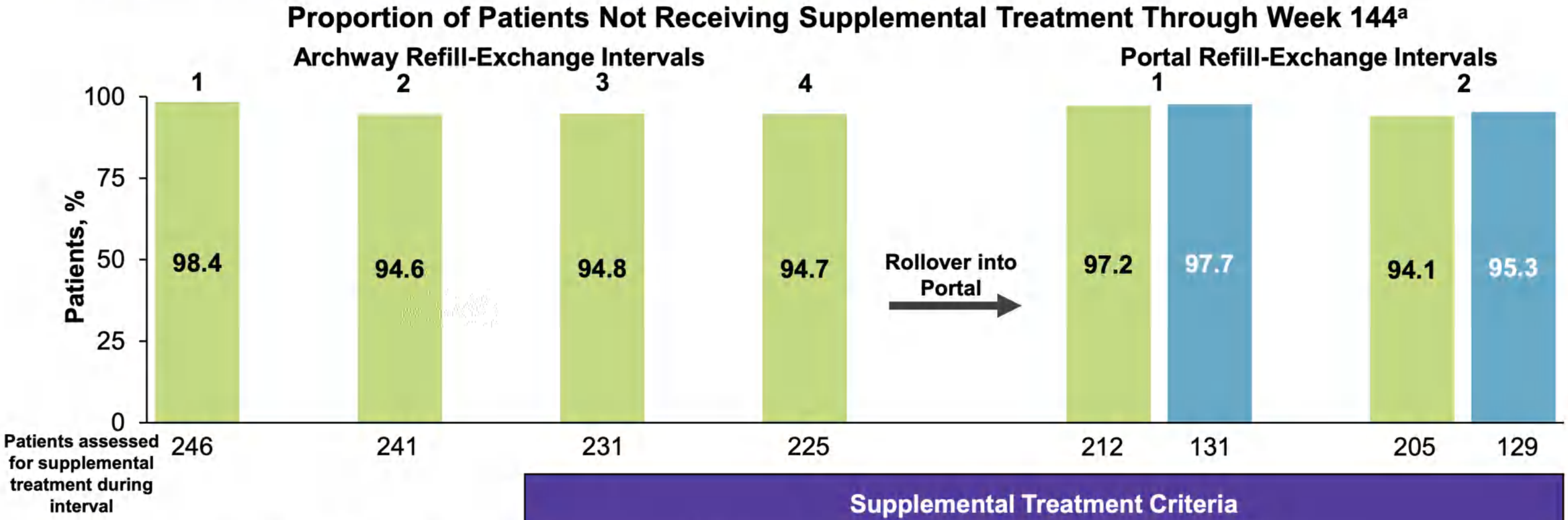
Archway, NCT03677934; Portal, NCT03683251. Archway efficacy population. Observed data. Baseline is defined as the last assessment on or before the first study treatment in Archway. The bars represent multiplicity-adjusted 95% CI. BCVA, best corrected-visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

PDS Q24W Maintained Retinal Anatomy Through Week 144



Archway, NCT03677934; Portal, NCT03683251. Archway efficacy population. Observed data. Baseline is defined as the last assessment on or before the first study treatment in Archway. The bars represent multiplicity-adjusted 95% CIs. CPT assessed by the central reading center with boundaries internal limiting membrane to inner third of the retinal pigment epithelium. CPT, center point thickness; PDS, Port Delivery System with ranibizumab; Q4W, every 4 weeks; Q24W, every 24 weeks.

~95% of PDS Q24W Patients Did Not Receive Supplemental Treatment Before Each Refill-Exchange Procedure



Supplemental Treatment Criteria	
BCVA-only	≥ 15 letter loss from the best-recorded on-study BCVA; or
CST-only	≥ 150 µm increase in CST on SD-OCT from the lowest on-study CST; or
BCVA+CST	≥ 100 µm increase in CST on SD-OCT from the lowest on-study CST, with ≥ 10 letter loss from best-recorded on-study BCVA

Archway, NCT03677934; Portal, NCT03683251. Observed data through the July 2022 clinical cutoff date; data collection ongoing. [a] Patients assessed at weeks 16, 20 40, 44, 64, 68, 88, 92, 112, 116, 136 and 140.
BCVA, best-corrected visual acuity; CST, central subfield thickness; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks; SD-OCT, spectral-domain optical coherence tomography.

Ocular Adverse Events of Special Interest[a] From Time of Implant Insertion: Archway Prior PDS Q24W Arm

MedDRA Preferred Term[b]	Archway Prior PDS Q24W (July 2022 Data-cut; n = 248)	
Overall number of AESIs	**142**	
Mean (range) follow-up time, weeks	**160.44 (2.0–200.3)**	
	All	**Vision-threatening***
Total number of patients with ≥ 1 AESI, n (%)	**74 (29.8%)**	**6 (2.4%)**
Cataract[c]	27 (10.9%)	0
Conjunctival bleb/conjunctival filtering bleb leak	21 (8.5%)	1 (0.4%)
Vitreous haemorrhage	19 (7.7%)	1 (0.4%)
Conjunctival erosion	13 (5.2%)	0
Conjunctival retraction	11 (4.4%)	0
Endophthalmitis[d]	5 (2.0%)	2 (0.8%)
Implant dislocation	6 (2.4%)	1 (0.4%)
Hyphema	3 (1.2%)	0
Rhegmatogenous retinal detachment	2 (0.8%)	1 (0.4%)

Patients were implanted **before** the 2020 Instructions for Use update which mandated an incision length of 3.5 mm

*An AE is considered to be vision-threatening if it is a serious adverse event and meets ≥ 1 the following: (1) causes a decrease of ≥ 30 letters in BCVA (compared with the last assessment of VA prior to the most recent treatment) lasting > 1 hour; (2) requires surgical intervention (ie, conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight; (3) associated with severe intraocular inflammation (eg, endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells in the vitreous)

Archway, NCT03677934; Portal, NCT03683251. Safety population; July 2022 CCOD. [a] Ocular AESIs potentially related to the PDS implant or implant insertion procedure. [b] Frequency counts by Preferred Term. Multiple occurrences of the same AE in an individual are counted only once for each column. [c] Includes the following terms: cataract, cataract nuclear, cataract cortical and cataract subcapsular. [d] The US Food and Drug Administration has issued a **boxed warning** for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab.[1] 1. Susvimo [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2022. AE, adverse event; AESI, adverse event of special interest; BCVA, best-corrected visual acuity; CCOD, clinical cutoff date; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks; VA, visual acuity.

Ocular Adverse Events of Special Interest[a] From Time of Implant Insertion: Archway Prior Injection Arm

MedDRA Preferred Term[b]	Archway Prior Injection Arm (July 2022 Data-cut; n = 132)	
Overall number of AESIs	**45**	
Mean (range) follow-up time, weeks	**77.49 (31.7–97.6)**	
	All	**Vision-threatening***
Total number of patients with ≥ 1 AESI, n (%)	**29 (22.0%)**	**0**
Cataract[c]	7 (5.3%)	0
Conjunctival bleb/conjunctival filtering bleb leak	15 (11.4%)	0
Vitreous haemorrhage	5 (3.8%)	0
Conjunctival erosion	3 (2.3%)	0
Conjunctival retraction	4 (3.0%)	0
Endophthalmitis[d]	3 (2.3%)	0
Implant dislocation	2 (1.5%)	0
Hyphema	1 (0.8%)	0
Rhegmatogenous retinal detachment	0	0

Patients were implanted **after** the 2020 Instructions for Use update which mandated an incision length of 3.5 mm

*An AE is considered to be vision-threatening if it is a serious adverse event and meets ≥ 1 the following: (1) causes a decrease of ≥ 30 letters in BCVA (compared with the last assessment of VA prior to the most recent treatment) lasting > 1 hour; (2) requires surgical intervention (ie, conventional surgery, vitrectomy, vitreous tap, or biopsy with intravitreal injection of anti-infective medications, or laser or retinal cryopexy with gas) to prevent permanent loss of sight; (3) associated with severe intraocular inflammation (eg, endophthalmitis, 4+ anterior chamber cell/flare or 4+ cells in the vitreous)

Archway, NCT03677934; Portal, NCT03683251. Safety population; July 2022 CCOD. [a] Ocular AESIs potentially related to the PDS implant or implant insertion procedure. [b] Frequency counts by Preferred Term. Multiple occurrences of the same AE in an individual are counted only once for each column. [c] Includes the following terms: cataract, cataract nuclear, cataract cortical and cataract subcapsular. [d] The US Food and Drug Administration has issued a **boxed warning** for the PDS because it has been associated with a 3-fold higher rate of endophthalmitis compared with monthly intravitreal injections of ranibizumab.[1] 1. Susvimo [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2022. AE, adverse event; AESI, adverse event of special interest; BCVA, best-corrected visual acuity; CCOD, clinical cutoff date; MedDRA, Medical Dictionary for Regulatory Activities; PDS, Port Delivery System with ranibizumab; VA, visual acuity.

88% of Patients Switching From Intravitreal Injections Preferred the PDS Over Intravitreal Injections

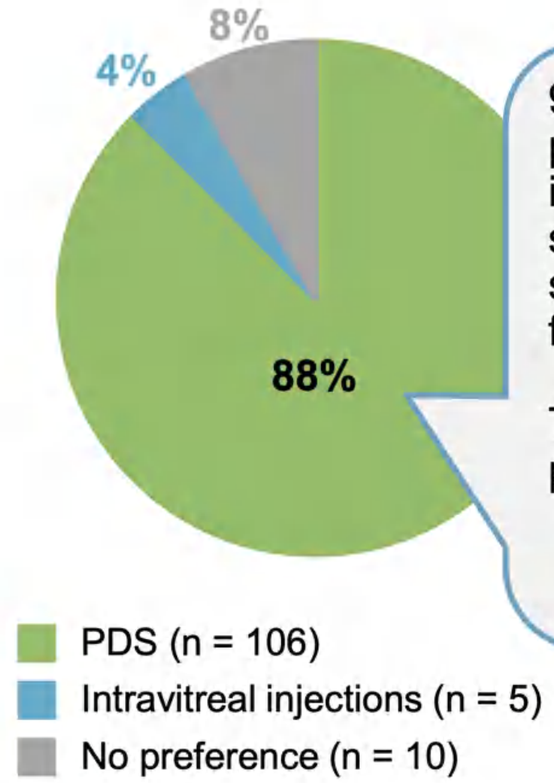
PDS Patient Preference Questionnaire (PPPQ)

- The PPPQ is a 3-item questionnaire that captures a patient's preference for treatment, the strength of their preference, and the reasons for their preference
- The PPPQ was administered to patients from the prior monthly ranibizumab arm in Archway who received the PDS in Portal

On average, patients received 22.9 injections in Archway before receiving the PDS in Portal

Responses to the PPPQ at Week 40[a]

(n = 121)[b]



90% of patients who preferred the PDS indicated a very strong or fairly strong preference for the PDS

Top reasons for preference:
- Fewer treatments
- Less discomfort

Archway, NCT03677934; Portal, NCT03683251. [a] Patients treated with intravitreal ranibizumab 0.5 mg in Archway who switched to PDS 100 mg/mL Q24W in Portal. [b] Percentages are based on total number of patients who completed the measure.
PDS, Port Delivery System with ranibizumab; PPPQ, PDS Patient Preference Questionnaire; Q24W, every 24 weeks.

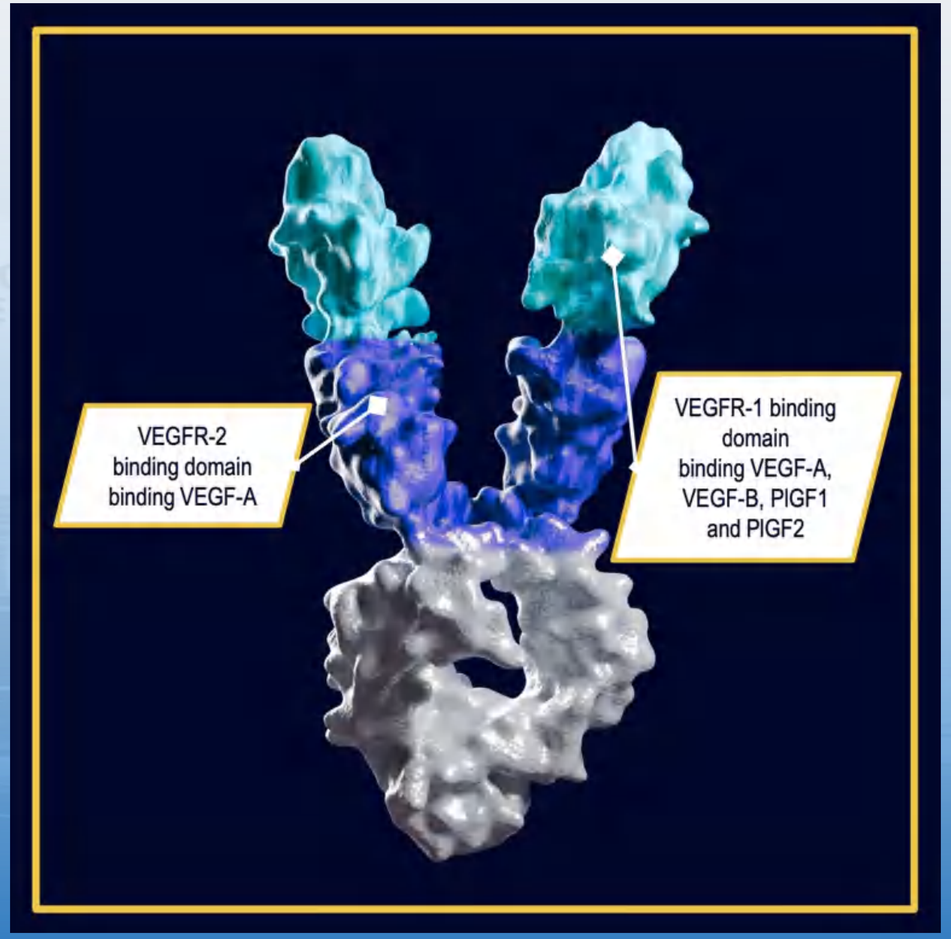
Efficacy and Safety Profile of PDS Q24W Maintained Over Longer Term

- PDS Q24W maintained vision and retinal anatomy improvements for up to 3 years, regardless of number of prior injections
- ~95% of PDS patients did not receive supplemental treatment in each treatment interval over 3 years
- Overall benefit-risk profile for PDS patients remains favorable
- No vision-threatening AEs reported in the recently implanted cohort which received surgeries in alignment with the updated Instructions for Use
- 88% of patients switching from intravitreal injections in Archway to the PDS in Portal preferred treatment with the PDS at week 40, consistent with previous results

Archway, NCT03677934; Portal, NCT03683251.
AE, adverse event; PDS, Port Delivery System with ranibizumab; Q24W, every 24 weeks.

Agents Seeking Approval

- Ophthalmic Bevacizumab
- High Dose Aflibercept



On-Label Ophthalmic Bevacizumab

The Majority of New Patient Starts are Off-Label Bevacizumab

New Patient Starts

66.3% of respondents (n=990) utilize off-label bevacizumab as a first-line agent[1]

Maintenance Therapy

42.8-50.2% of overall injections continue therapy on off-label[2,3]

- **Anti-VEGF is the standard-of-care** for the treatment of wAMD, DME and BRVO globally
- **~70% of Retinal Specialists in the US use off-label Avastin first-line for wAMD**

Source: Navigant Quantitative Survey (n=152), 2019

On-Label Ophthalmic Bevacizumab

ONS-5010 (bevacizumab-vikg) Investigational Therapy	
Patient Population	• Patients diagnosed with **wet AMD, DME, or BRVO**
Description	• Anti-VEGF **bevacizumab designed for ophthalmic indications** wet AMD, DME, and BRVO • Demonstrated high affinity to bind to all isoforms of VEGF A
Dosing and Administration	• Initially supplied in a glass vial for intravitreal 1.25 mg injection administered once monthly
Efficacy, Safety, and AEs	• NORSE TWO demonstrated significant efficacy and safety, and when combined with NORSE ONE and NORSE THREE provides the necessary registration database. These ONS-5010 data when taken as a whole continue to be consistent with previously published results for bevacizumab

On-Label Ophthalmic Bevacizumab

✓ U.S. FDA BLA Accepted with Target PDUFA of August 29, 2023

✓ Received Validation of Marketing Authorization Application by European Medical Agency

✓ Positive Signals

NORSE ONE

Clinical Experience Trial

1st Registration Trial

✓ Positive Top-Line Data

NORSE TWO

Pivotal Trial

2nd Registration Trial

✓ Completed

NORSE THREE

Open-Label Safety Study

Supports BLA Requirements

On-Label Ophthalmic Bevacizumab

NORSE TWO

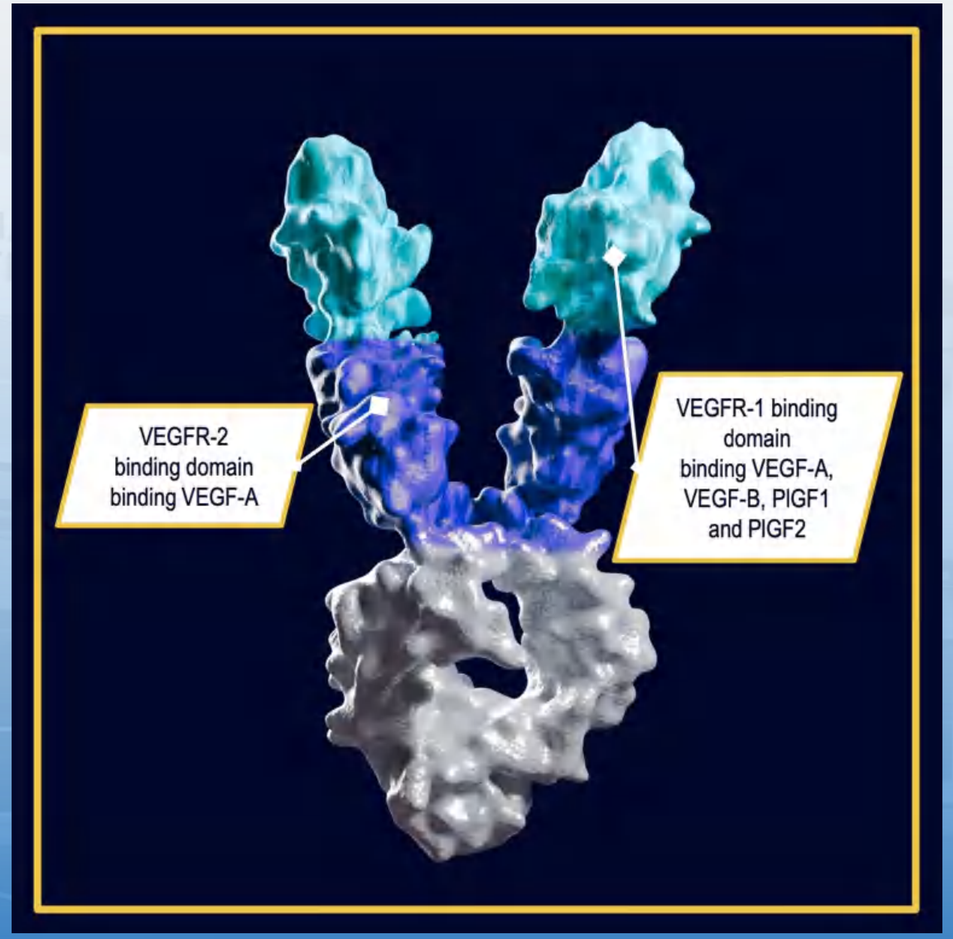
Pivotal Trial

2nd Registration Trial

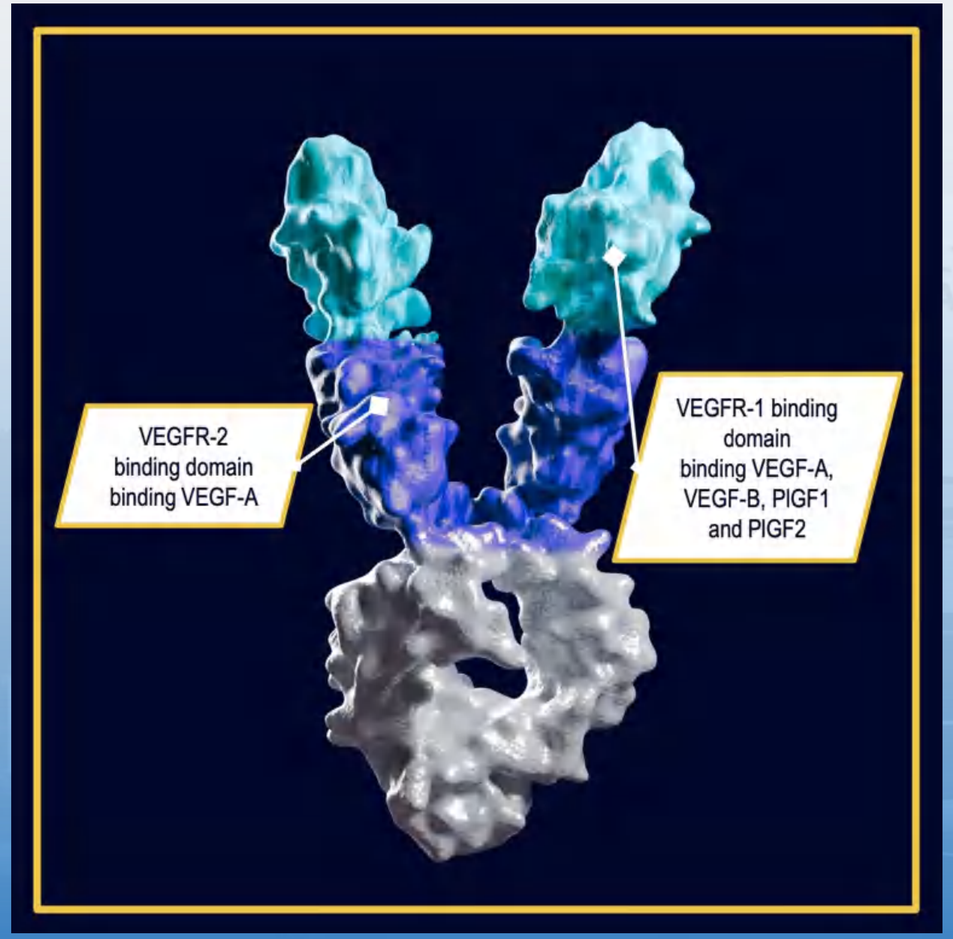
Key Outcomes:

- 41.7% of ONS-5010 subjects gained ≥3 lines of vision
- 56.5% of ONS-5010 subjects gained ≥ 10 letters of vision
- 68.5% of ONS-5010 subjects gained ≥ 5 letters of vision
- The **majority** of subjects maintained or gained BCVA during the study (defined as change from baseline in BCVA ≥ 0)
  - **≥ 80%** of subjects maintained BCVA each month
  - At 1 year, **86.4%** of subjects had maintained or gained BCVA, supporting the sustained positive effect of ONS-5010
- Only one ONS-5010 Ocular Inflammation AE Reported in NORSE TWO (Iritis)

High Dose Aflibercept



High Dose Aflibercept



- Novel intravitreal formulation delivers 8 mg in 70 µL injection (114.3 mg/mL)
- 4-times higher molar dose compared to aflibercept 2 mg is hypothesized to provide longer effective vitreal concentrations and enable a more sustained effect on VEGF signaling

Intravitreal Aflibercept 8 mg Injection in Patients with Neovascular Age-Related Macular Degeneration: 48-Week Results from the Phase 3 PULSAR Trial

Jean-François Korobelnik,[1] on behalf of the PULSAR study investigators

[1]CHU Bordeaux, Service d'Ophtalmologie, France; Univ. Bordeaux, INSERM, and Population Health Research Center, team LEHA, UMR 1219, F-33000, Bordeaux, France

Presented at the Retina Society 55th Annual Scientific Meeting; Pasadena, CA, USA; November 2–5, 2022

PULSAR Study Design

pulsar
nAMD

Multicenter, randomized, double-masked study in patients with treatment-naïve nAMD
Randomized at baseline 1 (2q8) : 1 (8q12) : 1 (8q16)

2q8
Aflibercept 2 mg every 8 weeks after 3 initial monthly injections
n=336

8q12
Aflibercept 8 mg every 12 weeks after 3 initial monthly injections
n=335

8q16
Aflibercept 8 mg every 16 weeks after 3 initial monthly injections
n=338

Primary endpoint at Week 48
Mean change in BCVA (non-inferiority)

Key secondary endpoint at Week 16
Proportion of patients without IRF and SRF in the center subfield

End of study at Week 96

BCVA, best corrected visual acuity; **IRF**, intraretinal fluid; **SRF**, subretinal fluid.

PULSAR: Dosing Schedule in Year 1

pulsar
nAMD

	Day 1	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48
2q8	X	X	X		X	o	X	o	X	o	X	o	X
8q12	X	X	X		o	X	o	o	X	o	o	X	o
8q16	X	X	X		o	o	X	o	o	o	X	o	o

DRM in Year 1

- **Weeks 16 or 20**: patients on 8q12 or 8q16 and meeting DRM criteria had treatment interval shortened to q8
- **Week 24**: patients on 8q16 and meeting DRM criteria had treatment interval shortened to q12
- **Subsequent dosing visits**: patients on 8 mg and meeting DRM criteria had treatment interval shortened by 4 weeks
- Minimum interval for all patients was q8

DRM criteria for dosing interval shortening

>5-letter loss in BCVA from Week 12 BCVA due to persistent or worsening nAMD

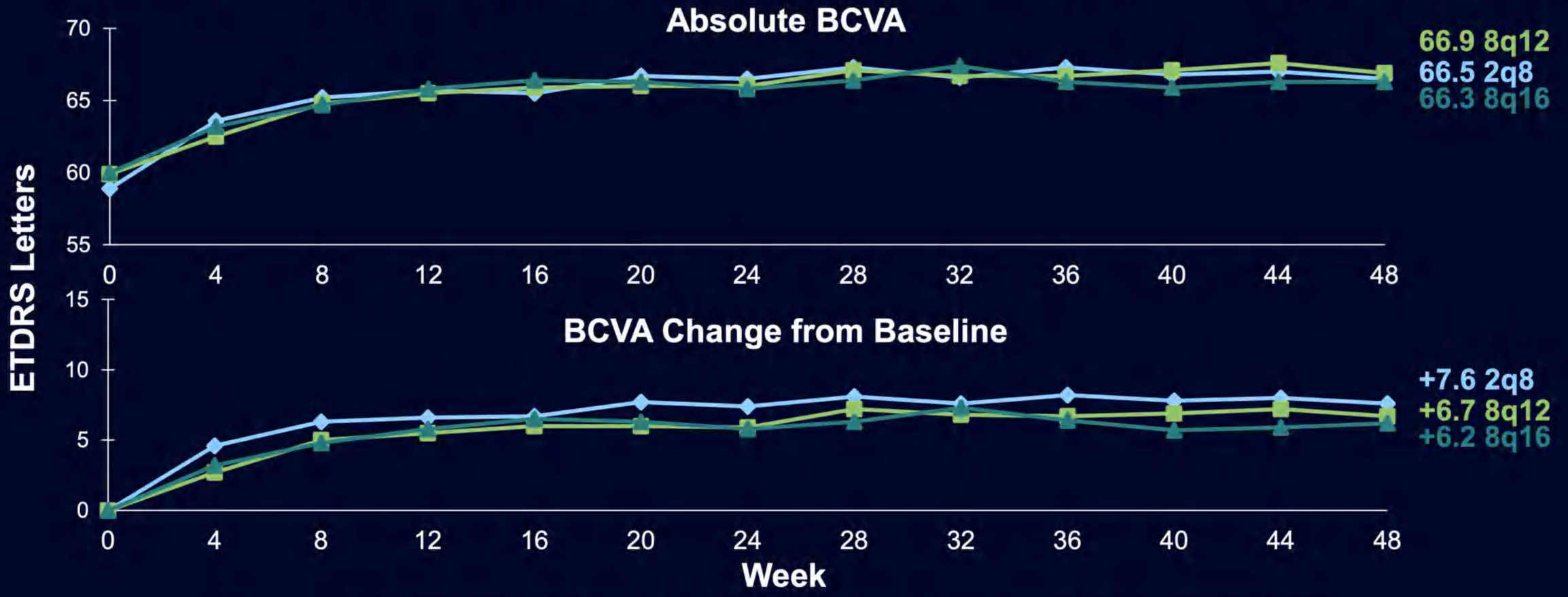
AND

>25 µm increase in CRT from Week 12 or new onset foveal neovascularization or foveal hemorrhage

Stippled boxes = initial treatment phase; X=active injection; o=sham injections
Note: Table does not reflect all dosing options once a patient is shortened. No extension of interval was allowed in Year 1.
CRT, central retinal thickness; **DRM**, dose regimen modifications; **OCT**, optical coherence tomography; **Wk**, week.

PULSAR: 48-Week BCVA Results
Primary Endpoint Met in Both 8mg Groups

pulsar
nAMD



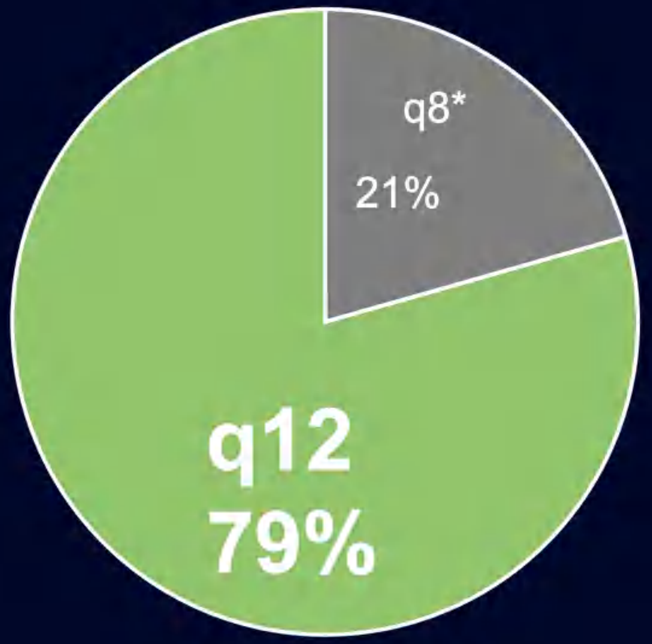
	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
2q8	7.0			
8q12	6.1	–0.97	–2.87, 0.92	p=0.0009
8q16	5.9	–1.14	–2.97, 0.69	p=0.0011

Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline).
ICE, intercurrent events; **MMRM**, mixed model for repeated measurements.

