Combination Therapy with Intravitreal Nesvacumab and Aflibercept for Neovascular Age-Related Macular Degeneration

Angiogenesis 2018

Allen C. Ho, MD
On behalf of the ONYX Investigators

Wills Eye Hospital

DISCLOSURES

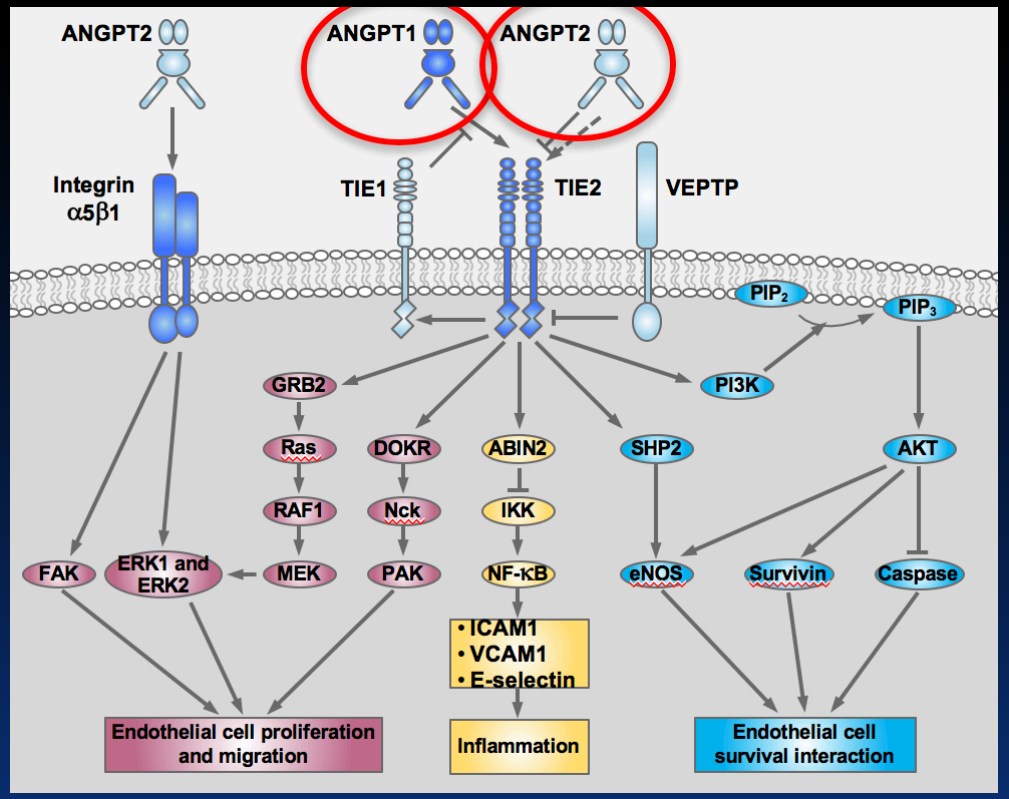
Aerpio (C)
Alcon (C, G)
Allergan (C, G)
Apellis (G)
Asclepix (C)
Beaver EndoOptiks (C)
Biotime (C)
C Kanghong Biotech (C)
Covalent (O)
DigiSight (C, O)
Genentech (C, G)
Iconic (G)
Iridex (C, G)
Janssen (C, G)
NEI/NIH (G)
ONL (C, O)
Ophthotech (C, G)
Optovue (C)
PanOptica (C, G, O)
PRN (C, O)
Regeneron (C, G)
Regenix (C)
Second Sight (C, G)
Tyrogenix (C)

Take Home Messages

- No significant differences in mean change in BCVA between combination of nesvacumab+aflibercept vs. IAI monotherapy
- No significant differences in mean change in CRT between combination of nesvacumab+aflibercept vs. IAI monotherapy
  - Trend towards greater proportion of patients achieving complete fluid resolution with HD combination
- Ocular and systemic safety of combination therapy consistent with IAI monotherapy

Background: Angiopoietin and TIE2 Receptor Pathway

- Angiopoietin family of angiogenic growth factors was discovered at Regeneron [1, 2]
- Genetic knockout of angiopoietins in mice resulted in profound angiogenic phenotypes
- Exploratory study of intravenous anti-angiopoietin 2 antibody (nesvacumab) conducted in cancer patients
- Clinical studies with intravitreal nesvacumab in combination with aflibercept conducted in AMD and DME



[1] Davis et al. Isolation of angiopoietin-1, a ligand for the TIE2 receptor, by secretion-trap expression cloning. Cell. 1996 Dec 27;87(7):1161-9.

