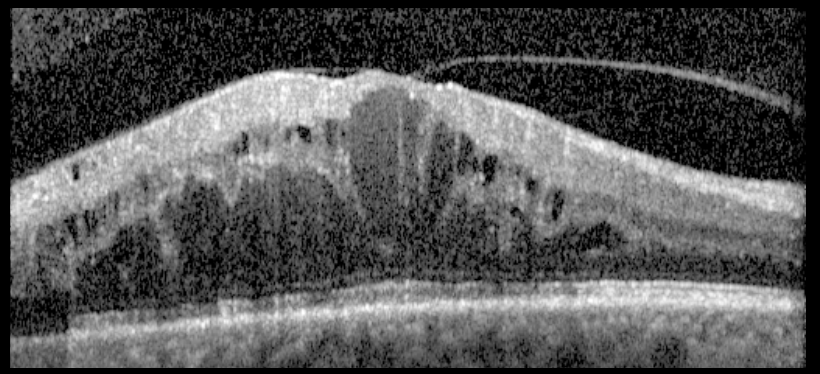
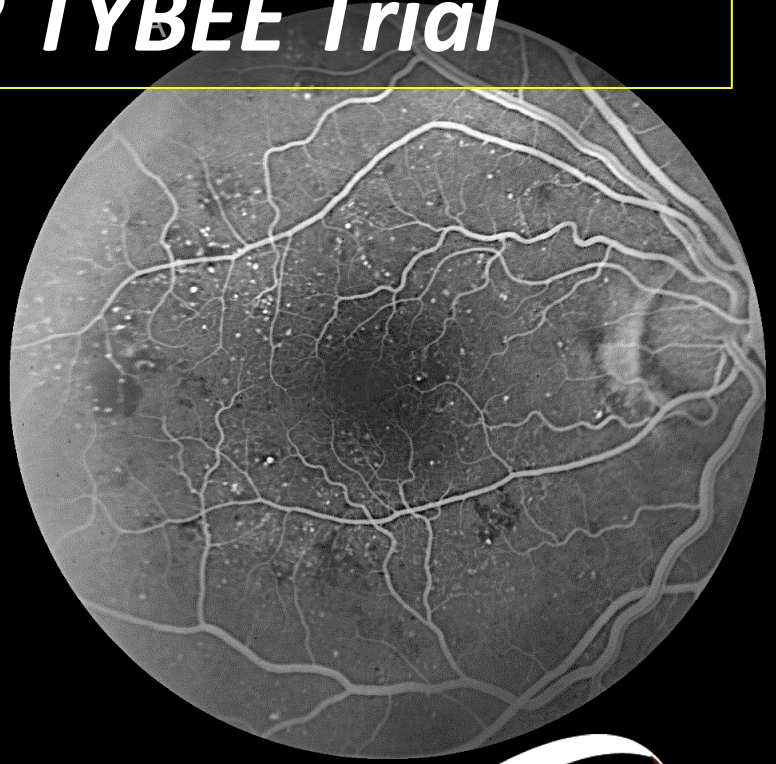
Suprachoroidal CLS-TA Plus Aflibercept Compared to Aflibercept Monotherapy for DME: *Results of the Randomized Phase 2 TYBEE Trial*





HOUSTON Methodist LEADING MEDICINE

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Retina Consultants Houston

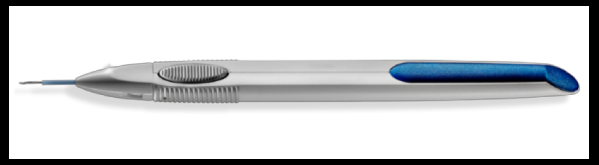
Disclosures

- Financial Disclosures
  - Adverum (C, R); Alimera Sciences (C); Allegro (C); Allergan(C, R); Alnylam (C); Apellis (C, R); Bayer (C); **Clearside Biomedical (C, R)**; DORC (C); EyePoint (C, R); Genentech/Roche (C, R); Kodiak (C); Neurotech (R); Notal Vision (C); Novartis (C, R); ONL Therapeutics (C); Opthea (R); PolyPhotonix (C); Recens Medical (C); Regeneron(C, R, S); Regenxbio (C, R); Samsung (R), Santen (C, R)
- Study Disclosures
  - This study includes research conducted on human subjects. Institutional Review Board approval was obtained prior to study initiation.

