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Suprachoroidal CLS-TA Plus Aflibercept Compared with Aflibercept Monotherapy for DME: *Primary and Selected Secondary Results of the Randomized Phase 2 TYBEE Trial*

Michael S. Ip, MD, Muneeswar Gupta Nittala and Swetha Velaga on behalf of the TYBEE Study Group

The Doheny Image Reading Center
Doheny Eye Institute
University of California - Los Angeles

Disclosures

- Financial Disclosures
  - Consultant: Boehringer Ingelheim, ThromboGenics, Genentech, Astellas, Allergan, Novartis, Alimera, Allegro
- Study Disclosures
  - This study includes research conducted on human subjects. Institutional Review Board approval was obtained prior to study initiation

Analyses of Phase 3 clinical trial data have indicated that even what seems to be persistent DME initially, may have good long-term results

Outcomes of Diabetic Macular Edema Eyes with Limited Early Response in the VISTA and VIVID Studies

Dante Pieramici, MD,[1] Rishi P. Singh, MD,[2] Andrea Gibson, PhD,[3] Namrata Saroj, OD,[3] Robert Vitti, MD,[3] Alyson J. Berliner, MD, PhD,[3] Oliver Zeitz, MD,[4,5] Carola Metzig, MD,[4] Yuhwen Soo, PhD,[3] Xiaoping Zhu, PhD,[3] David S. Boyer, MD[6]

Ophthalmology Retina 2018 2, 558-566DOI: (10.1016/j.oret.2017.10.014)

Original Investigation

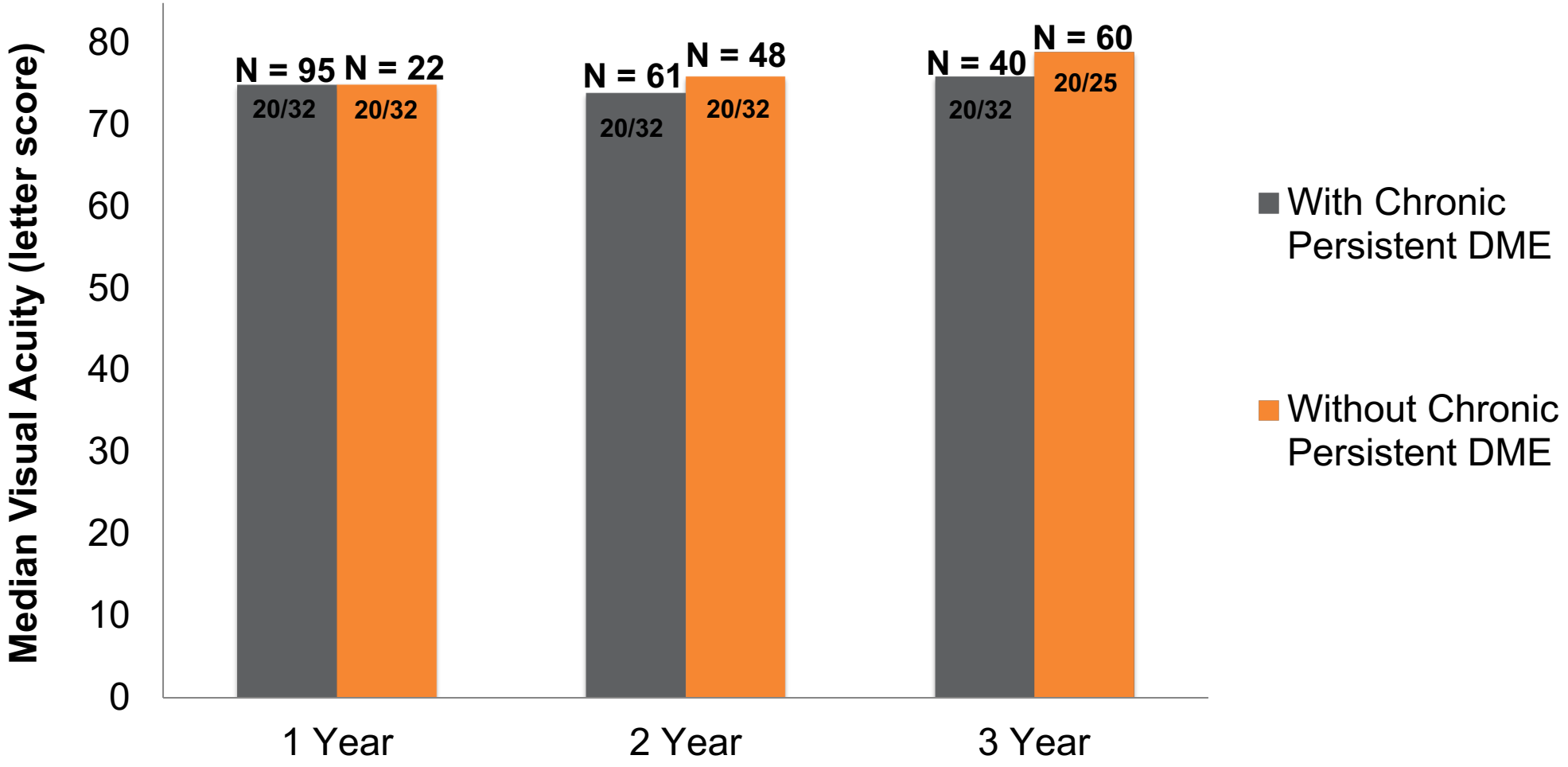
Persistent Macular Thickening After Ranibizumab Treatment for Diabetic Macular Edema With Vision Impairment

Susan B. Bressler, MD; Allison R. Ayala, MS; Neil M. Bressler, MD; Michele Melia, ScM; Haijing Qin, MS; Frederick L. Ferris III, MD; Christina J. Flaxel, MD; Scott M. Friedman, MD; Adam R. Glassman, MS; Lee M. Jampol, MD; Michael E. Rauser, MD; for the Diabetic Retinopathy Clinical Research Network

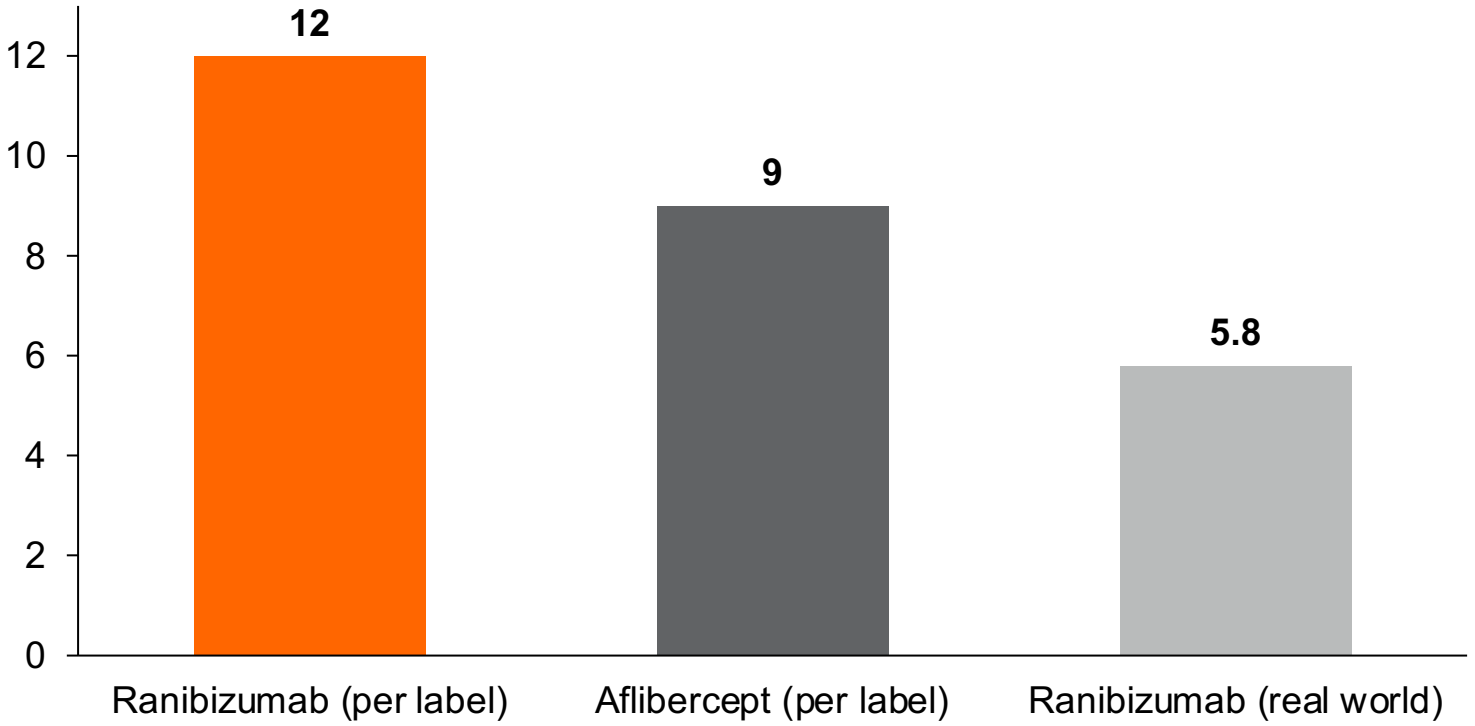
JAMA Ophthalmol. 2016;134(3):278-285.