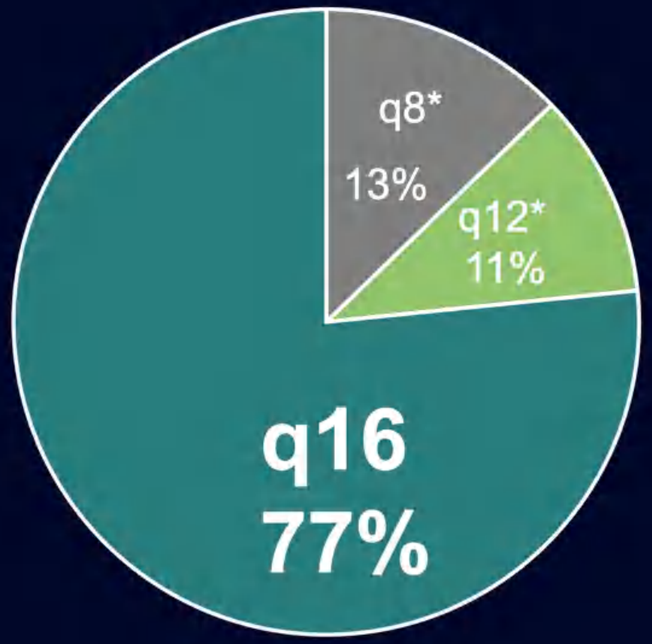
Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48

pulsar nAMD

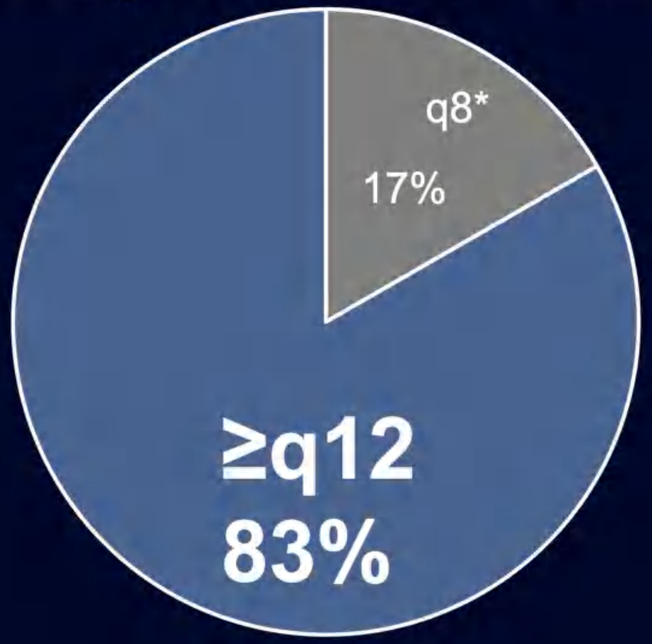
83% of 8 mg patients maintained dosing intervals ≥12 weeks



8q12 n=316^



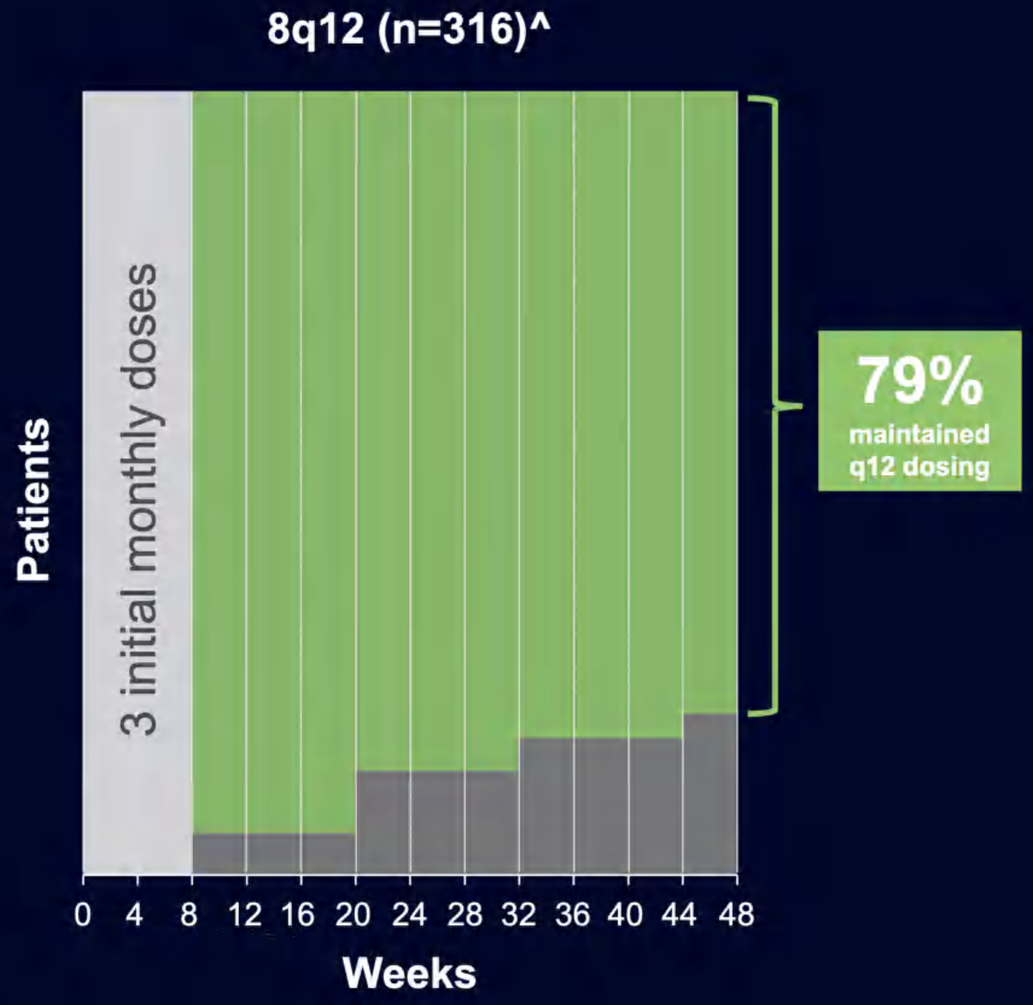
8q16 n=312^

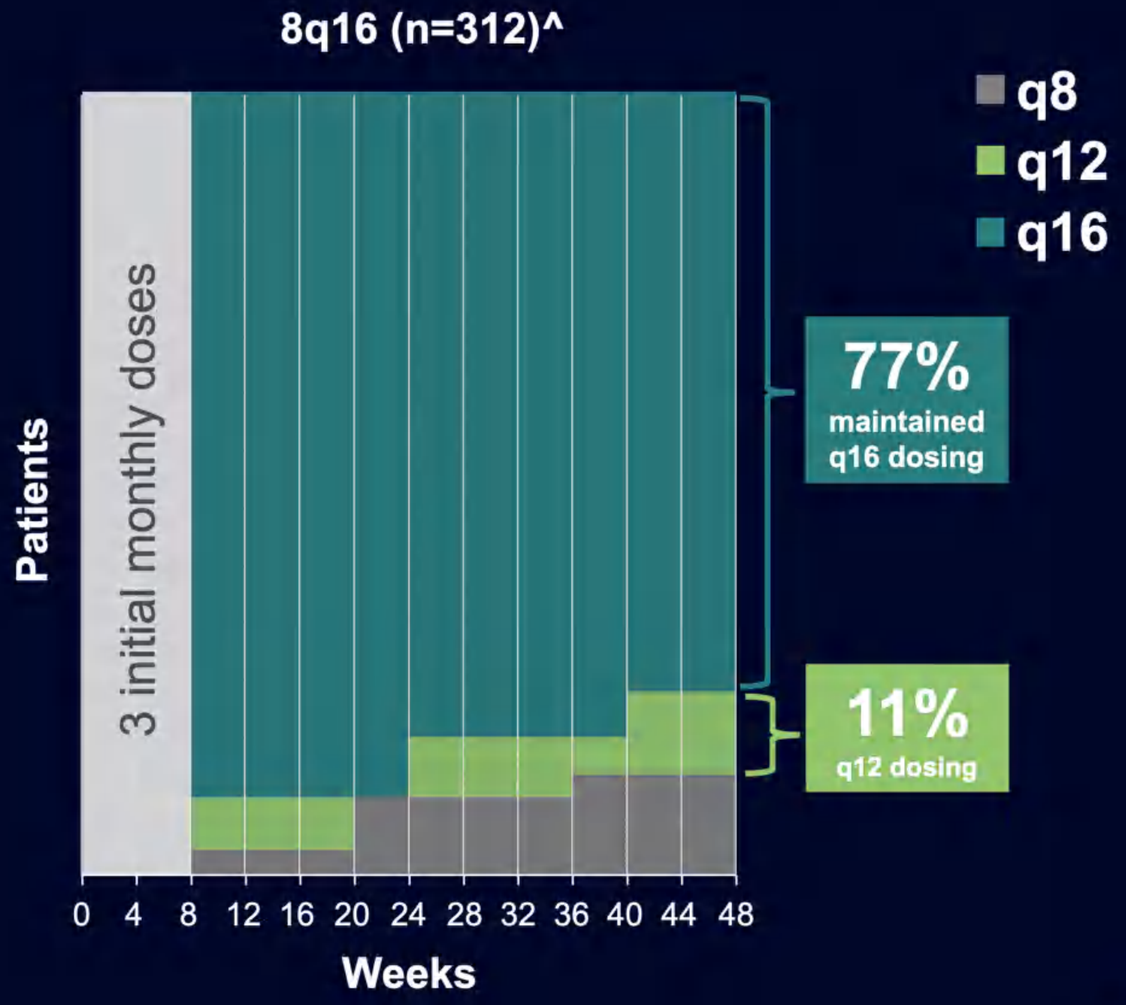


All 8 mg n=628^

Values may not add to 100% due to rounding.
*Patients shortened based on DRM assessments at some point through Week 48.
^Patients completing Week 48.

Proportion of Patients Maintaining q12- and q16-Week Intervals Through Week 48

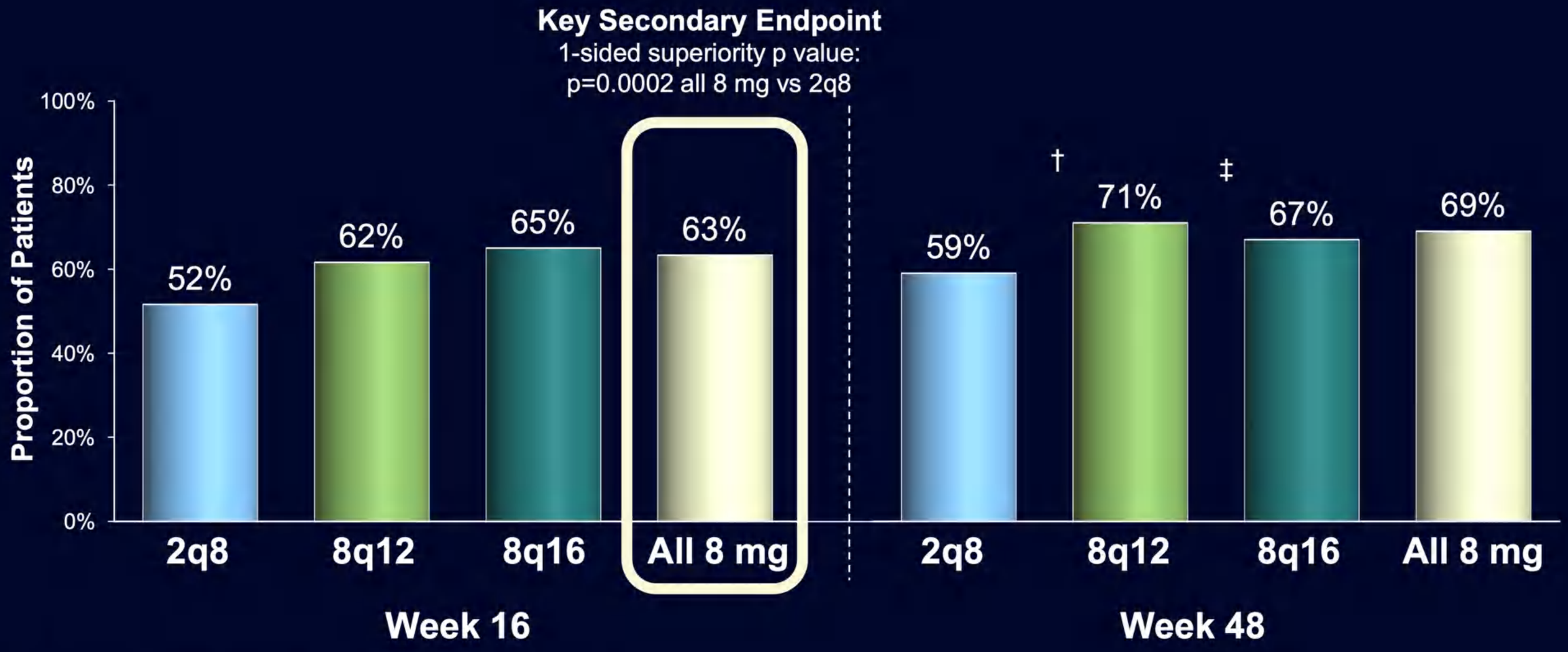




*Patients shortened based on DRM assessments at some point through Week 48.
^Patients completing Week 48.

Proportion of Patients Without Retinal Fluid in Center Subfield at Weeks 16 and 48

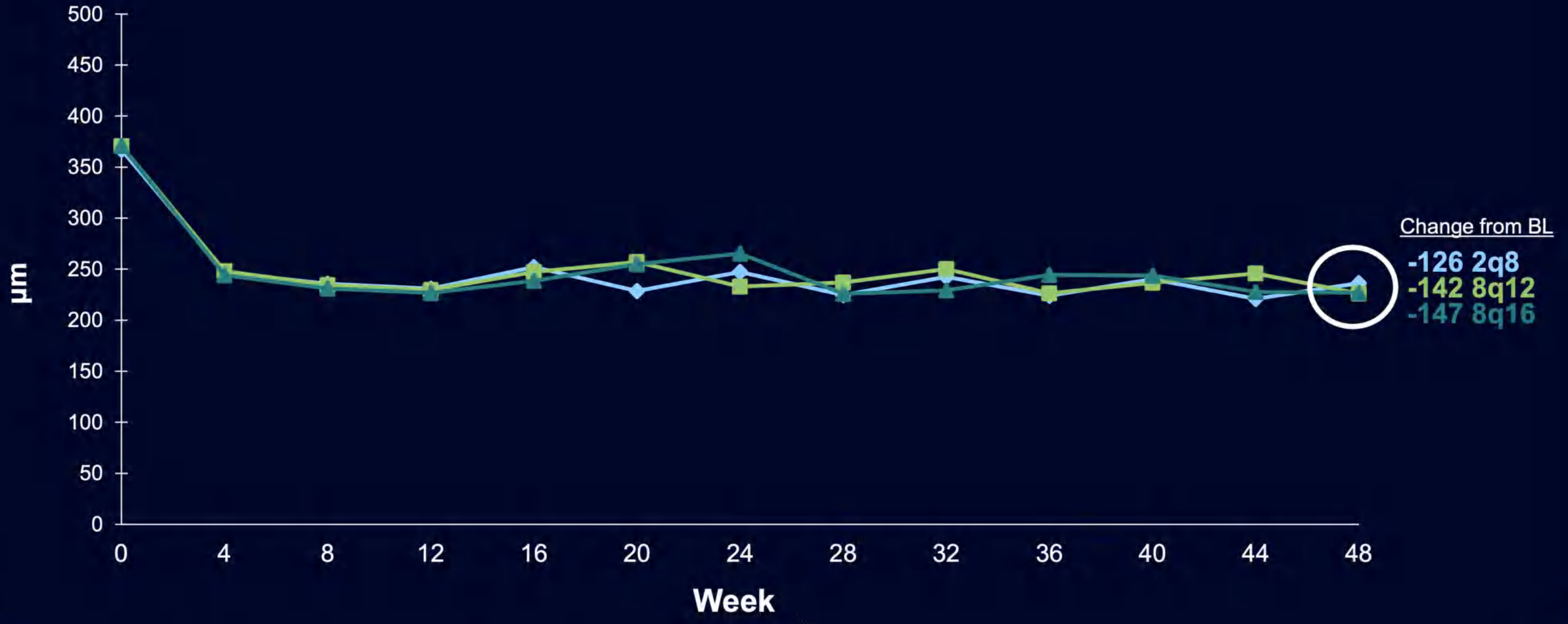
pulsar nAMD



Without retinal fluid defined as absence of IRF and SRF in center subfield.
LOCF (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338.
†p=0.0015 8q12 vs 2q8; ‡p=0.0458 8q16 vs 2q8.

Central Retinal Thickness

pulsar
nAMD



Observed values (censoring data post ICE); FAS: 2q8 n=336; 8q12 n=335; 8q16 n=338 (at baseline)

Most Frequent Ocular AEs Through Week 48

pulsar
nAMD

	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 AE (%)*	38.7%	38.5%	37.6%	38.0%
Cataract	3.0%	3.6%	3.6%	3.6%
Intraocular pressure increased	2.1%	3.3%	2.7%	3.0%
Retinal hemorrhage	4.2%	3.3%	3.0%	3.1%
Subretinal fluid	3.3%	3.0%	1.5%	2.2%
Visual acuity reduced	6.0%	3.6%	5.3%	4.5%
Vitreous floaters	3.3%	1.2%	3.6%	2.4%

*Any ocular treatment-emergent event in the study eye.
AE, adverse event; **SAE**, serious adverse event; **SAF**, safety analysis set.

Intraocular Pressure Through Week 48

pulsar
nAMD

	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with IOP ≥ 35 mmHg pre- or post-injection (%)	0.3%	0.9%	0.3%	0.6%

Pre-injection IOP values were similar to baseline values at all timepoints through Week 48

Intraocular Inflammation Through Week 48

pulsar
nAMD

	2q8	8q12	8q16	All 8 mg
N (SAF)	336	335	338	673
Patients with ≥ 1 IOI AE (%)*	0.6%	1.2%	0.3%	0.7%

No cases of endophthalmitis or occlusive retinal vasculitis
Reported IOI terms: chorioretinitis, iridocyclitis, iritis, vitreal cells, vitritis

*Treatment-emergent events.

Examples of Current Trials

- Gene Therapy
- Tyrosine Kinase Inhibitors
- VEGF-C & -D Blockade

- Delivery Methods
  - Intravitreal Injection
  - Suprachoroidal Injection
  - Subretinal Injection

RGX–314 for Treatment of Neovascular Age-related Macular Degeneration (nAMD)

RGX–314 PRODUCT CANDIDATE

Vector: AAV8 | **Gene:** anti-VEGF fab

Route of administration:

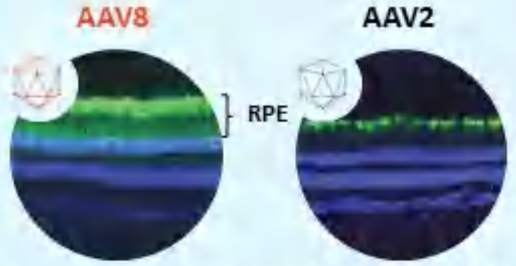
Subretinal (nAMD) or

Suprachoroidal (nAMD/DR)

Mechanism of action:

Reducing leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab

Improved AAV vector technology



More efficient gene delivery to the RPE[1]

+

Leveraging current standard of care in transgene

- FDA-approved mAbs and mAb fragments that inhibit VEGF are the current standard of care for treatment of nAMD
- **RGX–314 gene encodes an anti-VEGF mAb fragment (fab)**

=

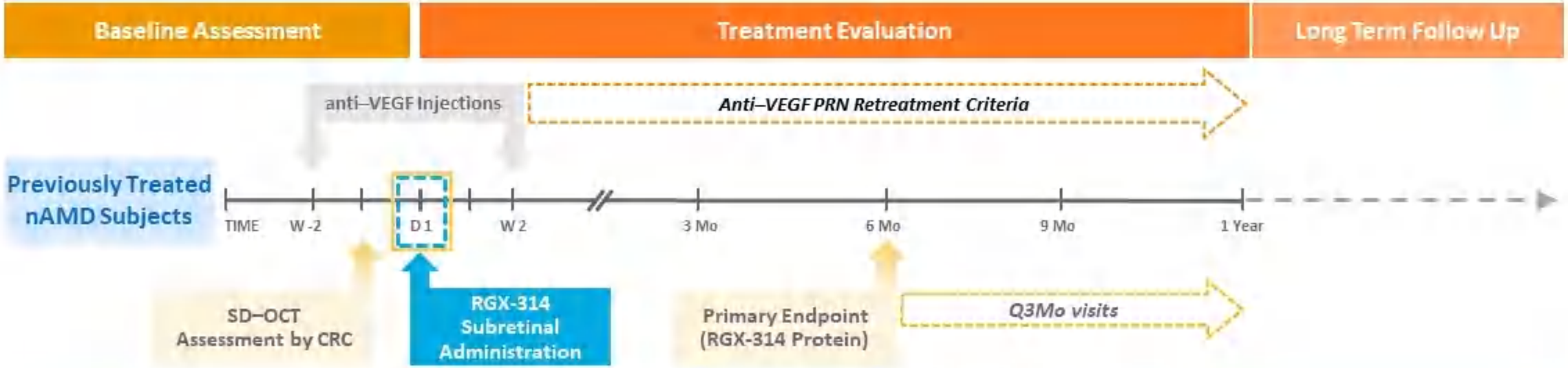
RGX–314: AAV8 encoding anti–VEGF fab

Potential for long-term therapeutic anti-VEGF expression

1. Vandenberghe et al. 2011 Science Translational Medicine.

AAV: Adeno-Associated Virus

RGX-314 Phase II Clinical Trial in nAMD: A Pharmacodynamic (PD) Study



No prophylactic steroids given beyond routine vitrectomy SOC

✓ Fully Enrolled

DOSE 1 (High)
$1.3x10^{11}$ GC/eye

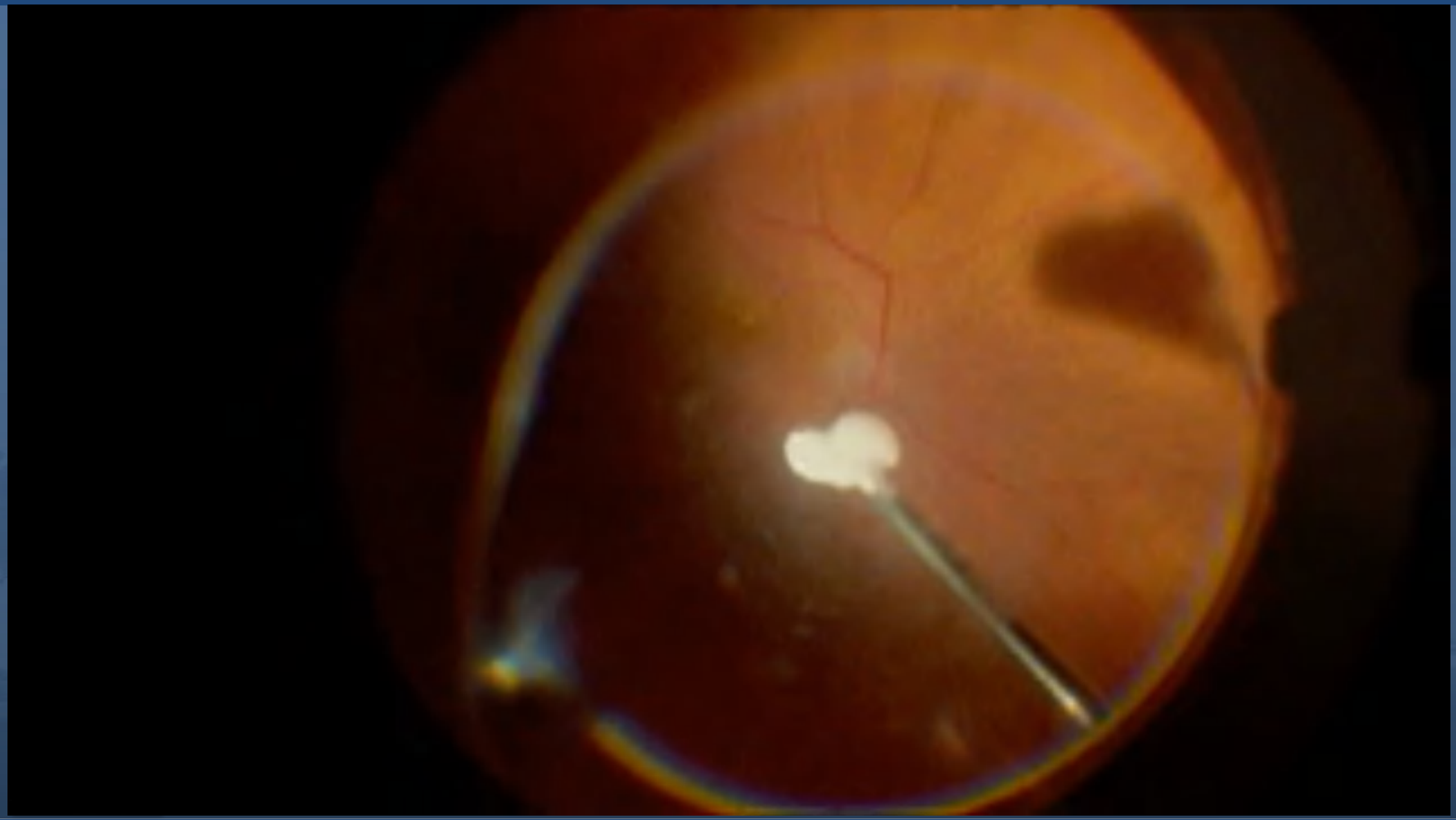
BRX ✓ RGX-314 n=15 → HS ✓ RGX-314 n=15

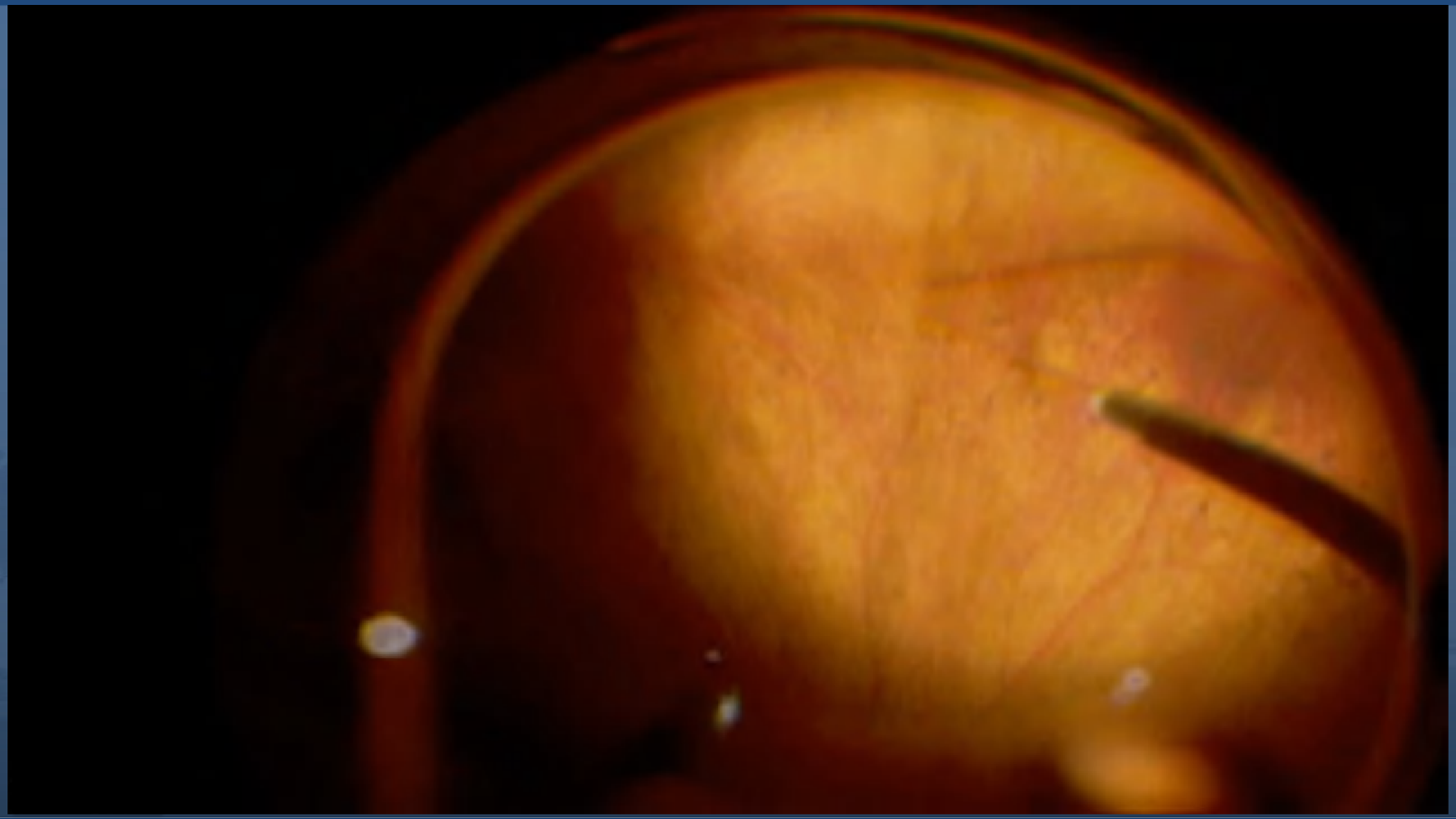
DOSE 2 (Low)
$6.4x10^{10}$ GC/eye

BRX ✓ RGX-314 n=15 → HS RGX-314 n=15

ENROLLING

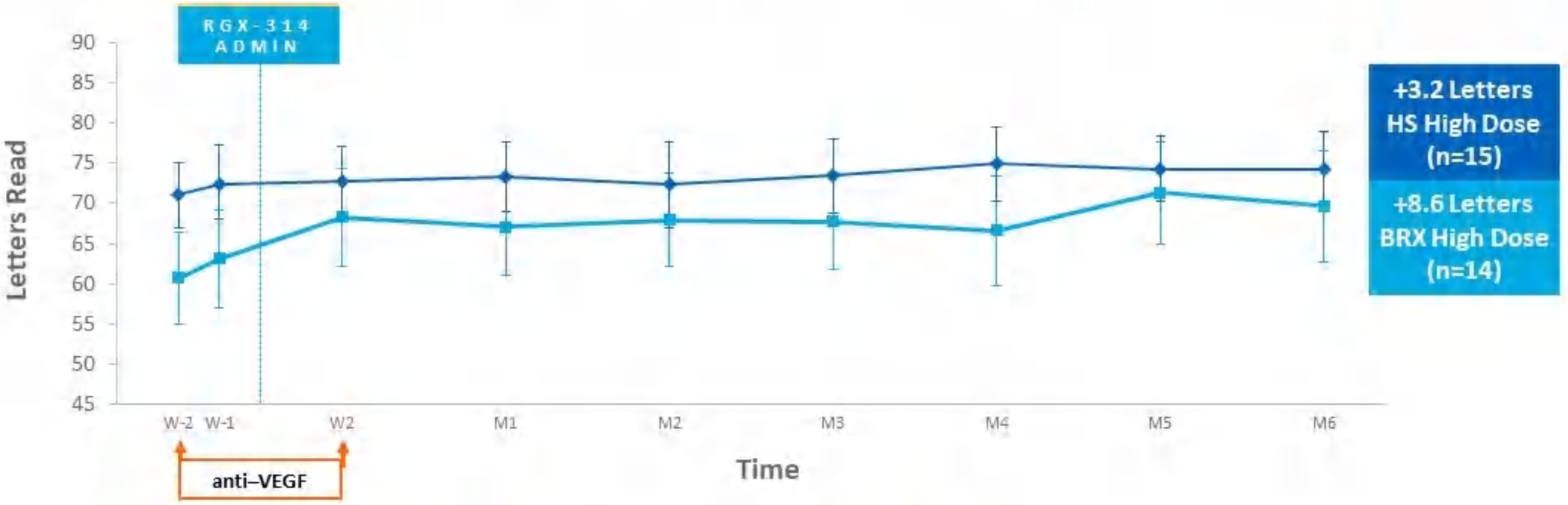
Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.
BRX: Bioreactor; HS: Hyperstack; SOC: standard of care





High Dose Cohorts: Mean change in BCVA from Baseline Through Month 6

BEST CORRECTED VISUAL ACUITY (BCVA) 95% CI

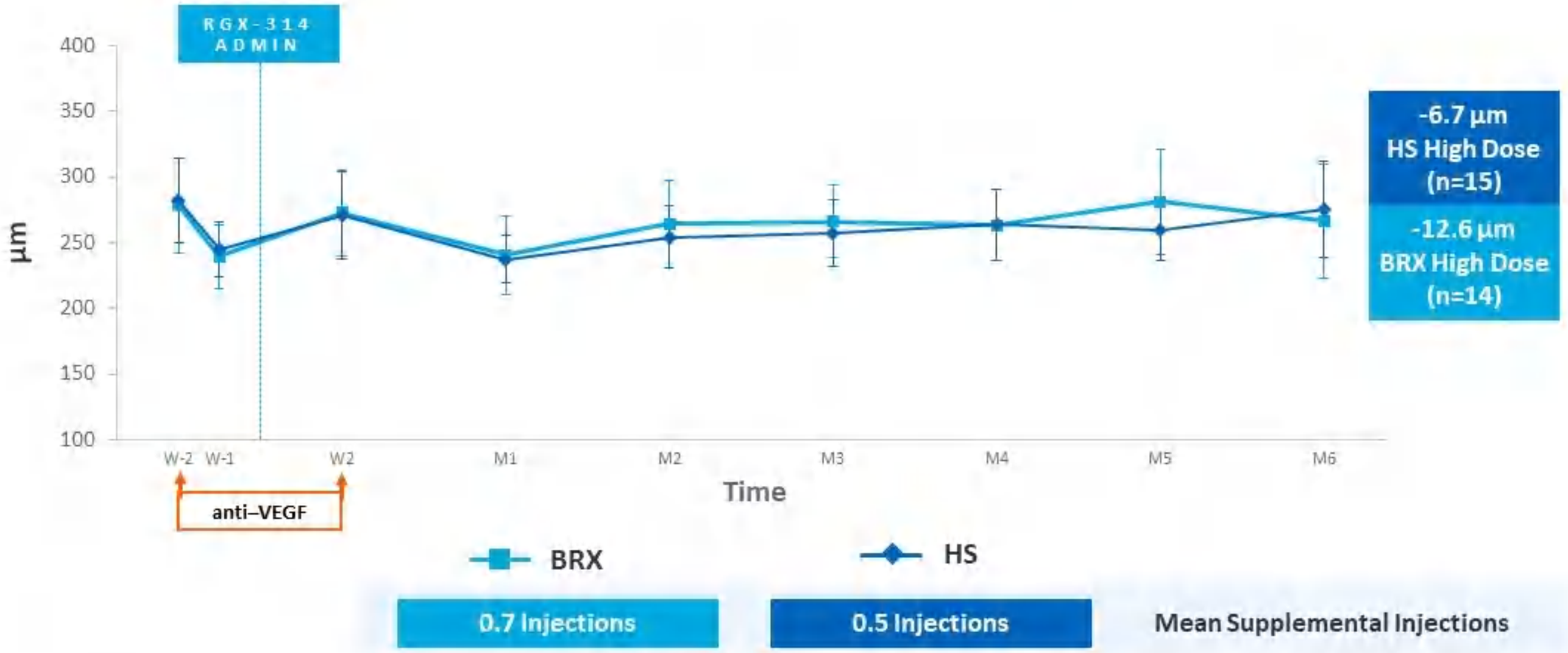


Data cut: November 14, 2022.
BRX: Bioreactor; HS: Hyperstack

Wykoff, Angiogenesis 2023

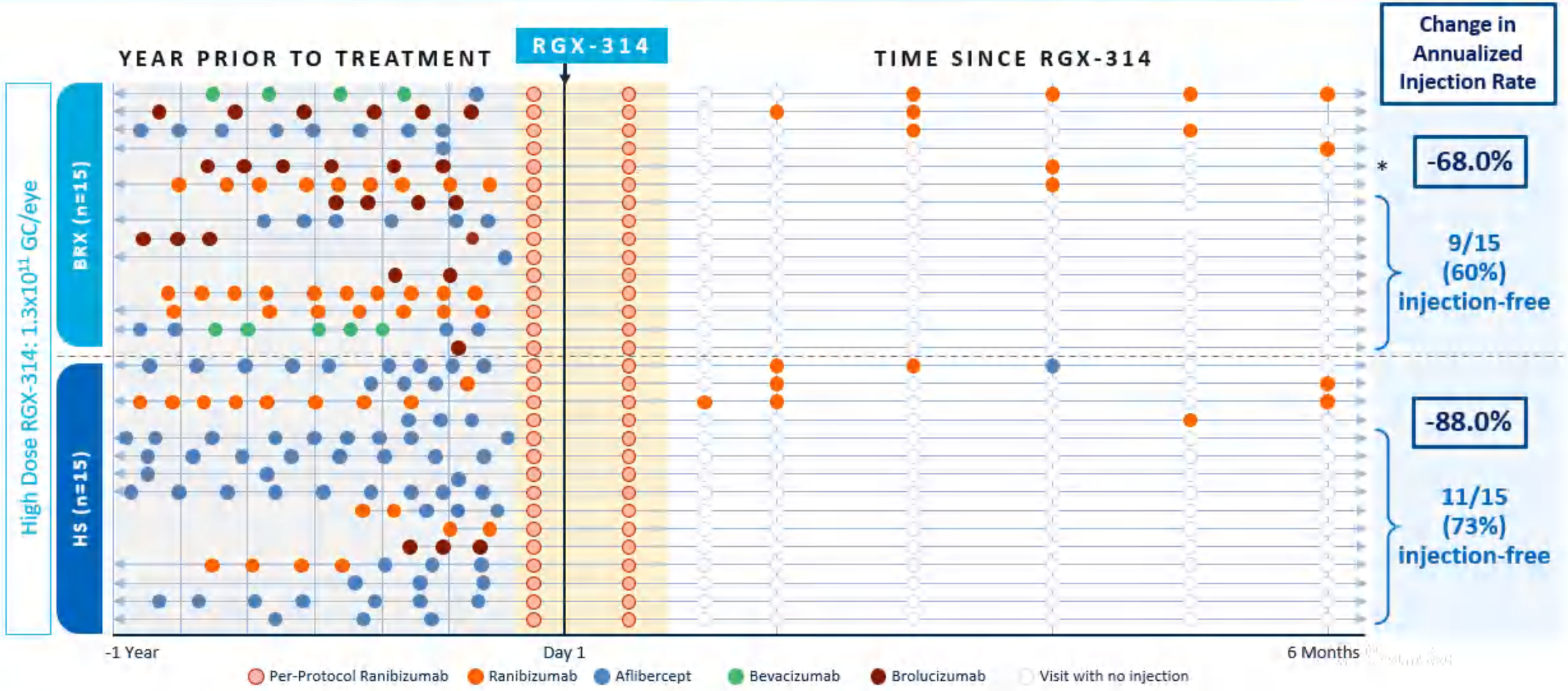
High Dose Cohorts: Mean CRT from Screening Through Month 6