FDA-Approved Pharmaceutical Treatment Options for DME

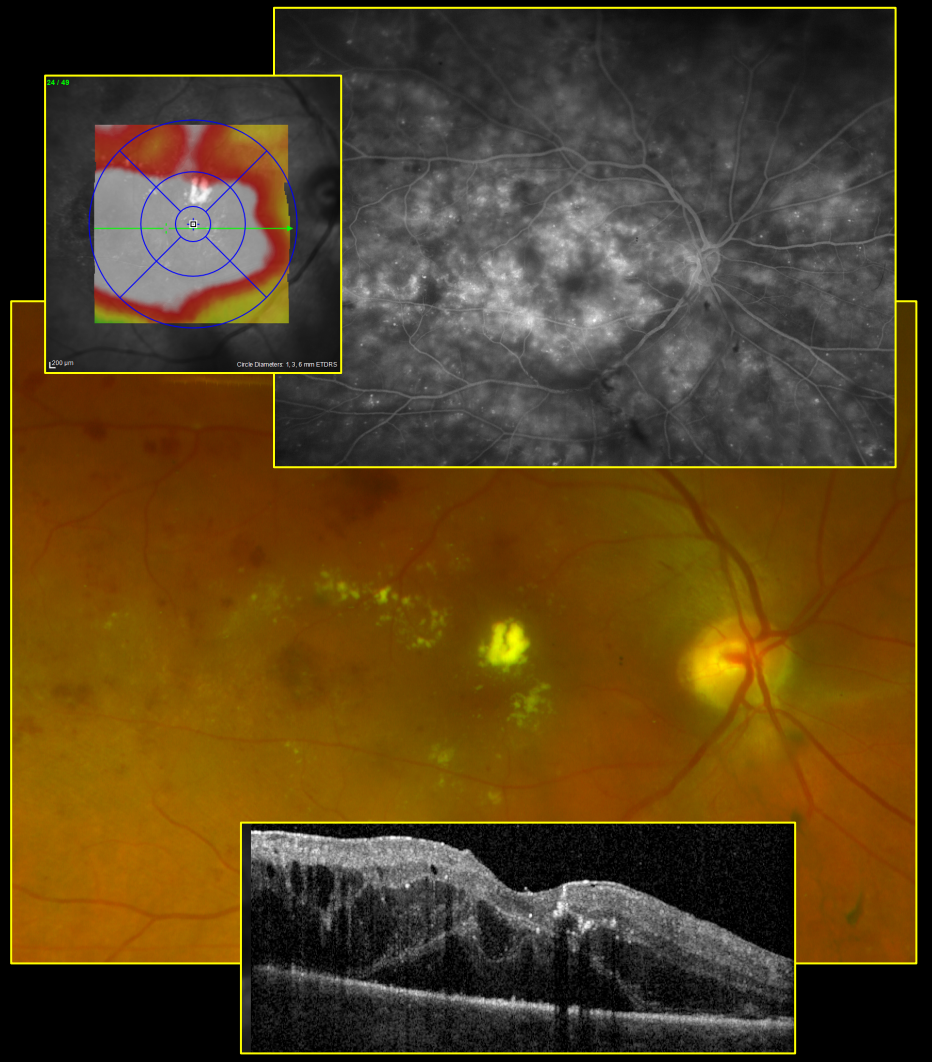
Ranibizumab

Dexamethasone



Aflibercept

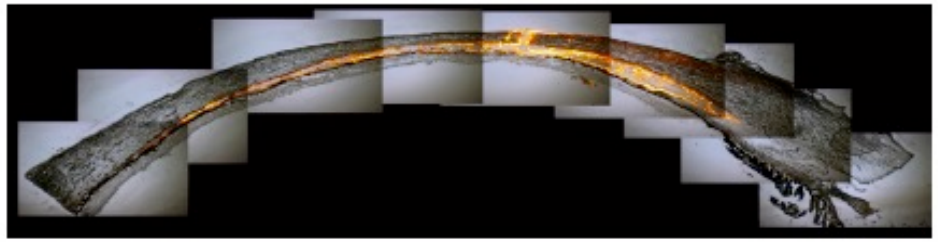
Fluocinolone Acetonide



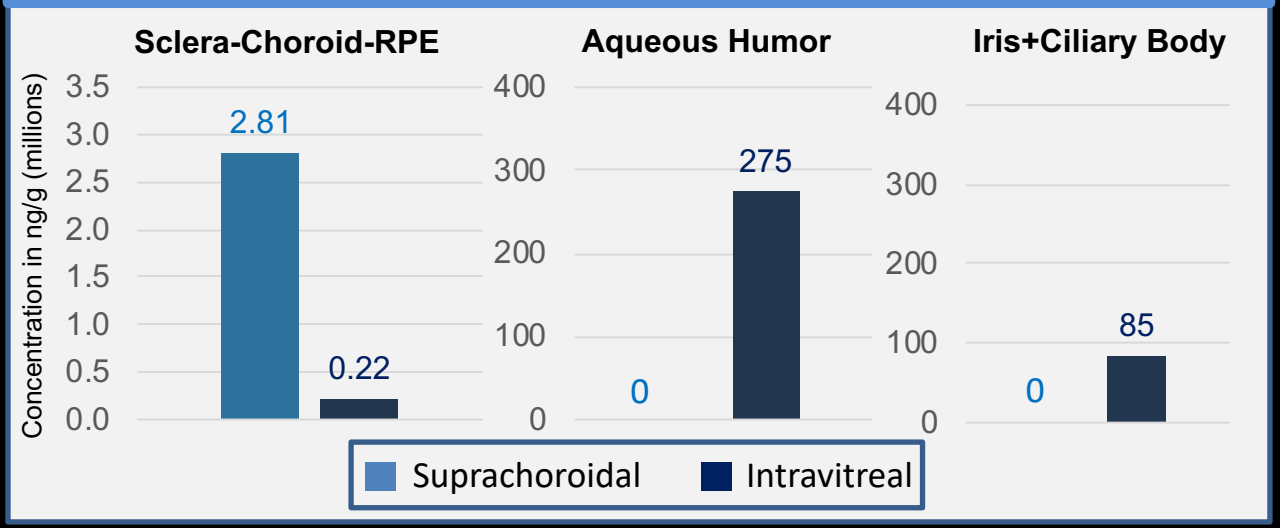
Suprachoroidal Space (SCS) Delivery of Corticosteroids

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

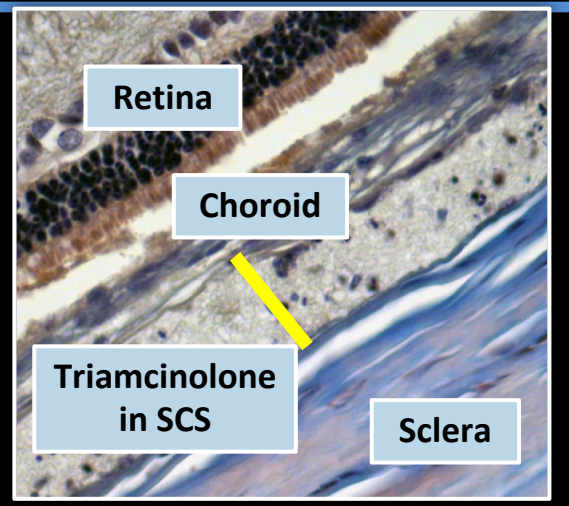
Fluorescent particles s/p SCS injection in a pig eye