Protocol I: Median Visual Acuity

in Persistent DME Cohort

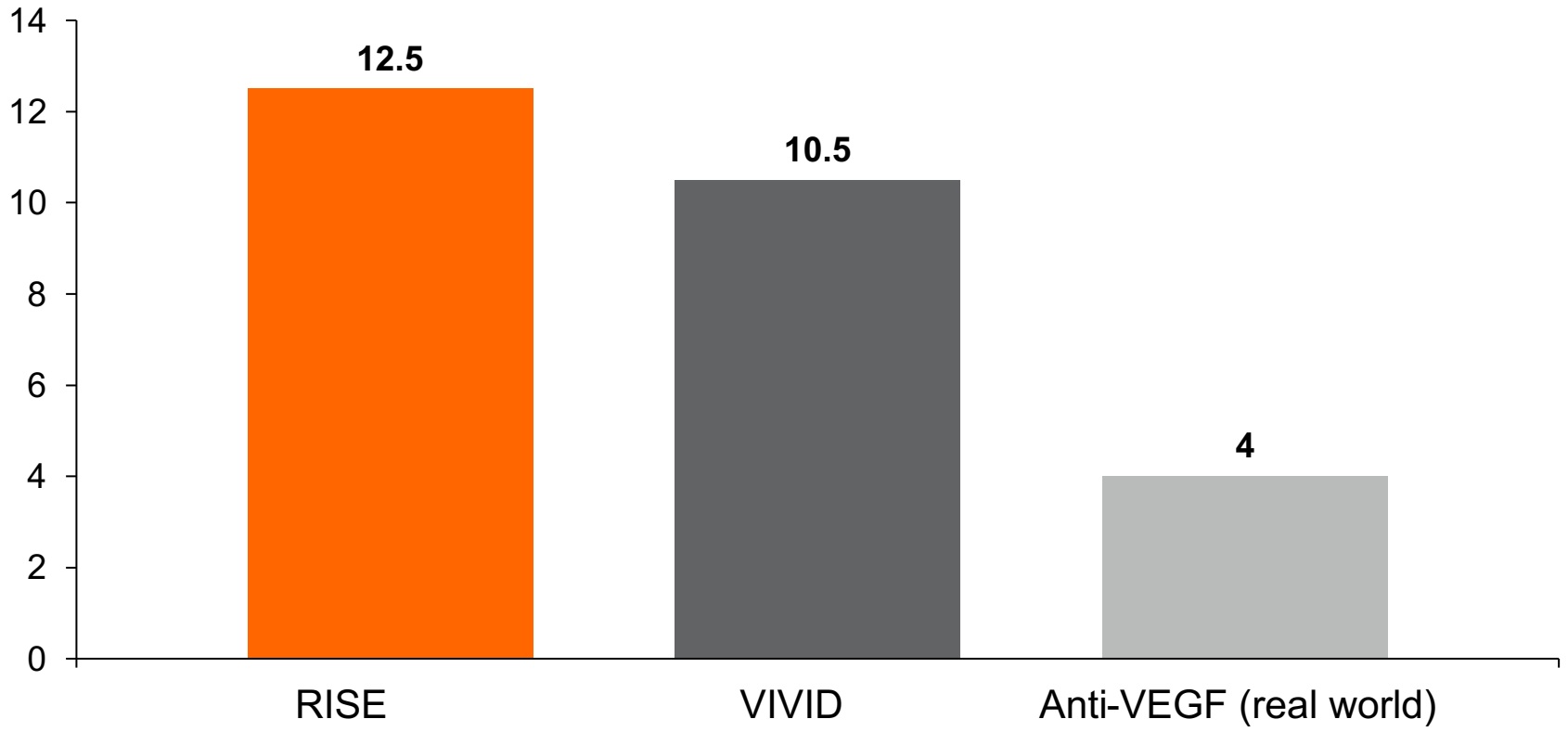


Real-world data suggests DME patients are undertreated



Ciulla et al – AAO 2019

Real-world outcomes are much worse than clinical trials in DME

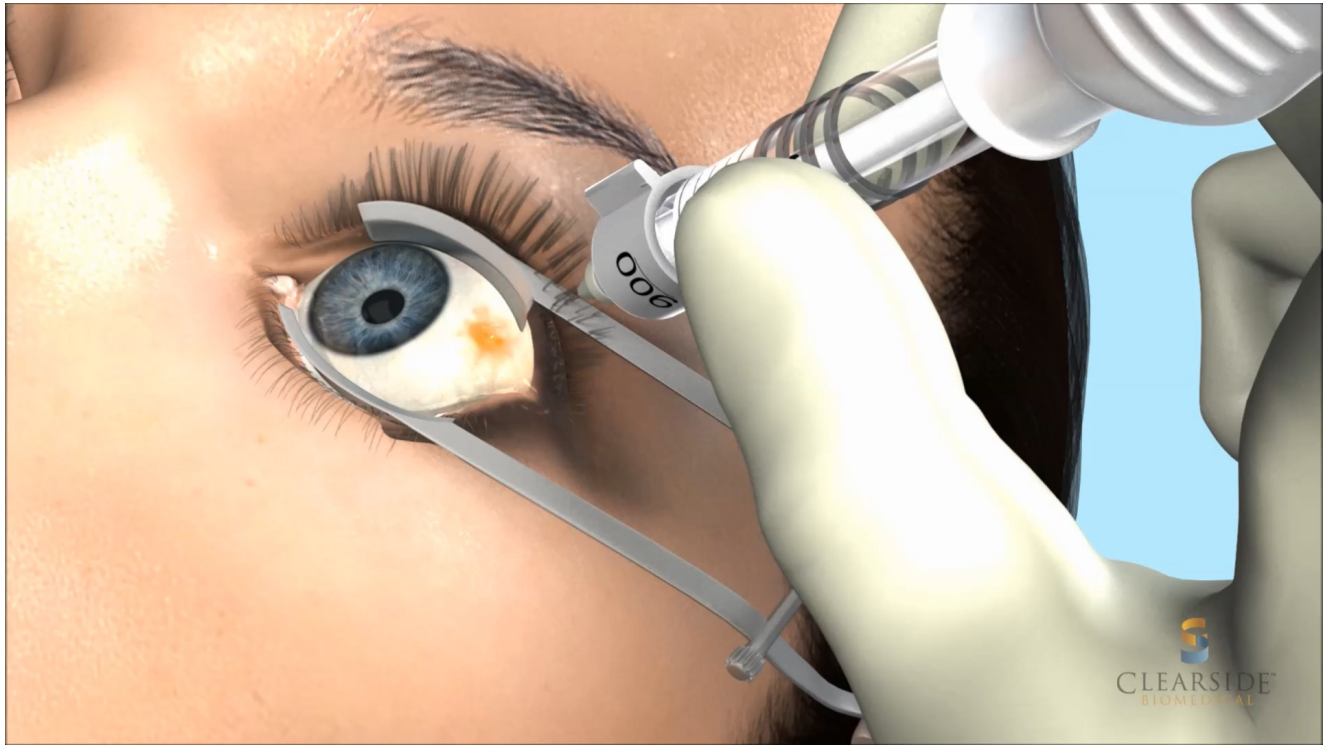


Wecker et al (BJO 2016)