MEAN CENTRAL RETINAL THICKNESS (CRT) 95% CI



Data cut: November 14, 2022.
BRX: Bioreactor; HS: Hyperstack

High Dose Cohort Injections: Pre and Post RGX-314 (n=30) – 6 Month Data



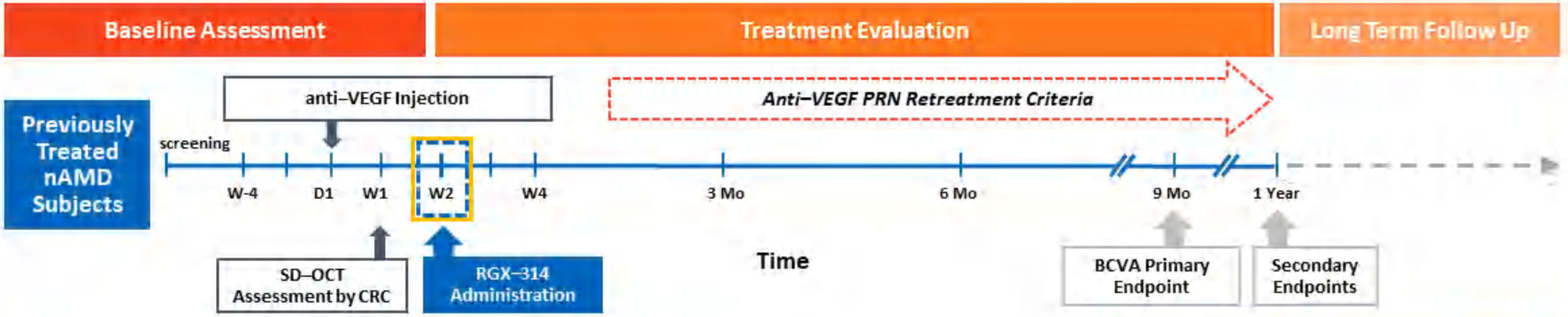
Data cut: November 14, 2022.
*Patient received an incomplete dose at time of subretinal procedure. BRX: Bioreactor; HS: Hyperstack

Safety Summary

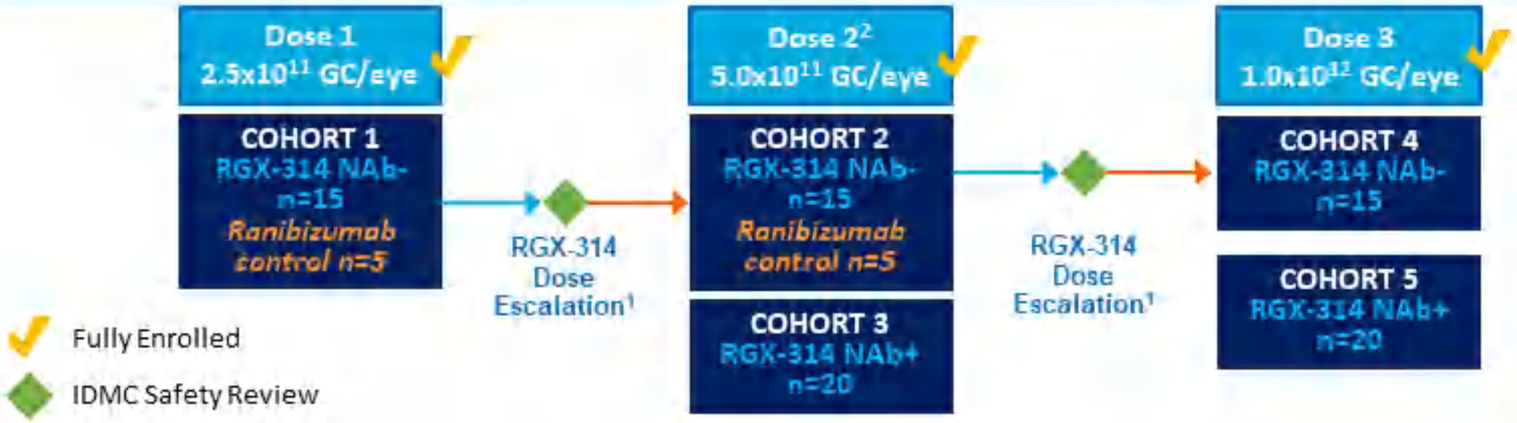
- **RGX–314 was well–tolerated in all cohorts (n=46)**
- 5 SAEs reported in 4 patients, none considered drug-related
- Common AEs[1] in the study eye in the High Dose cohorts (BRX: n=15 and HS: n=15) were similar through 6-months and included:
    - Post-operative conjunctival hemorrhage (40% of all patients; 40% of BRX cohort and 40% of HS cohort) – 100% mild (n=12), all resolved within days to weeks
    - Post-operative inflammation[2] (30% of all patients; 27% of BRX cohort and 33% of HS cohort) – 89% mild (n=8), 11% moderate (n=1), and all resolved within days to weeks
    - Retinal pigmentary changes all occurring in periphery (13% of all patients; 13% of BRX cohort and 13% of HS cohort) – 100% mild (n=4)

Data cut: November 14, 2022.
1. Includes AEs for total group ≥10% with onset up to 6m visit. Subjects are counted once for each Preferred Term regardless of the number of events.
2. Post-operative inflammation is defined as inflammation AEs which occurred within 30 days of subretinal procedure.
SAE: Serious Adverse Event; AE: Adverse event; BRX: Bioreactor; HS: Hyperstack

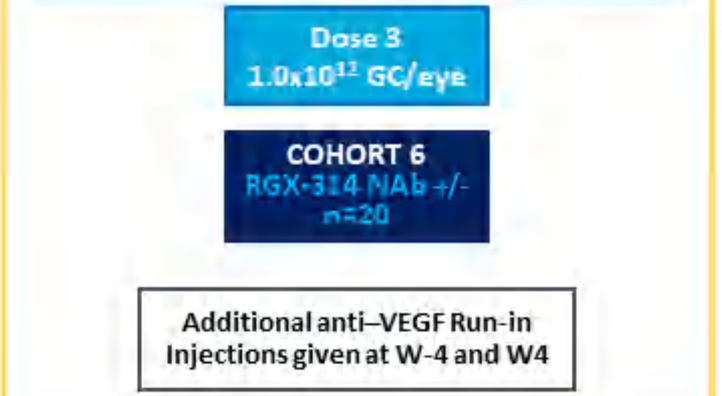
AAVIATE®: Study Design with Addition of Cohort 6



No prophylactic steroids given for Cohorts 1–5



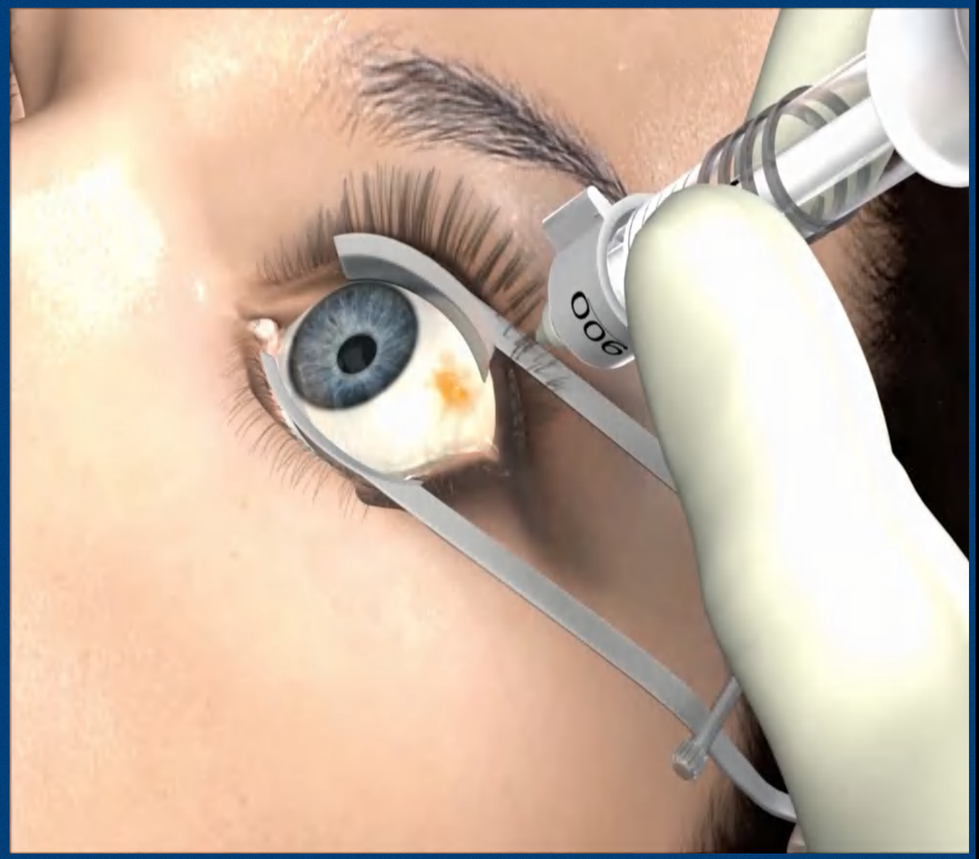
Prophylactic ocular steroids added for Cohort 6



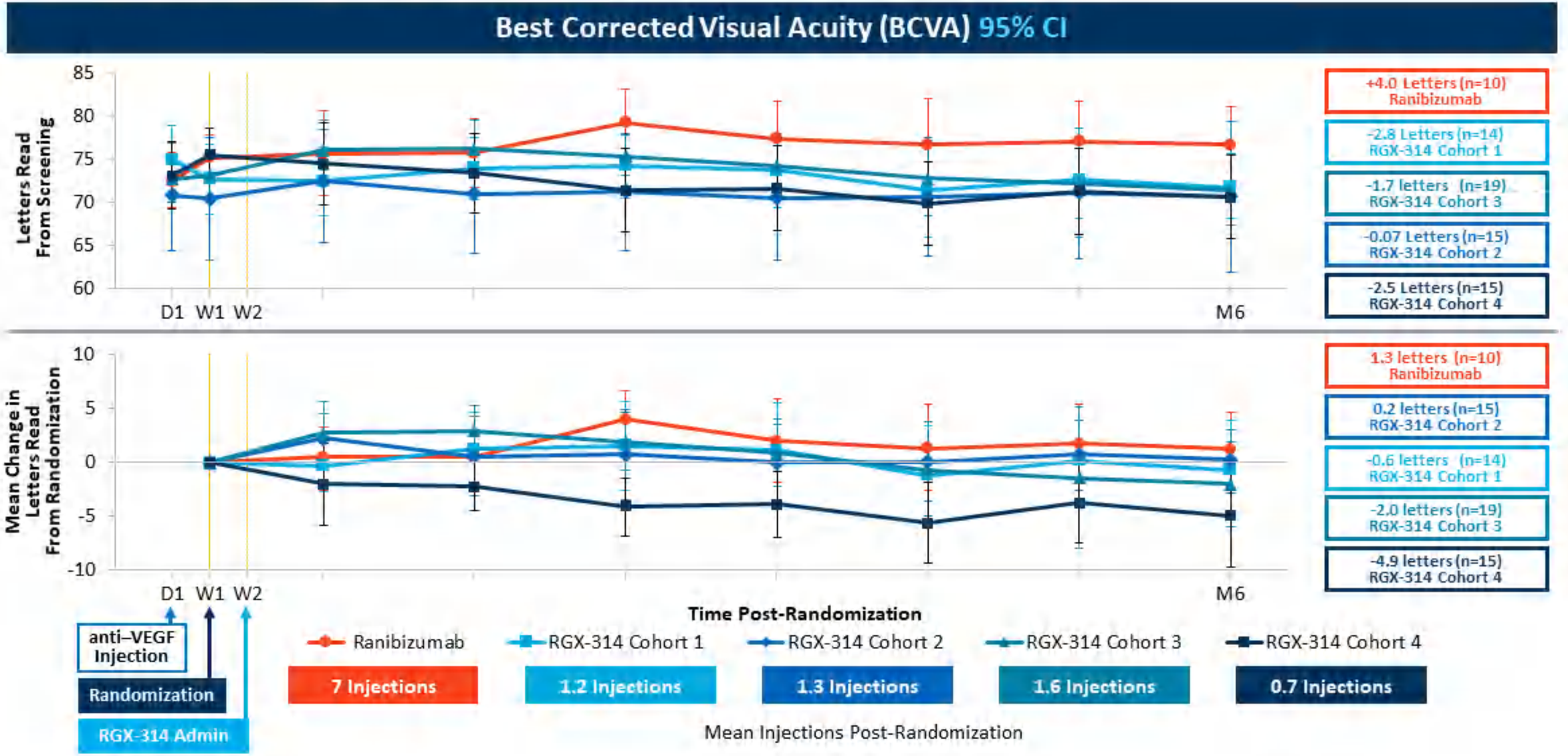
1. Dose escalation safety review to occur two weeks after final subject in each cohort has been dosed.
2. Subjects in Cohort 2 received two doses of 100µL, all other cohorts received one dose of 100µL.

NAb+ = AAV8 neutralizing antibody positive; NAb- = AAV8 neutralizing antibody negative/low

Suprachoroidal

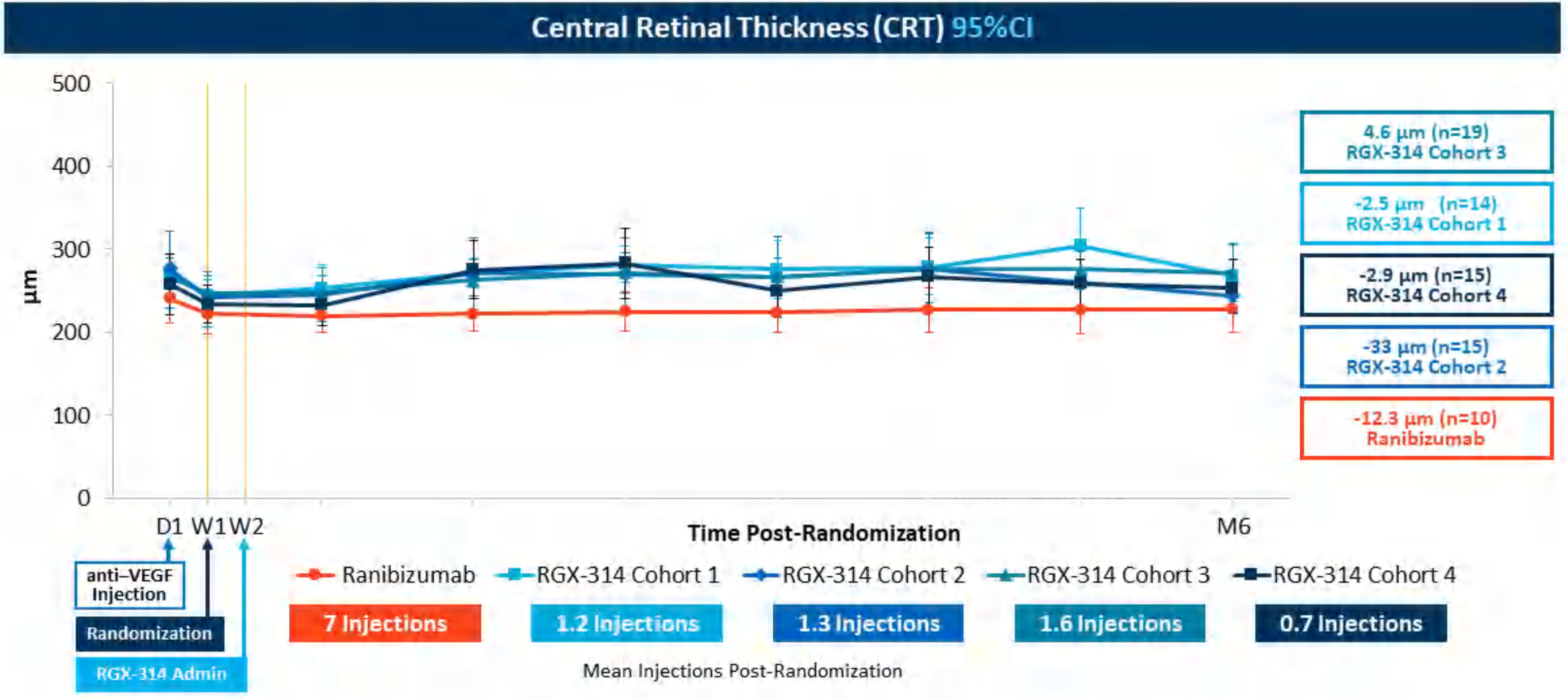


Cohorts 1-4: Mean BCVA Through Month 6



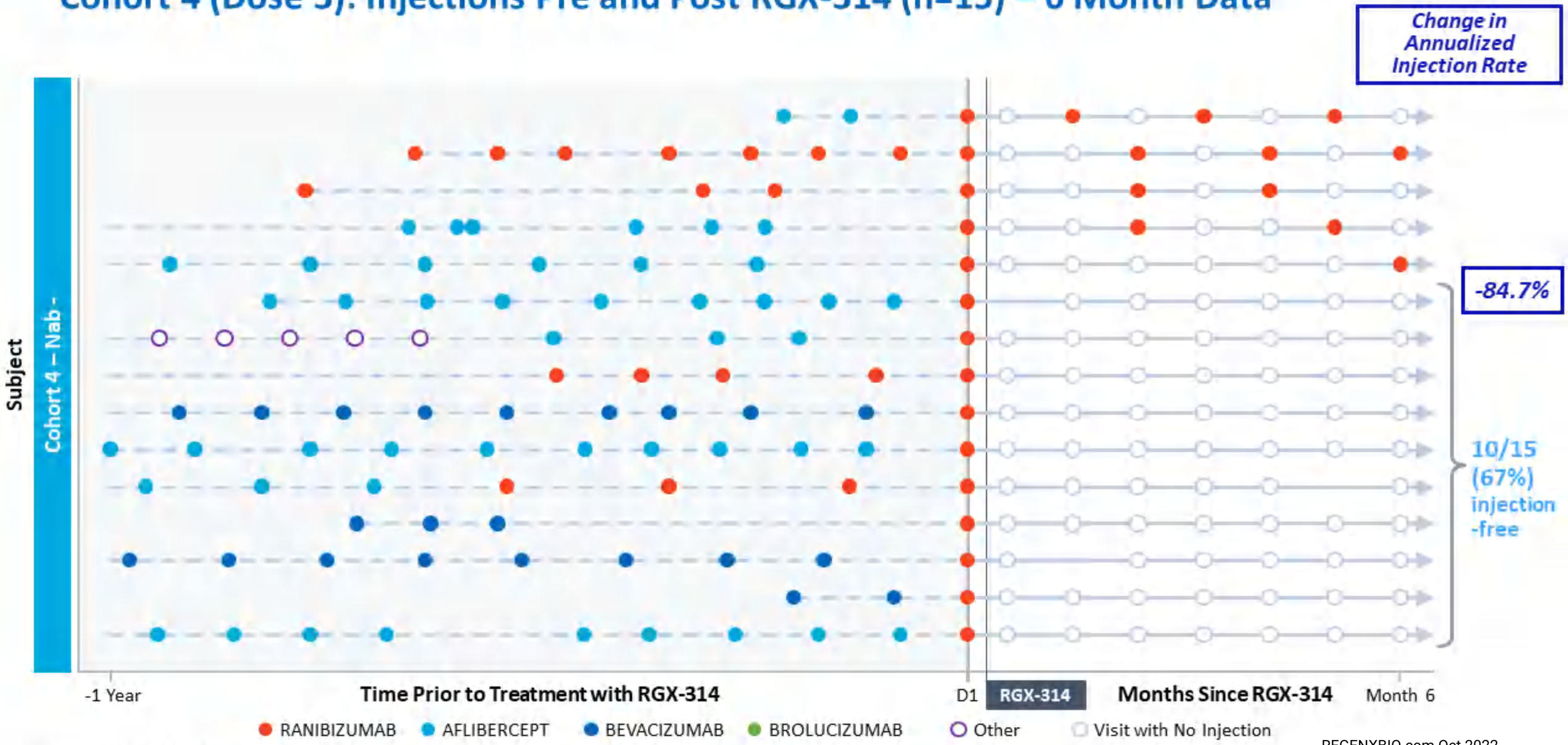
Data cut: August 1, 2022.

Cohorts 1–4: Mean CRT from Day 1 (Screening) Through Month 6



Data cut: August 1, 2022.

Cohort 4 (Dose 3): Injections Pre and Post RGX-314 (n=15) – 6 Month Data



Data cut: August 1, 2022.

REGENXBIO.com Oct 2022

AAVIATE® Safety Summary

- RGX–314 was well–tolerated in Cohorts 1–5 (n=85) with follow-up ranging from 1–12 months post dosing
  - 15 SAEs: None considered drug-related
  - No cases of chorioretinal vasculitis or occlusion, or hypotony were observed

Cohort 1 to 4: Common Ocular TEAEs[1] in the Study Eye through 6 Months	Cohort 1 Dose 1 NAb- (N=15)	Cohort 2 Dose 2 NAb- (N=15)	Cohort 3 Dose 2 NAb+ (N=20)	Cohort 4 Dose 3 NAb - (N=15)	Total (N=65)
Intraocular Inflammation[2]	4 (26.7%)	3 (20.0%)	2 (10.0%)	6 (40.0%)	15 (23.1.%)
Conjunctival Hemorrhage	5 (33.3%)	2 (13.3%)	3 (15.0%)	1 (6.7%)	11 (16.9%)
Intraocular Pressure Increased[3]	1 (6.7%)	2 (13.3%)	3 (15.0%)	3 (15.0%)	9 (13.8%)
Conjunctival Hyperemia	2 (13.3%)	1 (6.7%)	1 (5.0%)	3 (20.0%)	7 (10.8%)
Episcleritis[4]	0	3 (20.0%)	2 (10.0%)	2 (13.3%)	7 (10.8%)

No meaningful differences based on **baseline AAV8 NAbs**

Data cut: August 01, 2022.
1. Includes AEs for total group ≥10% with onset up to 6m visit.
2. All cases were mild to moderate (range +0.5 to 2+), most presented 2-6 weeks post injection, predominantly as anterior cells on slit lamp examination. Resolved on topical corticosteroids.
3. Intraocular pressure increased and ocular hypertension have been combined into one group. All mild to moderate and all controlled.
4. All mild (grade 1), presented 2-6 weeks post injection and resolved on topical corticosteroid or NSAID treatment.

Ixoberogene soroparvovec (Ixo-vec) Intravitreal Gene Therapy for Neovascular Age-Related Macular Degeneration

Szilárd Kiss, MD

Director of Clinical Research, Associate Professor of Ophthalmology

Weill Cornell Medical College

46th Annual Macula Society Meeting • February 15-18 2023

OPTIC Study: 2-Year Safety and Efficacy of Ixo-vec for nAMD

OPTIC
Gene Therapy in nAMD

Primary Objective

- Assess the safety and tolerability of a single IVT injection of Ixo-vec

Secondary Objective

- Evaluate vision maintenance (BCVA)
- Evaluate anatomy (SD-OCT)
- Assess the need for supplemental therapy

	Prophylaxis Steroid Regimen
Cohort 1 (n=6) 6 x 10^{11} high dose	Oral*, 13d
Cohort 2 (n=6) 2 x 10^{11} low dose	Oral*, 13d
Cohort 3 (n=9) 2 x 10^{11} low dose	Eye Drops**, 6 wks
Cohort 4 (n=9) 6 x 10^{11} high dose	Eye Drops**, 6 wks

Supplemental Aflibercept (2 mg IVT) Criteria:

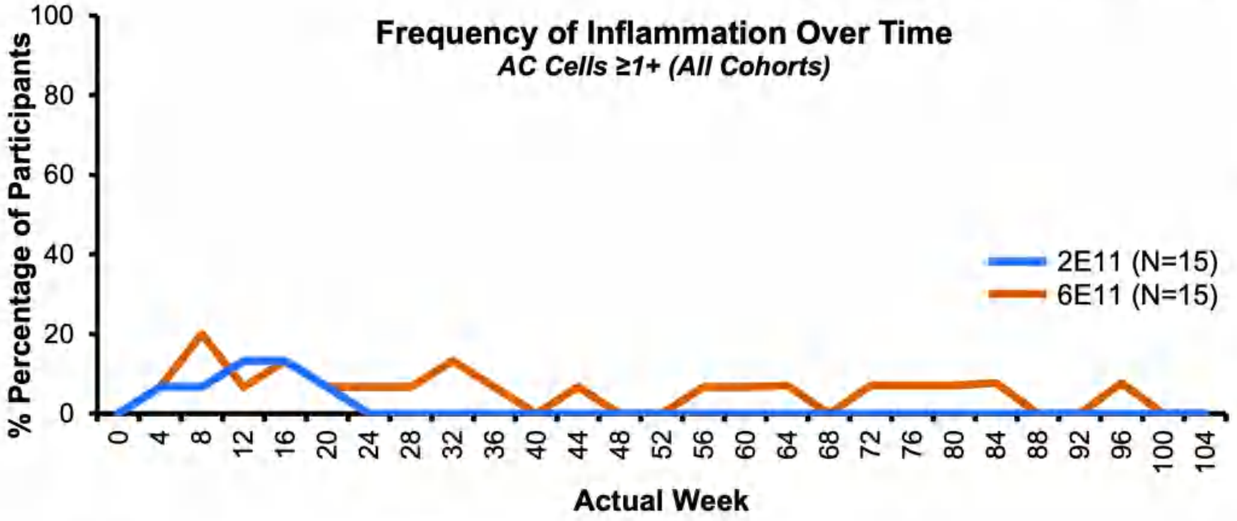
1. Loss of ≥10 letters in BCVA (ETDRS) from baseline that is attributed to intraretinal or subretinal fluid observed by the investigator
2. Increase in central subfield thickness >75 µm from baseline
3. Presence of vision-threatening hemorrhage due to AMD

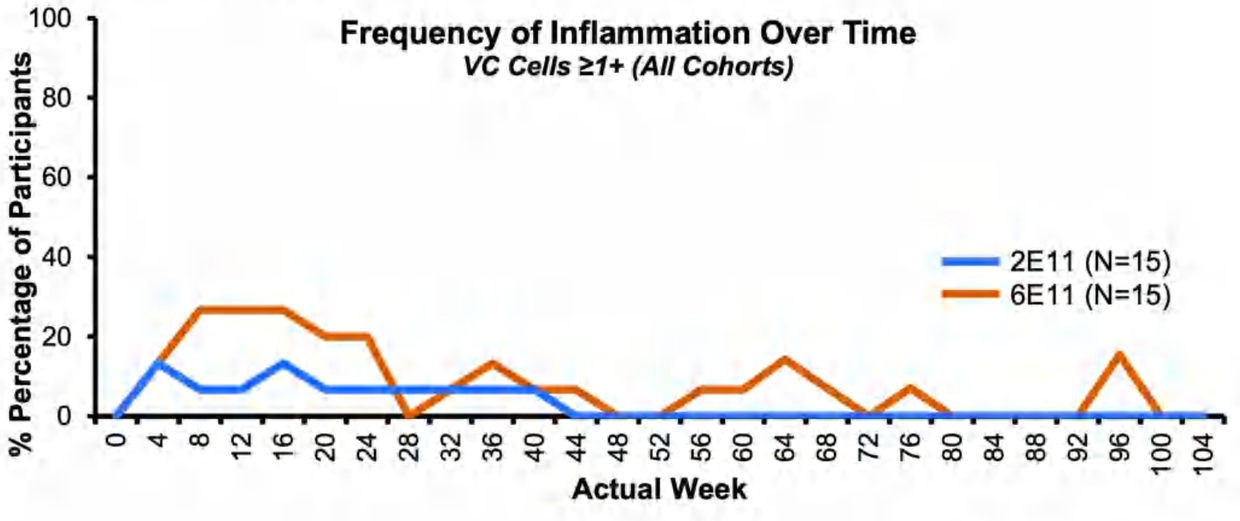
*Subjects received prophylaxis of 60 mg oral prednisone for 6 days starting at Day –3 followed by 7-day taper. **Subjects received prophylaxis of QID difluprednate eye drops for 3 weeks starting at Day 1 followed by a 3-week taper.
Final analysis includes all participants regardless of baseline neutralizing antibody titer.
AAV, adeno-associated virus; AMD, age-related macular degeneration; BCVA, best corrected visual acuity; CST, central subfield thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IVT, intravitreal therapy; QID, four times daily; SD-OCT, spectral domain optical coherence tomography; NCT03748784.

Ixo-vec OPTIC Study Safety Summary

- Despite short corticosteroid prophylaxis, Ixo-vec was generally well tolerated. The most common AE was dose-dependent, mild to moderate inflammation responsive to topical corticosteroids
- At Year 2, inflammation at the 2×10^{11} dose resolved, and no participants required corticosteroids
- Across all cohorts, most Ixo-vec-related ocular AEs were mild (83.7%) to moderate (15.6%)
- Most commonly reported ocular AE was anterior chamber cell
- Two Ixo-vec related SAEs were reported: uveitis (responsive to topical corticosteroids) and dry AMD
- No vasculitis, retinitis, choroiditis, vascular occlusions, endophthalmitis, or clinically relevant low IOP events were observed at either dose

Frequency of Inflammation Decreases Over Time





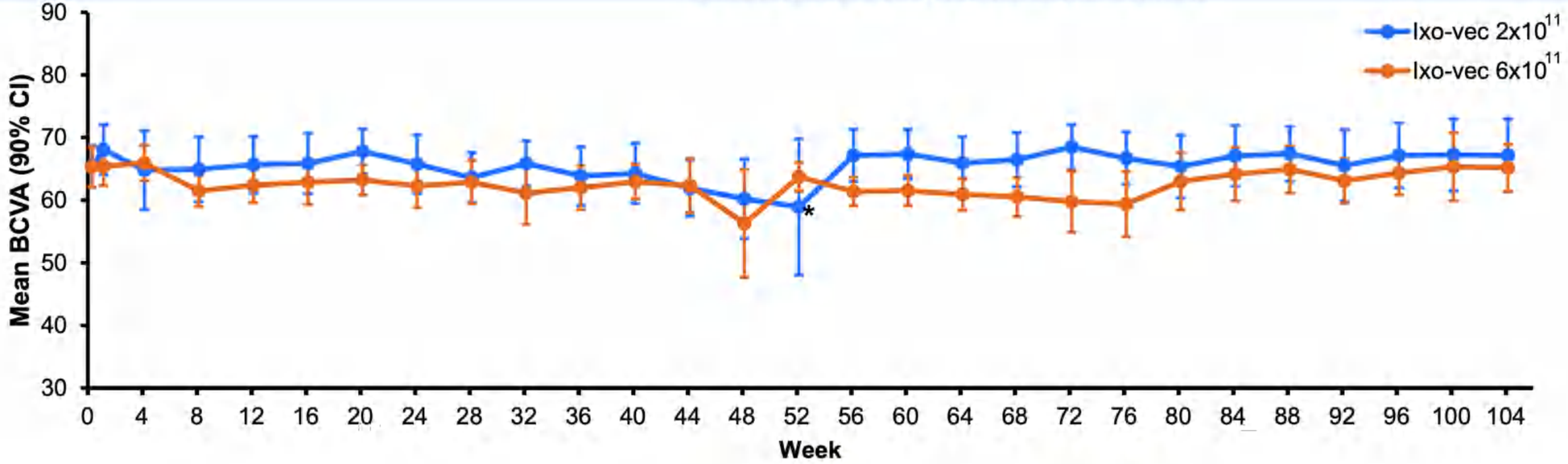
AC, aqueous cells; AE, adverse event; SAE, serious adverse event; VC, vitreous cells.

Final 2-Year Analysis

Ixo-vec Maintains or Improves BCVA and CST Through 2 Years

OPTIC
Gene Therapy in nAMD

Mean BCVA (90% CI) by Cohort and Week

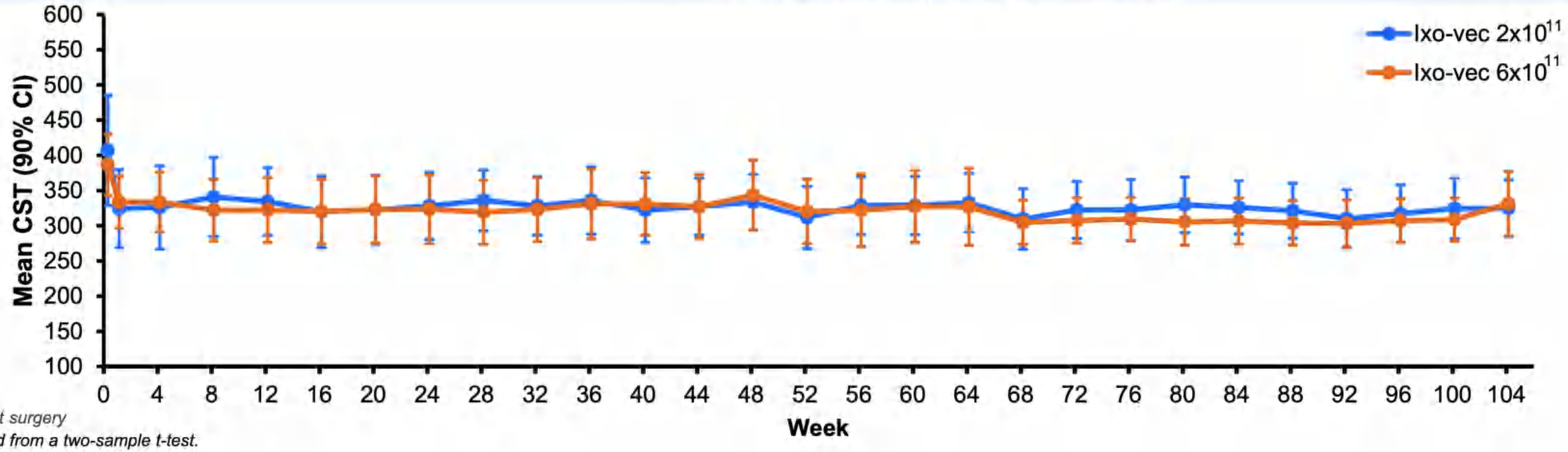


Mean BCVA (letters) change from baseline to last visit (90% CI)

+0.2 (-4.6, 5.0)
2x10^11 vg/eye

-0.2 (-3.4, 3.0)
6x10^11 vg/eye

Mean CST (90% CI) by Cohort and Week



Mean CST (µm) change from baseline to last visit (90% CI)

-60.2 (-99.1, -21.3)
p = 0.017**
6x10^11 vg/eye

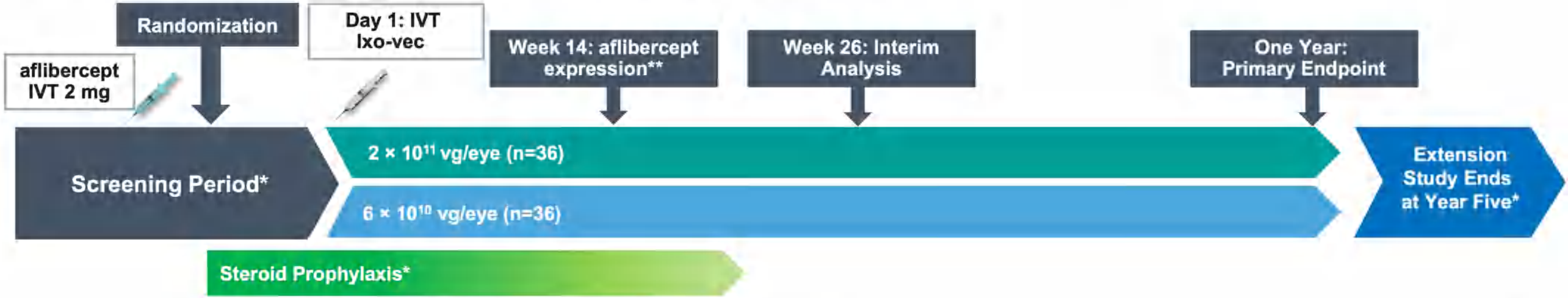
-92.9 (-153.3, -32.6)
p = 0.017**
2x10^11 vg/eye

*Cataract surgery
**Derived from a two-sample t-test.