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



Triamcinolone acetonide s/p SCS injection in a rabbit eye

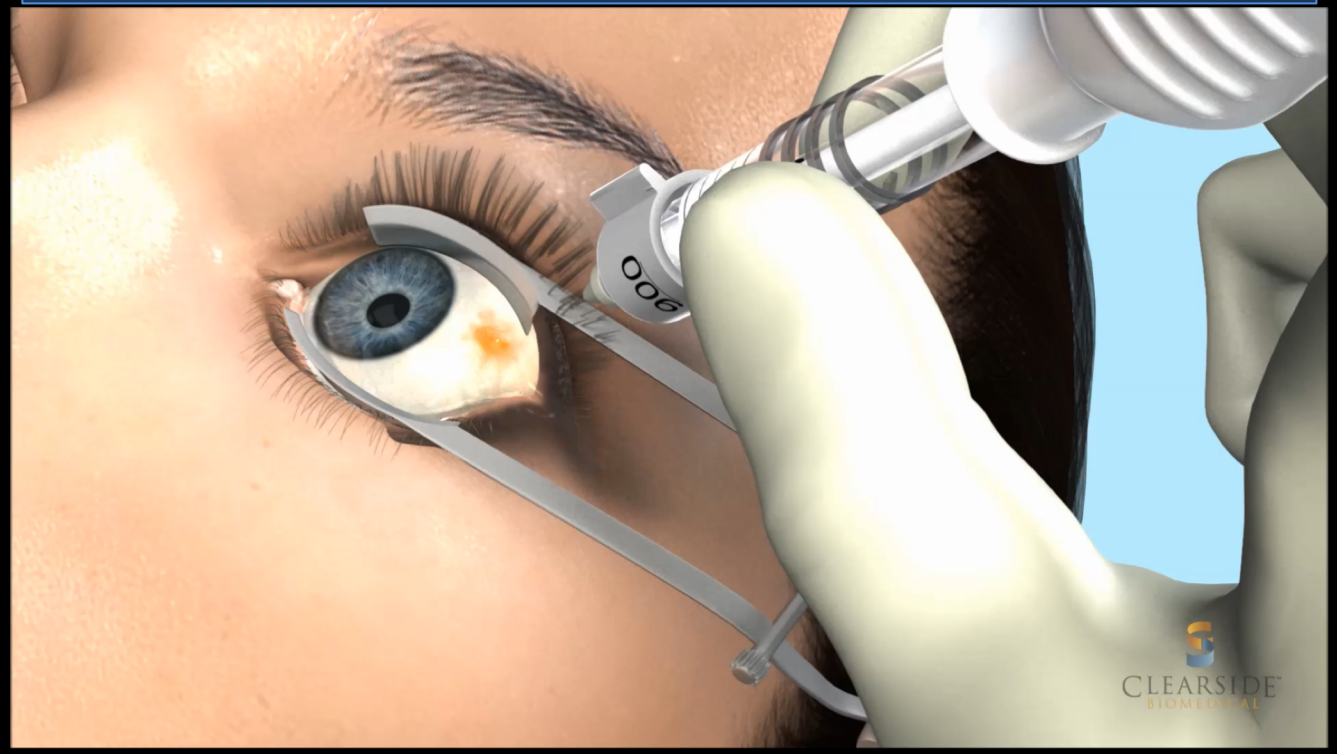


Olsen *AJO* 2006
Patel *IOVS* 2012
Edelhauser ARVO 2013

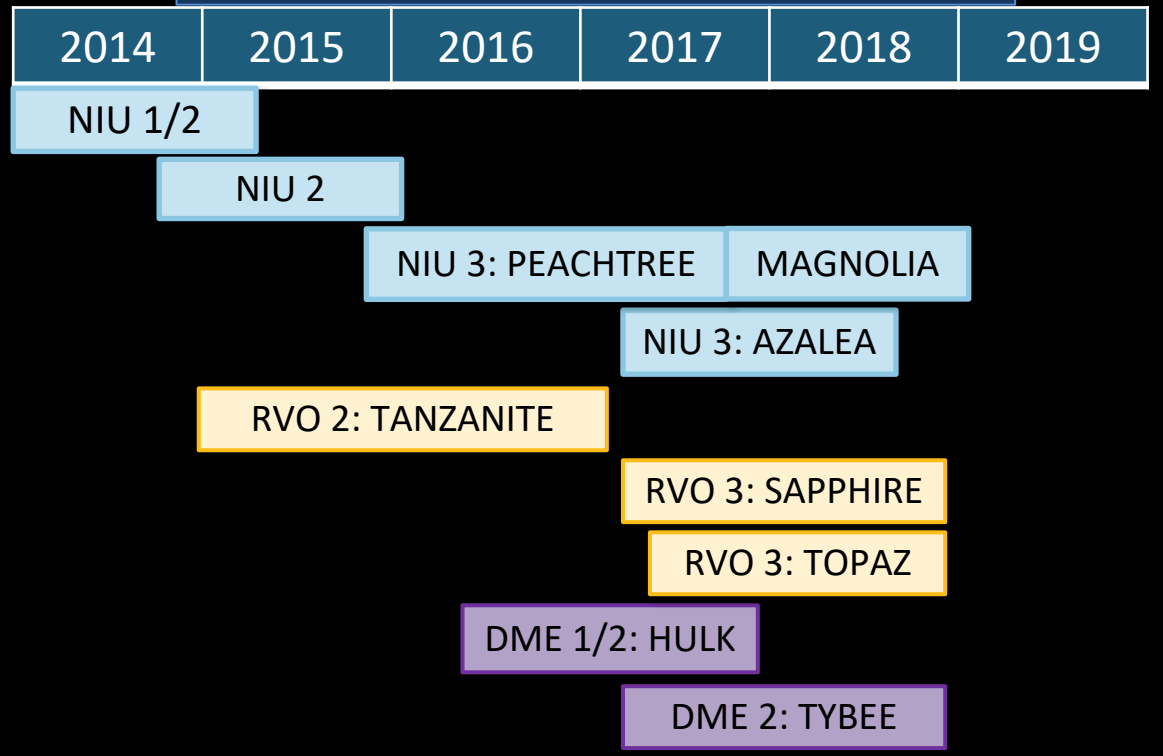
SCS Microinjector

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

Illustration of CLS-TA Suprachoroidal Delivery



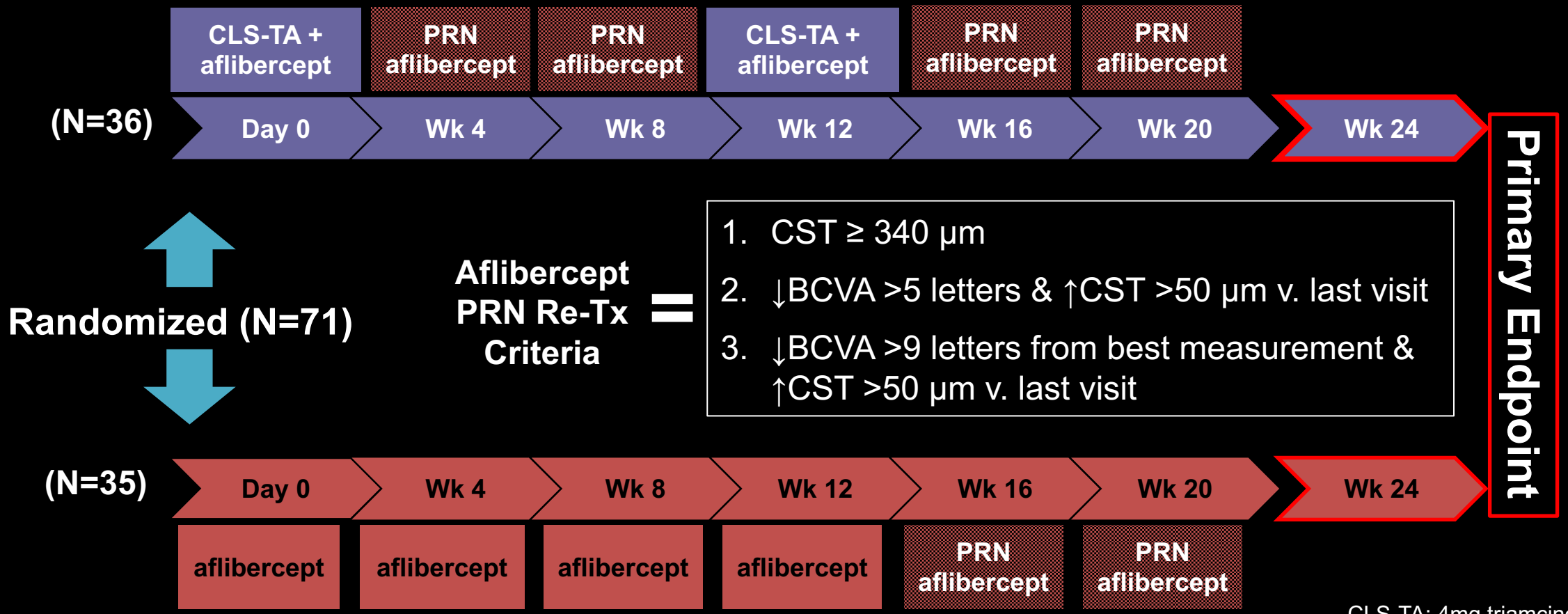
CLS-TA Clinical Trial Program



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

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

TYBEE *Key Inclusion & Exclusion Criteria*

Inclusion

- Naïve to local pharmacologic treatment for DME in the study eye
- DME with central involvement (> 300 µm) in the central subfield on SD-OCT
- ETDRS BCVA score of ≥ 20 letters read and ≤ 70 letters read in the study eye (approximate 20/40-20/400 Snellen)

Exclusion

- Cataract surgery, PPV, PRP or focal laser within 90 days
- Glaucoma or “steroid-responder” to prior corticosteroid exposure
- IOP > 21 mmHg, or IOP < 22 on > 1 IOP-lowering medication
- Any uncontrolled systemic disease that, in the opinion of the Investigator, would preclude participation in the study

TYBEE *Endpoints*

- **Primary**
  - Mean change in BCVA from baseline at Week 24
- **Secondary**
  - Mean BCVA change from baseline over time
  - Mean CST changes from baseline over time and at week 24
  - The number of additional intravitreal aflibercept injections required
  - Change in diabetic retinopathy status over 24 weeks