SCS Microinjector

Specifically for Suprachoroidal Delivery of Preservative Free Triamcinolone Acetonide (CLS-TA)

Illustration of CLS-TA Suprachoroidal Delivery



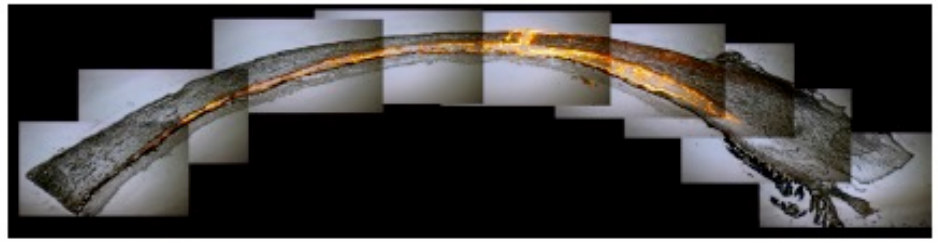
Goldstein *TVST* 2016

CLS-TA: Non-preserved, terminally sterilized, aqueous suspension of triamcinolone acetonide administered as a single injection of 4 mg in 0.1mL

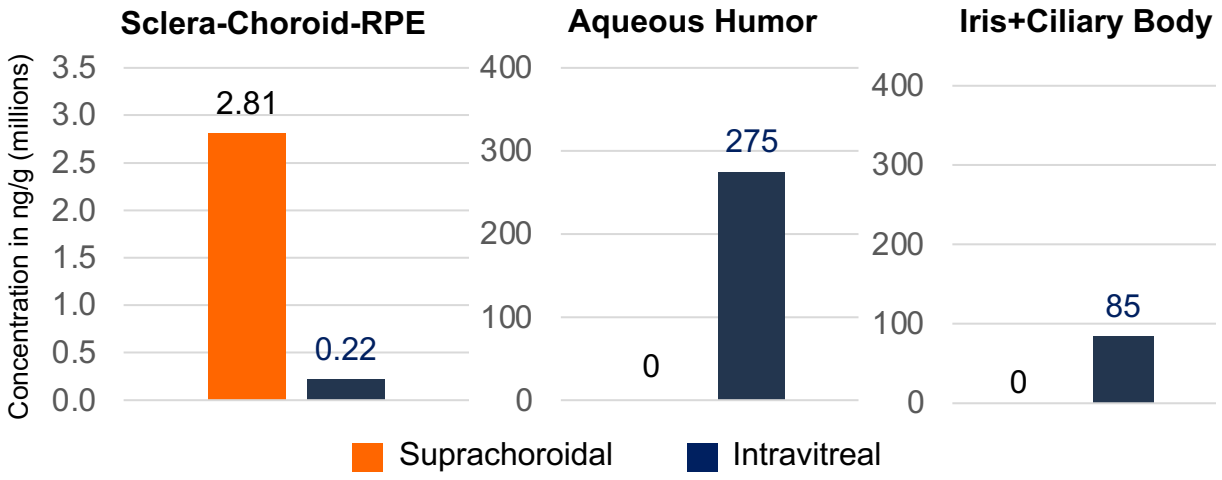
Suprachoroidal Space (SCS) Delivery of Corticosteroids

- Maximize drug levels in retina
- Minimize drug levels in AC
- Potential to:
  - Reduce cataract acceleration
  - Reduce incidence of increased IOP

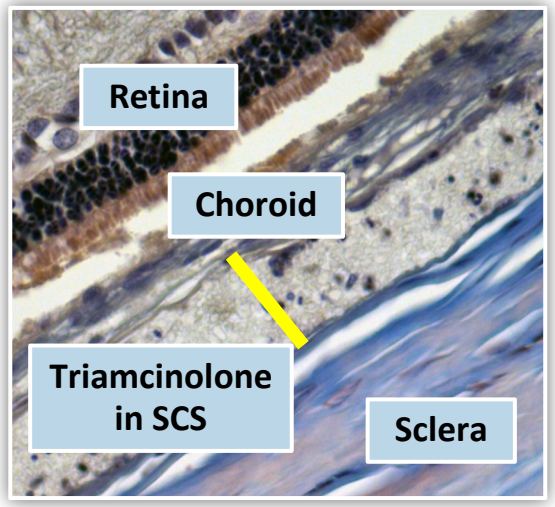
Fluorescent particles s/p SCS injection in a pig eye



Greater Posterior & Less Anterior Exposure with SCS: Rabbit Eyes (Day 14)