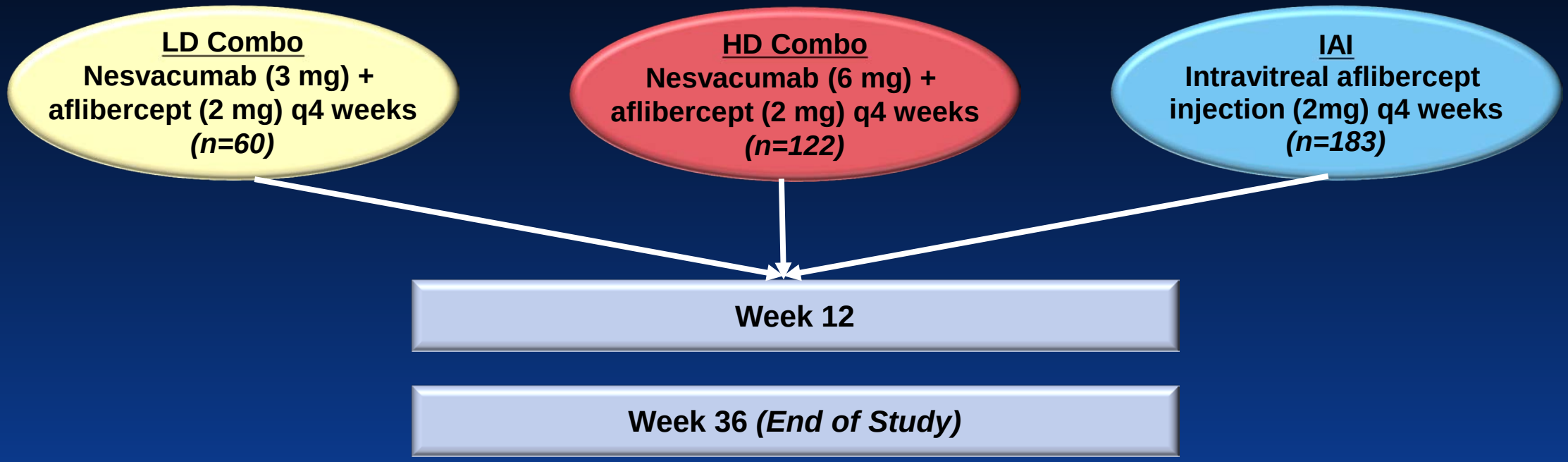
[2] Maisonpierre et al. Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Science. 1997 Jul 4;277(5322):55-60.

Study Design
Baseline - Week 12

Multiple-dose, double masked, randomized, controlled study in patients with treatment naïve AMD
Randomized 1:2:3

Key Eligibility Criteria

- BCVA ETDRS letter score equivalent to 20/40 to 20/320
- Active subfoveal CNV secondary to AMD, including juxtafoveal lesions that affect the fovea



LD: Low Dose; HD: High Dose

Patients Disposition and Demographics

	LD	HD	IAI	Total
	(n=60)	*(n=122)*	*(n=183)*	*(N=365)*
Patients completing Week 12 , n(%)	59 (98.3%)	121 (99.2%)	181 (98.9%)	361 (98.9%)
Mean Age, years (SD)	**79.3 (9.33)**	**79.4 (8.91)**	**78.4 (8.37)**	**78.9 (8.71)**
Female, n (%)	41 (68.3%)	75 (61.5%)	110 (60.1%)	226 (61.9%)
Race, n (%)				
White	59 (98.3%)	116 (95.1%)	178 (97.3%)	353 (96.7%)
Black or African American	0	1 (0.8%)	1 (0.5%)	2 (0.5%)
Asian	1 (1.7%)	3 (2.5%)	2 (1.1%)	6 (1.6%)
American Indian or Alaska Native	0	1 (0.8%)	0	1 (0.3%)
Native Hawaiian or Other Pacific Islander	0	1 (0.8%)	0	1 (0.3%)
Other	0	0	2 (1.1%)	2 (0.5%)