Final 2-Year Analysis

LUNA Phase 2 Study in nAMD - Study Design

Objective: The LUNA trial is a multicenter, double-masked, randomized, parallel-group Phase 2 study evaluating a one-time IVT injection of either of two doses of Ixo-vec (ADVM-022), including 2 × 10^{11} vg/eye dose and a new, lower 6 × 10^{10} vg/eye dose in 72 patients



Study Population

- nAMD diagnosis
- 50 years or older
- Demonstrated response to anti-VEGF treatment

Prophylactic Regimens

- **Durezol® topical 22 weeks (n=18)**
- **Ozurdex® IVT (n=18)**
- **Durezol® topical 22 weeks + Prednisone oral 10 weeks (n=18)**
- **Ozurdex® IVT + Prednisone oral 10 weeks (n=18)**

Primary Endpoints

- Mean change in best corrected visual acuity (BCVA) from baseline to one year
- Incidence and severity of adverse events

Secondary Objectives

- Evaluate the effect of Ixo-vec on Best Corrected Visual Acuity (BCVA)
- Assess the durability of a single IVT injection of Ixo-vec
- Evaluate the effect of Ixo-vec on Central Subfield Thickness (CST)
- Assess the effectiveness of prophylactic corticosteroid treatment regimens in minimizing post-prophylactic inflammation

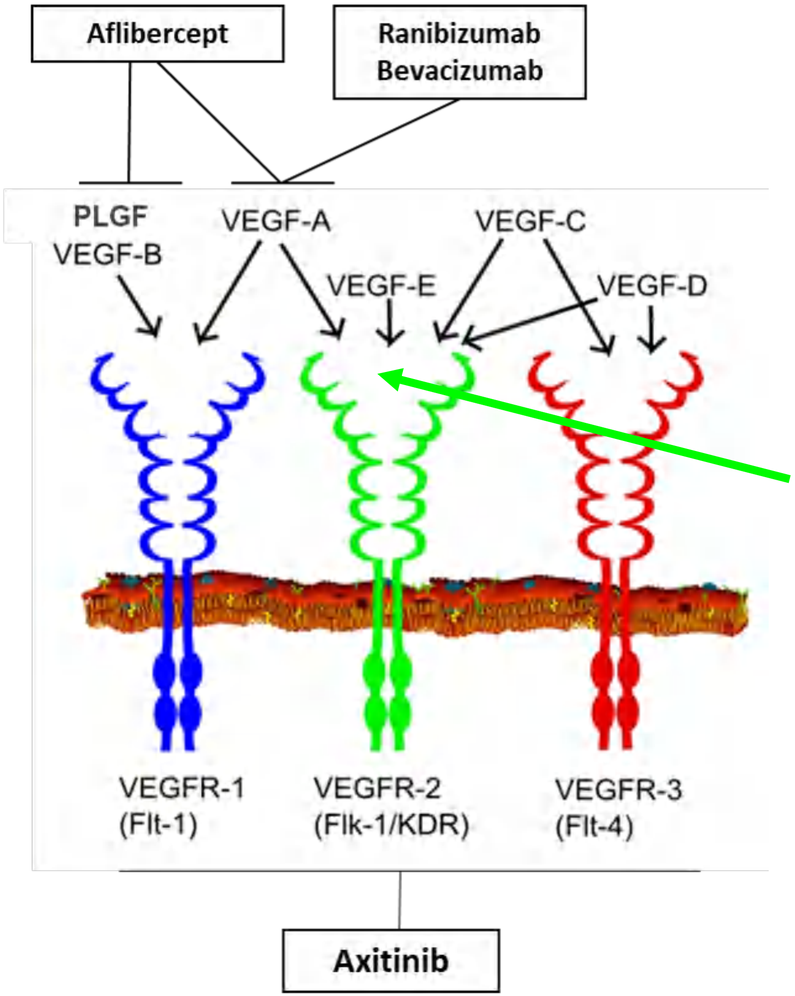
**Study timeline and length of arrows depicted are not to scale*
***Additional levels of aflibercept expression will be measured throughout*

CLS-AX

(axitinib injectable suspension)
for Suprachoroidal Injection

Axitinib: a Highly Potent, Pan-VEGF TKI to Treat Wet AMD

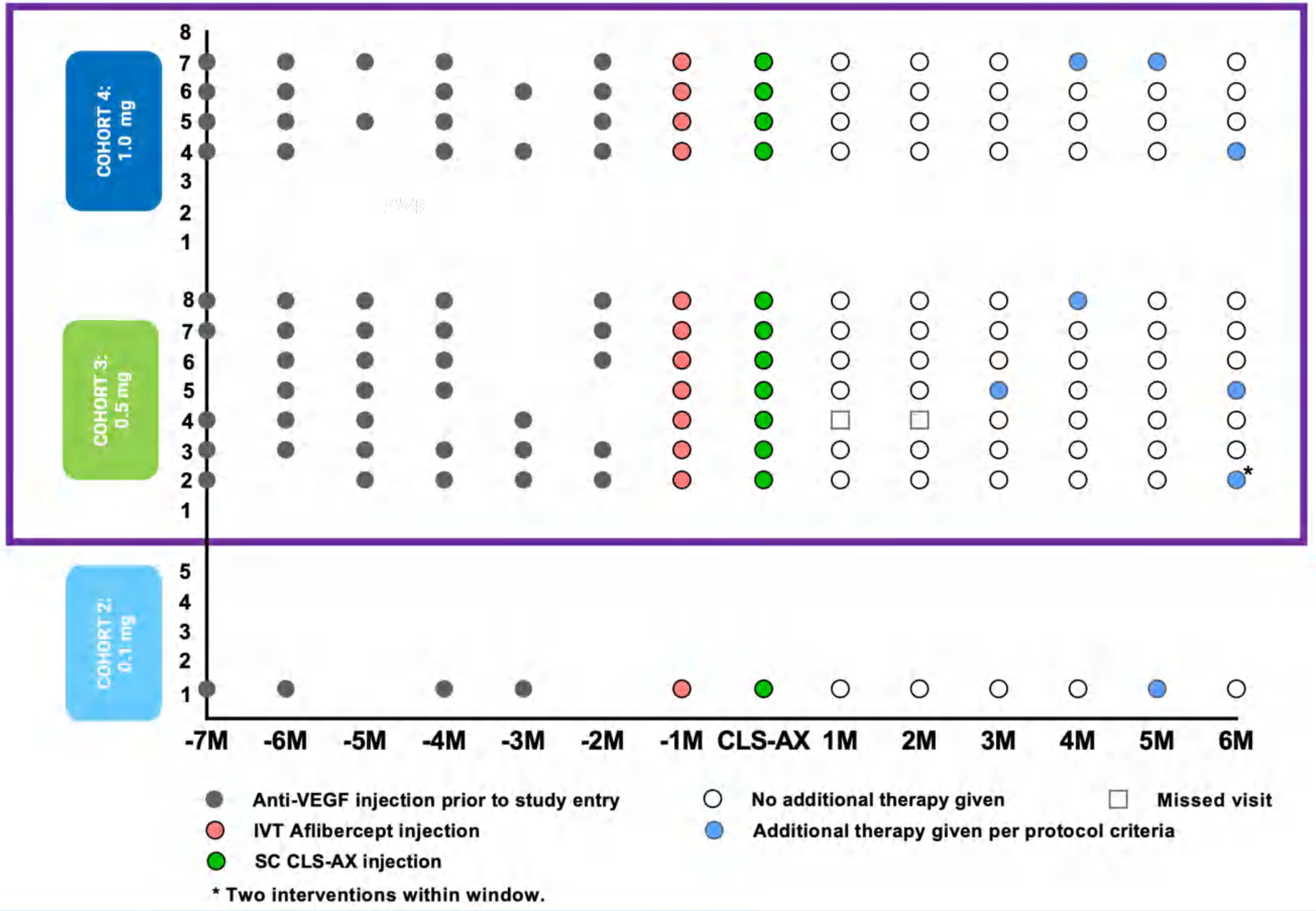
- Axitinib's intrinsic pan-VEGF inhibition through receptor blockade
  - Approved treatments are focused VEGF-A inhibitors
- Inhibits **VEGFR-1**, **VEGFR-2**, **VEGFR-3** receptors
  - More active than anti-VEGF-A in *in-vitro* angiogenesis model[1-2]
- Highly potent tyrosine kinase inhibitor (TKI)
  - >10x more potent than other TKIs in preclinical studies
  - Better ocular cell biocompatibility than other TKIs[3]
  - More active than other TKIs for experimental corneal neovascularization in preclinical models
- Preclinical data showed axitinib inhibition and regression of angiogenesis



VEGF Receptor-2 primarily mediates angiogenesis

Sources: 1. Cabral T et al. Bevacizumab Injection in Patients with Neovascular Age-Related Macular Degeneration Increases Angiogenic Biomarkers. Ophthalmol Retina. 2018 January ; 2(1): 31–37. doi:10.1016/j.oret.2017.04.004. | 2. Lieu et al. The Association of Alternate VEGF Ligands with Resistance to Anti-VEGF Therapy in Metastatic Colorectal Cancer. PLoS ONE 8(10): e77117. | 3. Theile et al. Multikinase Inhibitors as a New Approach in Neovascular Age-Related Macular Degeneration (AMD) Treatment: In Vitro Safety Evaluations of Axitinib, Pazopanib and Sorafenib for Intraocular Use. Klin Monatsbl Augenheilkd 2013; 230: 247-254. | Image by Mikael Häggström, used with permission. Häggström, Mikael (2014). "Medical gallery of Mikael Häggström 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.008. ISSN 2002-4436. Public Domain.

Extension Study (6 Month Data): Prior Anti-VEGF Therapies and Additional Therapies Per Protocol Criteria



DURABILITY

Cohorts 3 & 4

No Additional Therapy

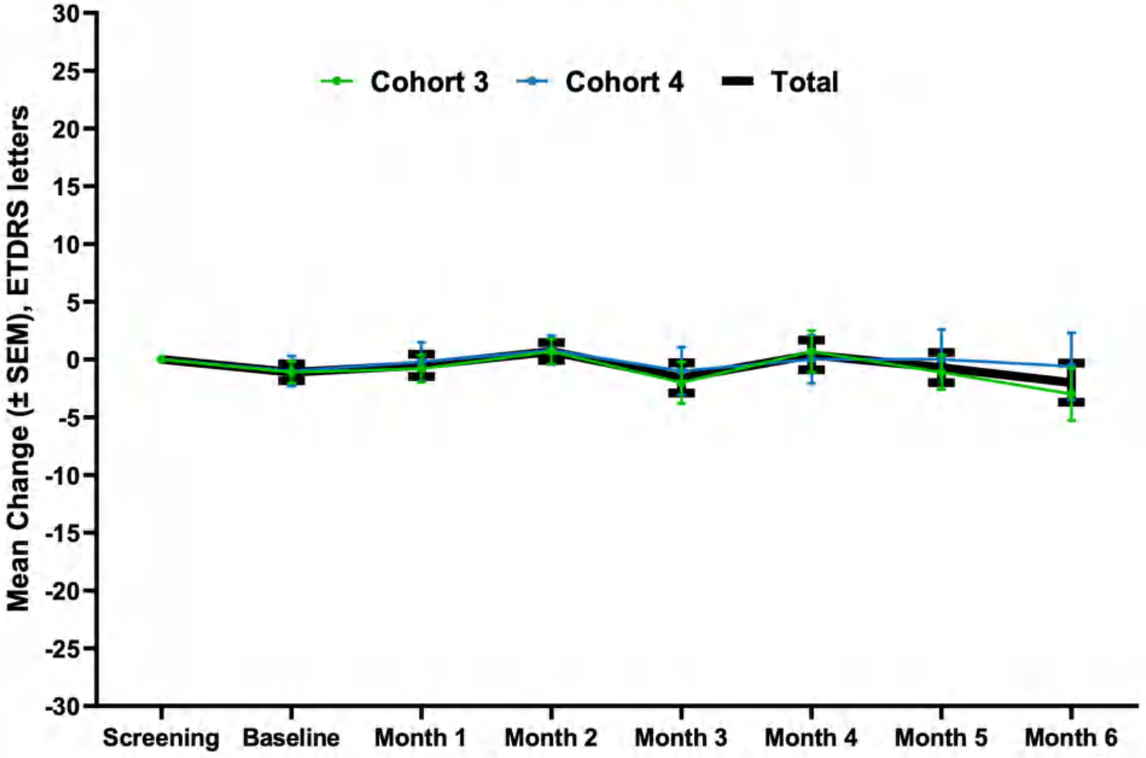
≥ 3 Months: 11/11 (100%)
≥ 4 Months: 10/11 (91%)
≥ 6 Months: 8/11 (73%)
> 6 Months: 6/11 (55%)

Excludes patients whose first additional therapy was not per protocol-defined criteria.
Source: Clearside data on file.

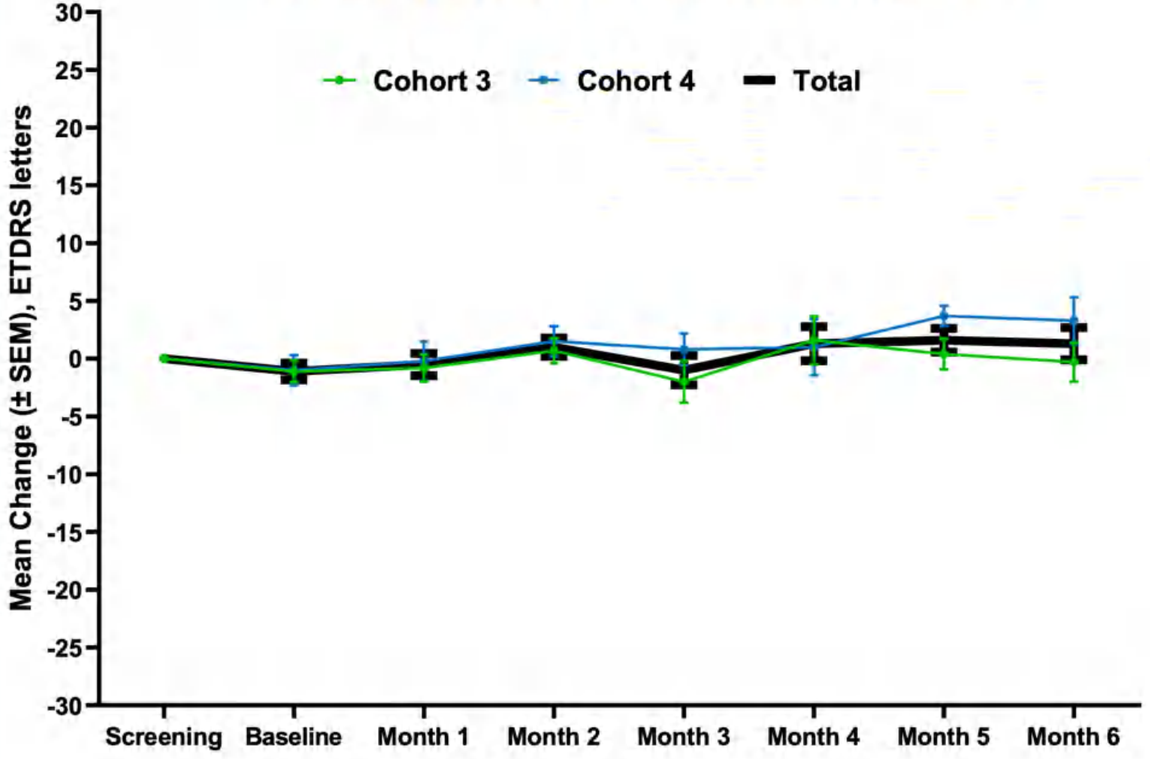
Extension Study (6 Month): Stable Visual Acuity

Mean Best Corrected Visual Acuity Letter Score, Change from Screening

All Data



Excluding Data After Additional Treatment

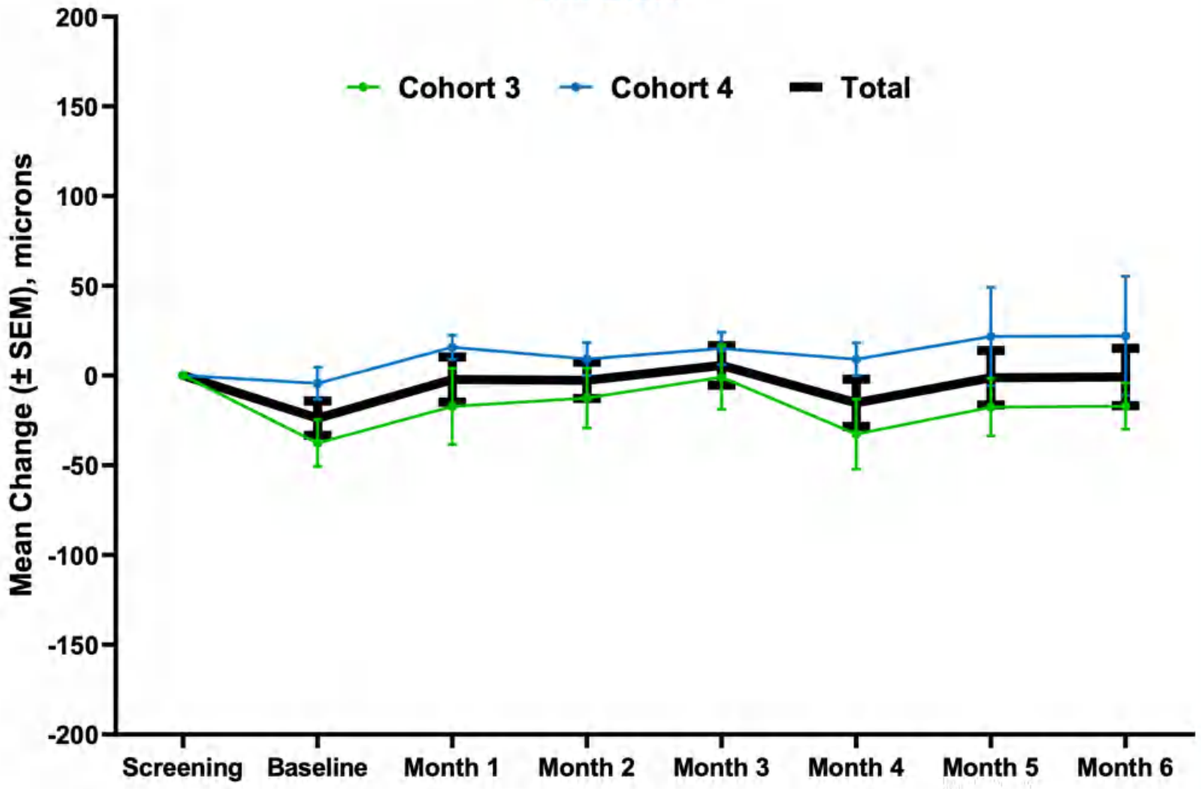


Source: Clearside data on file.

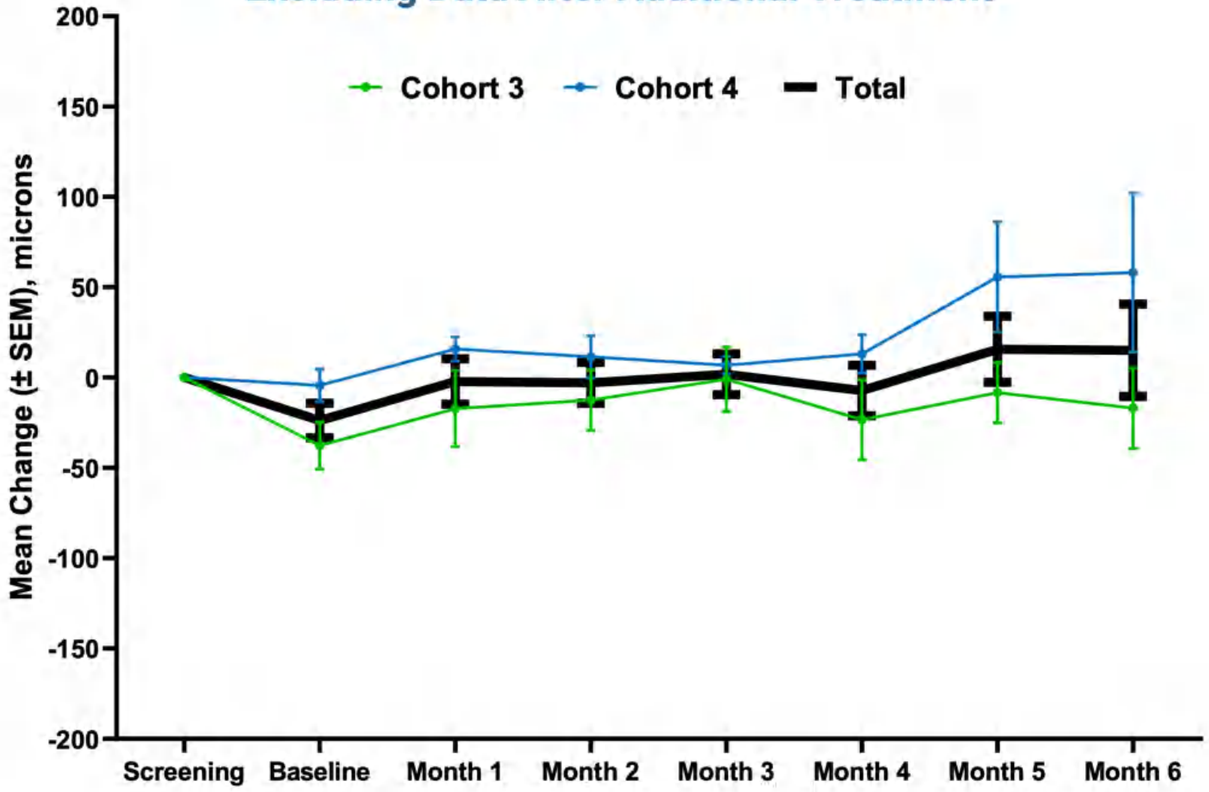
Extension Study (6 Month): Stable Central Subfield Thickness

Mean Central Subfield Thickness, Change from Screening

All Data



Excluding Data After Additional Treatment



Source: Clearside data on file.

OASIS (3 Month) and Extension Study (6 Month) Cohorts 3 and 4: Promising CLS-AX Safety Data, Durability and Biologic Effect

SAFETY DATA

- Excellent safety profile at all doses and timepoints
- No Serious Adverse Events
- No dose limiting toxicities
- No Adverse Events (AEs) from inflammation
- No AEs related to intraocular pressure

DURABILITY

- In OASIS, to 3 months:
  - ≥72% reduction in treatment burden
- In Extension Study, to 6 months:
  - ≥77% reduction in treatment burden
  - Patients not requiring additional therapy:
    - ≥ 3 Months: 11/12 (92%)
    - ≥ 4 Months: 10/12 (83%)
    - **≥ 6 Months: 8/12 (67%)**
    - **> 6 Months: 6/12 (50%)**

BIOLOGIC EFFECT

- Stable mean Best Corrected Visual Acuity (BCVA)
- Stable mean Central Subfield Thickness (CST)
- On optical coherence tomography (OCT), anatomical signs of tyrosine kinase inhibitor (TKI) biologic effect were observed in anti-VEGF treatment-experienced sub-responders

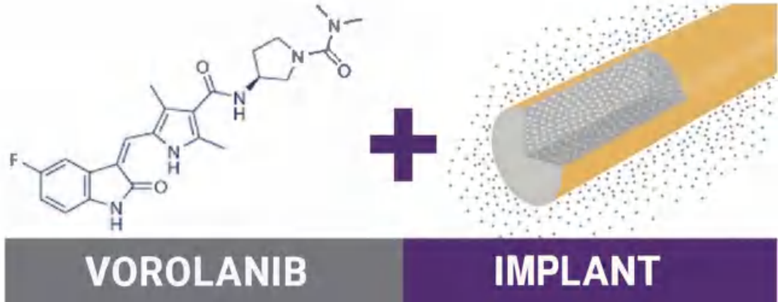
NEXT STEPS

- Expect to initiate Phase 2b clinical trial in Q1 2023 with primary endpoint readout anticipated in mid-2024

Source: Clearside data on file.

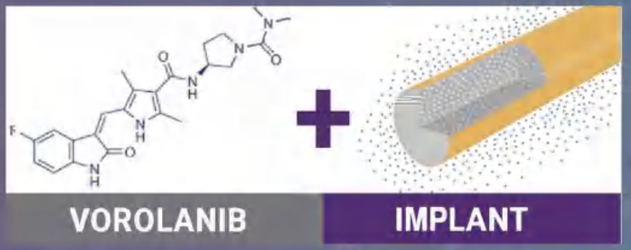
8-month Results of a Tyrosine Kinase Inhibitor (Vorolanib) in a Bio-erodible Durasert® Implant for Previously Treated Wet AMD: The DAVIO Trial

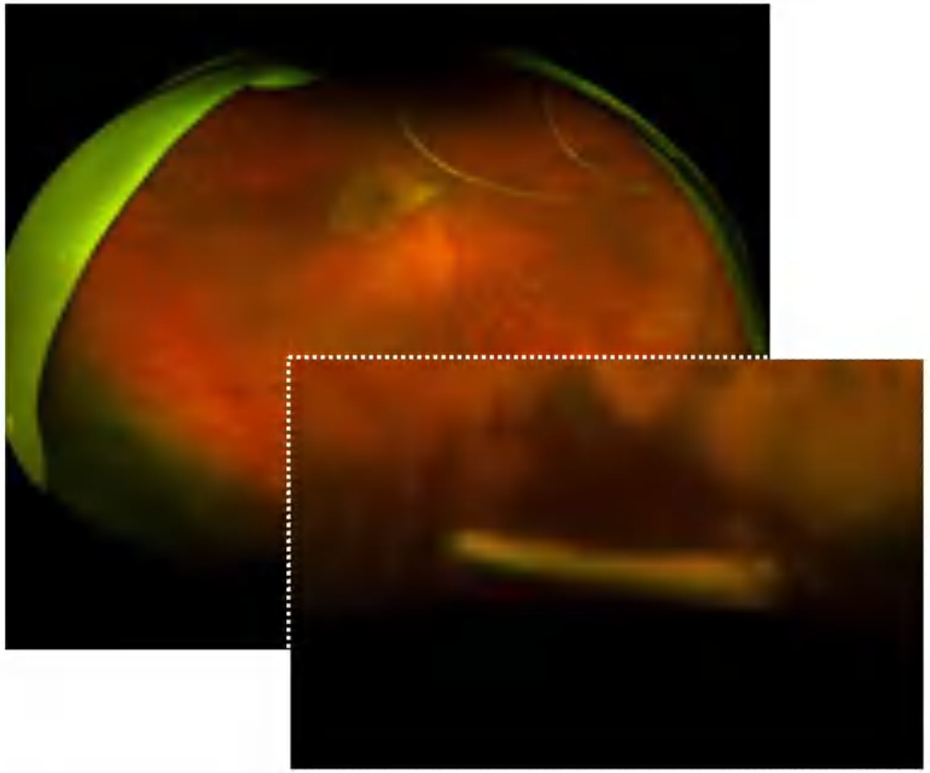
Mark R Barakat, M.D.
Retinal Consultants of Arizona



EYP-1901 – A Novel Approach to Wet AMD Therapy

Vorolanib in Bioerodible Implant





EYP-1901 insert at month 5 post-injection

Bioerodible Durasert® Platform: injectable, sustained-delivery technology

Intravitreal implant like fluocinolone 0.18mg implant

- One difference: No polyimide shell → Bioerodible

Drug release dynamics*

- Initial burst from surface of implant
- Constant, zero-order kinetic release rate for months
- Designed for approximately six month or longer efficacy

*Data on file
Jay Duker at Angiogenesis Meeting 2022

DAVIO Primary Endpoint – Safety Up to 8 Months

Positive Overall Safety Data

No ocular serious adverse events (SAEs) reported
No drug-related systemic SAEs reported

Ocular AEs of particular interest:

- No vitreous floaters
- No endophthalmitis
- No retinal detachment
- No implant migration in the anterior chamber
- No retinal vasculitis
- No posterior segment inflammation

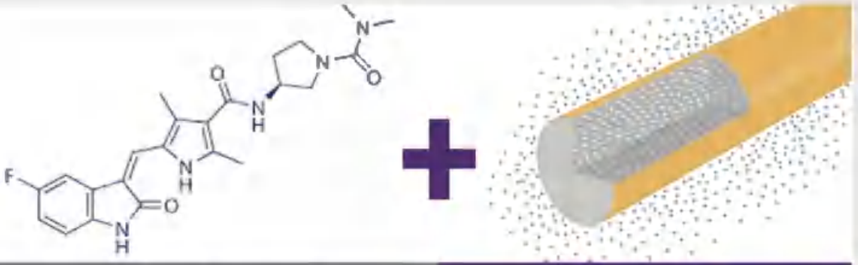
Ocular AEs Observed:

- One eye: mild asymptomatic anterior chamber cell/flare; *Treated with steroid eyedrops – resolved in 8 days –no sequelae or recurrence*
- One eye: asymptomatic vitreous hemorrhage from injection; Observed

AC, anterior chamber; AE, adverse event; BCVA, best corrected visual acuity; SAE, serious adverse event

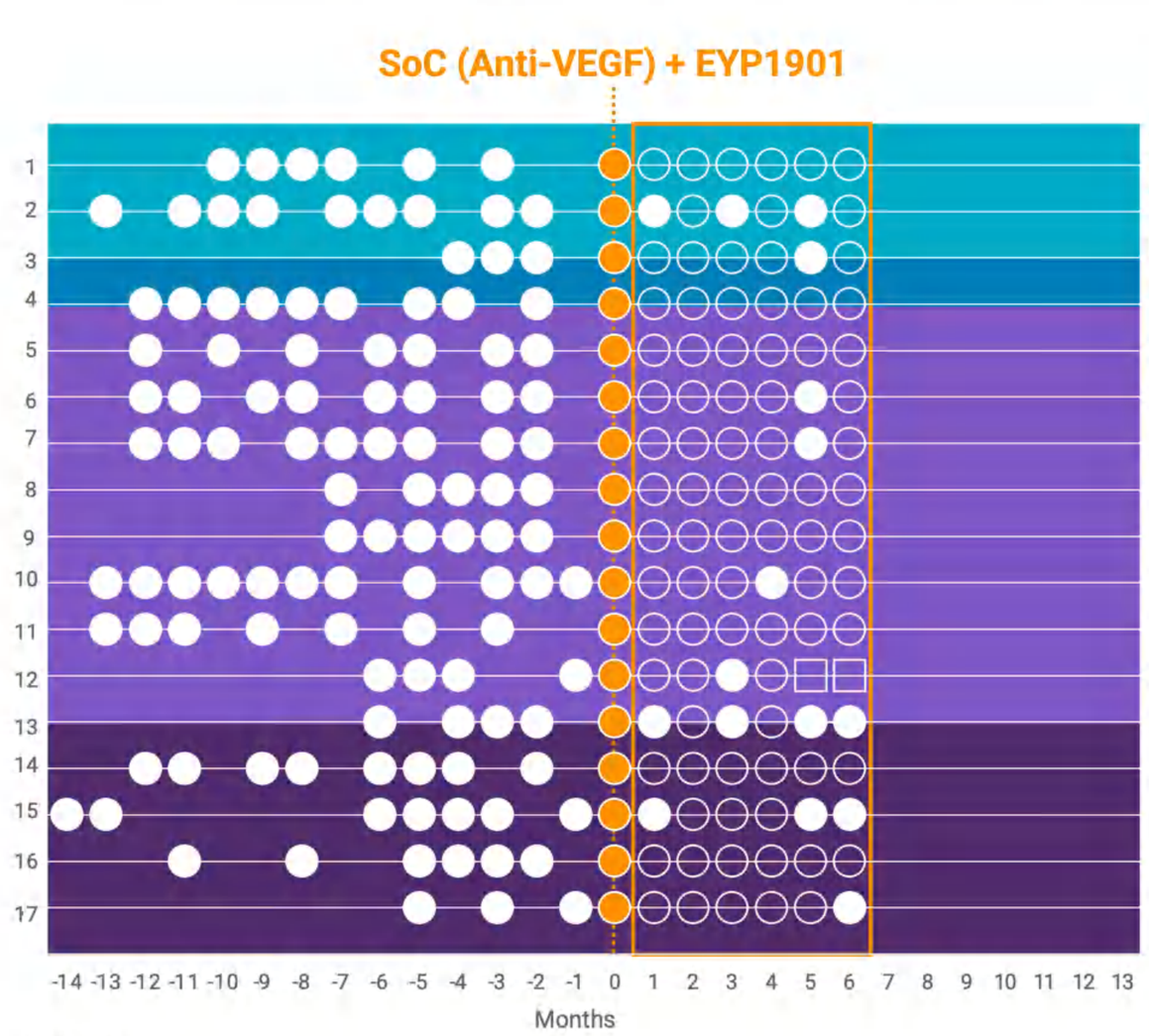
Clinically Significant Reduction in Treatment Burden - 79% at 6 Months

EYP-1901 PHASE 1 DAVIO STUDY



VOROLANIB + IMPLANT

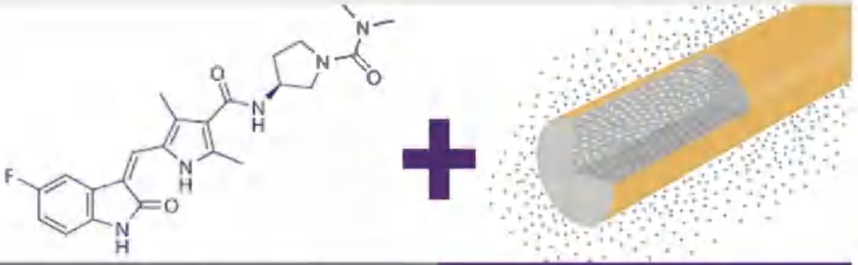
SOC Anti-VEGF Injections Before and After Treatment