Triamcinolone acetonide s/p SCS injection in a rabbit eye



Olsen *AJO* 2006
Patel *IOVS* 2012
Edelhauser ARVO 2013

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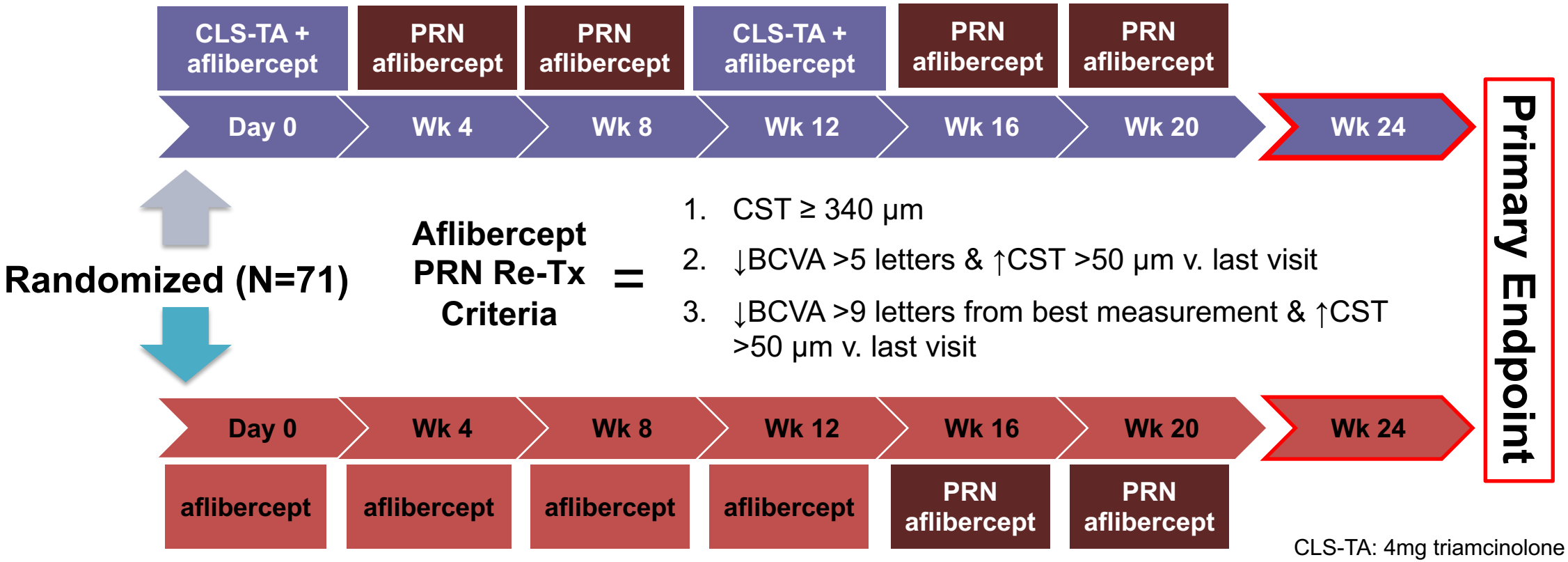
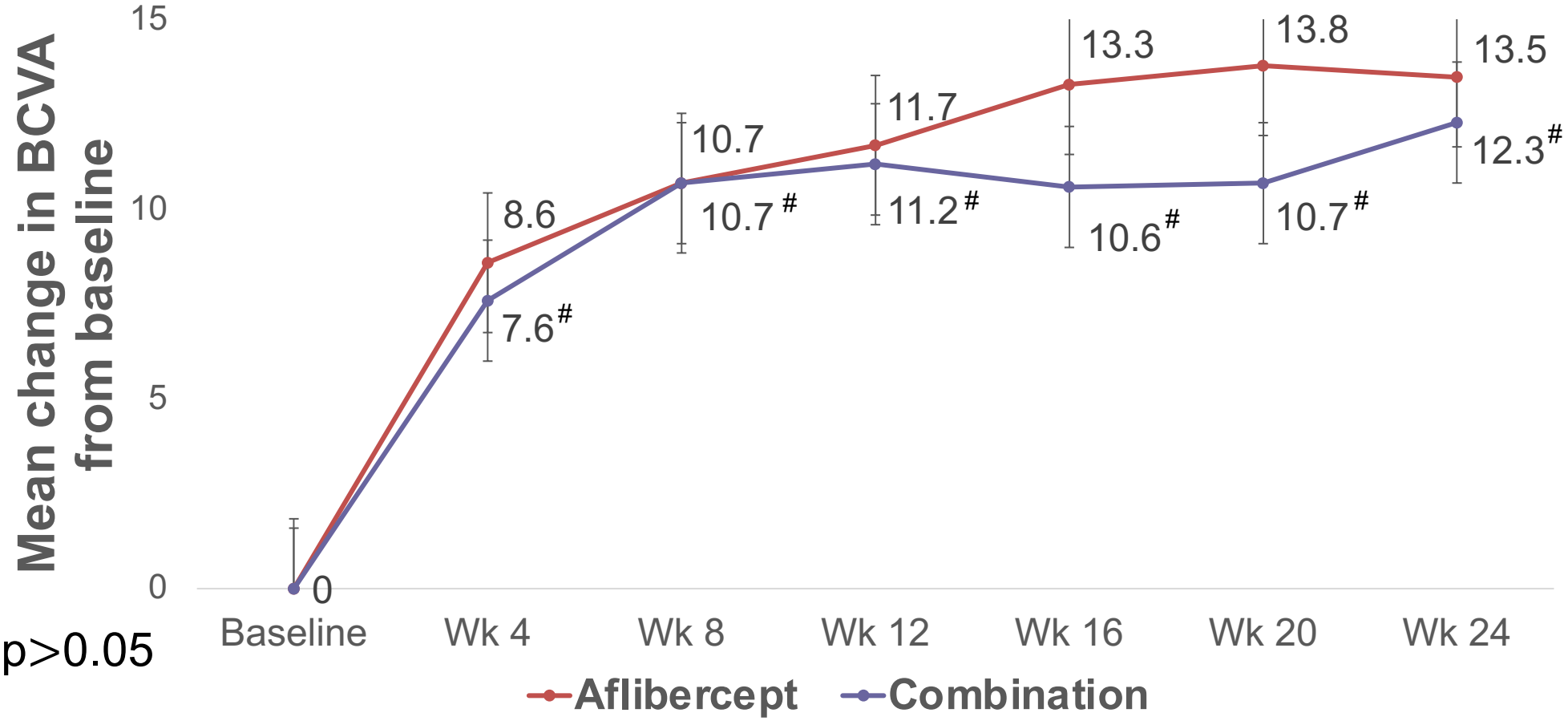
TYBEE Phase 2 Double-Masked 6-Month DME Trial



- Sham CLS-TA injections were administered to the aflibercept arm at Day 0 and Wk12.
- Sham aflibercept injections were administered to the combination arm at Wk4 and Wk8

CLS-TA: 4mg triamcinolone acetonide (0.1 mL of 40 mg/mL suspension) delivered into suprachoroidal space. Aflibercept: 2 mg/0.05 mL