SAF

Baseline Disease Characteristics

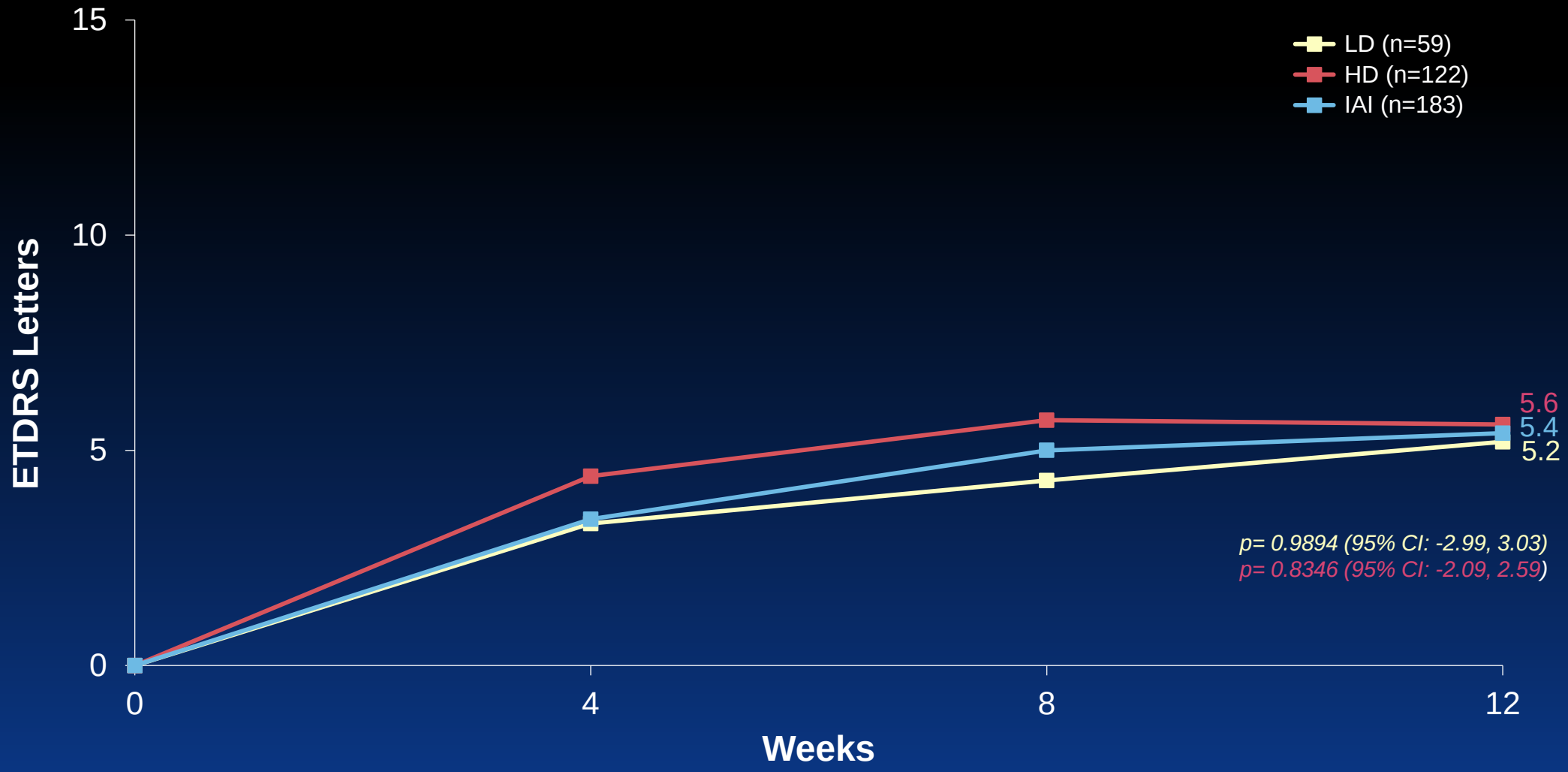
	LD	HD	IAI	Total
	(n=59)	*(n=122)*	*(n=183)*	*(N=364)*
Mean ETDRS BCVA, letters (SD)	58.2 (11.62)	55.7 (12.27)	55.5 (13.54)	56.0 (12.83)
Mean Lesion Size, mm^2 (SD)	6.9 (4.79)*	8.7 (6.48)	8.7 (5.54)	8.4 (5.79)
Patients with lesion size >4 DA, n (%)	14 (23.7%)	38 (31.1%)	57 (31.1%)	109 (29.9%)
Mean CRT, um (SD)	484.2 (179.57)	521.1 (191.43)	496.2 (161.91)	502.6 (175.25)
CNV Subtype, n (%)				
Occult	29 (49.2%)	62 (50.8%)	105 (57.4%)	196 (53.8%)
Minimally Classic	23 (39.0%)	45 (36.9%)	58 (31.7%)	126 (34.6%)
Predominantly Classic	7 (11.9%)	15 (12.3%)	20 (10.9%)	42 (11.5%)