TYBEE *Baseline Demographics*

	Aflibercept (N=35)	**Combination** (N=36)
Age (years) - Median	59.0	60.5
Gender: Women	31.4%	27.8%
Ethnicity: Hispanic	25.7%	33.3%
Race		
White	91.4%	86.1%
Black/African American	5.7%	8.3%
Other	2.9%	5.6%
Type 2 diabetes	97.1%	97.2%
HbA1C - Median	7.6	7.2
Days since DME Diagnosis	88.0	83.7

TYBEE *Baseline Ocular Characteristics*

	Aflibercept (N=35)	**Combination** (N=36)
Mean visual acuity score (~Snellen Equivalent)	58.3 (20/80)	56.0 (20/80)
Mean OCT CST (µm)	502.8	513.8
Diabetic Retinopathy Severity		
Mild NPDR	5.7%	8.3%
Moderate NPDR	51.4%	41.7%
Severe NPDR	28.6%	41.7%
PDR	14.3%	5.6%

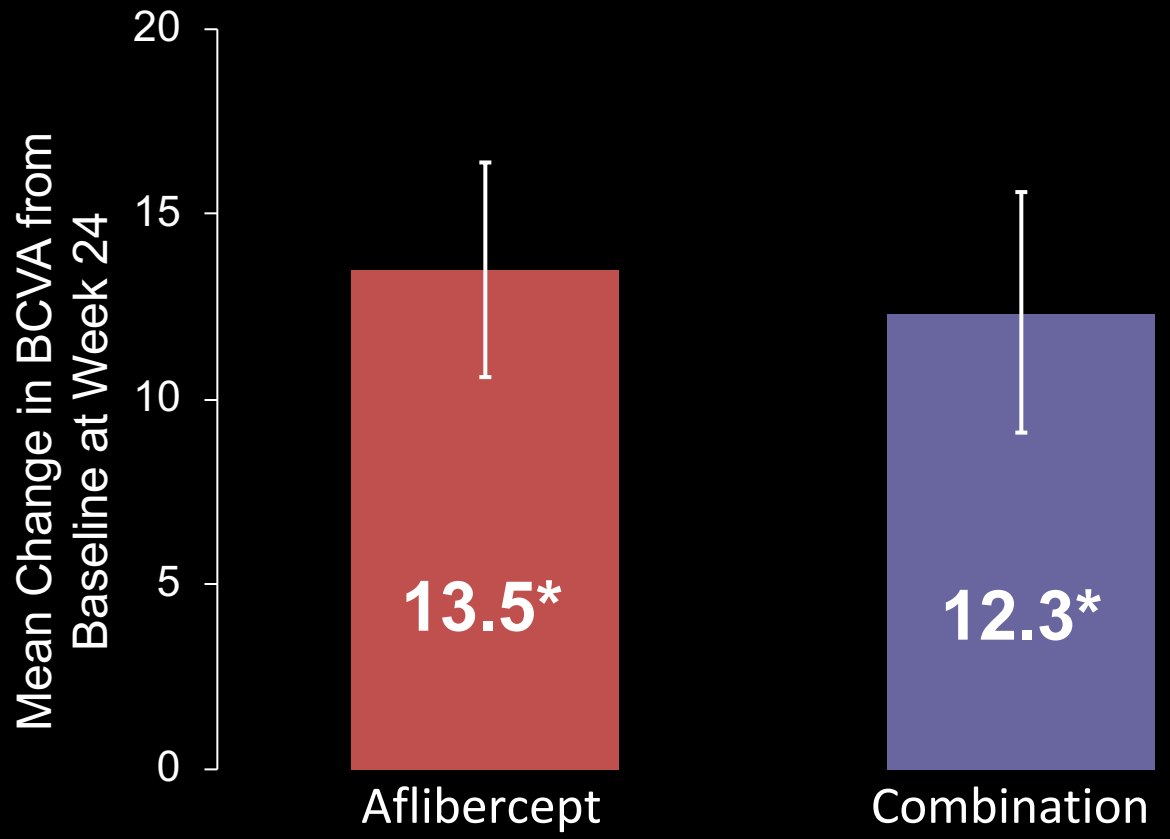
TYBEE *Patient Disposition*

	Aflibercept (N=35) n (%)	**Combination** (N=36) n (%)	**Overall (N=71) n (%)**
Safety Population	35 (100)	36 (100)	**71 (100)**
Per Protocol	31 (88.6)	25 (69.4)	**56 (78.9)**
Completed the Study	33 (94.3)	30 (83.3)	**63 (88.7)**

All safety analyses were conducted using the safety population
All efficacy analyses were conducted using the per protocol population (Patients with major protocol violations were not included)

Sample size determined such that the difference in BCVA between combination and monotherapy arms could be estimated within +/- 5 ETDRS letters. VISTA&VIVID 24-week data used to estimates variance: pooled standard deviation was 9.17 letters; with 28 subjects per arm, 2-sided 90% confidence interval with a distance from the mean difference to the limits (half of interval width) was expected to be less than 5 letters.