Mean Change in BCVA

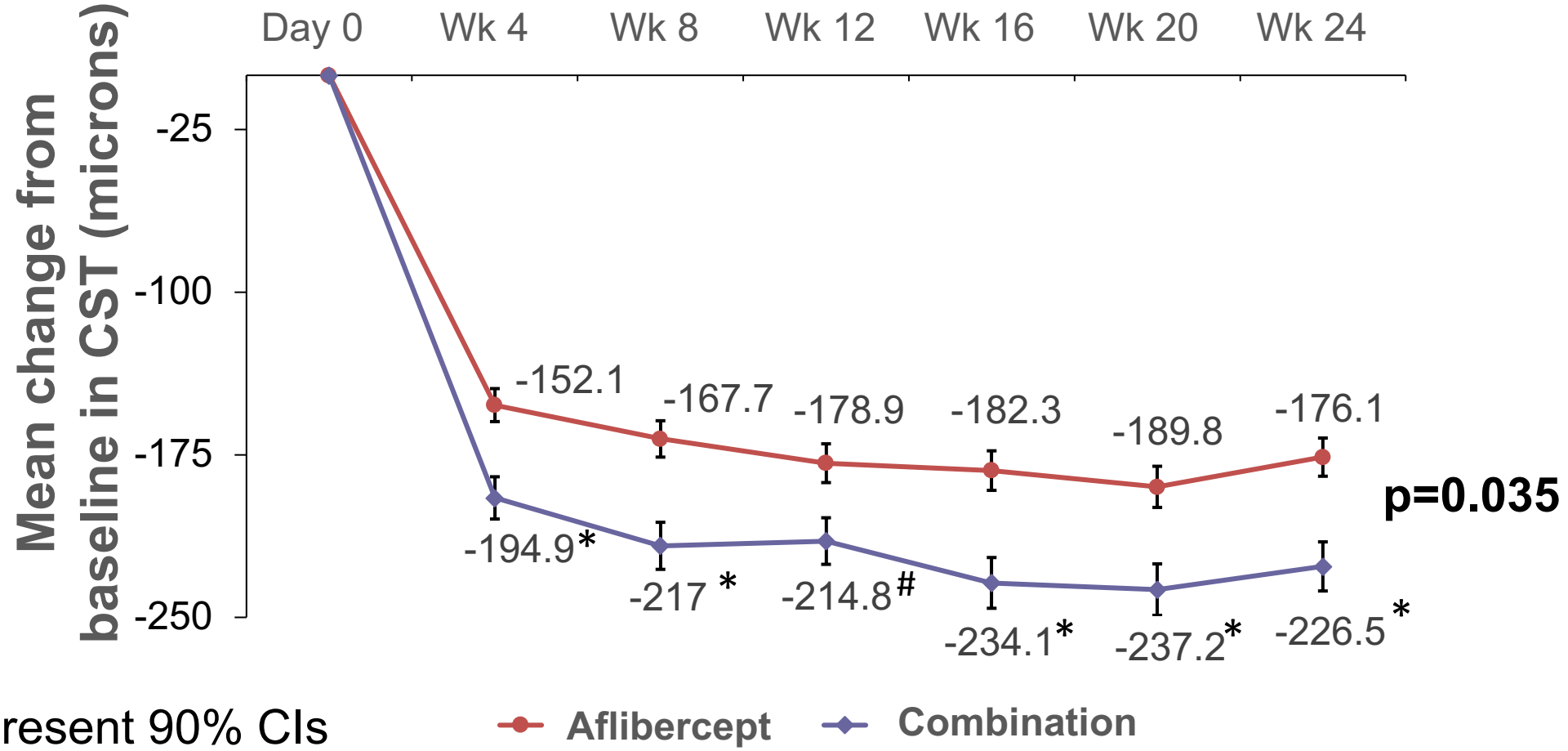


p=0.66

all p>0.05

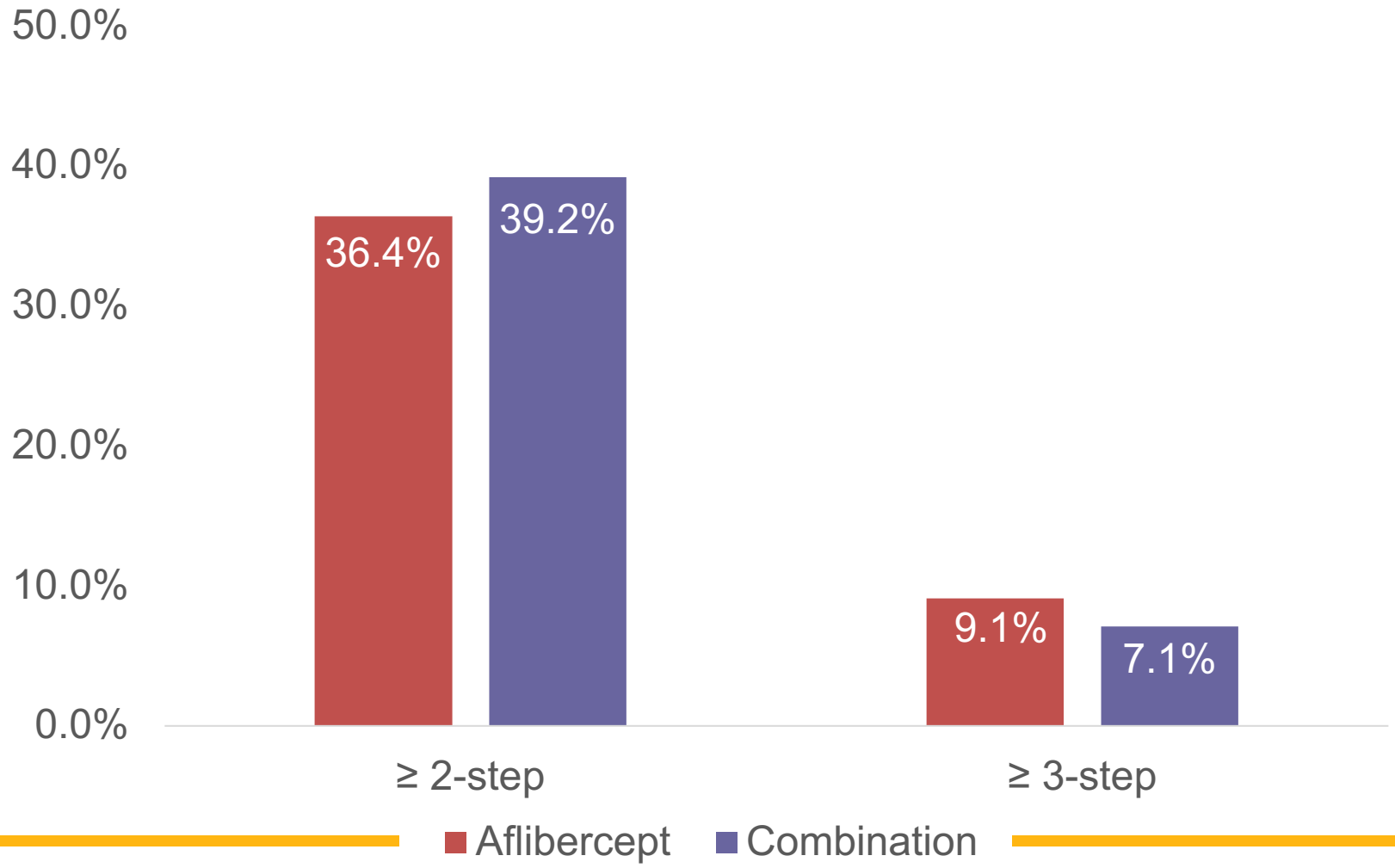
Baseline BCVA: Aflibercept: 58; Combination 56

Greater CST reduction observed with combination treatment vs. aflibercept monotherapy

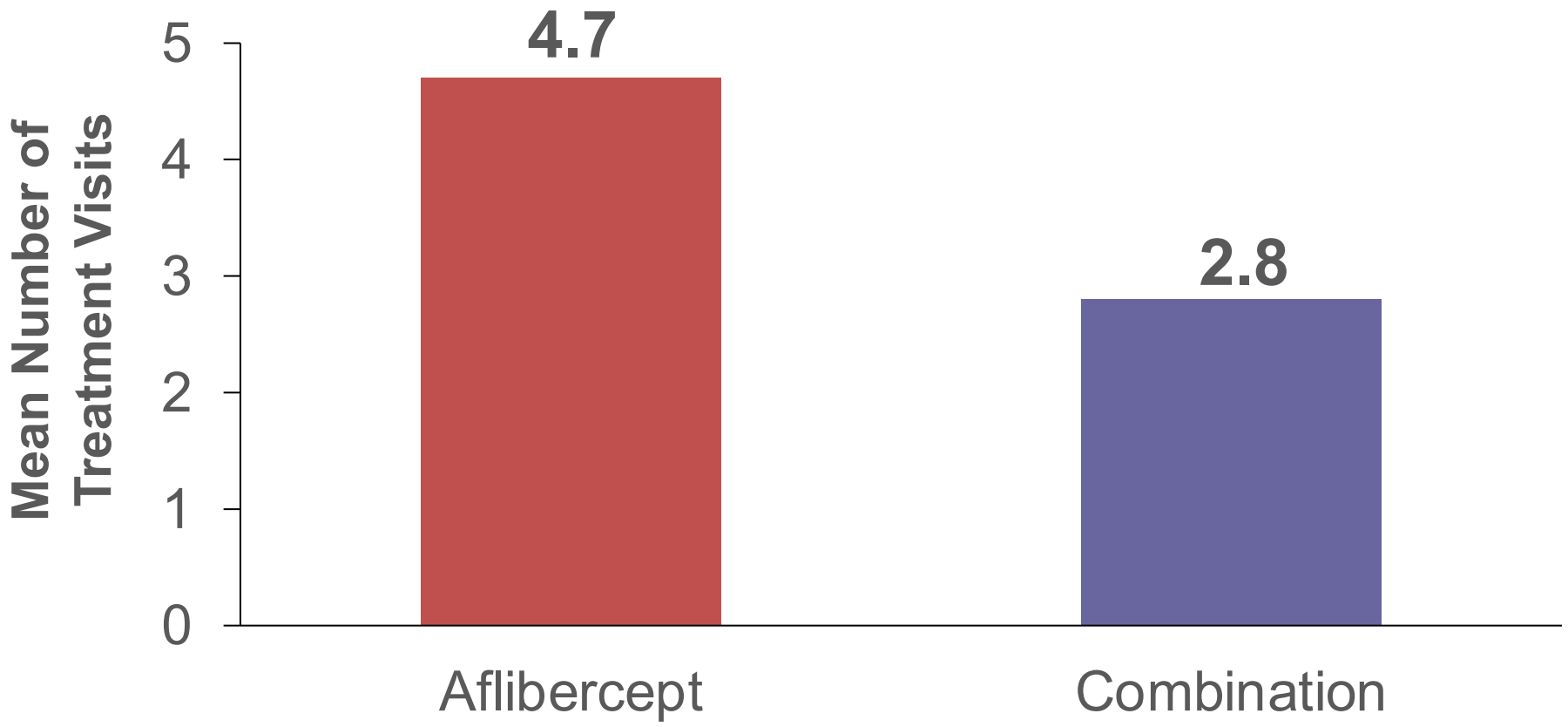


* p≤0.05
# p>0.05
Error bars represent 90% CIs

≥2- and ≥3-Step DRSS Improvements at Week 24



Combination treatment resulted in fewer treatment visits vs. aflibercept monotherapy



All Serious Adverse Events

Adverse Event Term	Aflibercept n (%)	Combination n (%)
Acute left ventricular failure	1 (2.9)	0 (0)
Acute myocardial infarction	1 (2.9)	0 (0)
Anemia	0 (0)	2 (5.6)
Cardiac arrest	0 (0)	1 (2.8)
Diabetes	0 (0)	1 (2.8)
Diabetic neuropathic ulcer	1 (2.9)	0 (0)
Fractures	0 (0)	2 (5.6)
Hepatorenal syndrome	0 (0)	1 (2.8)
Kidney disease	0 (0)	1 (2.8)
Orthostatic hypotension	0 (0)	1 (2.8)
Osteomyelitis	1 (2.9)	0 (0)
Pneumonia	0 (0)	3 (8.3)