INTERIM DATA – MONITORED THROUGH 6 MONTHS

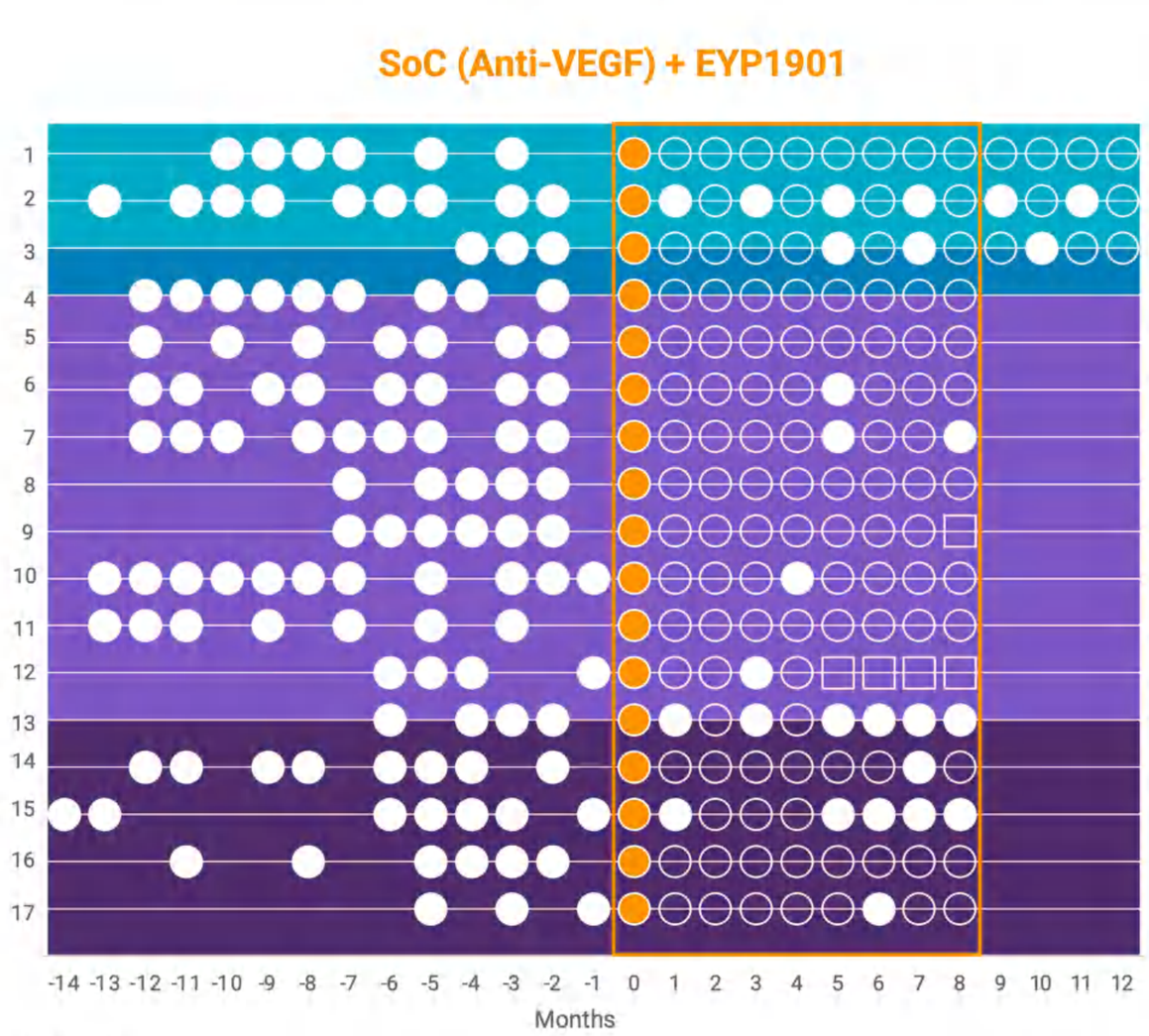
Clinically Significant Reduction in Treatment Burden - 75% at 8 Months

EYP-1901 PHASE 1 DAVIO STUDY



VOROLANIB + IMPLANT

SOC Anti-VEGF Injections Before and After Treatment



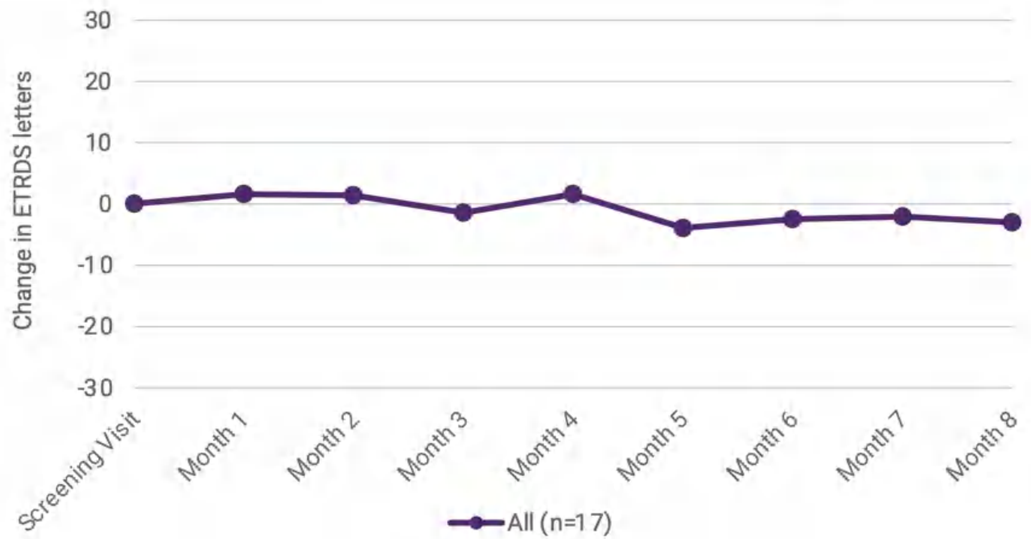
INTERIM DATA – MONITORED THROUGH 6 MONTHS

Jay Duker at Angiogenesis Meeting 2022

Results at 8 Months: Mean BCVA and CST are Stable After Single EYP-1901 Treatment

For all 17 eyes at 8 months
BCVA = -3.0 letters

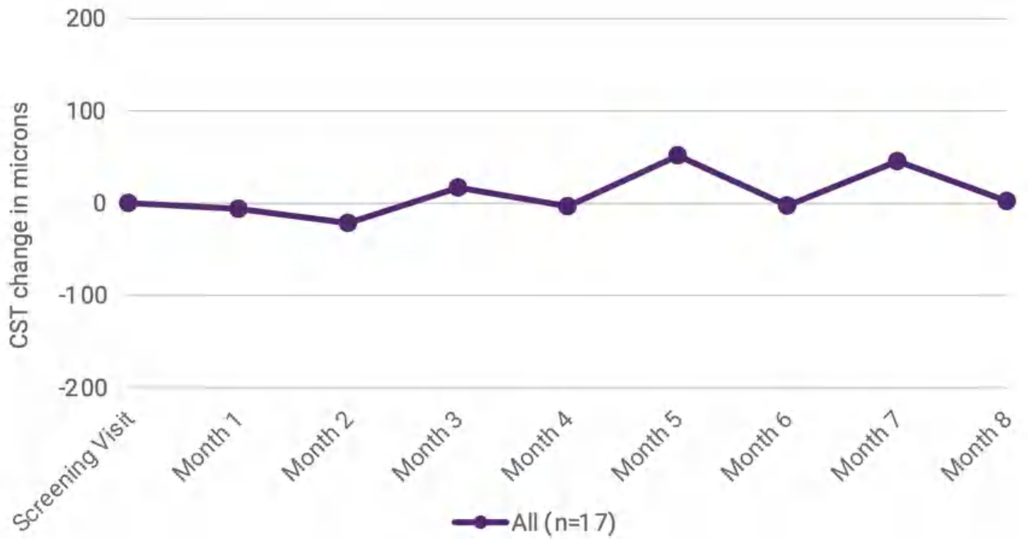
Mean change in BCVA from screening visit



BCVA: best corrected visual acuity

For all 17 eyes at 8 months
CST on OCT = + 2.4 microns

Mean change in CST from screening visit



OCT: optical coherence tomography; CST: central subfield thickness

INTERIM DATA – MONITORED THROUGH 6 MONTHS

Update on a Hydrogel-Based Intravitreal Axitinib Implant (OTX-TKI) for the Treatment of Neovascular Age-related Macular Degeneration

Andrew A. Moshfeghi, MD[1]

On behalf of the clinical study investigators: Stephen S. Couvillion, MD[2]; David A. Eichenbaum, MD[3]; Arshad M. Khanani, MD[4]; Nathan C. Steinle, MD[5]; Charles C. Wykoff, MD, PhD[6]; Samantha Xavier, MD[7]

[1]Keck School of Medicine, USC Roski Eye Institute, University of Southern California, Los Angeles, CA; [2]California Retina Consultants, Bakersfield, CA; [3]Retina Vitreous Associates of Florida, St Petersburg, FL; [4]Sierra Eye Associates, Reno, NV; [5]California Retina Consultants, Santa Barbara, CA; [6]Retina Consultants of Texas, Houston, TX; [7]Florida Eye Clinic, Altamonte Springs, FL

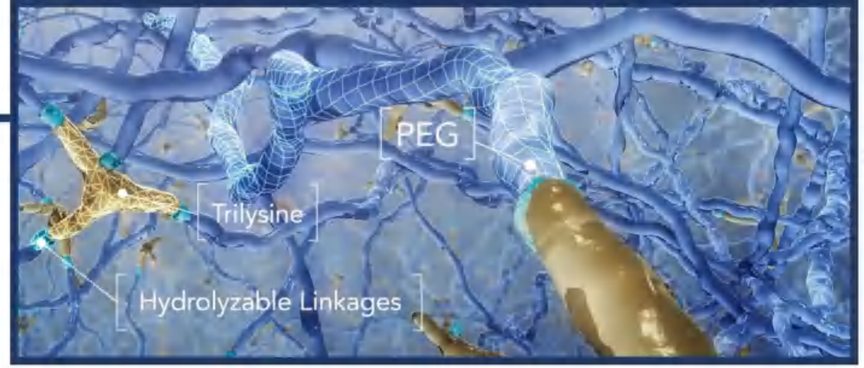
Angiogenesis, Exudation, and Degeneration Meeting
Virtual | February 11, 2023

OTX-TKI: Hydrogel Delivery of Axitinib

HYDROGEL DELIVERY PLATFORM

BIORESORBABLE, TARGETED, SUSTAINED DRUG DELIVERY

OTX's proprietary bioresorbable polymer matrix, a polyethylene glycol (PEG) hydrogel is a versatile platform for localized sustained drug delivery



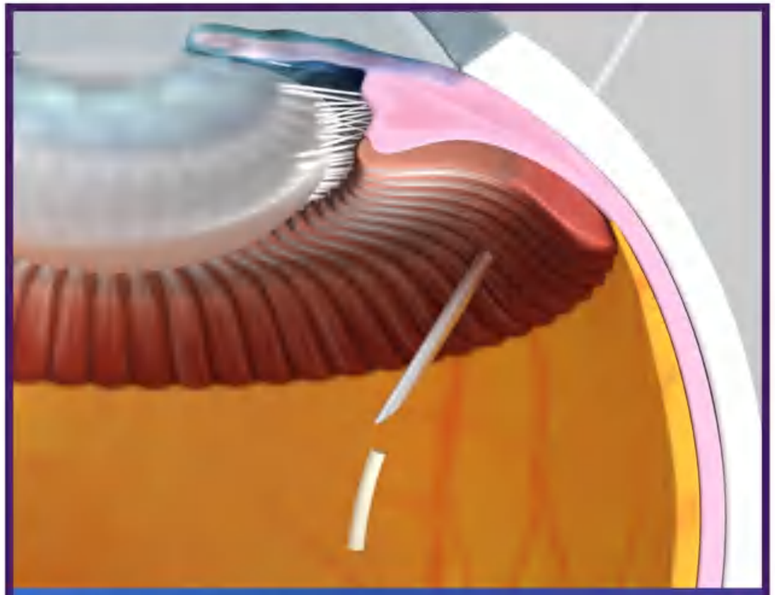
AXITINIB

MULTI-TARGET TYROSINE KINASE INHIBITOR FOR RETINAL VASCULAR DISEASES

Axitinib is a highly selective inhibitor of all VEGF and PDGF receptors with high affinity and low solubility compared to other ocular TKIs[1]

Drug	Inhibitory Concentrations for VEGFR2/KDR (IC_{50} in nM) (lower values indicate higher affinity)
Axitinib[2]	**0.2**
Sunitinib[3]	43
Vorolanib[3]	52

OTX-TKI: AXITINIB IN A HYDROGEL INTRAVITREAL IMPLANT



- **Single implant**
- **Completely bioresorbable**
- **Target release for 6-12 months**
- **Administered by a 25G or smaller needle**

References: 1. Zhao Y, et al. *Oncologist*. 2015;20(6):660-673. **2.** Gross-Goupil M, et al. *Clin Med Insights Oncol*. 2013;7:269-277. **3.** Eyepoint Pharmaceuticals, Inc. Form 8-K. Published online September 15, 2020. Accessed August 24, 2022. https://sec.report/Document/0001564590-20-043596/
KDR=kinase insert domain receptor; PDGF=platelet-derived growth factor; VEGF=vascular endothelial growth factor

Safety Summary Up to Month 10: OTK-TKI was generally well tolerated with a favorable safety profile

- No reports of drug-related ocular or systemic SAEs in either arm
- One event of acute endophthalmitis in OTX-TKI arm which occurred following mandated aflibercept injection at Month 1
  - Reported as moderate
  - Injection procedure related
  - Unrelated to the study drug
  - Resolved after intravitreal antibiotic injection, with vision returning to baseline
- All events were mild except
  - Acute endophthalmitis SAE (moderate and resolved) and worsening of cataract (moderate) in OTX-TKI arm
  - Elevated IOP in aflibercept arm (moderate and resolved)

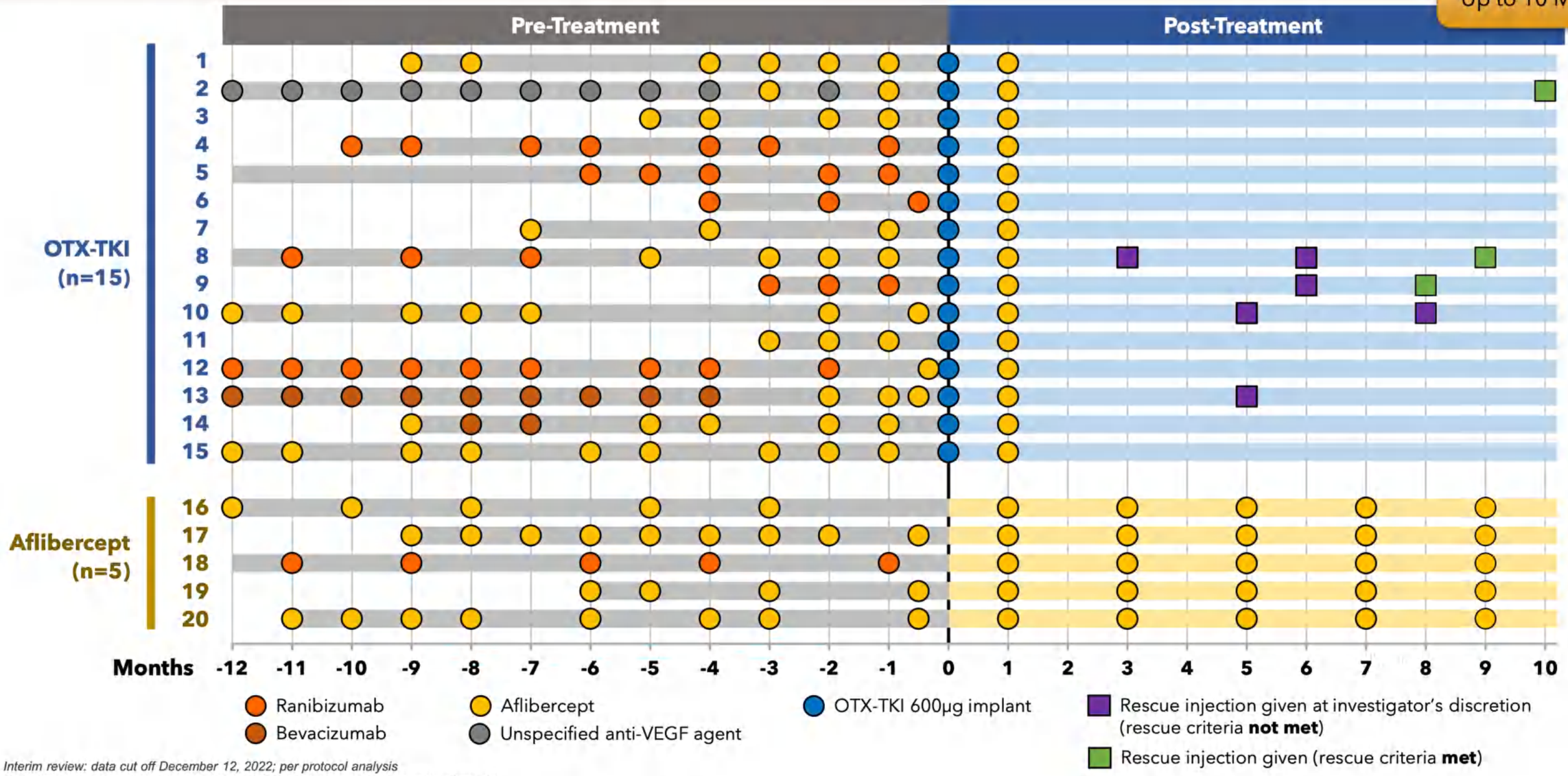
Subjects with Adverse Events in the Study Eye	OTX-TKI n=16	Aflibercept n=5
Elevated IOP	0	1**
Retinal detachment	0	0
Retinal vasculitis	0	0
Implant migration into the anterior chamber	0	NA
Acute Endophthalmitis	1*	0
Subjects with Ocular Adverse Events Reported by Severity		
Ocular AEs	16	3
Mild	14	2
Moderate	2*	1**
Severe	0	0
Serious AEs	1*	0

*Moderate and serious ocular AE in OTX-TKI arm was Acute Endophthalmitis 6 days after mandated aflibercept injection at Month 1
**Moderate AE in Aflibercept arm was Elevated Intraocular pressure

Interim review: data cut off December 12, 2022
IOP=intraocular pressure; SAE=serious adverse event

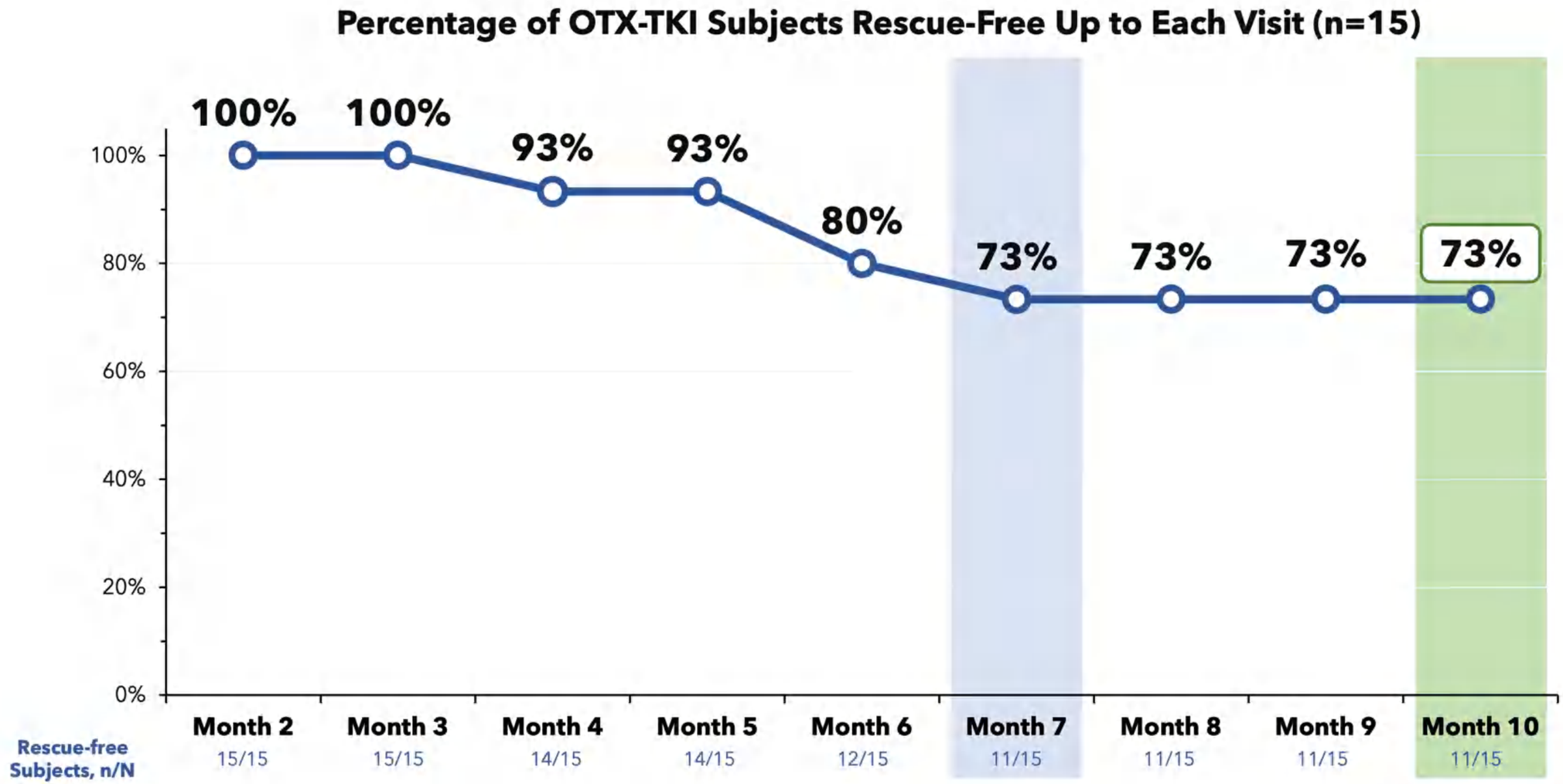
Reduction in Anti-VEGF Injections Following OTX-TKI Up to Month 10

Treatment Reduction
Up to 10 Months: 92%



Interim review: data cut off December 12, 2022; per protocol analysis
Reduction in treatment burden calculation includes all rescue injections up to Month 10
Sham injection was given at Month 0 in the Aflibercept Arm and at Month 3, 5, 7 and 9 in the OTX-TKI Arm (not shown).

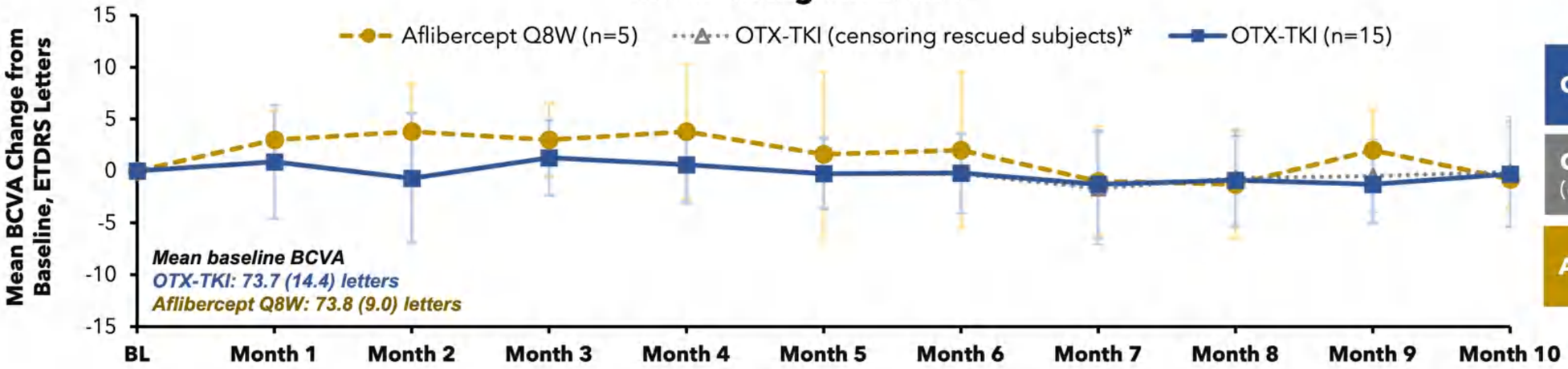
OTX-TKI Demonstrated Extended Duration of Action with 73% of Subjects Rescue-Free Up to 10 months



Interim review: data cut off December 12, 2022
Rescue-free rate calculations: If subjects received rescue anti-VEGF therapy at a study visit, those were reflected to the count at the following study visit in the graph above

Vision and CSFT with OTX-TKI were Comparable to Aflibercept Q8W Up to Month 10

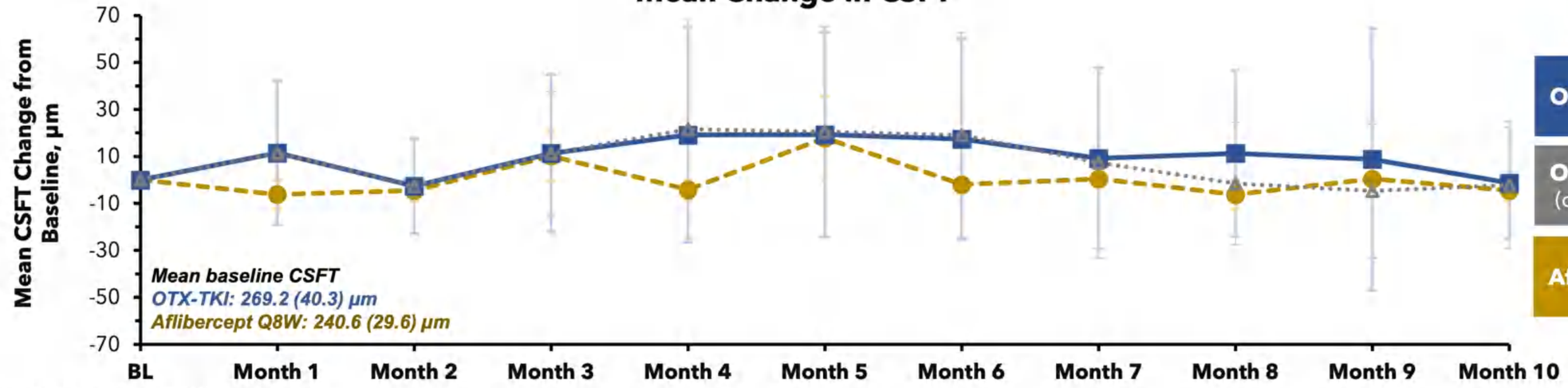
Mean Change in BCVA



Mean (SD) change in BCVA from baseline to Month 10:

- **OTX-TKI: -0.3 (5.1) letters**
- **OTX-TKI: -0.1 (5.3) letters** (censoring rescued subjects)
- **Aflibercept Q8W: -0.8 (2.8) letters**

Mean Change in CSFT



Mean (SD) change in CSFT from baseline to Month 10:

- **OTX-TKI: -1.3 (23.7) µm**
- **OTX-TKI: -2.1 (26.9) µm** (censoring rescued subjects)
- **Aflibercept Q8W: -4.5 (4.4) µm**

Interim review: data cut off December 12, 2022
Error bars represent standard deviation; n=14 in OTX-TKI arm at Months 2 and 7 due to missed visits
**Sample size for OTX-TKI (censoring rescued subjects): n=15 at Baseline and Months 1 and 3; n=14 at Month 2 (missed visit) and Months 4 and 5; n=12 at Month 6 and n=11 at Month 7, 8, 9, and 10*
BCVA=best corrected visual acuity; BL=baseline; CSFT=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study

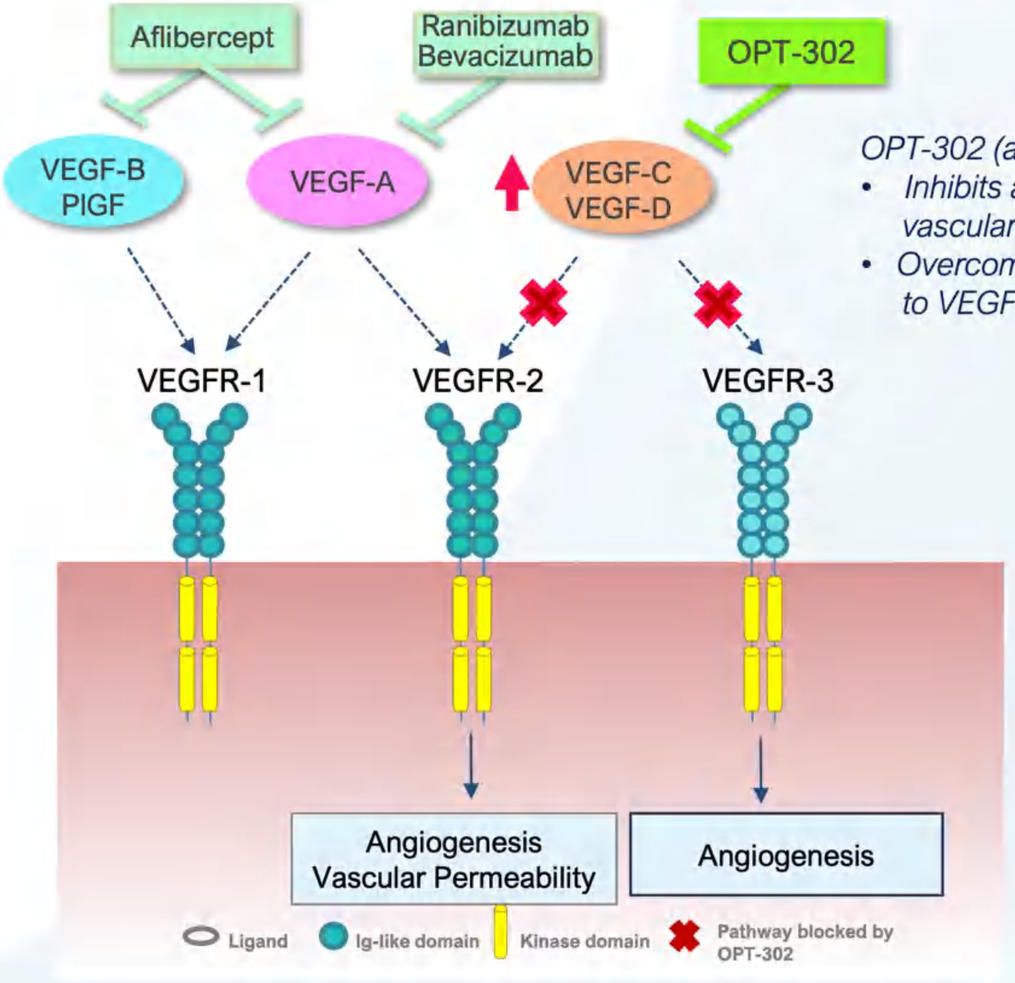
New approach in wet-AMD treatment: Efficacy and safety of dual inhibition of VEGF-C/-D and VEGF-A with OPT-302 combination therapy

Caroline R. Baumal

New England Eye Center, Tufts Medical Center, Boston, Massachusetts, USA

OPT-302 combination therapy offers broader inhibition of VEGF receptor signaling by targeting VEGF-C /-D and VEGF-A

Used in combination with any VEGF-A inhibitor, OPT-302 **completely blocks ligand signaling of the VEGFR-2 and VEGFR-3 receptors**, inhibiting the most important pathways driving angiogenesis and vascular leakage



OPT-302 (anti-VEGF-C/-D):

- *Inhibits angiogenesis & vascular leakage*
- *Overcomes escape mechanism to VEGF-A suppression*

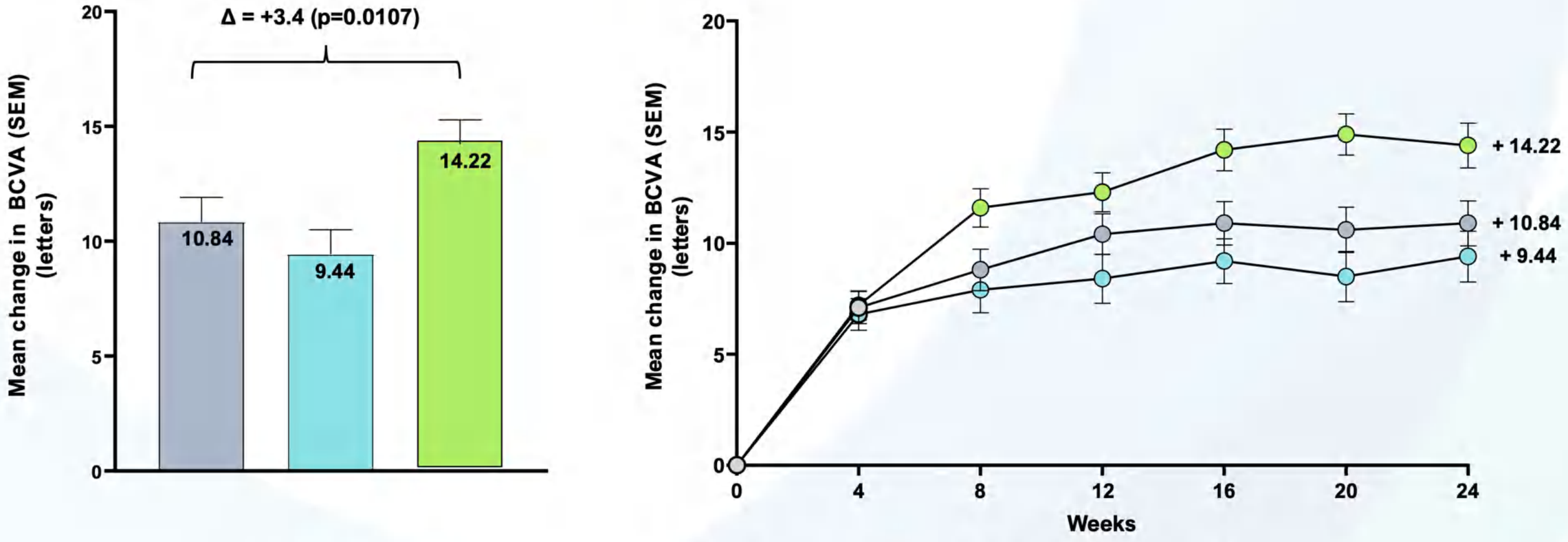
VEGF-A inhibition elevates VEGF-C and VEGF-D which can contribute to sub-optimal clinical efficacy of anti-VEGF-A treatments

[a] *Bevacizumab is used 'off-label' for the treatment of nAMD*
Dugel PU, et al Ophthalmology Retina. 2020; 4: 250–263.