Mean Change in BCVA from Baseline at Week 24

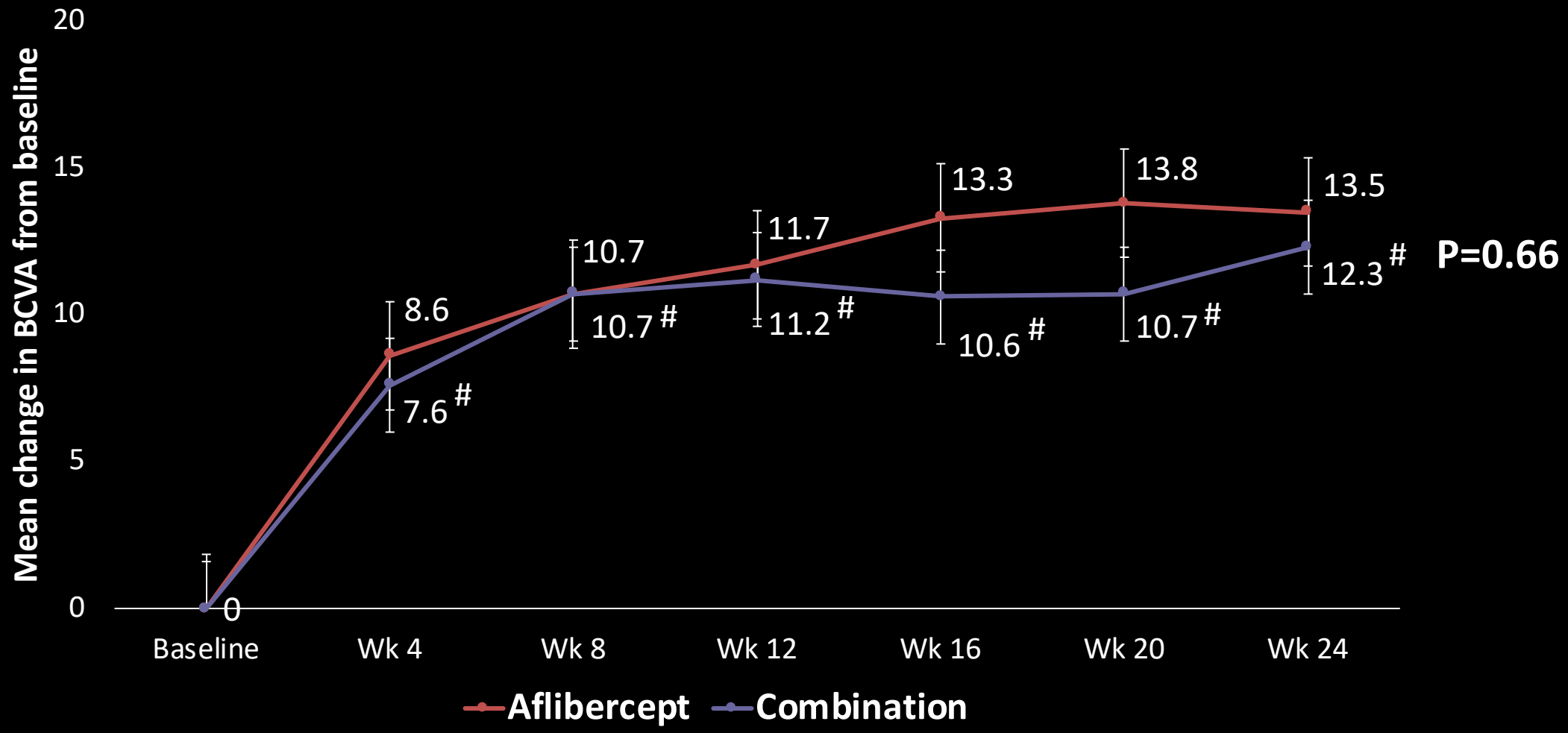


Baseline BCVA: Aflibercept: 58; Combination 56

Error bars represent 90% CIs

- Each arm shows a statistically significant improvement in BCVA from baseline (*p<0.001)
- At week 24, mean BCVA change from baseline was not significantly different between the arms (p>0.05)

Mean Change in BCVA

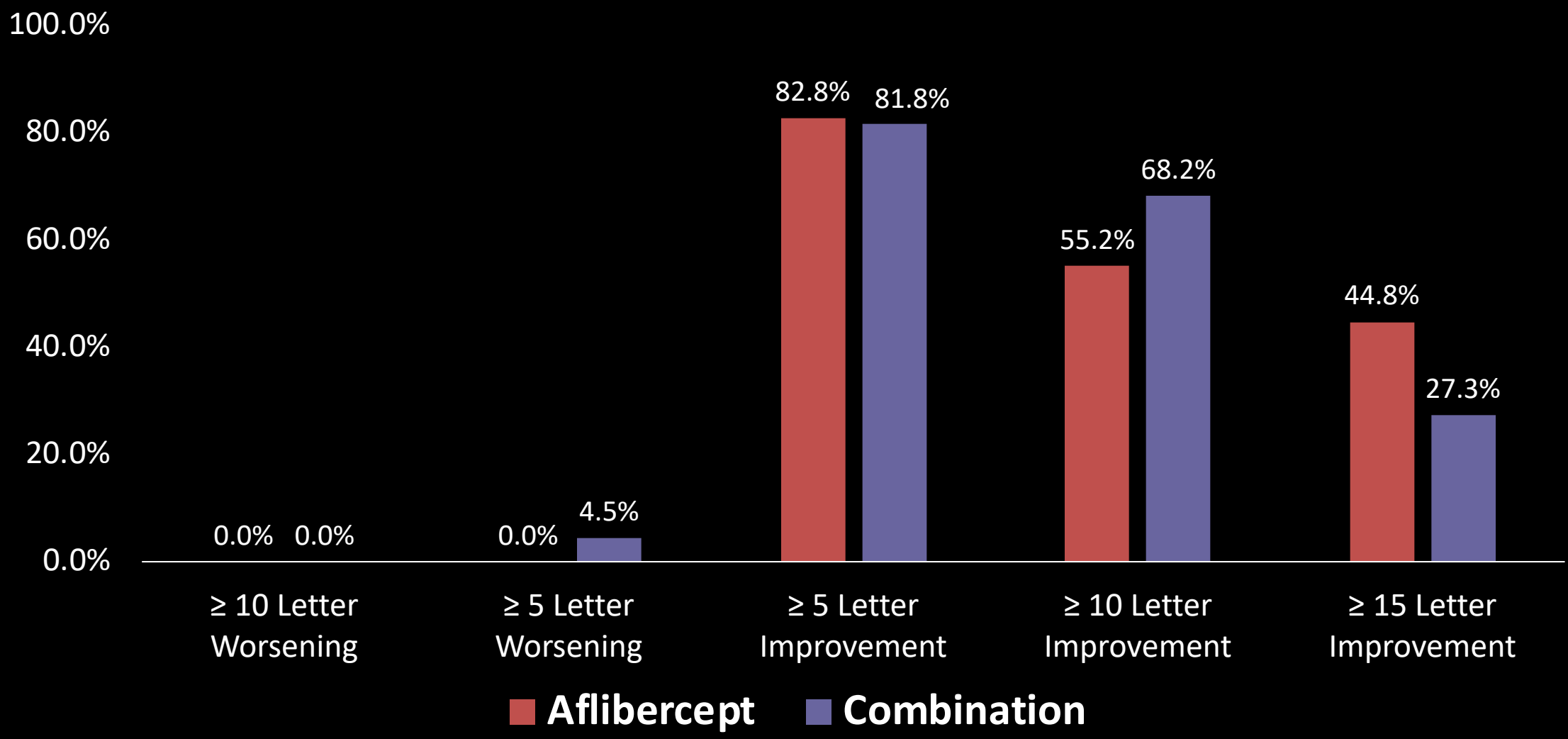


all p>0.05

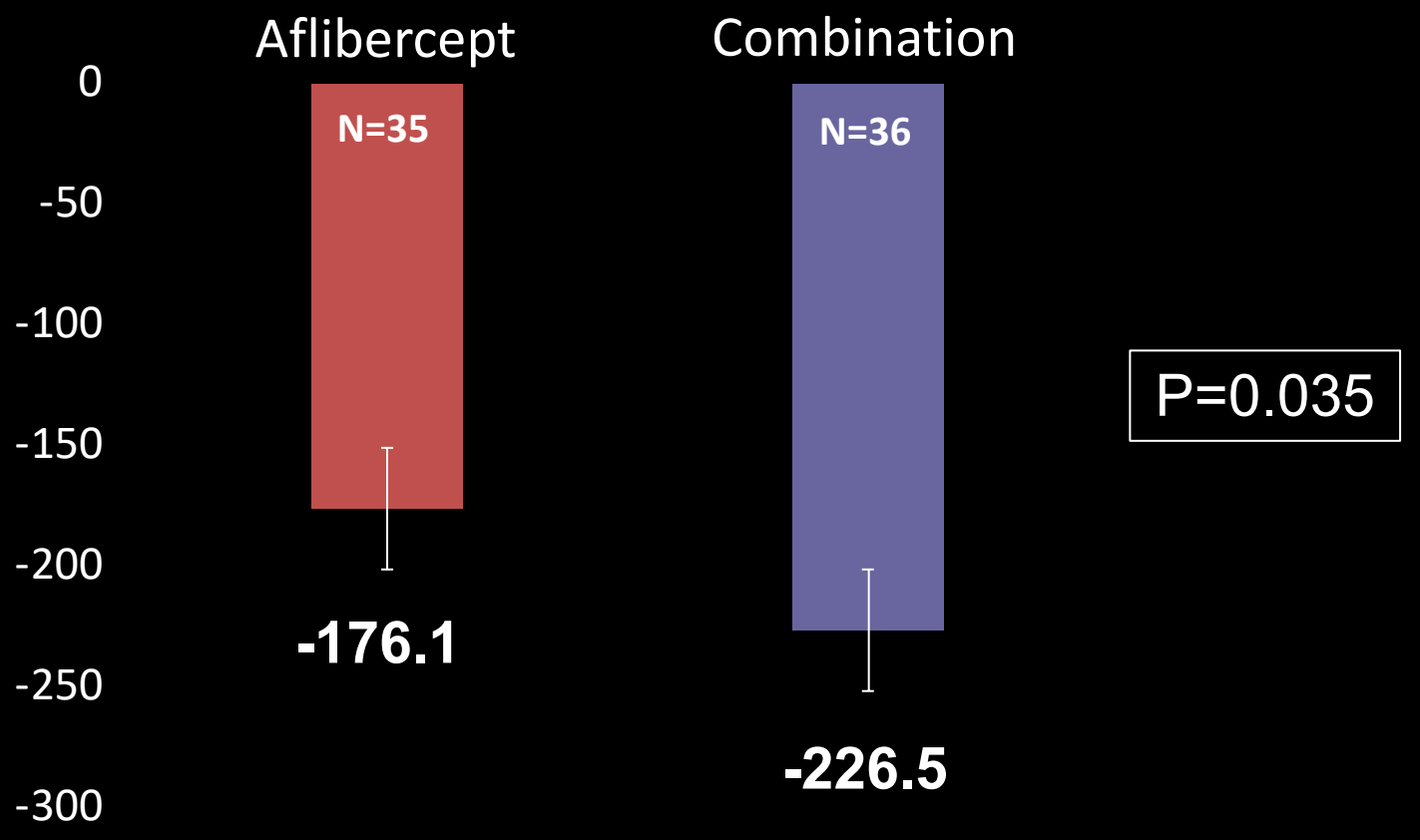
Baseline BCVA: Aflibercept: 58; Combination 56