No SAE assessed as related to study drug or study procedure in either arm

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All Ocular Adverse Events

Adverse Event Term	Aflibercept n (%)	Combination n (%)
Conjunctival hemorrhage	1 (2.9)	2 (5.6)
Cataract*	1 (2.9)	2 (5.6)
Conjunctival opacity	0	1 (2.8)
Dry eye	0	1 (2.8)
Eye irritation	0	1 (2.8)
Eye pain	1 (2.9)	0
Macular hole	0	1 (2.8)
Ocular hypertension	0	1 (2.8)
Punctate keratitis	0	1 (2.8)
Retinal detachment	0	1 (2.8)
Retinal exudates	1 (2.9)	0
Visual acuity reduced	0	1 (2.8)
Vitreous detachment	1 (2.9)	0
Vitreous floaters	1 (2.9)	0
IOP increased	1 (2.9)	3 (8.3)
Sensation of foreign body	0	1 (2.8)
Visual field defect	0	1 (2.8)

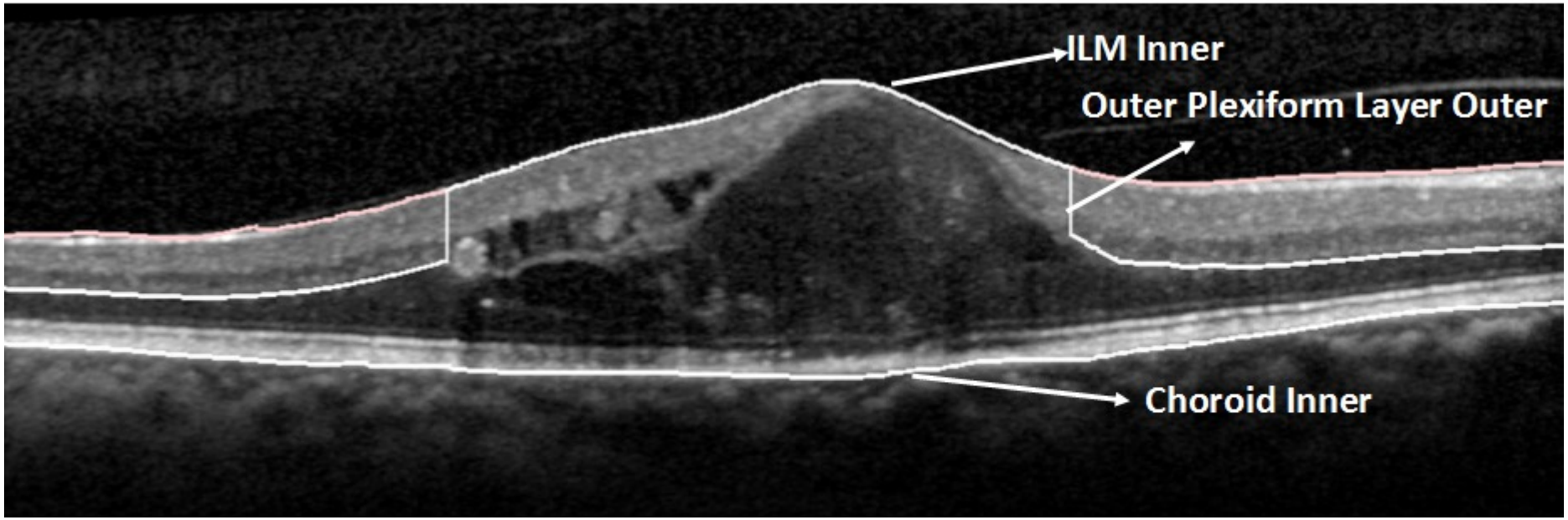
* Includes “Cataract Nuclear”

Analysis: Disorganization of the Inner Retinal layers (DRIL)

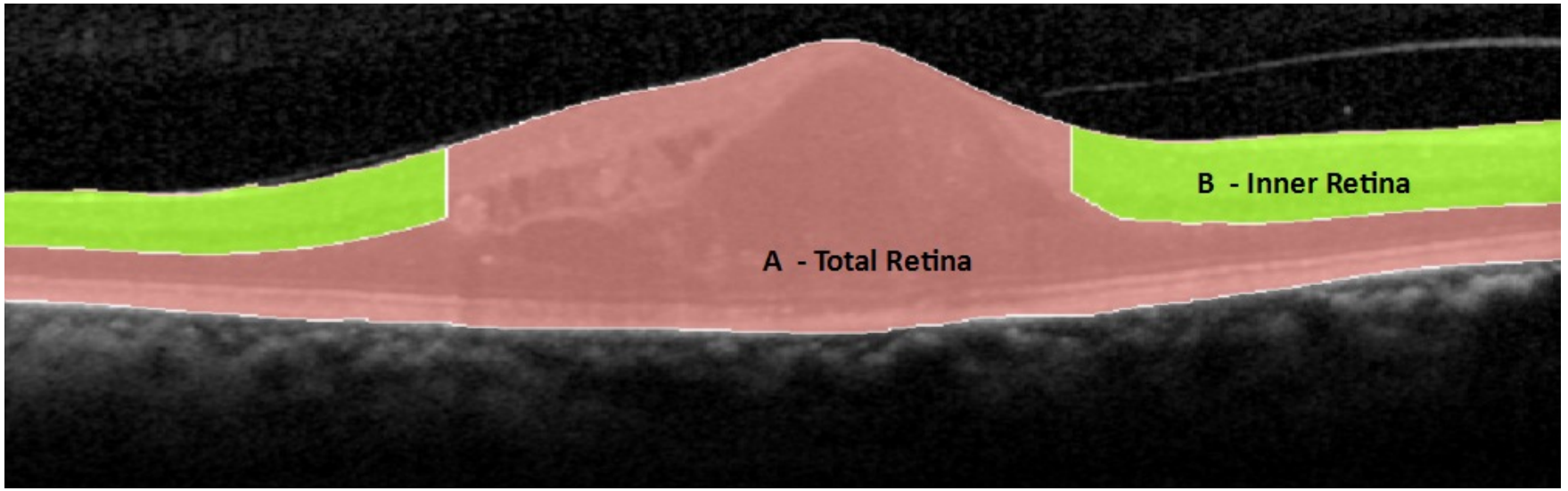
Disorganization of the inner retinal layers was defined as the horizontal extent (μm) for which 1 or more boundaries between the inner retinal layers (ganglion cell layer and inner plexiform layer complex, inner nuclear layer, and outer plexiform layer) were not separately identifiable

Spectralis OCT Case Illustration

Manual delineation of DRIL by snapping the outer plexiform layer to the inner limiting membrane in each B-scan of the macular volume.