Superiority in visual acuity for OPT-302 (2 mg) combination therapy versus ranibizumab monotherapy

Primary endpoint met in Phase 2b wet AMD study

Mean Change in BCVA Baseline to Week 24



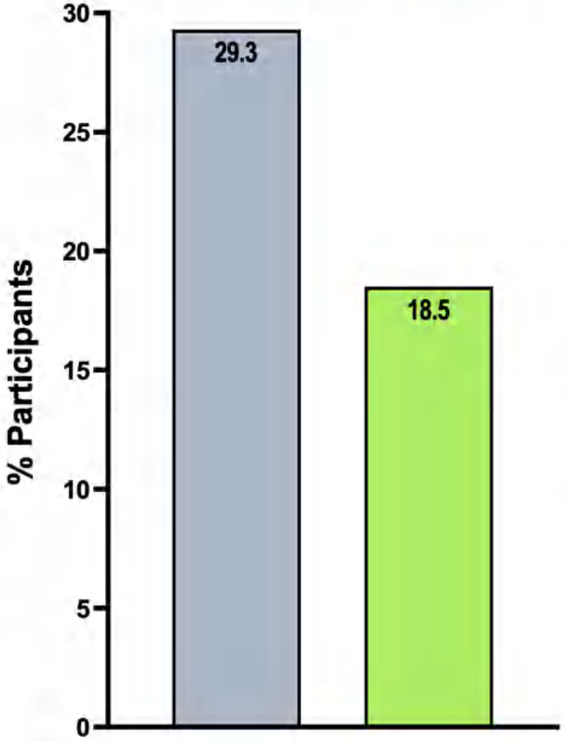
mITT; BCVA – Best Corrected Visual Acuity
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM

Improved anatomy for OPT-302 (2 mg) combination therapy versus ranibizumab monotherapy

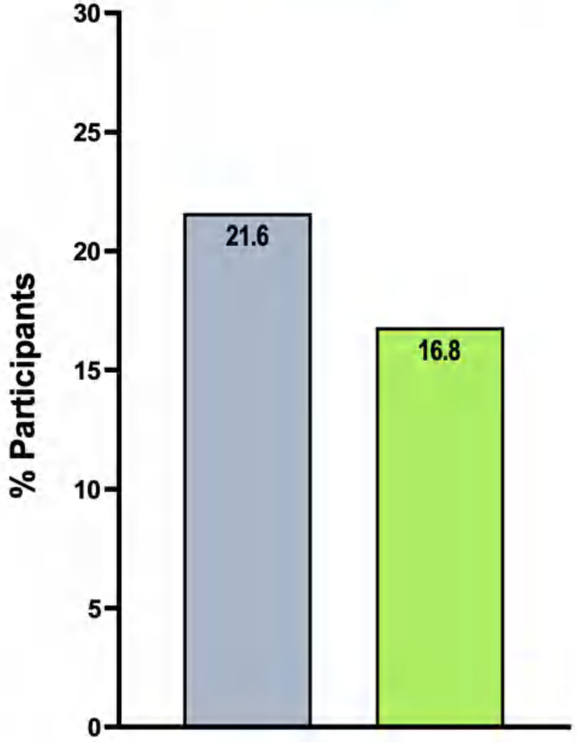
Phase 2b wet AMD study

SD-OCT at Week 24

↓ Presence of sub-retinal fluid

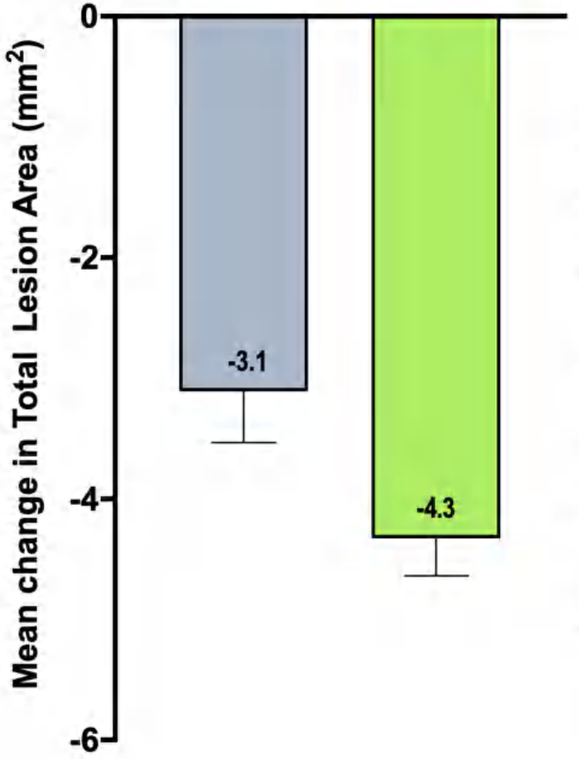


↓ Presence of Intraretinal cysts

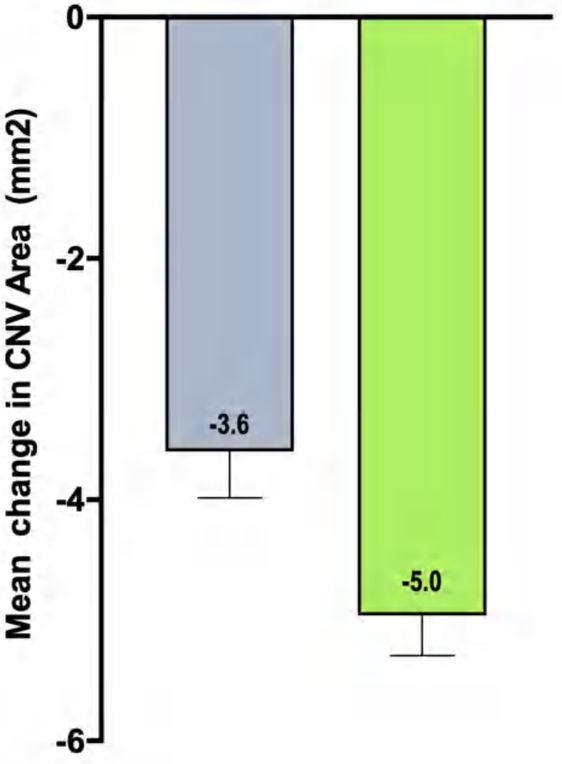


FA at Week 24

↓ Total Lesion Area



↓ CNV Area



Sham + 0.5 mg ranibizumab (n=116)

2.0 mg OPT-302 + 0.5 mg ranibizumab (n=120)

Safety: Phase 2b wet AMD study

OPT-302 combination therapy well-tolerated and comparable to ranibizumab monotherapy

N Participants (%)	Sham + ranibizumab N=121	0.5 mg OPT-302 + ranibizumab N=120	2.0 mg OPT-302 + ranibizumab N=124
Treatment emergent AEs (TEAEs)	84 (69.4%)	87 (72.5%)	93 (75.0%)
Ocular AEs - Study Eye – related to study product(s)[1]	17 (14.0%)	17 (14.2%)	19 (15.3%)
Ocular AEs - Study Eye – Severe[2]	1 (0.8%)	2 (1.7%)	1 (0.8%)
Serious AEs	10 (8.3%)	16 (13.3%)	7 (5.6%)
Ocular SAEs in Study Eye	0 (0.0%)	2[3] (1.7%)	0 (0.0%)
Intraocular inflammation[4] – Study Eye	2[5,6] (1.7%)	2[3] (1.7%)	1[5] (0.8%)
Participants with AEs leading to study discontinuation	1[7] (0.8%)	0 (0.0%)	0 (0.0%)
Any APTC event	0 (0.0%)	1[8] (0.8%)	0 (0.0%)
Deaths	2[9] (1.7%)	0 (0.0%)	0 (0.0%)

Safety population analysed according to medication received

[1] *Assessed by investigator to be "possibly related", "probably related" or "definitely related" to administration of study drug(s)*

[2] *Assessed by Investigator to be National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or above, or, if CTCAE grade is unavailable, an AE assessed as "causing an inability to perform normal daily activities"*

[3] *SAE of endophthalmitis, with AEs of hypopyon and anterior chamber cell (n=1), SAE of vitritis (n=1)*

[4] *AEs considered to be indicative of intraocular inflammation, defined prior to database lock as: Endophthalmitis, iritis, vitritis, iridocyclitis, uveitis, hypopyon, viral iritis, or anterior chamber inflammation*

[5] *Transient anterior chamber cell (trace 1-4 cells)*

[6] *Not reported as a TEAE*

[7] *Squamous cell carcinoma of the lung diagnosed shortly after Baseline visit*

[8] *Non-fatal myocardial infarction*

[9] *Pneumonia (n=1), infective endocarditis (n=1)*

Non-Exudative AMD with Geographic Atrophy

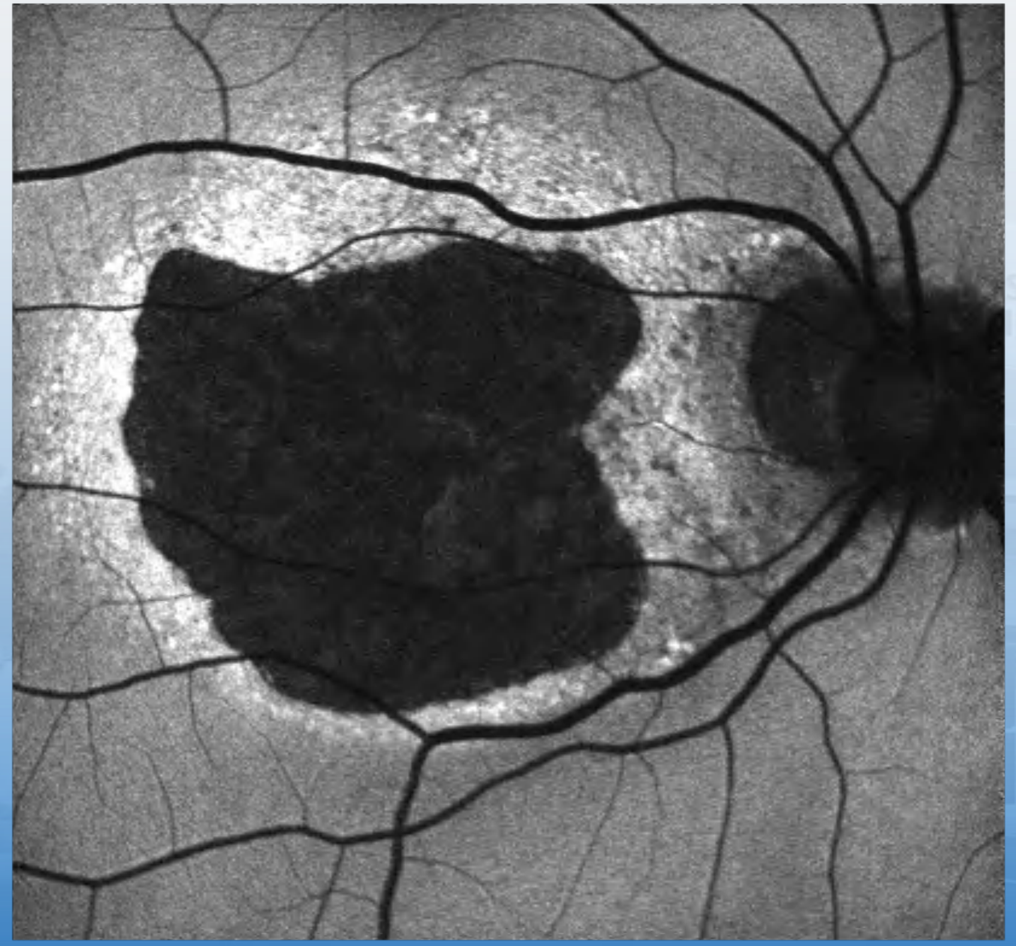


Image courtesy of Frank Holz

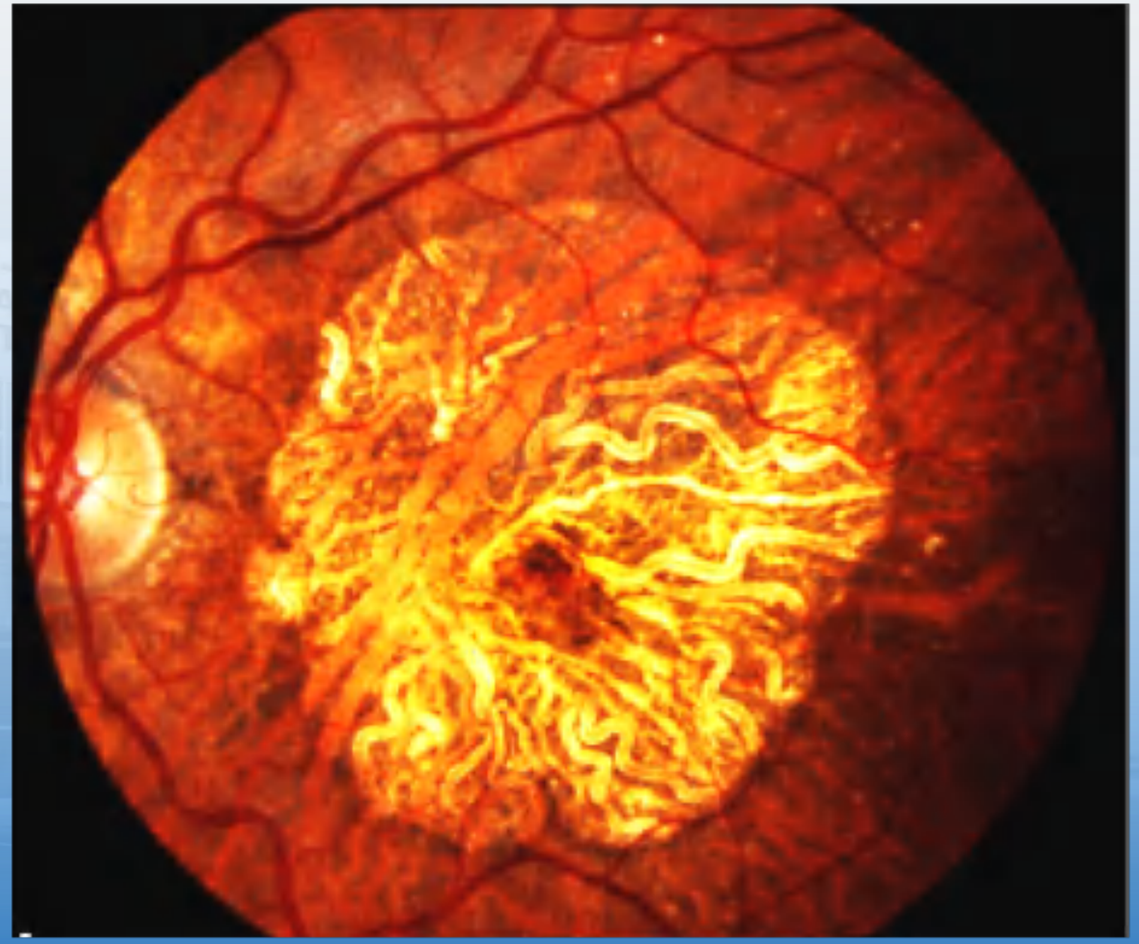
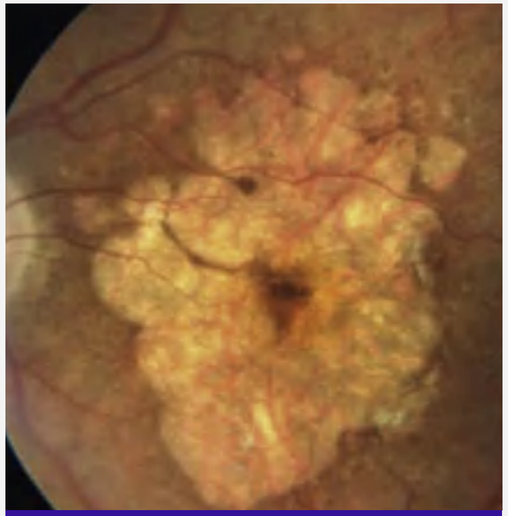


Image courtesy of Brandon Lujan

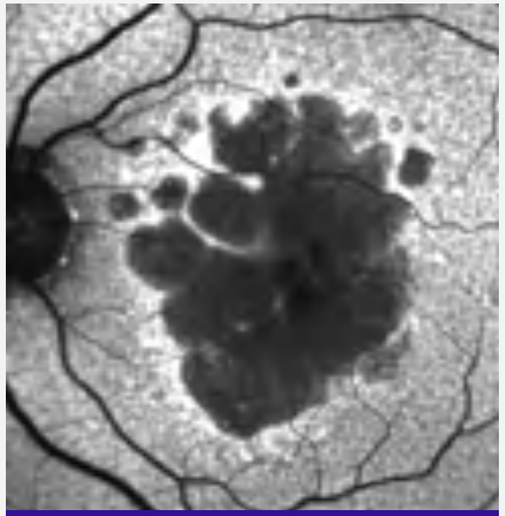
Multiple imaging modalities are used to visualize GA lesions[1,2]

Each modality has its strengths and weaknesses

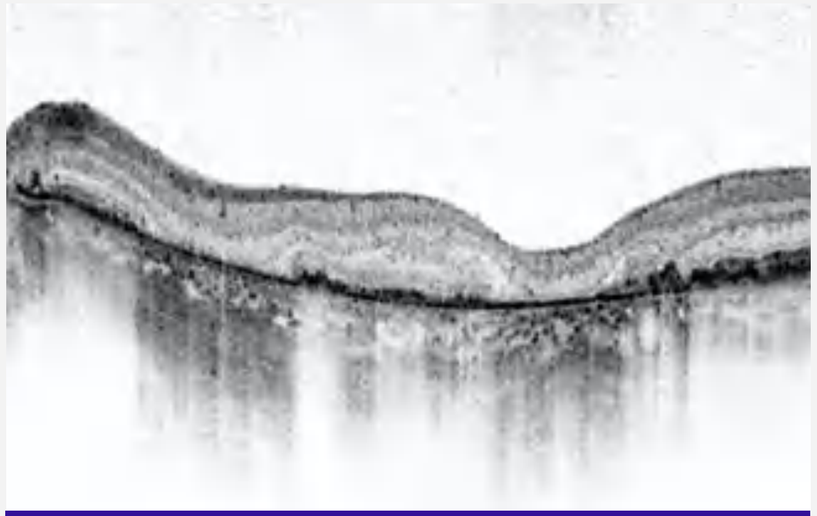
Multimodal imaging may be needed to obtain the most reliable detection and measurement of atrophy



COLOR FUNDUS PHOTOGRAPHY



FUNDUS AUTOFLUORESCENCE



OPTICAL COHERENCE TOMOGRAPHY

Images: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

GA, geographic atrophy.

1. Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **2.** Holz FG, et al. *Ophthalmology*. 2017;124:464-478.

CAM findings: OCT established to be the optimal imaging modality for defining AMD/Atrophy

OCT: study of AMD progression and early end point development allows specific layers (photoreceptors, RPE) to be evaluated

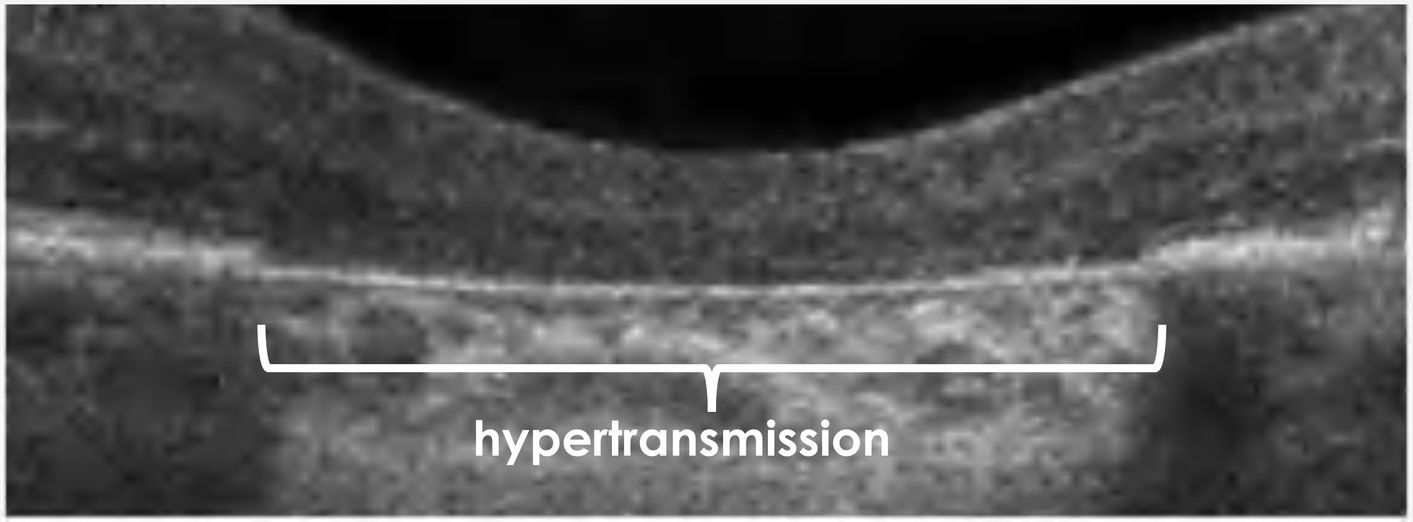


Image: Sadda SR, et al. *Ophthalmology*. 2018;125:537-548.

Other imaging methods would be used to corroborate or support OCT-based observations

AMD, age-related macular degeneration; CAM, Classification of Atrophy Meeting; OCT, optical coherence tomography; RPE, retinal pigment epithelium.
Sadda SR, et al. *Ophthalmology*. 2018;125:537-548.

Non-Exudative (Dry) AMD

- Smoking Cessation
- AREDS2 Vitamins
- Anything Else?

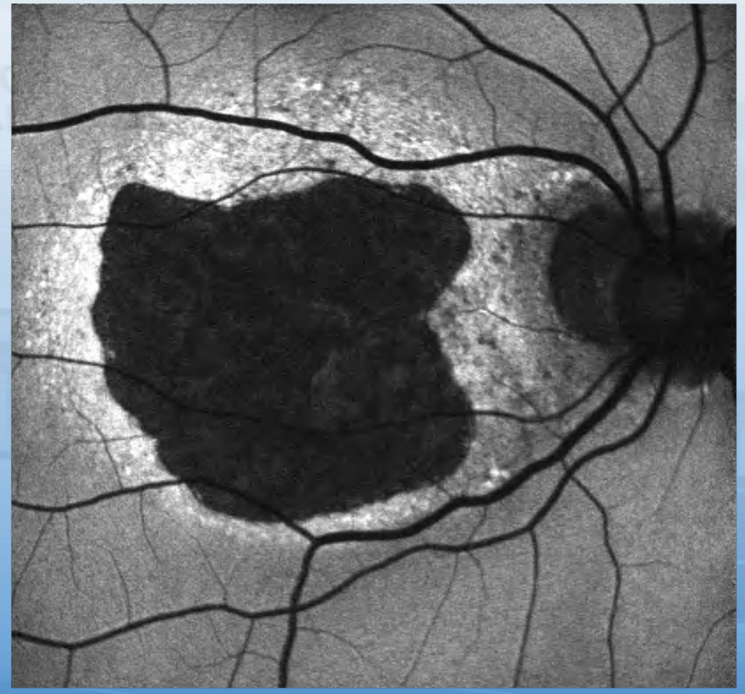


Image courtesy of Frank Holz

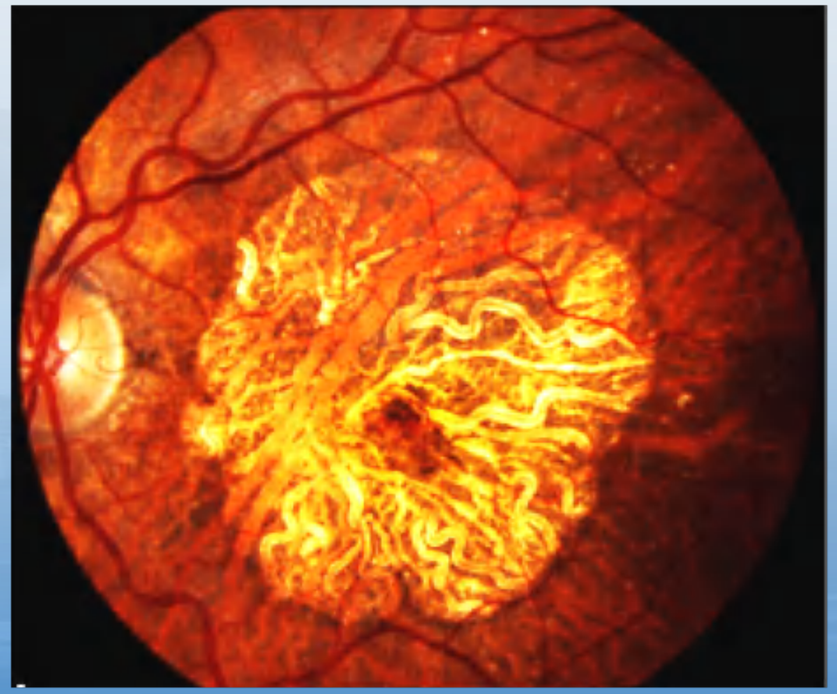


Image courtesy of Brandon Lujan

Current Hypothesis for GA Pathophysiology > Multifactorial

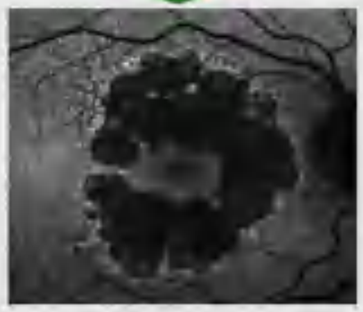
Oxidative stress **Genetic predisposition** **Environment**

Complement deposition between retinal pigment epithelium (RPE) and Bruch's membrane[1]

Loss of complement regulation[2]

Blood-retina barrier breakdown[2]

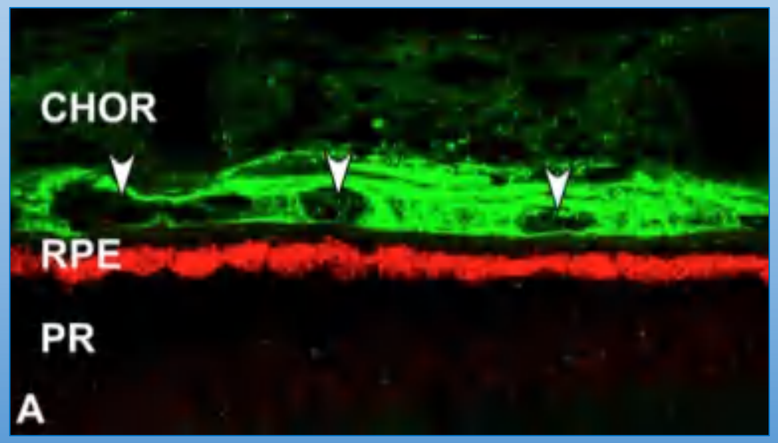
Geographic atrophy



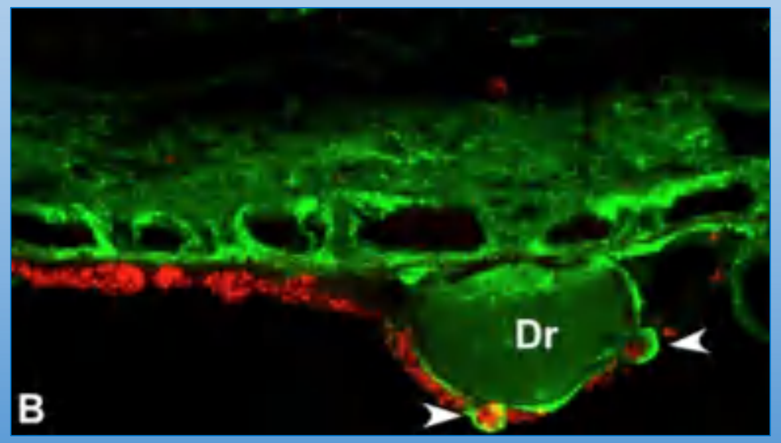
1. Age-Related Eye Disease Study Research Group. Arch Ophthalmol. 2001;119(10):1417-1436; 2. Ambati J, et al. Nat Rev Immunol. 2013;13(6):438-451. Images courtesy of Caroline R. Baumal, MD, FASRS.

Histopathology of AMD Eyes

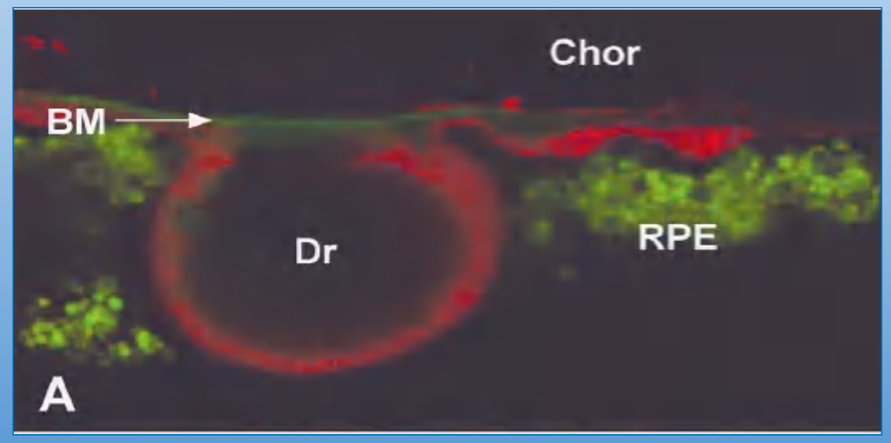
C3 and C5 accumulation in drusen, Bruch's Membrane and Inner Choroid



C3
(green)



C3
(green)



C5
(red)

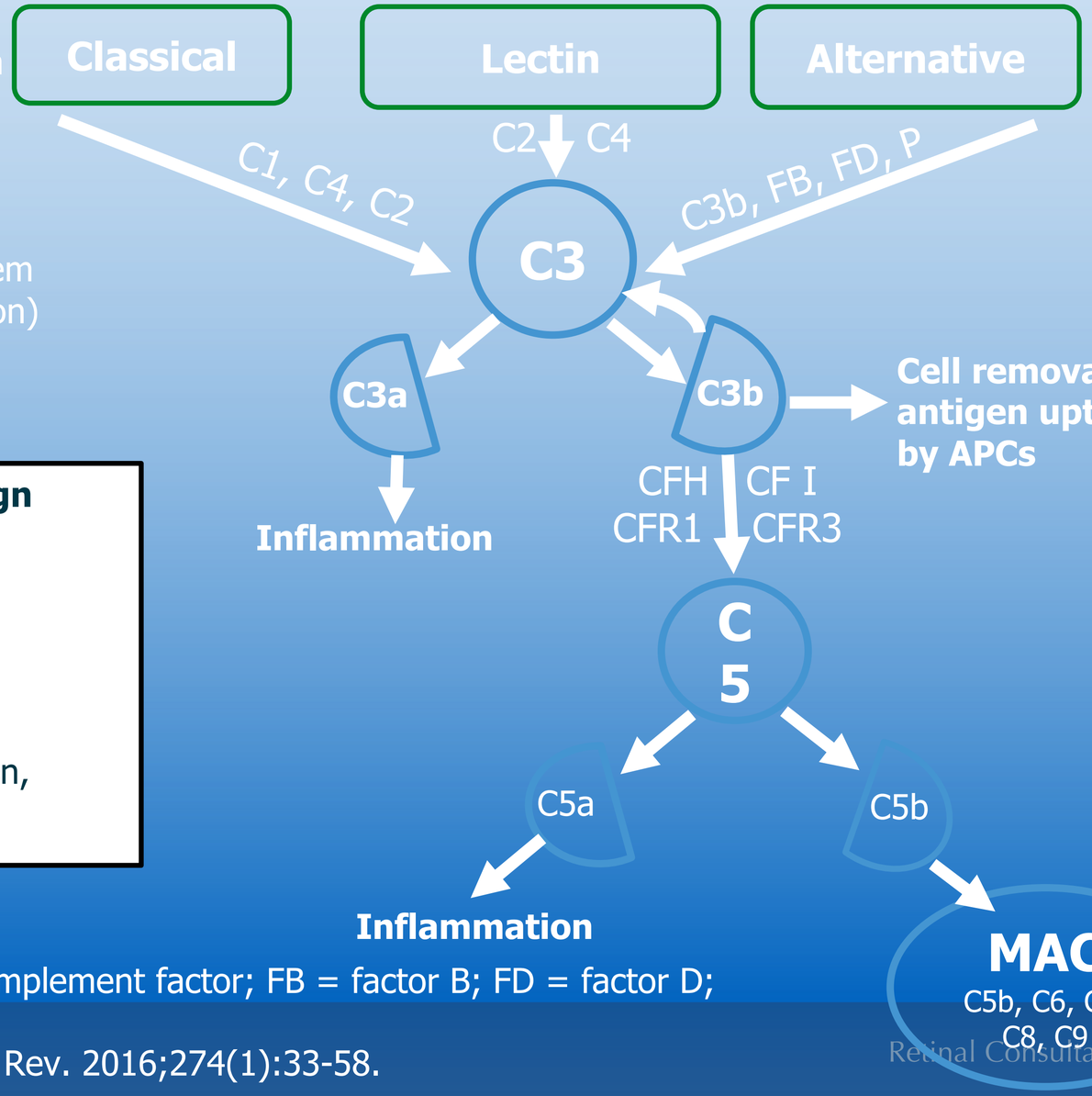
(A) Arrowheads indicate cross-sections of choroidal capillaries; (B) Arrowheads indicate C3 immunoreactivity is also present in the extracellular space between the RPE and Bruch's membrane and in the cytoplasm of some RPE cells. BM = Bruch's membrane; Chor/CHOR = choroid; Dr = drusen; PR = photoreceptor layer.

Anderson DH, et al. Prog Retin Eye Res. 2010;29(2):95-112; Anderson DH, et al. Am J Ophthalmol. 2002;134(3):411-431.