Error bars represent 90% CIs

≥5 & ≥10 Letter Worsening & Improvement at Week 24



Mean Change in CST from Baseline at Week 24

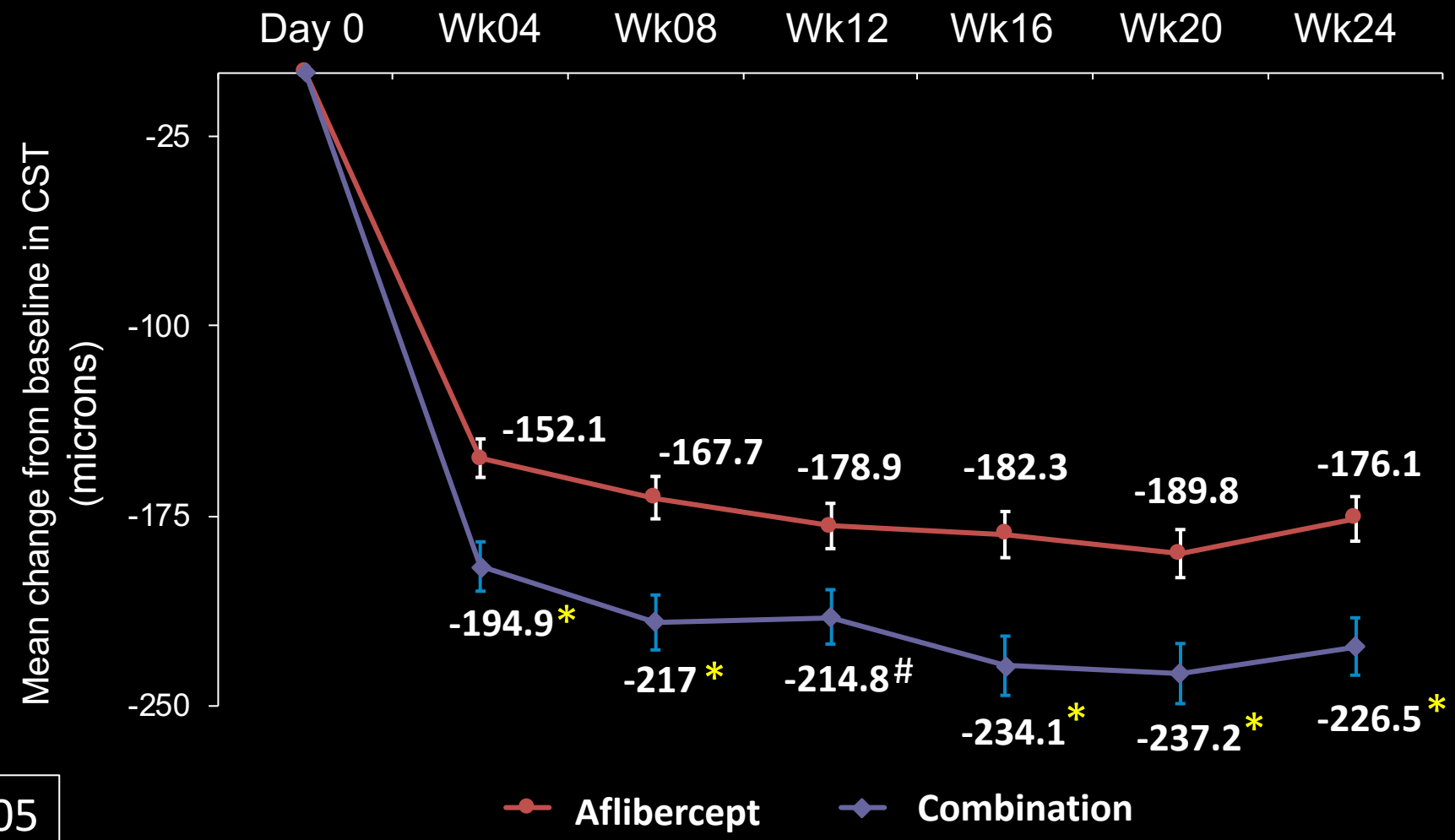


Baseline CST in microns: Aflibercept: 503; Combination 514

Error bars represent 90% CIs

- Each arm shows a statistically significant improvement in CST from baseline at week 24 (*p<0.001)
- The combination arm led to a statistically significant improvement in CST relative to the aflibercept arm (p=.035)