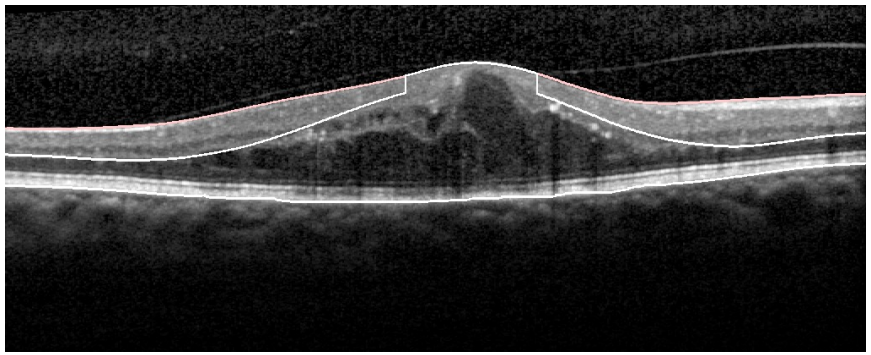


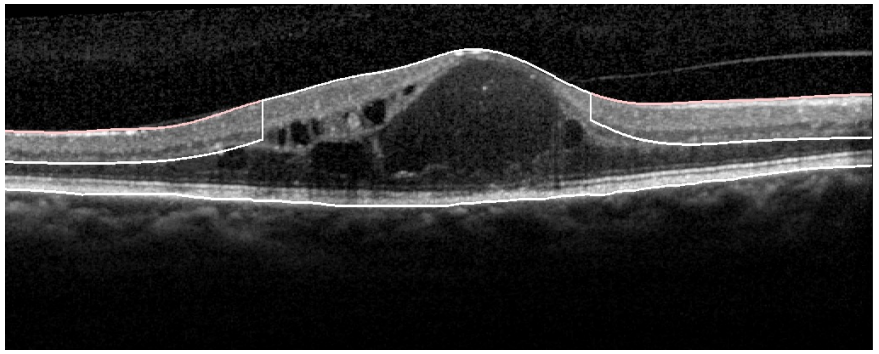
Spectralis Case Illustration

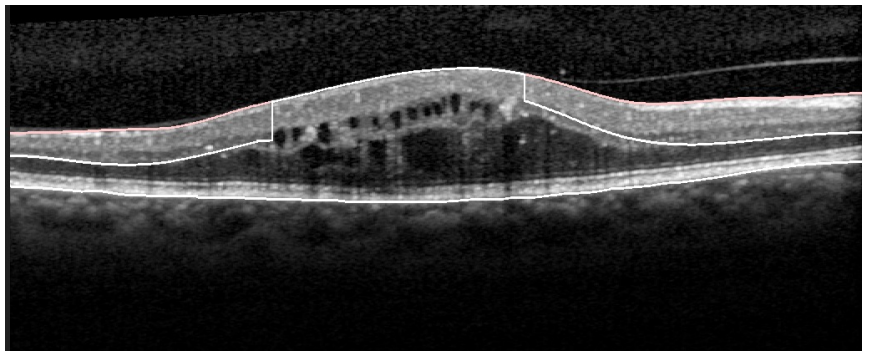


A – B = DRIL Area

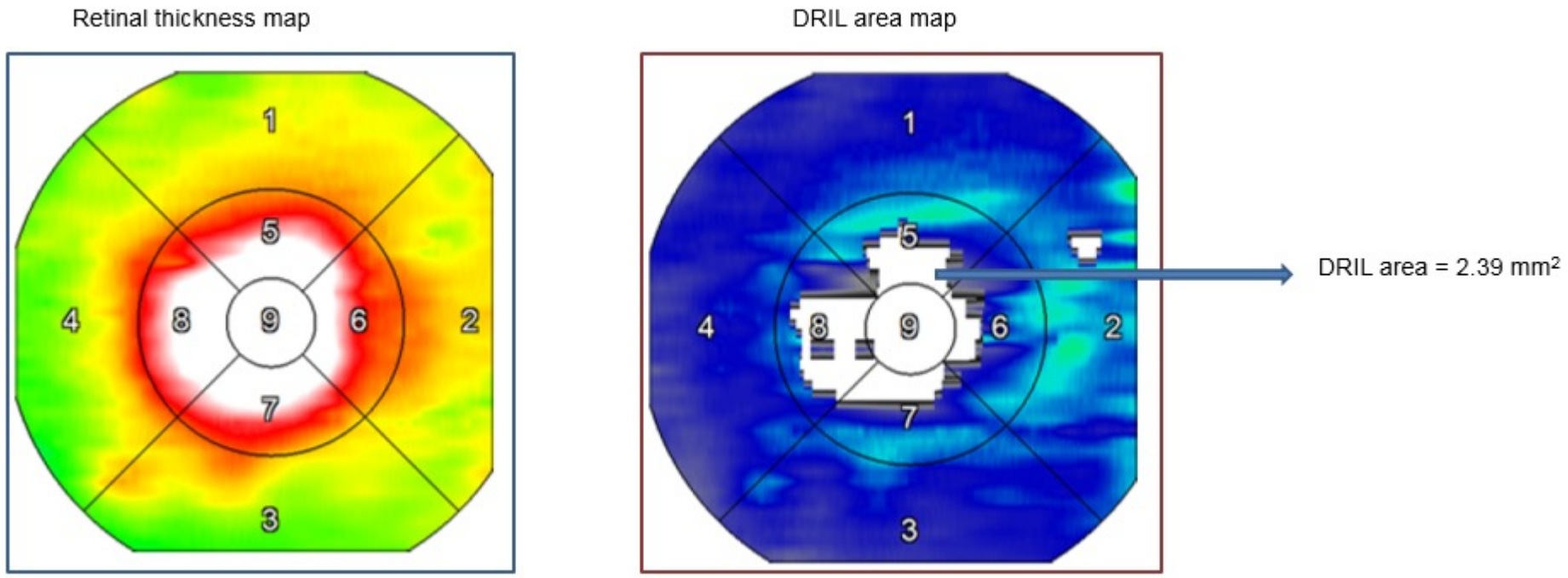
Total Retina – Inner Retina = DRIL Area





DRIL area map from volume scans



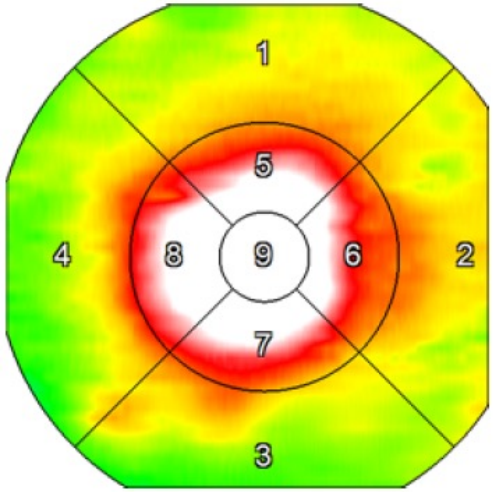
MRN: 4011-03
Patient: TYBEE, 4011-03
DateOfBirth: 1900-01-01
Gender: M
StudyDate: 2017-09-14 19:48:59
Author: swetha

OD

Protocol: Volume
ReportDate: 2019-03-21 12:36:17
AnnotationLastChangeDate: 1600-12-31 16:00:00
NumBScans: 49
Comment:

Retina Thickness

ILM -- Inner to Choroid -- Inner



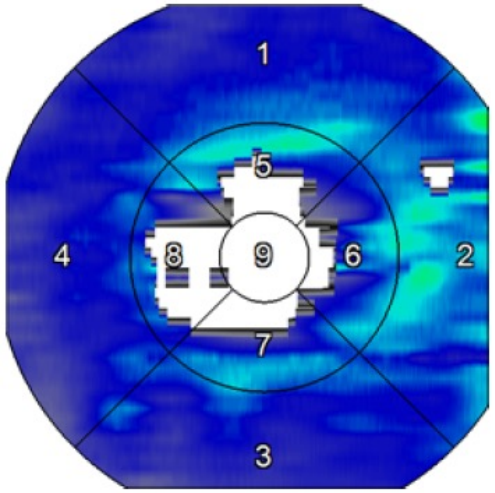
Field No.	Mean (um)	Volume (mm^3)	Mean Intensity	Area (mm^2)	Dist to Max (mm)
1	307.1	1.55	0.5078	5.05	542.53
2	316.1	1.33	0.5402	4.20	541.28
3	292.3	1.29	0.5532	4.42	541.96
4	296.0	1.53	0.4872	5.18	542.60
5	445.6	0.70	0.3986	1.58	542.33
6	419.4	0.66	0.4382	1.57	541.56
7	446.4	0.70	0.4170	1.56	541.92
8	479.7	0.75	0.3513	1.57	542.39
9	639.9	0.50	0.2746	0.78	542.10
Total Scan	338.4	9.84	0.4761	29.03	[illegible]
Very Center	700.8	0.00	0.2133	0.00	542.07

A

A – B = DRIL Area
Total Retina – Inner Retina = DRIL Area
29.03 – 26.64 = 2.39 mm2