Complement Cascade

Complement system and AMD
1st line defense of immune system
Protection from microorganisms
innate immunity
- Not adaptable
- Does not change as we age

Activated by adaptive immune system
(through antigen antibody interaction)



3 Separate Pathways
- Activation
- Converge on C3

Classical: antigen-antibody complexes

Lectin: polysaccharides on microorganisms

Alternative: pathogen cell surfaces and nonspecific/ spontaneous activation

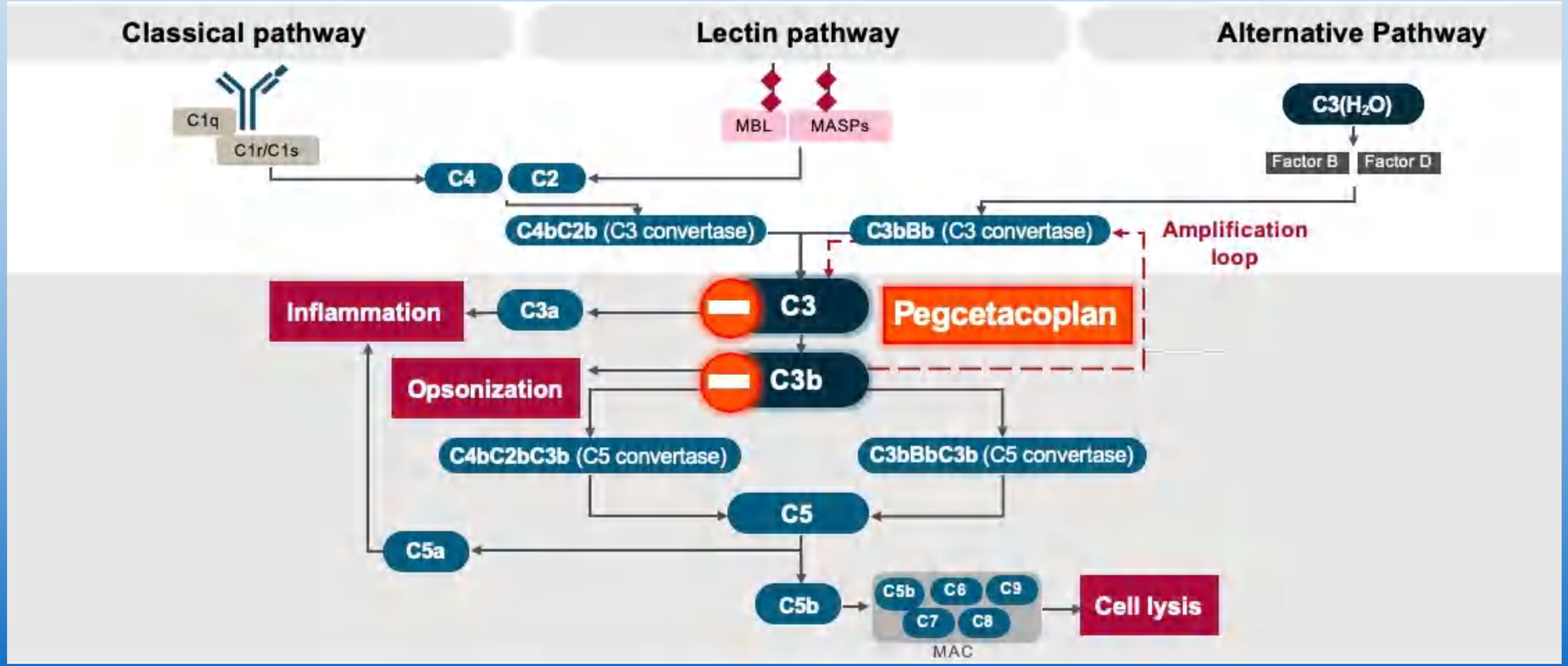
For detection and removal foreign pathogens

-30 proteins

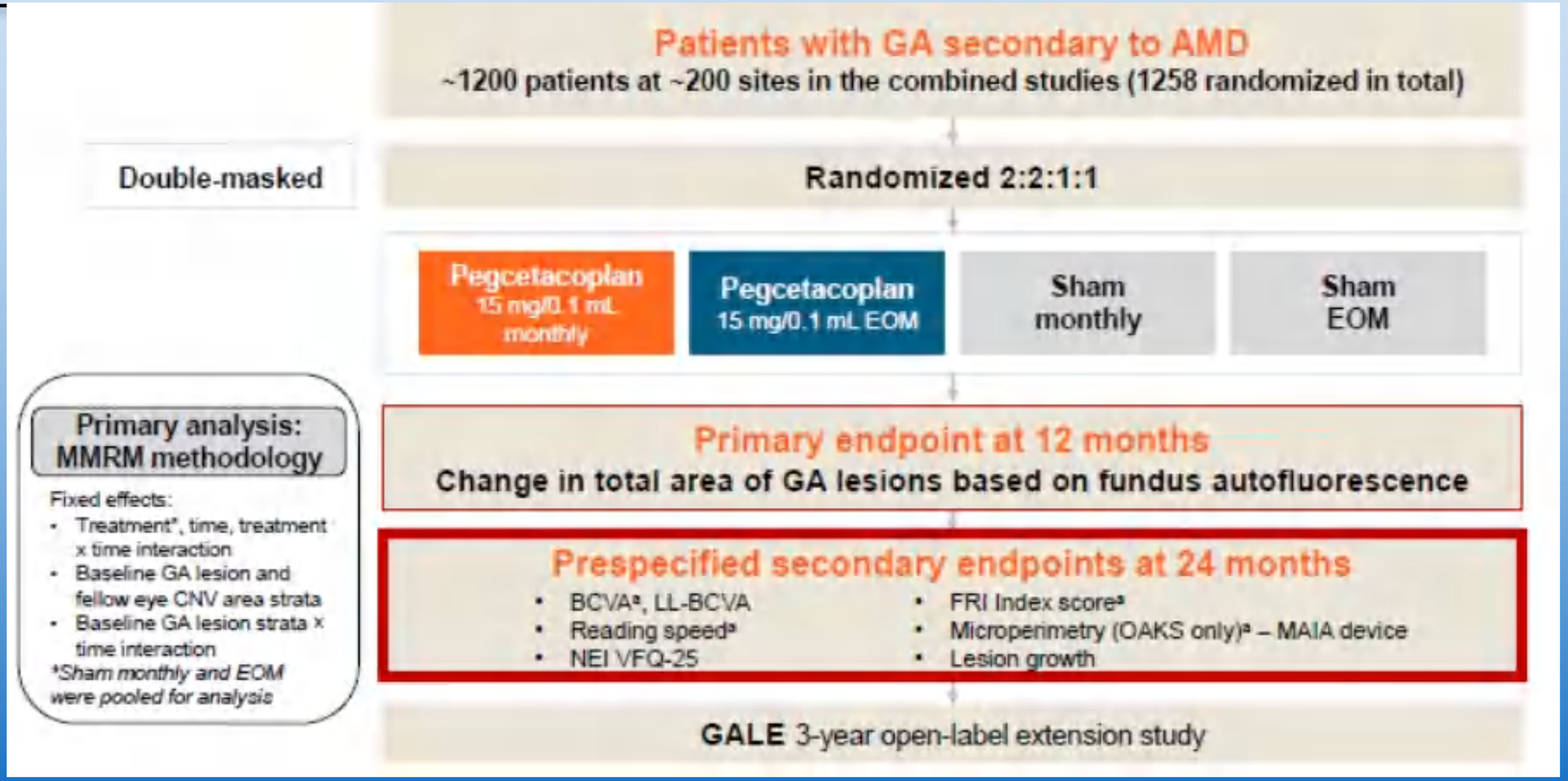
Activation
- Inflammation
- Opsonization/phagocytosis
- MAC-mediated lysis, cell secretion, proliferation

APC = antigen presenting cell; CF = complement factor; FB = factor B; FD = factor D; MAC = membrane attack complex.
Adapted from Ricklin D, et al. Immunol Rev. 2016;274(1):33-58.

Pegcetacoplan Binds to C3 and C3b

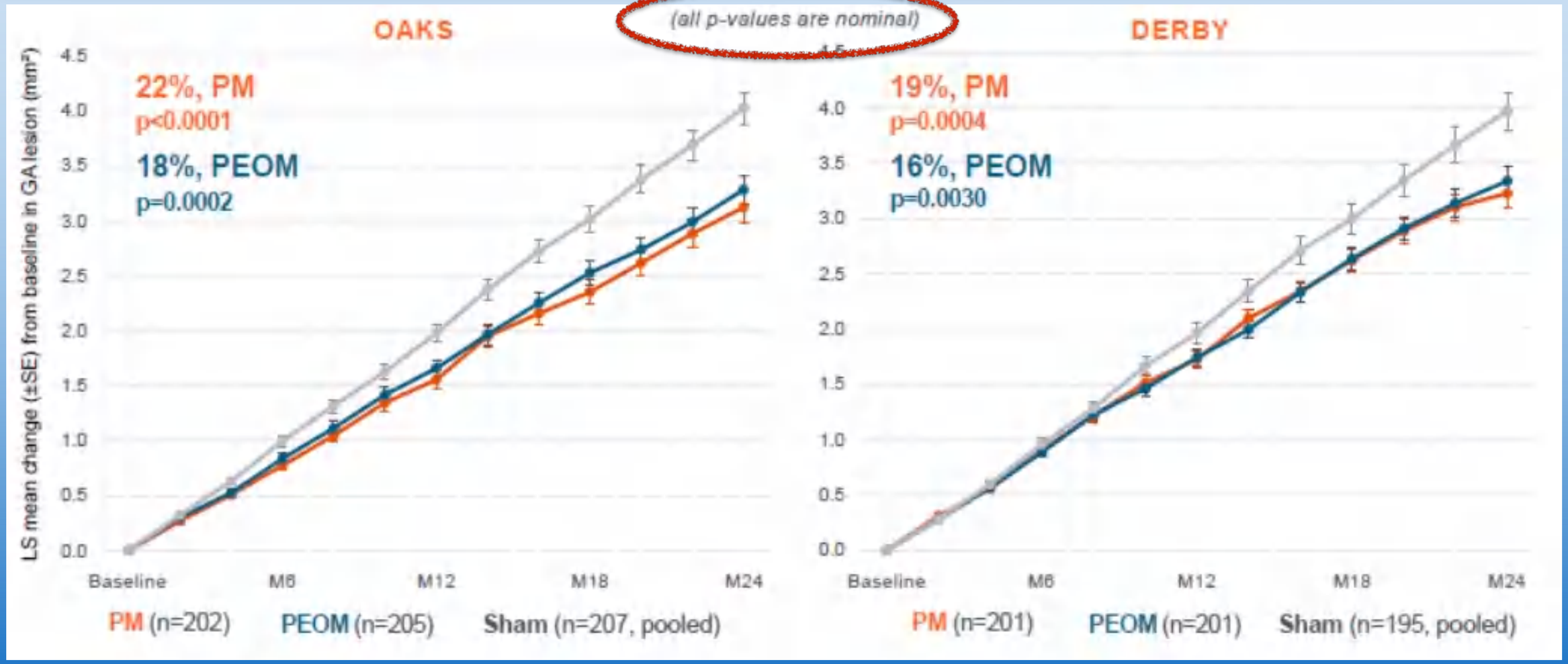


Design of the Phase 3 OAKS and DERBY Studies



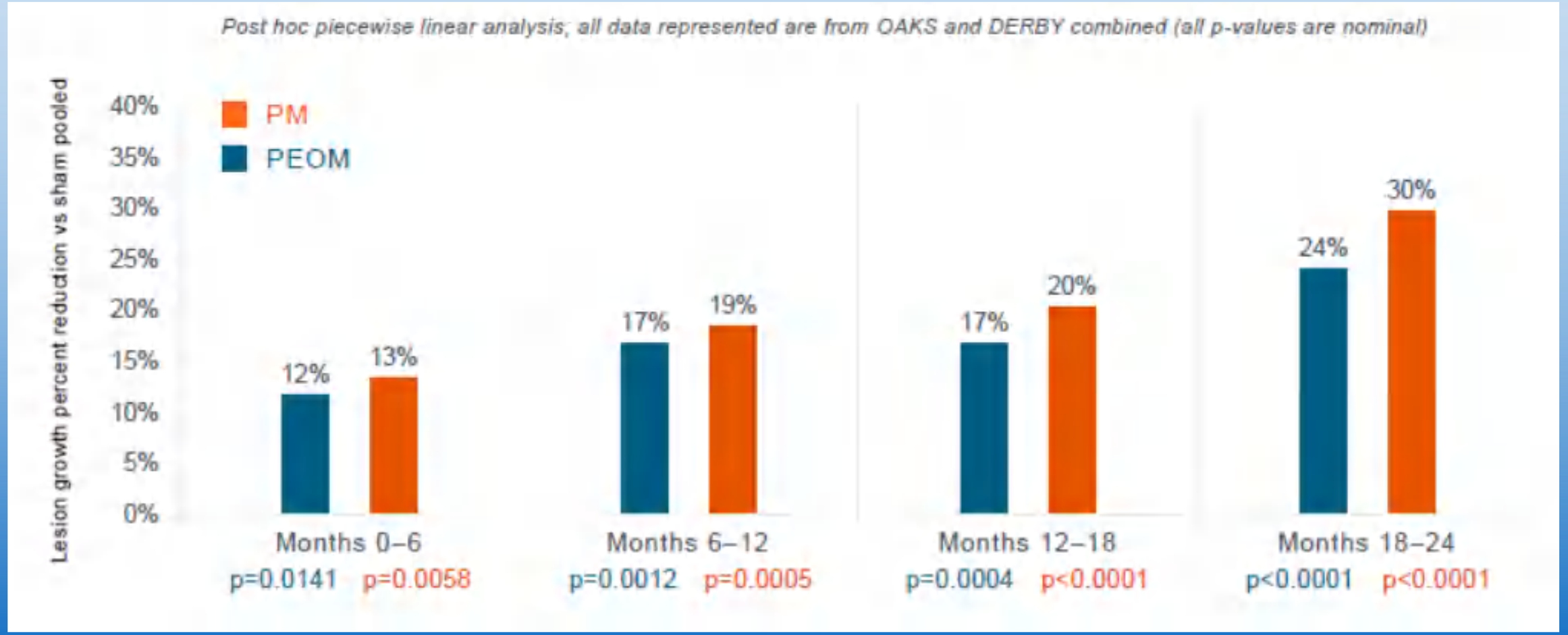
OAKS (NCT03525613), DERBY (NCT03525600), GALE (NCT04770545). *Key secondary endpoints. AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; EOM = every other month; FRI = Functional Reading Independence; GA = geographic atrophy; LL = low luminance; MAIA = macular integrity assessment; MMRM = mixed-effects model for repeated measures; NEI-VFQ = National Eye Institute Visual Function Questionnaire. Wykoff C, et al. Presented at: AAO annual meeting. September 30-October 3, 2022; Chicago, IL.

Reductions in GA Lesion Growth at Month 24

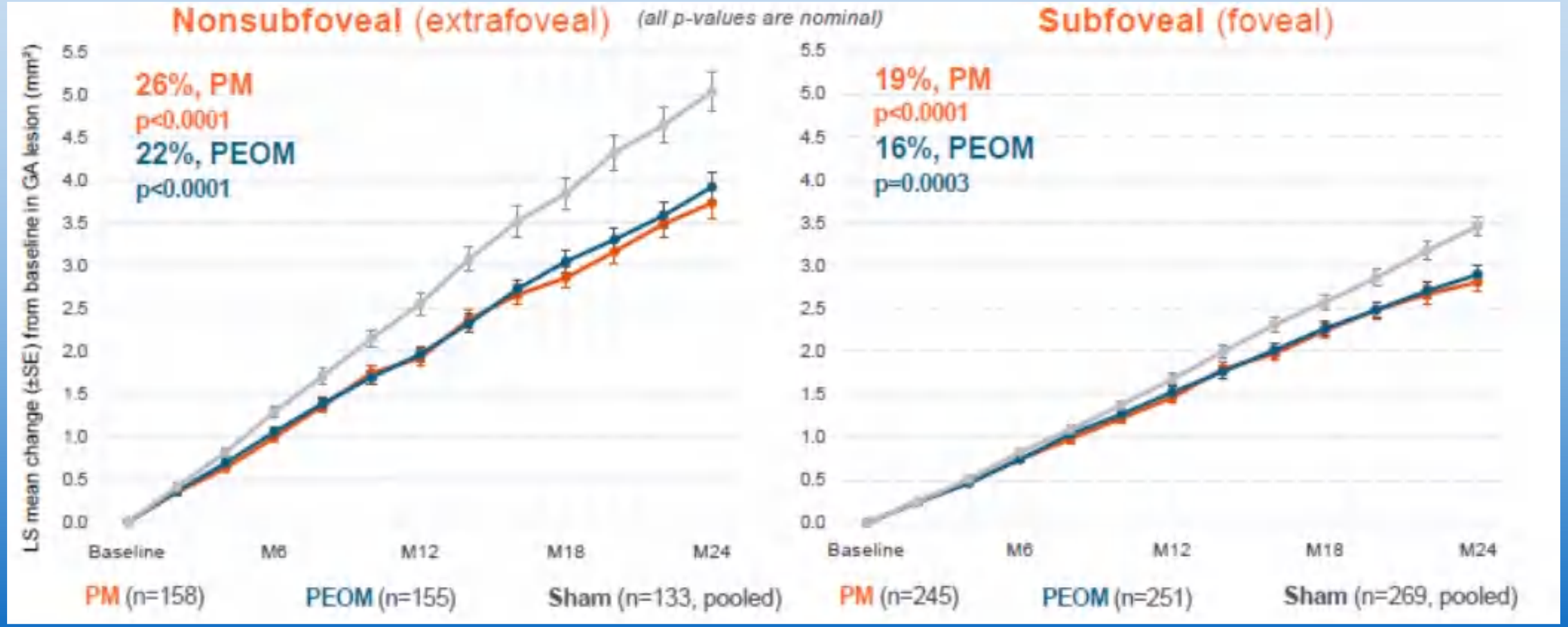


LS means estimated from a MMRM. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye. Heier J, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

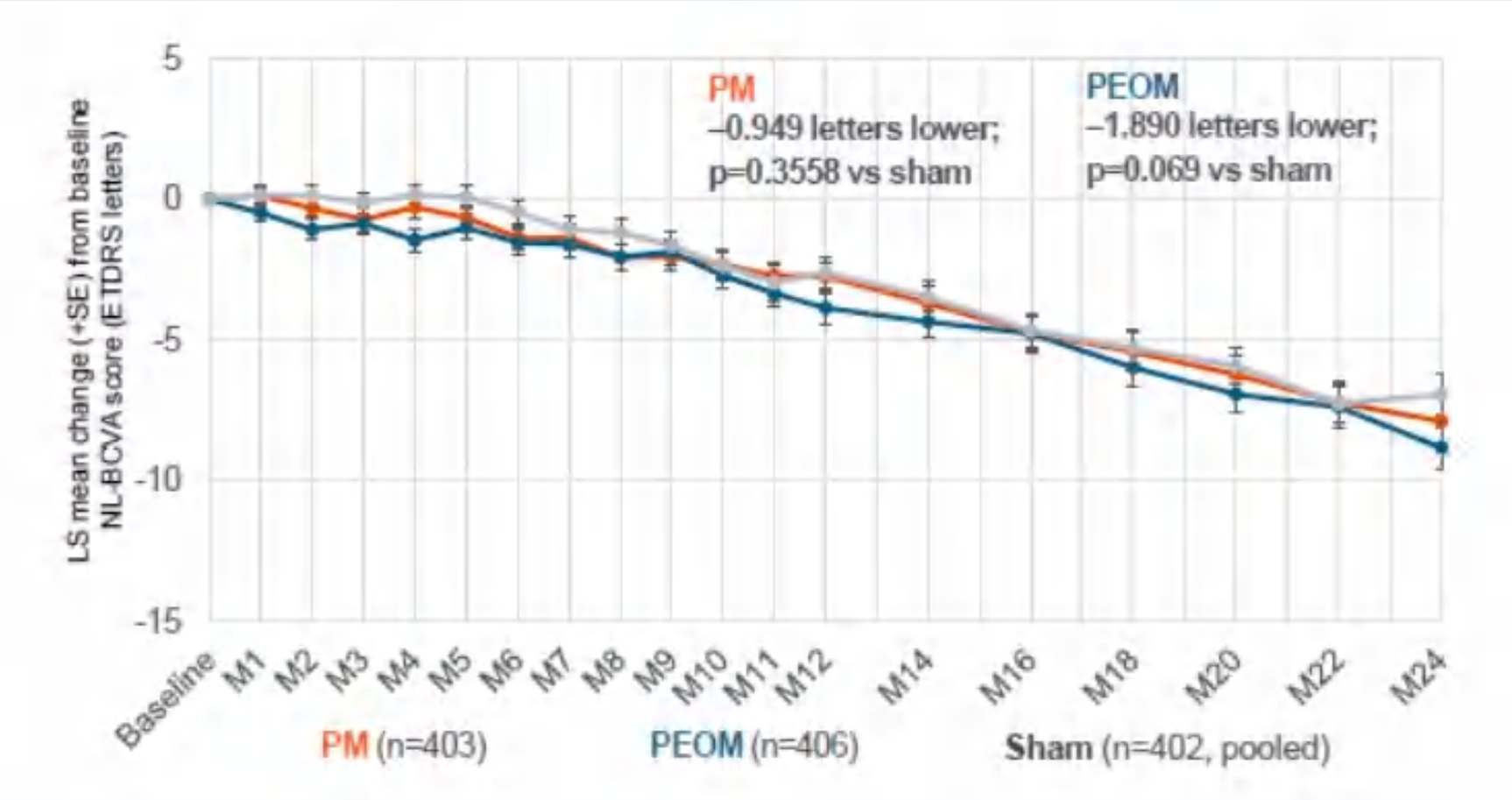
Combined Reductions in GA Lesion Growth Over 6-Month Periods



Combined Reductions in GA Lesion Growth by Lesion Location



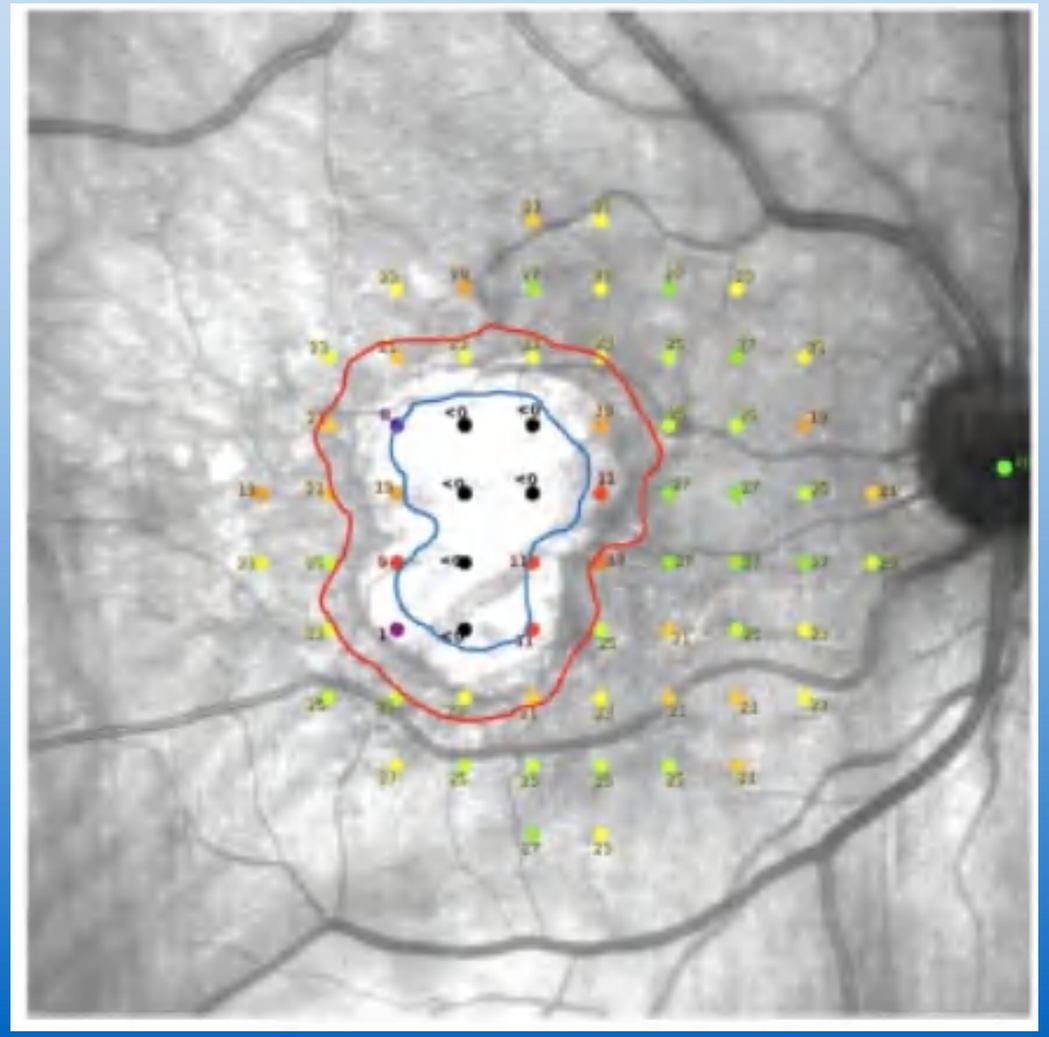
Combined BCVA in the Study Eye Over 24 Months



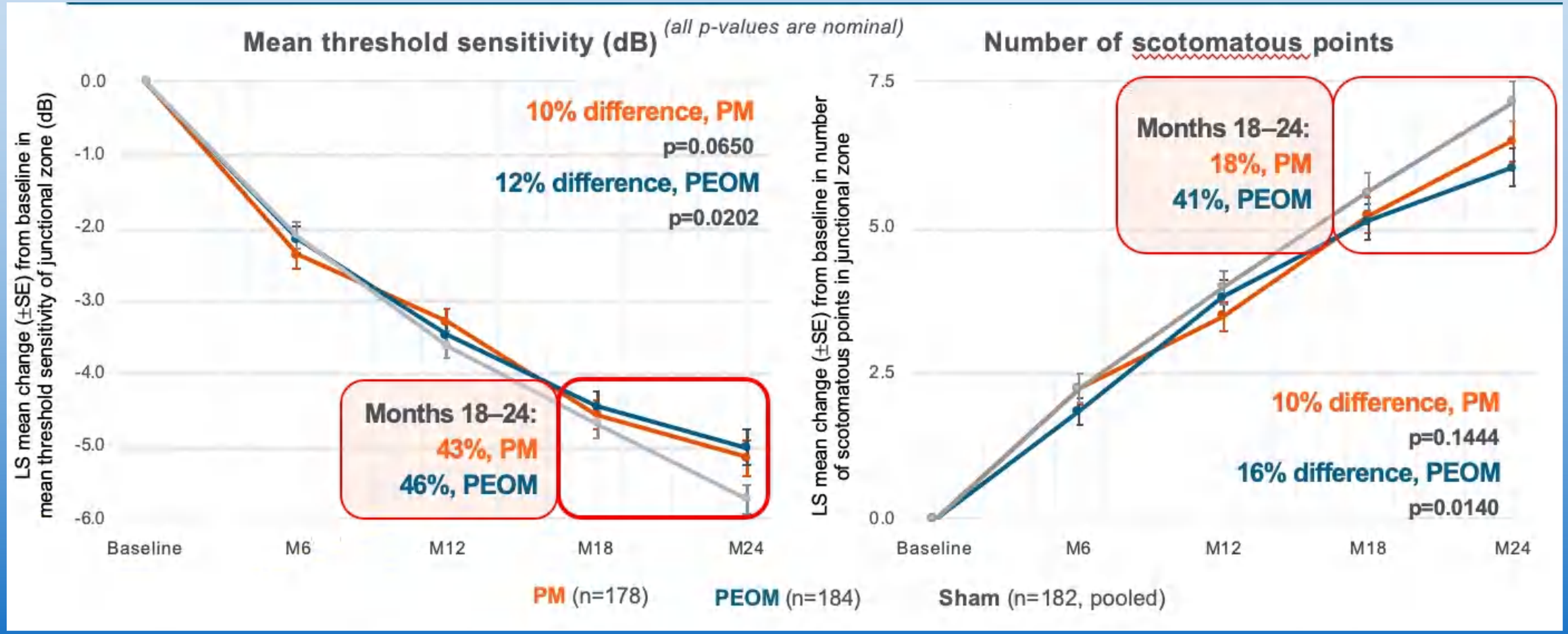
LS means estimated from a MMRM. The mITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye. Wycoff C, et al. Presented at: AAO 2022. September 30-October 3, 2022; Chicago, IL.

Microperimetry: Post Hoc Analysis of the Junctional Zone

- Hypothesis: linear expansion of GA lesions of ~100-150 microns/year[1] means that pegcetacoplan preservation of retinal tissue may primarily be reflected in preserved photoreceptor function in retina near GA lesion borders at baseline
- Functional zone (area within 250 microns of each side of GA lesion border) was created on FAF for each patient
- Microperimetry endpoints were assessed within this region[a]



Microperimetry Junctional Perilesional Analysis
(Post Hoc) Signal of Functional Preservation



TEAEs in OAKS and DERBY Over 24 Months

	PM (N=213)	PEOM (N=212)	Sham pooled (N=211)	PM (N=206)	PEOM (N=208)	Sham pooled (N=206)
All TEAEs, n (%)	192 (90.1%)	187 (88.2%)	175 (82.9%)	178 (86.4%)	180 (86.5%)	169 (82.0%)
Ocular TEAEs in study eye, patients, n (%)	133 (62.4%)	123 (58.0%)	98 (46.4%)	125 (60.7%)	108 (51.9%)	95 (46.1%)
Non-ocular TEAEs, patients, n (%)	174 (81.7%)	165 (77.8%)	154 (73.0%)	163 (79.1%)	142 (68.3%)	146 (70.9%)
Serious ocular TEAEs in the study eye, n (%) M	5 (2.3%) 7	4 (1.9%) 4	1 (0.5%) 1	4 (1.9%) 4	2 (1.0%) 4	2 (1.0%) 2
Endophthalmitis	2 (0.9%) 2	3 (1.4%) 3	0	0	0	0
Optic ischemic neuropathy	2 (0.9%) 2	0	0	1 (0.5%) 1	0	0
Retinal detachment	1 (0.5%) 1	1 (0.5%) 1	0	0	0	0
Uveitis	0	0	0	0	2 (1.0%) 2	0
Vitritis	0	0	0	2 (1.0%) 2	0	0
Visual acuity reduced	0	0	1 (0.5%) 1	0	1 (0.5%) 1	0
Papilledema	1 (0.5%) 1	0	0	0	0	0
Iridocyclitis	0	0	0	0	1 (0.5%) 1	0
Retinal tear	0	0	0	1 (0.5%) 1	0	0
Dry AMD	0	0	0	0	0	1 (0.5%) 1
Macular hole	0	0	0	0	0	1 (0.5%) 1
Hyphema	1 (0.5%) 1	0	0	0	0	0

New-Onset wet AMD in Study Eye at M12 & 24: Combined

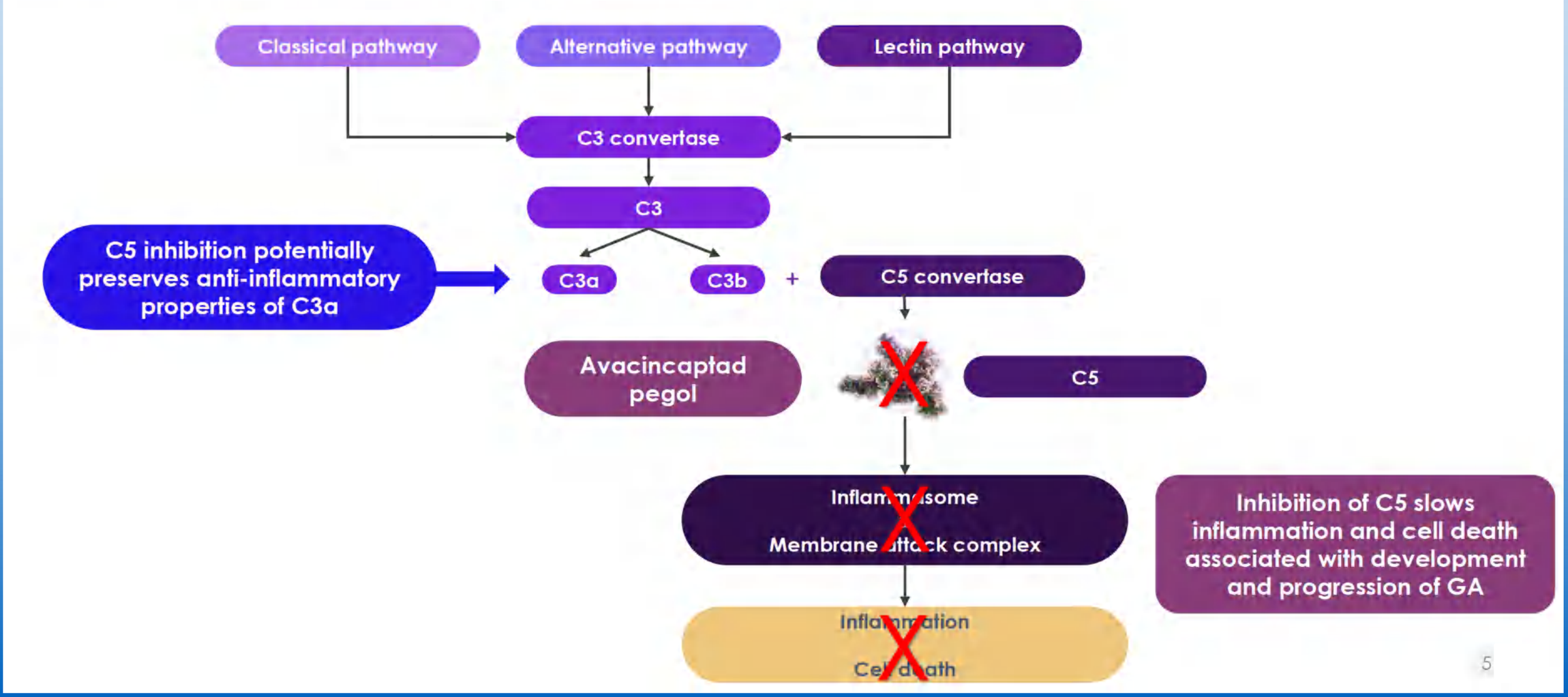
Measure, n (%)	PM (N=419)	PEOM (N=420)	Sham Pooled (N=417)
New-onset investigator-determined eAMD			
12 months	25 (6.0)	17 (4.1)	10 (2.4)
New-onset investigator-determined eAMD			
24 months – cumulative	51 (12.2)	28 (6.7)	13 (3.1)
Confirmed by reading center, 24 months	37 (8.8)	23 (5.5)	11 (2.6)

At the time of investigator-reported eAMD, 100% of patients had available SD-OCT and 82% had available FA for reading center evaluation