Mean Change in CST



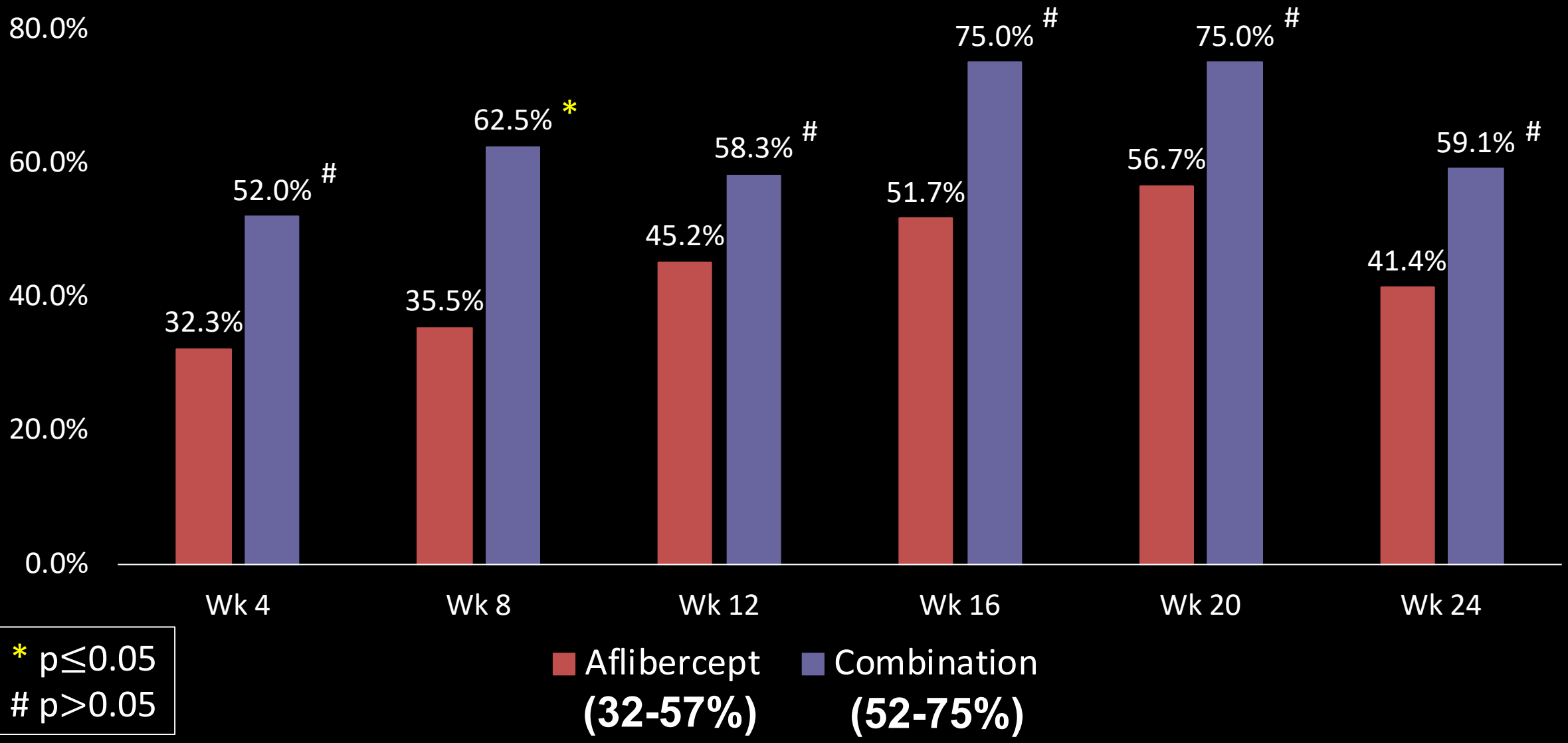
p=0.035

* p≤0.05
# p>0.05

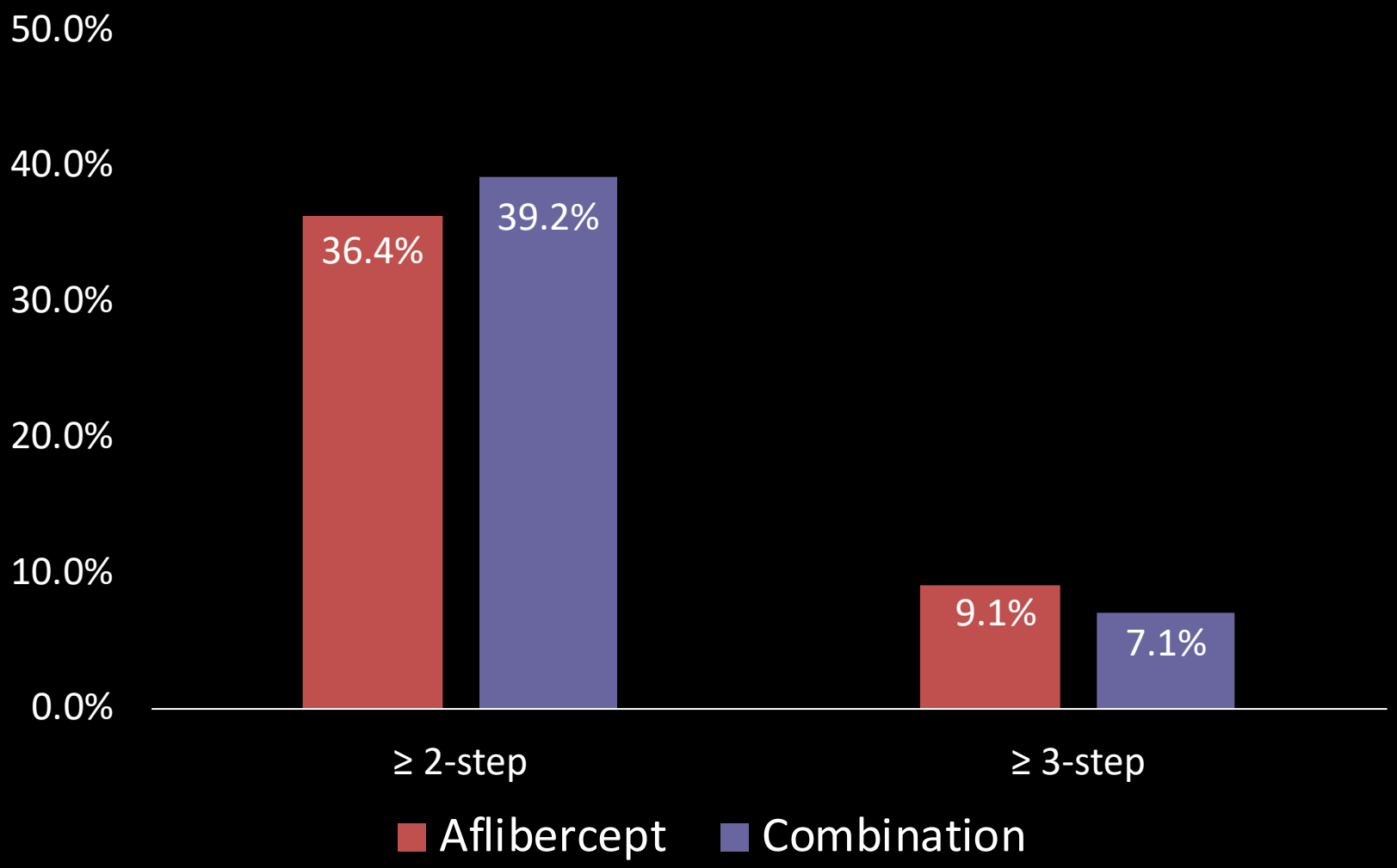
Baseline CST in microns: Aflibercept: 503; Combination 514

Error bars represent 90% CIs

Resolution of Excess CST (CST <300 microns)