Inner Retina Thickness

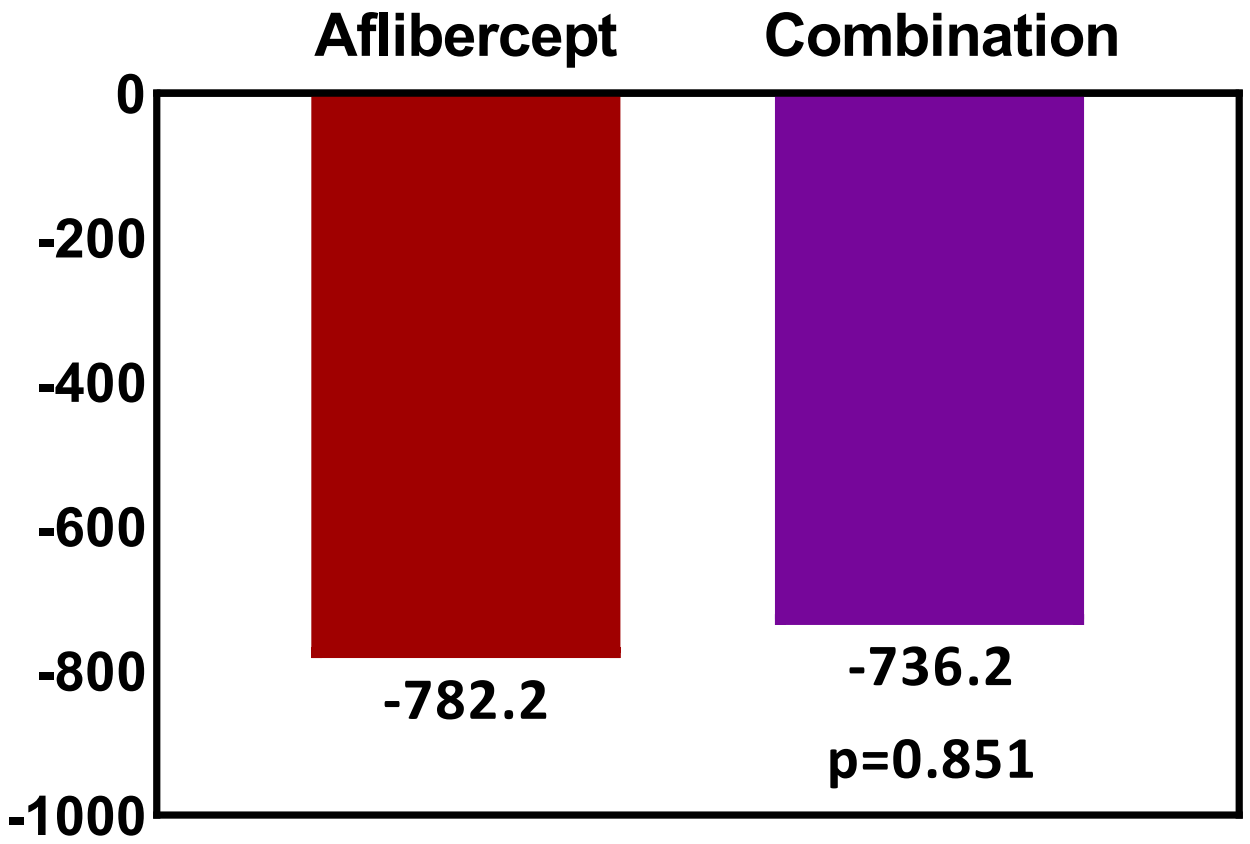
ILM -- Inner to Outer Plexiform Layer -- Outer



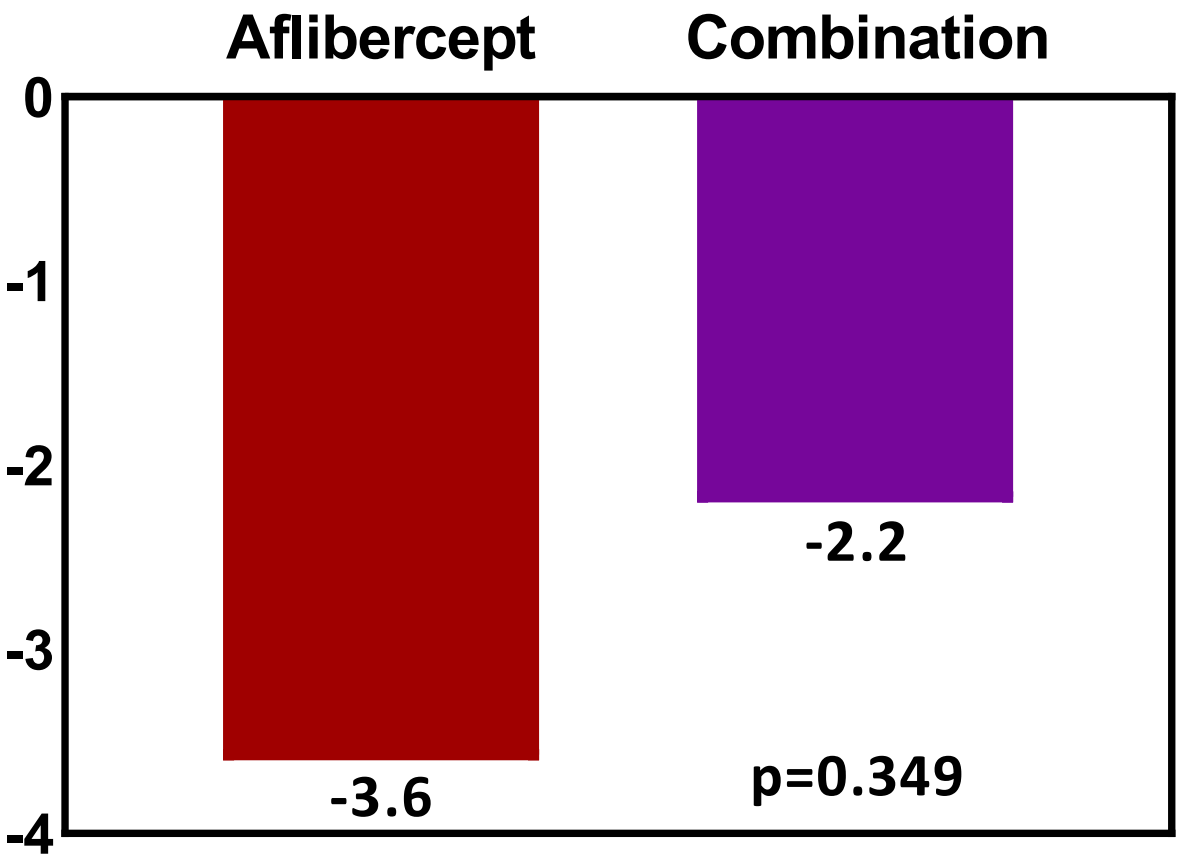
Field No.	Mean (um)	Volume (mm^3)	Mean Intensity	Area (mm^2)	Dist to Max (mm)
1	158.9	0.80	0.5395	5.05	542.60
2	177.6	0.75	0.5817	4.14	541.60
3	151.2	0.67	0.6004	4.42	541.21
4	146.9	0.76	0.5164	5.18	543.63
5	120.9	0.19	0.5217	1.17	542.85
6	138.4	0.22	0.5404	1.40	541.43
7	125.1	0.20	0.5719	1.24	541.14
8	77.4	0.12	0.4776	0.91	542.77
9	0.7	0.00	0.5372	0.01	542.18
Total Scan	142.5	4.15	0.5548	26.64	[illegible]
Very Center	0.0	0.00	NaN	0.00	542.07

B

Similar improvement in maximum extent of DRIL (μm)



Similar improvement in area of DRIL (mm^2)



TYBEE: Conclusion

- Similar BCVA improvements with combination aflibercept & suprachoroidal CLS-TA treatment vs aflibercept monotherapy.
- CST improvement was significantly greater with combination treatment vs aflibercept monotherapy.
- Other anatomic outcomes such as DRSS and changes in ***DRIL (maximum extent and area) were similar*** when comparing combination aflibercept & suprachoroidal CLS-TA treatment vs aflibercept monotherapy.
- Fewer treatments in the combination arm compared to aflibercept monotherapy: 4.7 vs 2.8 mean treatment visits.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