FDA Approved in February 2023

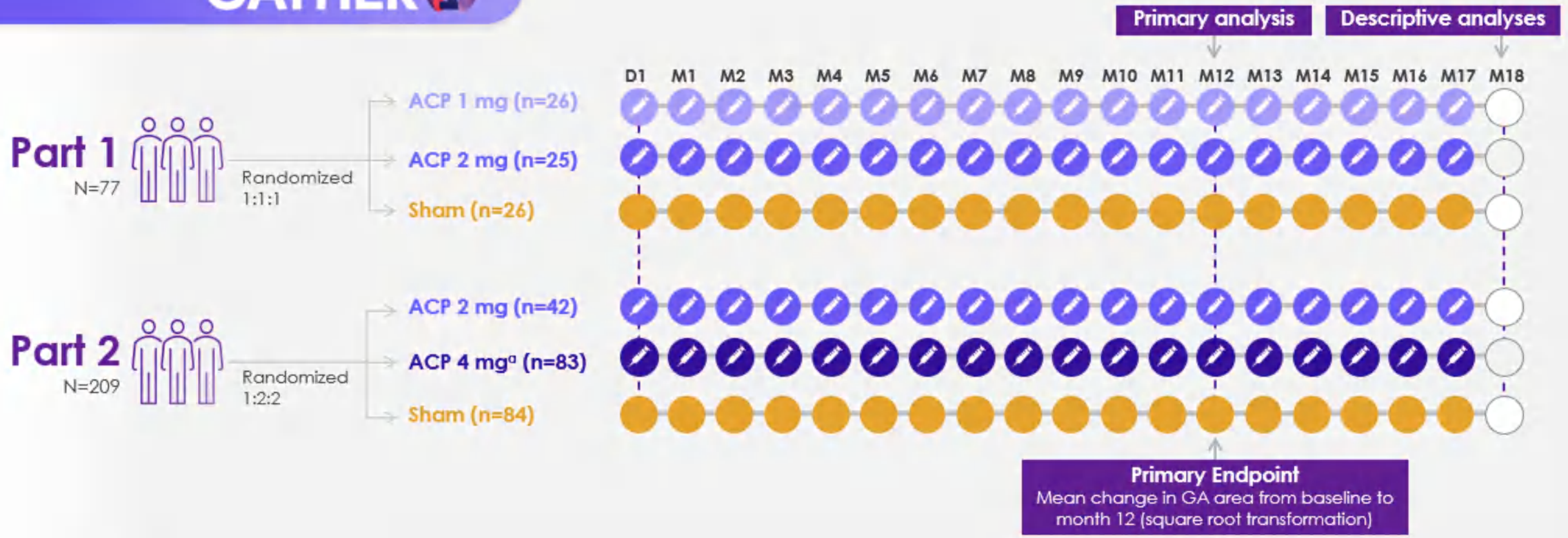
- The vast majority of CNV lesions that developed were occult lesions
- Patients who developed eAMD continued treatment with study drug and received on-label anti-VEGF therapy at the discretion of the investigator
- No patients in the pegcetacoplan study arms discontinued the studies due to eAMD

Avacincaptad Pegol Is a Pegylated RNA Apatamer Designed to be a Specific Inhibitor of Complement C5



GATHER1 – A phase 2/3, international, prospective, randomized, double-masked, sham-controlled study

GATHER1



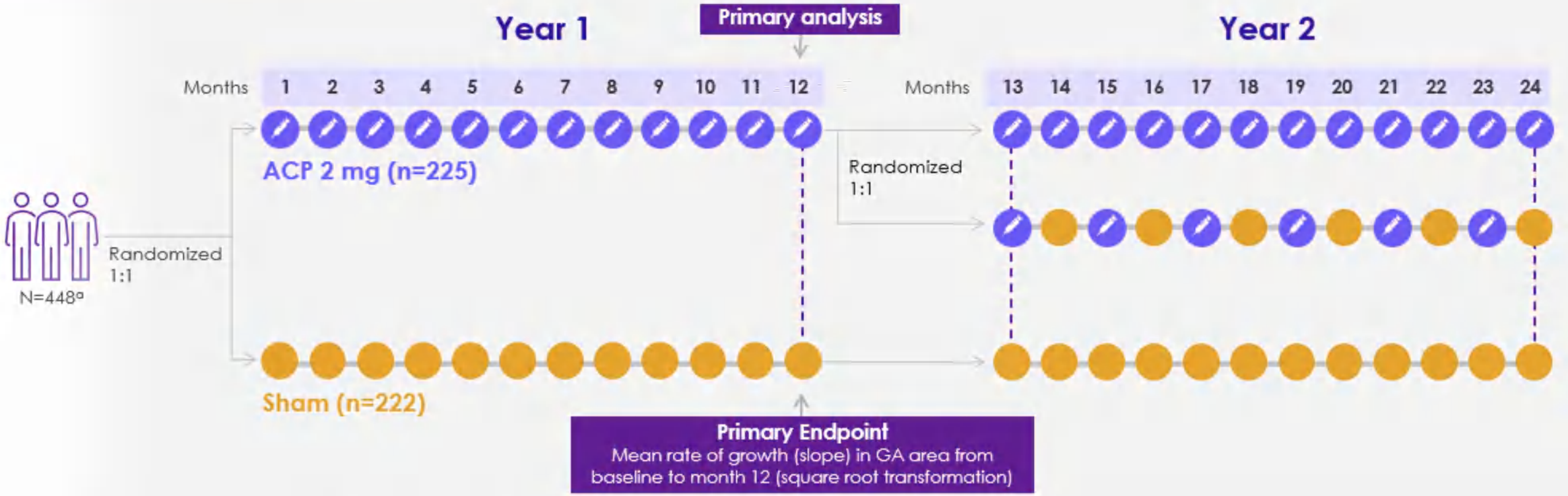
[a]2 injections of 2 mg per eye.

ACP, avacincaptad pegol; D, day; FAF, fundus autofluorescence; GA, geographic atrophy; M, month

1. Jaffe GJ, et al. Ophthalmology. 2021;128:576-586; **2.** Data on file. IVERIC Bio. **3.** Zimura in Subjects With Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration. ClinicalTrials.gov Identifier: NCT02686658. Updated March 21, 2022. https://clinicaltrials.gov/ct2/show/study/NCT02686658

GATHER2 – A phase 3, international, multicenter, prospective, randomized, double-masked, sham-controlled study

GATHER 2



[a]448 randomized, with 447 treated (one patient in sham not receiving treatment after randomization).
ACP, avacincaptad pegol; GA, geographic atrophy.

1. Khanani AM, et al. Presented at: AAO; September 30-October 3, 2022. **2.** A Phase 3 Safety and Efficacy Study of Intravitreal Administration of Zimura (Complement C5 Inhibitor). ClinicalTrials.gov Identifier: NCT04435366. Updated September 28, 2022. https://clinicaltrials.gov/ct2/show/NCT0443

Key Inclusion and Exclusion Criteria

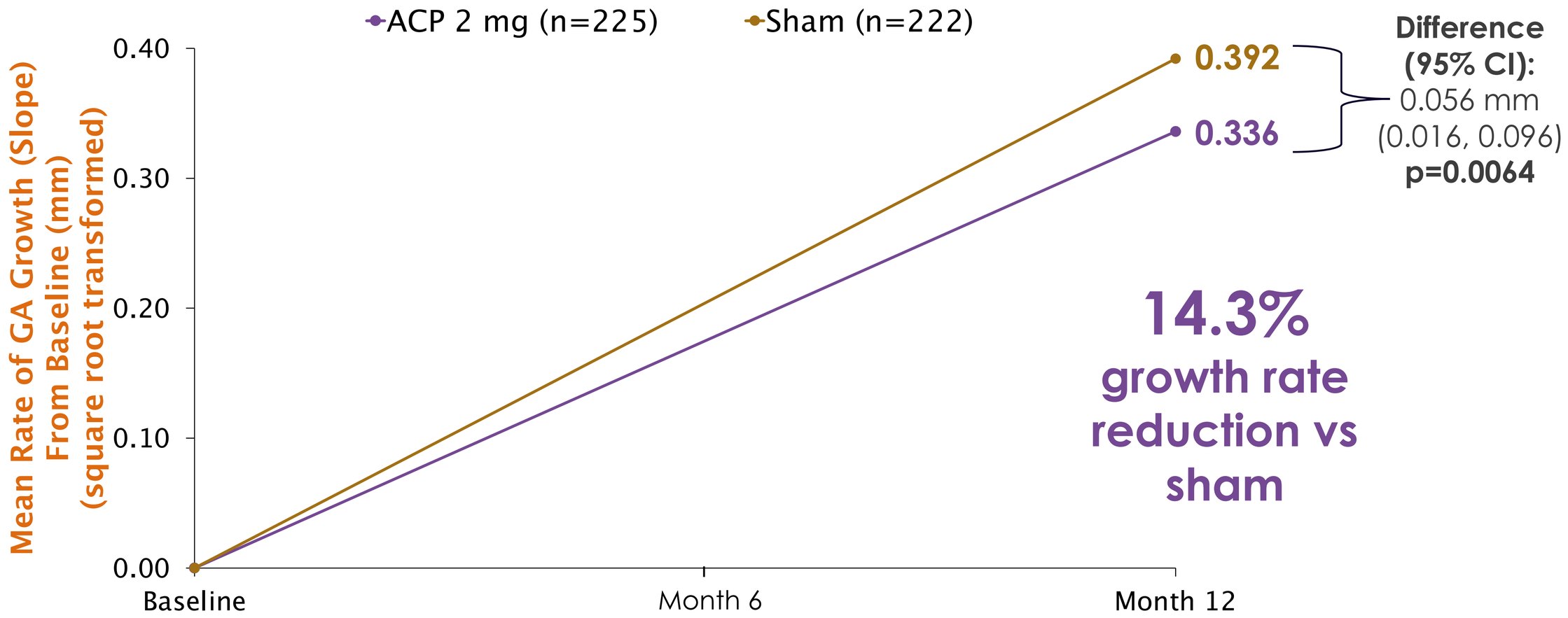
Inclusion Criteria

- Age ≥50 years
- BCVA between 20/25 and 20/320
- GA lesion:
  - Non-center point involving
  - GA in part within 1500 µm from the foveal center
  - Total area between 2.5 mm^2 and 17.5 mm^2 (1 – 7 DA, respectively)
  - If multifocal lesions, at least 1 lesion had to be ≥1.25 mm^2 (0.5 DA)

Exclusion Criteria

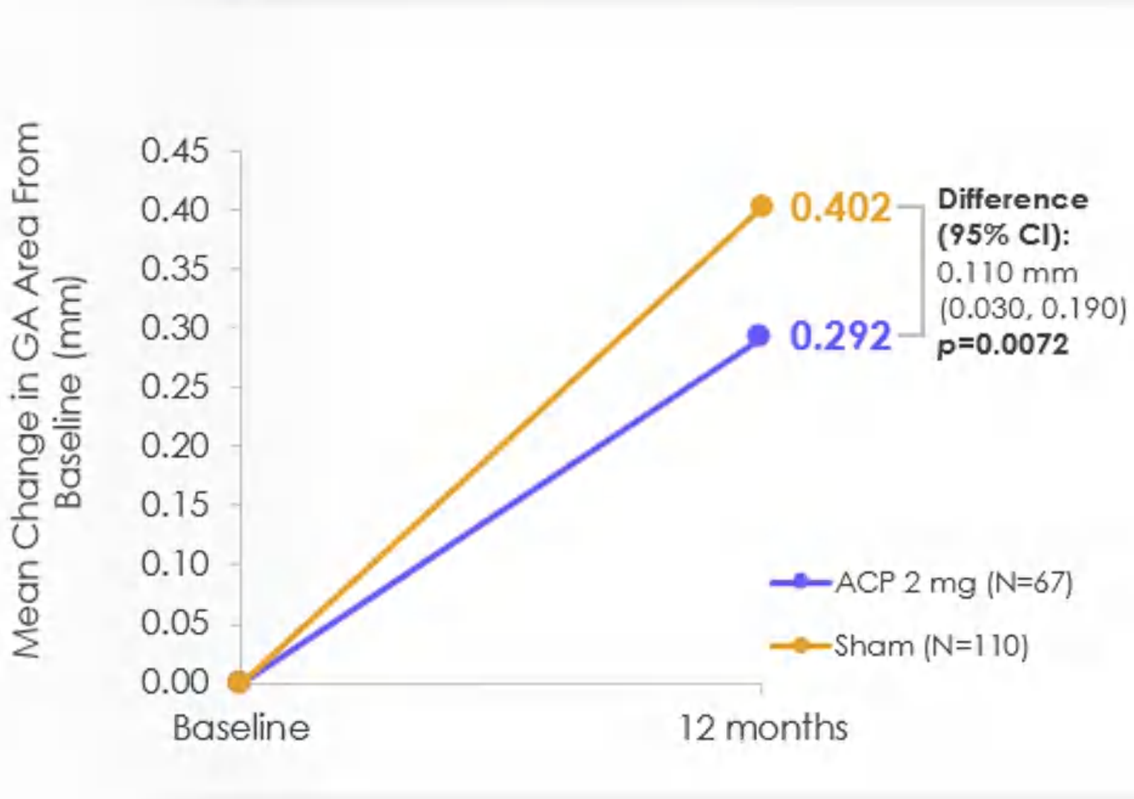
- Evidence of CNV in either eye at baseline
- GA secondary to any condition other than AMD in either eye
- Any prior treatment for AMD or any prior intravitreal treatment for any indication in either eye (except oral vitamin or mineral supplements)
- Any ocular condition in study eye that could progress during the study and potentially affect central vision or otherwise act as a confounding factor
- Any sign of diabetic retinopathy in either eye

GATHER 2: Primary Endpoint (Slope Analysis)

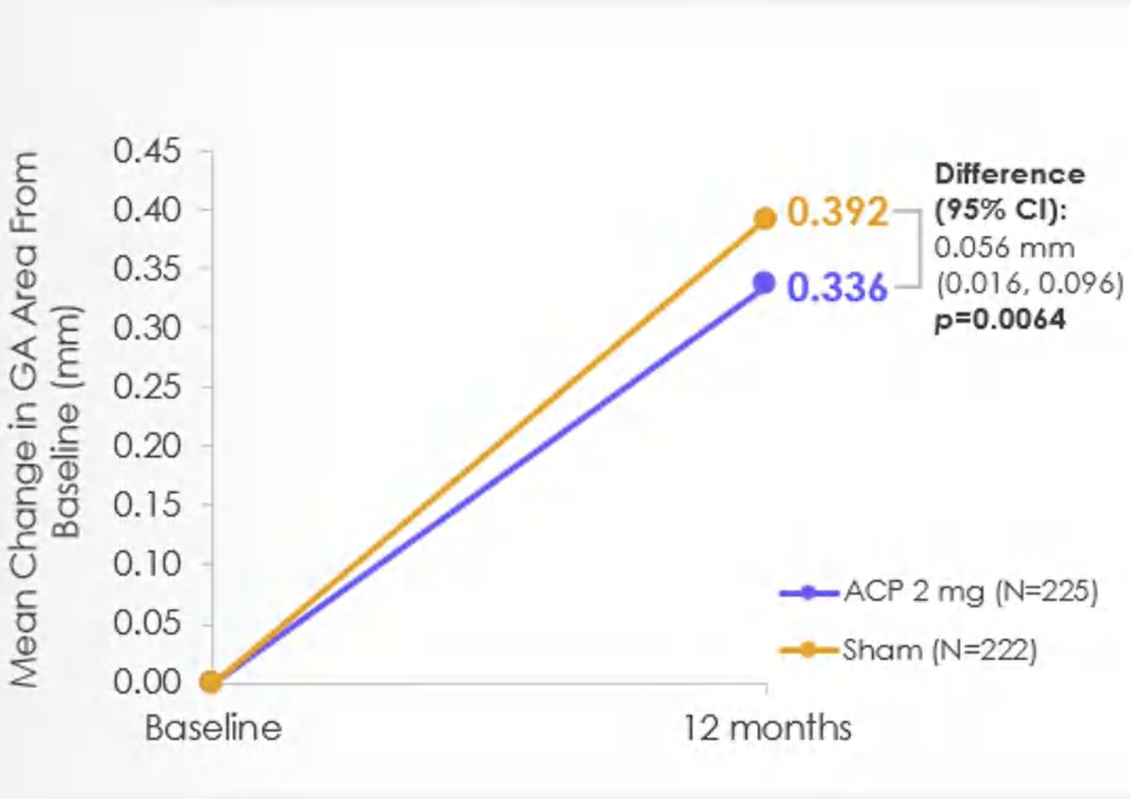


GATHER 1/2 Met the Primary Endpoint

GATHER 1



GATHER 2



GATHER1: Benefit of ACP Increases With Duration of Therapy Over 18 Months

MEAN RATE OF GROWTH IN GA AREA AS MEASURED BY SQUARE ROOT TRANSFORMATION OVER 18 MONTHS

Avacincaptad 2 mg vs sham

Based on LSMEANS from MRM model; ITT population Hochberg procedure was used for significance testing; prespecified and descriptive analysis. These least squares means are estimates of the MRM model, drawing on all available data, including data from groups with different randomization ratios in Part 1 and Part 2, and should not be interpreted as directly observed data. *18-month P values are descriptive in nature.

GATHER 1/2: Treatment-Emergent Adverse Events

	GATHER 2 12 months[1]		GATHER 1 12 months[1,2,a]	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
TEAEs, n (%)	**178 (79.1)**	**157 (70.7)**	**50 (74.6)**	**77 (70.0)**
Ocular in study eye	110 (48.9)	83 (37.4)	35 (52.2)	38 (34.5)
Non-ocular	125 (55.6)	127 (57.2)	39 (58.2)	60 (54.5)
Serious TEAEs, n (%)	**30 (13.3)**	**37 (16.7)**	**7 (10.4)**	**20 (18.2)**
Ocular in study eye	2 (0.9)	2 (0.9)	0	0
Non-ocular	29 (12.9)	35 (15.8)	7 (10.4)	20 (18.2)
TEAEs leading to study drug discontinuation, n (%)	**6 (2.7)**	**2 (0.9)**	**0**	**1 (0.9)**
Ocular in study eye	2 (0.9)	0	0	0
Non-ocular	4 (1.8)	2 (0.9)	0	1 (0.9)

Ocular TEAEs ≥2% in Study Eye

Ocular TEAEs, n (%)	GATHER2 12 months[1]		GATHER1 12 months[1,2,a]	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Conjunctival hemorrhage	27 (12.0)	17 (7.7)	10 (14.9)	13 (11.8)
Punctate keratitis	11 (4.9)	14 (6.3)	4 (6.0)	8 (7.3)
Conjunctival hyperemia	12 (5.3)	13 (5.9)	3 (4.5)	4 (3.6)
Choroidal neovascularization	**15 (6.7)**	**9 (4.1)**	**6 (9.0)**	**3 (2.7)**
Dry eye	8 (3.6)	8 (3.6)	0	2 (1.8)
Eye pain	9 (4.0)	6 (2.7)	2 (3.0)	3 (2.7)
Vitreous detachment	7 (3.1)	6 (2.7)	2 (3.0)	5 (4.5)
Visual acuity reduced	3 (1.3)	5 (2.3)	2 (3.0)	4 (3.6)
Vision blurred	6 (2.7)	2 (0.9)	1 (1.5)	2 (1.8)
Visual impairment	6 (2.7)	2 (0.9)	0	0
Intraocular pressure increased	**21 (9.3)**	**2 (0.9)**	**4 (6.0)**	**1 (0.9)**
Vitreous floaters	6 (2.7)	1 (0.5)	1 (1.5)	1 (0.9)
Visual acuity reduced transiently	6 (2.7)	1 (0.5)	---	---
Blepharitis	6 (2.7)	0	0	1 (0.9)
Ocular hypertension	5 (2.2)	0	---	---

Exudative MNV in the Study Eye

	GATHER2 12 months[1]		GATHER1 12 months[2,a]	
	ACP 2 mg (N=225)	Sham (N=222)	ACP 2 mg (N=67)	Sham (N=110)
Total CNV, n (%)	**15 (6.7)**	**9 (4.1)**	**6 (9.0)**	**3 (2.7)**
eMNV, n (%)	11 (4.9)	7 (3.2)	4 (6.0)	3 (2.7)
neMNV, n (%)	1 (0.4)	0	2 (3.0)	0
Peripapillary NV, n (%)	3 (1.3)	2 (0.9)	0	0

- Exudation status was read by the CORE Reading Center at Cole Eye Institute of the Cleveland Clinic
- OCT images were read to determine the number of CNV cases that were (1) macular neovascularization (MNV), versus peripapillary neovascularization and (2) exudative vs. non-exudative

The Reading Center classifies cases of MNV as exudative or non-exudative based on the following OCT criteria:

- **"eMNV"** is MNV that presents with new onset fluid in either the subretinal space or the intraretinal space
- **"neMNV"** is MNV which does not present with new onset fluid in the subretinal or intraretinal spaces. In some cases, isolated fluid may be present in the sub-RPE space. A case is considered to be neMNV when the MNV may not be visible but both a double-layer sign and sub-RPE fluid are present

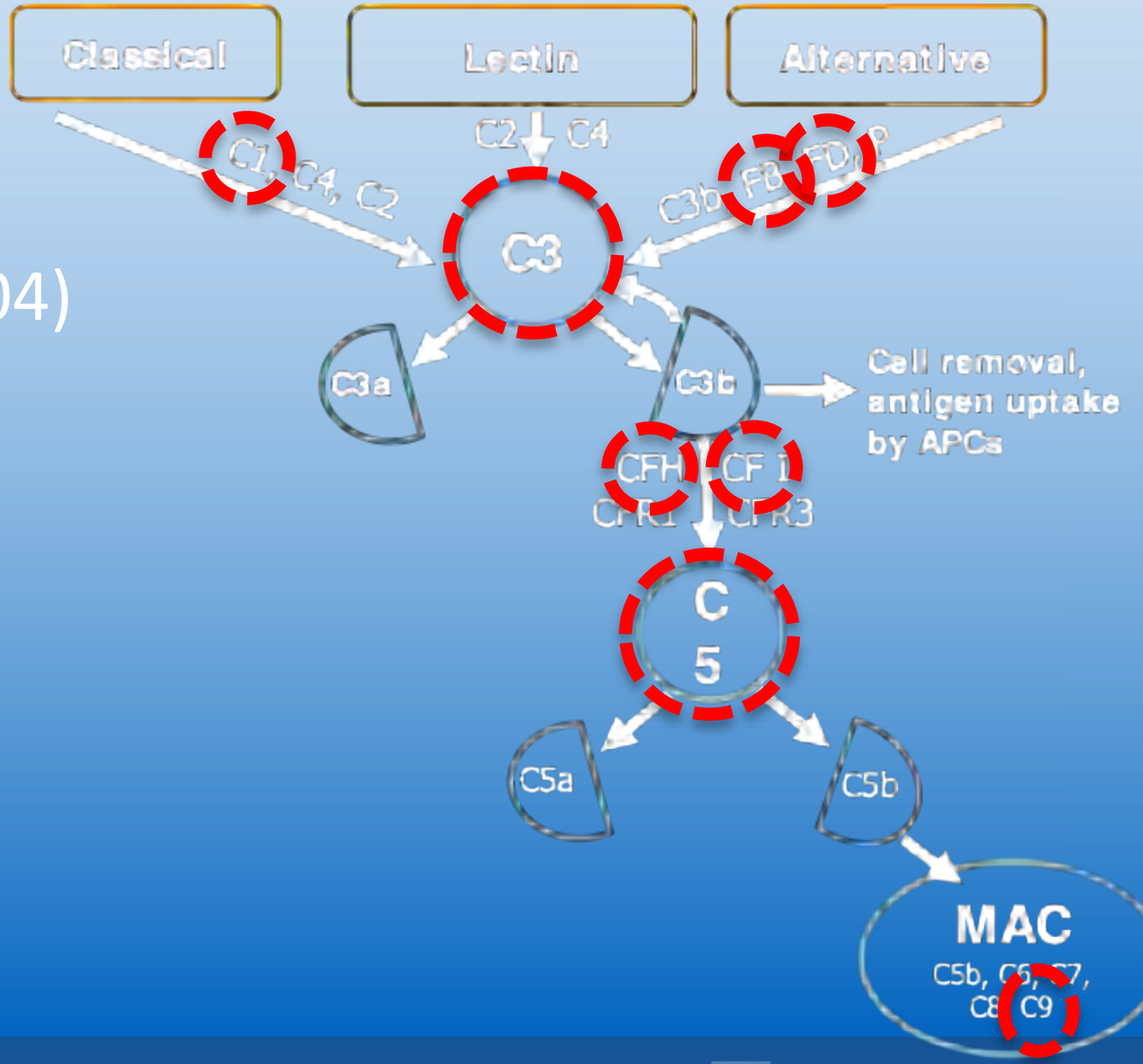
What’s Next?

Complement Therapies for GA Under Study

Down-stream
Anti-C3 (NGM621)
C3 degrader (CB 2782)
CFI (GT005 gene therapy; CB 4332; GEM 104)
CFH (GEM103)
sCD59 (JNJ1887)

Classical-specific
Anti-C1q (ANX007)

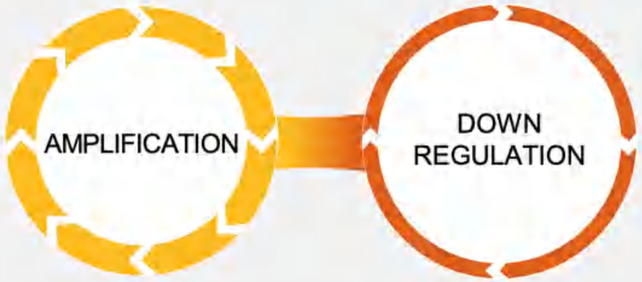
Alternative-specific
Reduce CFB (IONIS-FB-LRx)
Oral Factor D inhibitor (ALXN 2040)



Gene Therapy

One-time Gene Therapy May Offer Durable Therapeutic Effect With Single Intervention

Complement system is always 'on'

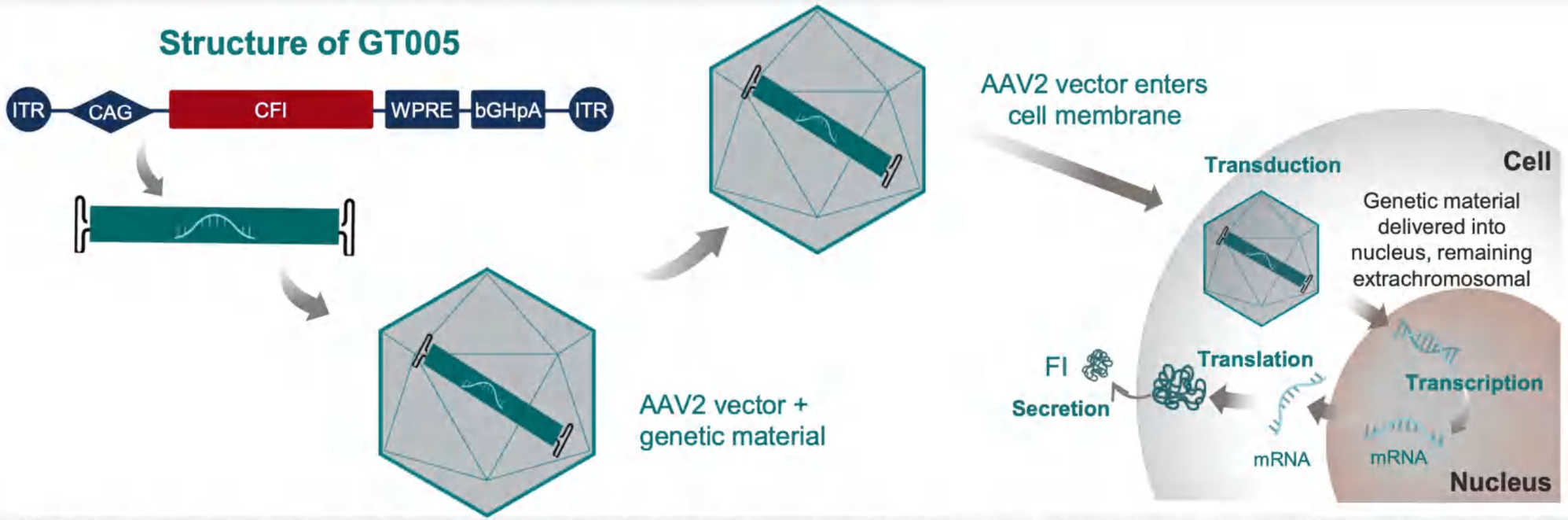


IVT therapies require repeat injections to maintain effect

Gene therapy designed to provide durable effect with single administration

GT005

GT005* Is an AAV2-Based Gene Therapy Designed to Induce Expression of FI[1,2]



*GT005 is an investigational medication being studied as a treatment for geographic atrophy. It has not been approved for use by the FDA or any health authority and its efficacy and safety profiles have not been established.

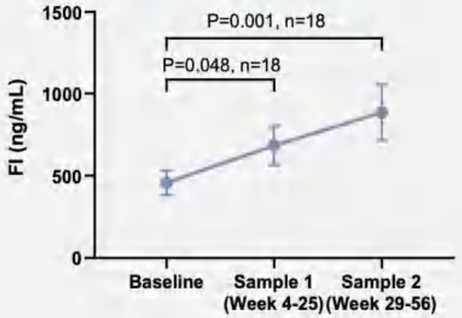
AAV=Adeno-associated virus. bGHpA=poly A signal. CAG=CAG promotor. ITR=Inverse terminal repeat. mRNA=Messenger ribonucleic acid. WPRE=Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element.

1. Goswami R, et al. *Front Oncol*. 2019;9:297. 2. Wang D, et al. *Nat Rev Drug Discov*. 2019;18:358-78.

GT005

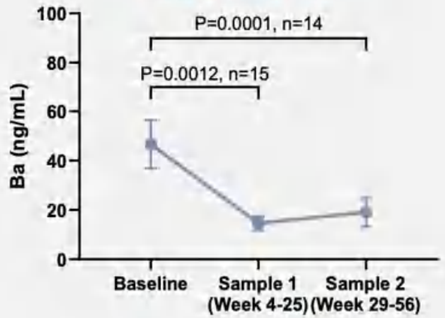
GT005 Generated Sustained Increases in Vitreous FI and Decreases in Downstream Proteins Involved in Overactivation of Complement System

Vitreous FI

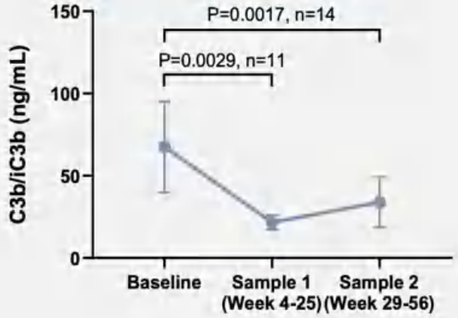


- Significant increases compared to baseline in vitreous FI post GT005

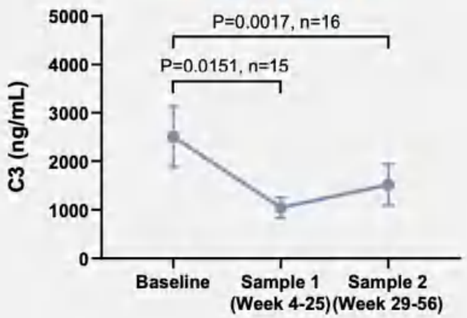
Vitreous Ba



Vitreous C3b/iC3b



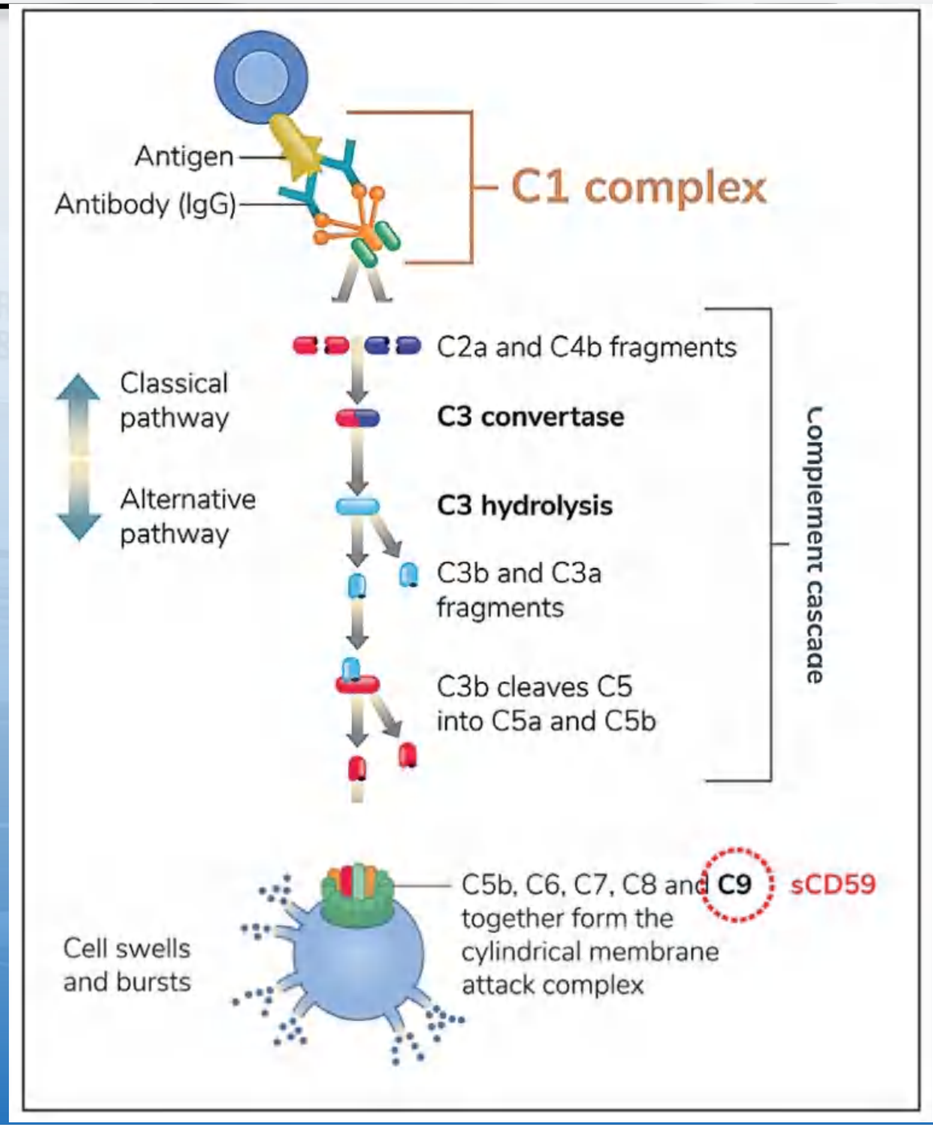
Vitreous C3



- GT005 not only impacts complement activation (Ba, C3b/iC3b) but also input of C3 to the ocular complement system
- Reduction of chronic inflammatory drive would result in an overall reduction in production of C3

Data shown as mean + SEM; Stats: Wilcoxon matched paired analysis. Data on file as of January 2022.

JNJ1887



https://www.retina-specialist.com/article/gene-therapy-in-amd-promises-and-challenges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Thank You!