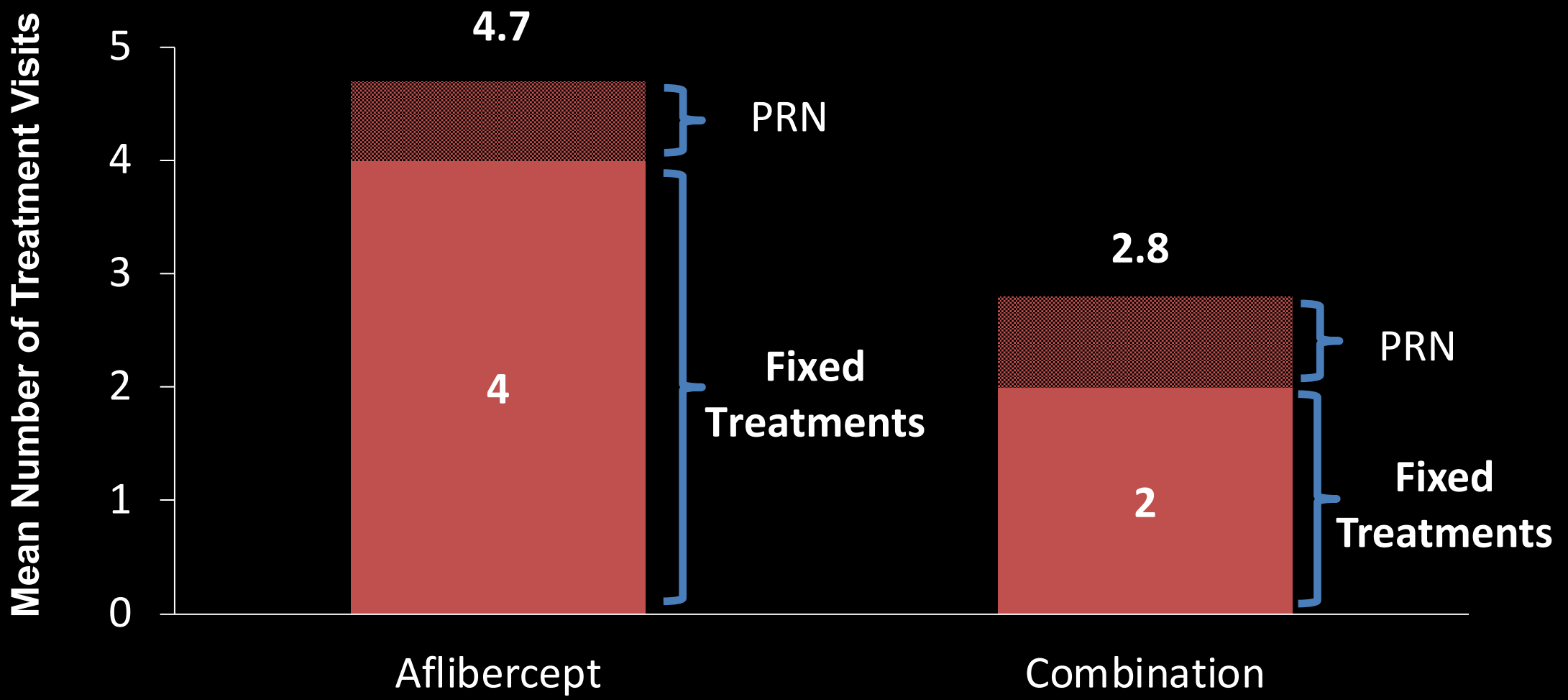


≥2- and ≥3-Step DRSS Improvements at Week 24



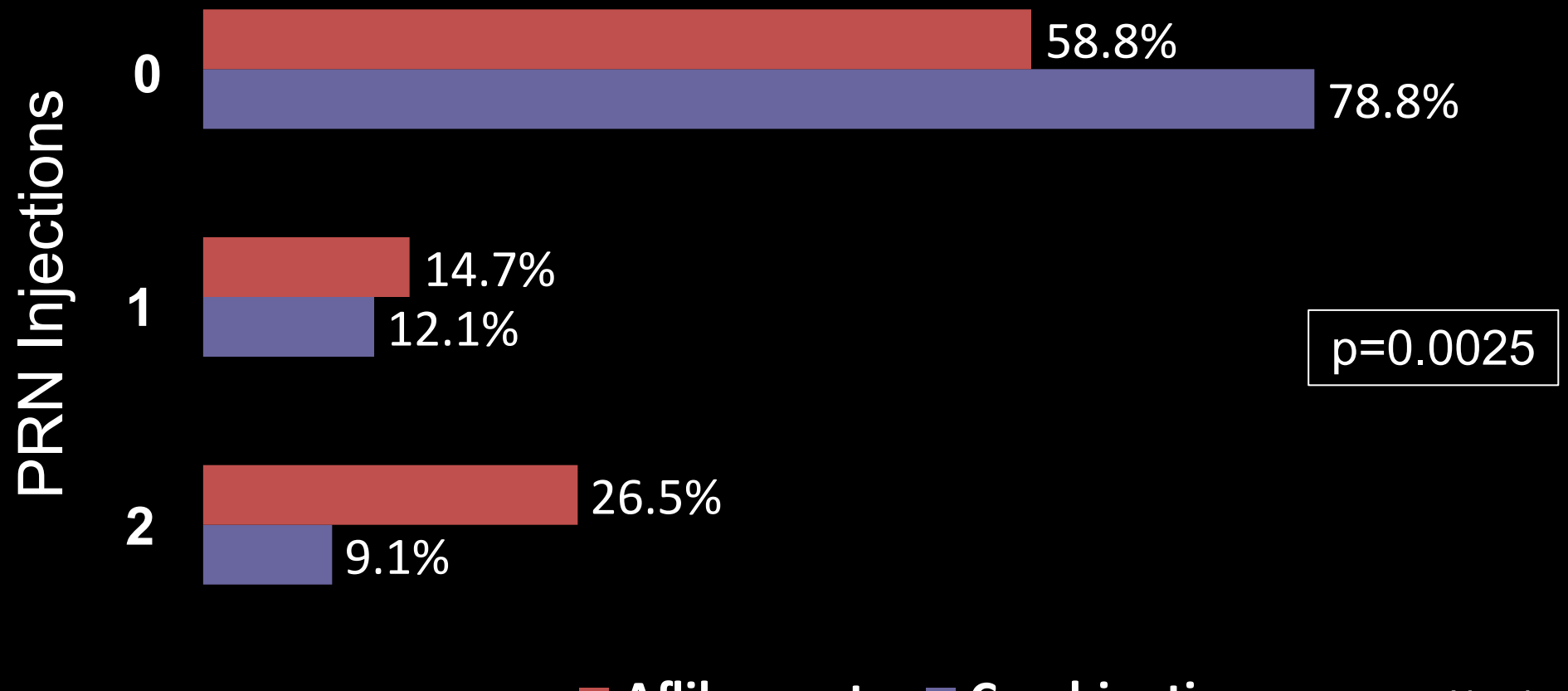
Mean Number of Treatment Visits

Through Week 24



Aflibercept Injections Delivered

During Matched PRN Phase (Weeks 16-20)



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

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”

Ocular Adverse Events >3%

	Aflibercept (N=35)	Combination (N=36)
IOP increased	1 (2.9)	3 (8.3)
Cataract*	1 (2.9)	2 (5.6)
Conjunctival hemorrhage	1 (2.9)	2 (5.6)

* Includes “Cataract Nuclear”

IOP Related Findings

	Aflibercept (N = 35) n (%)	**Combination** (N = 36) n (%)
IOP elevation ≥ 10 mmHg above baseline at any visit	0	5 (13.9)
IOP measurement ≥ 30 mmHg at any visit	0	3 (8.3)
Given IOP-lowering medications	0	3 (8.3)

TYBEE Conclusion

Phase II double-masked 6-month trial of DME eyes

- Similar BCVA improvements with aflibercept monotherapy (+13.5 letters) compared to combination aflibercept & suprachoroidal CLS-TA (+12.3 letters)
- CST improvement was significantly greater with combination aflibercept & suprachoroidal CLS-TA (-227 um) compared to aflibercept monotherapy (-176 um) (P=0.035).
- Fewer treatments in the combination arm compared to aflibercept monotherapy: 4.7 vs 2.8 mean treatment visits
- IOP elevation ≥ 10 mmHg above baseline at any visit in combination arm compared to aflibercept monotherapy: 13.9% vs 0%.