*p=0.0248 vs. IAI

FAS

Mean Change in Best-Corrected Visual Acuity

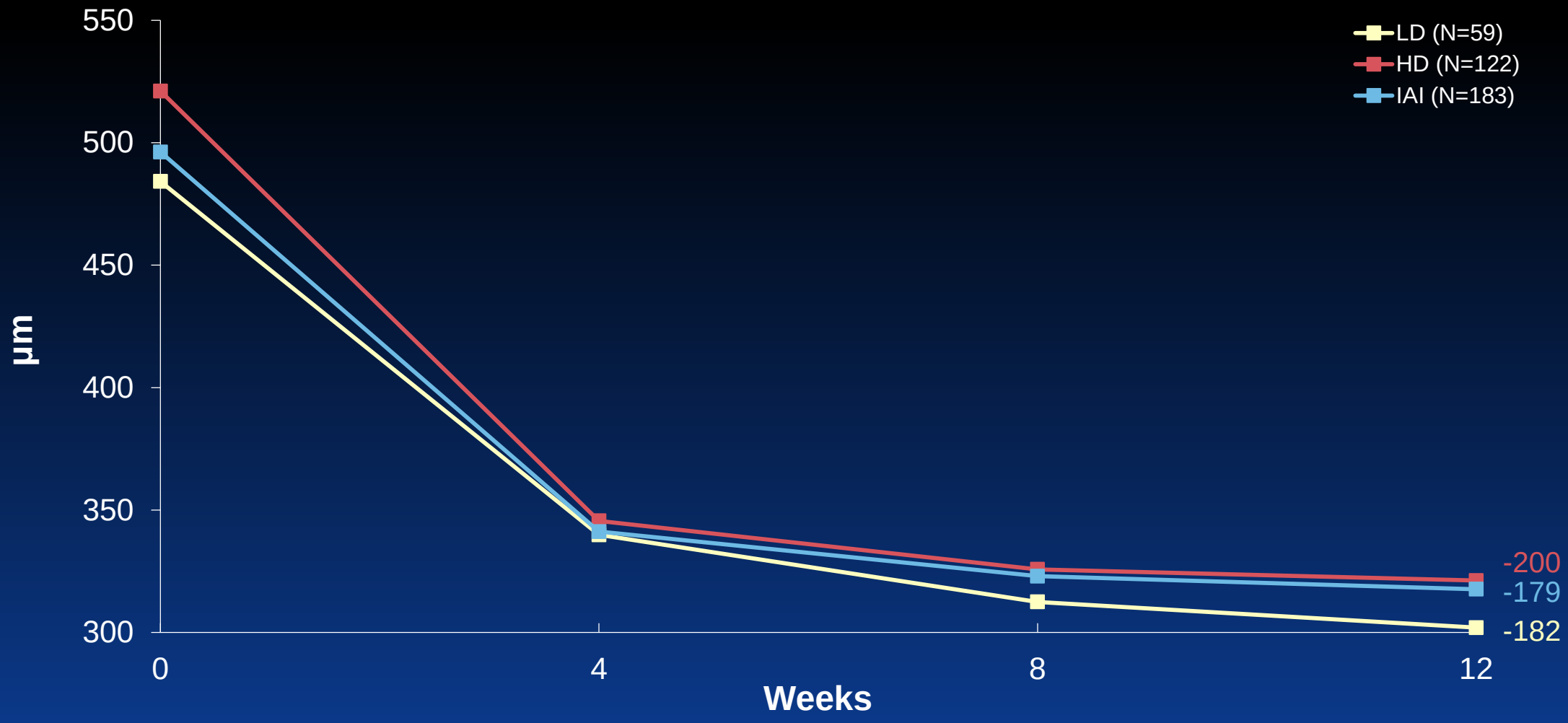
Baseline - Week 12



FAS, LOCF

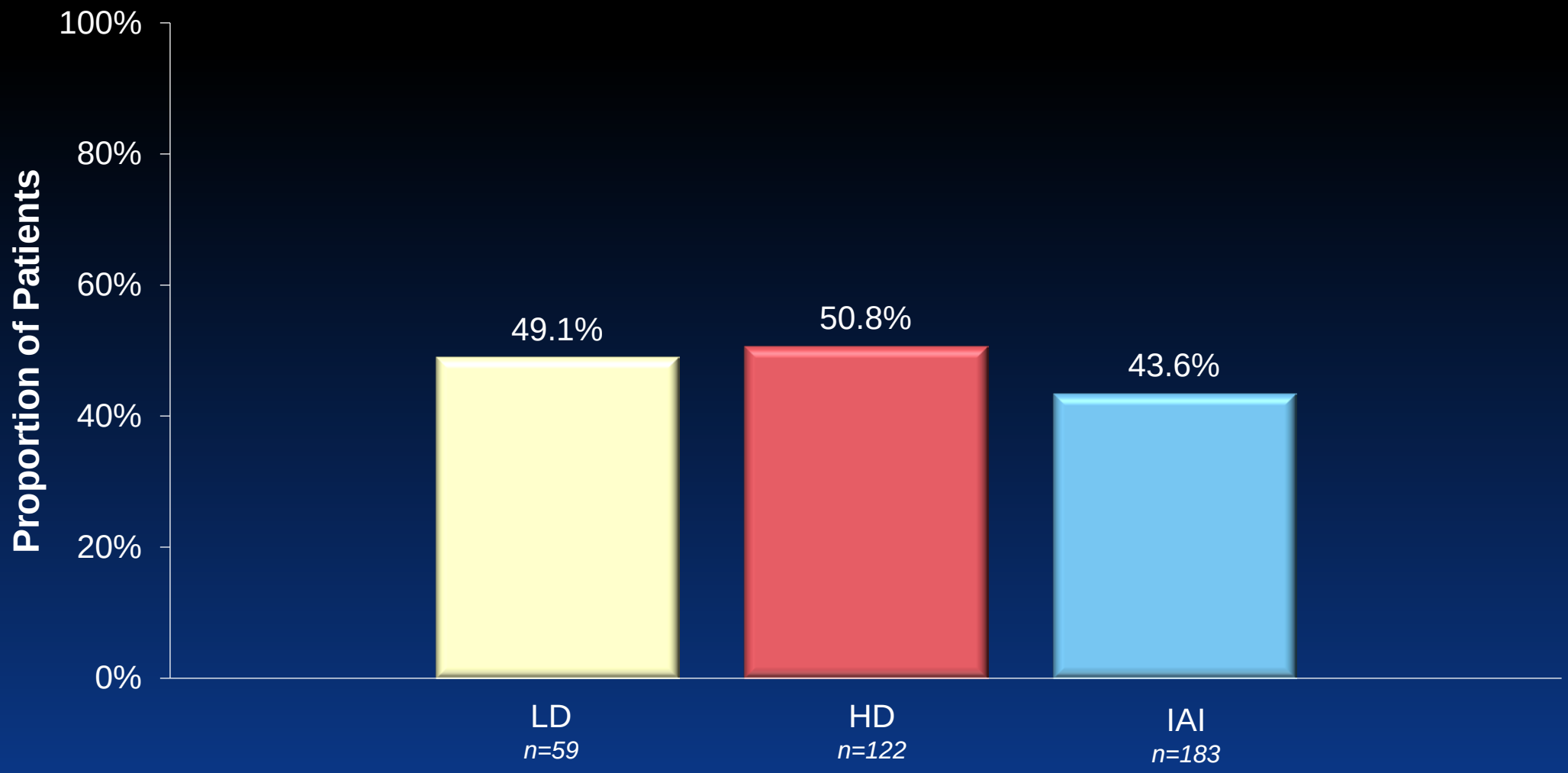
Mean Absolute Central Retinal Thickness

Baseline - Week 12



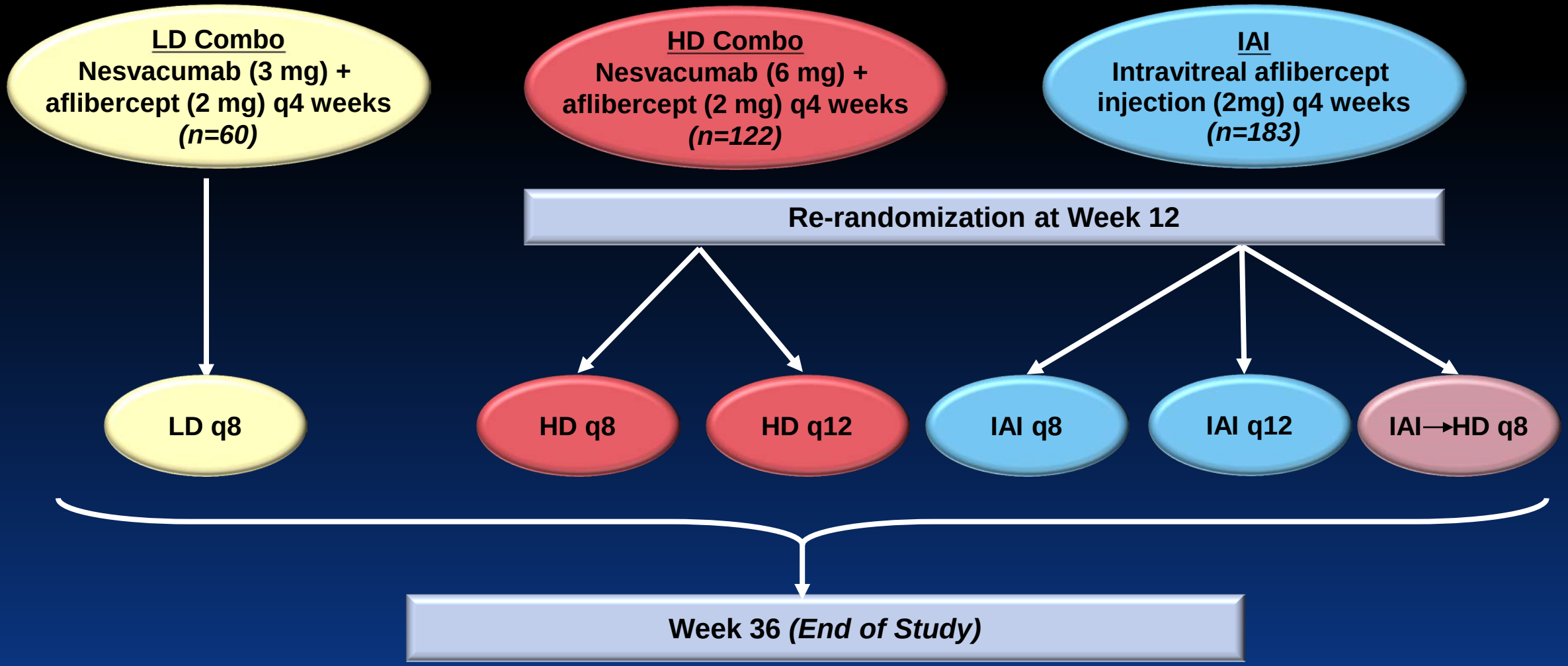
FAS, LOCF

Proportion of Patients With Complete Resolution of Fluid at Week 12



FAS, LOCF

Study Design
Week 12 – Week 36



Stratification for re-randomization based on VA outcomes at week 12
LD: Low Dose; HD: High Dose

Week 36

Patient Disposition

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
Number of patients in the Secondary Randomization Set, n (%)	*(n=58)*	*(n=57)*	*(n=62)*	*(n=60)*	*(n=62)*	*(n=58)*
Number of patients completing week 36, n (%)	57 (98.3%)	53 (93.0%)	60 (96.8%)	59 (98.3%)	60 (96.8%)	54 (93.1%)

FAS -Secondary randomization set

Baseline Disease Characteristics

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI HD q8
	(n=58)	*(n=57)*	*(n=62)*	*(n=60)*	*(n=62)*	*(n=58)*
Mean ETDRS BCVA, letters (SD)	58.3 (11.71)	55.4 (12.24)	55.9 (12.38)	54.6 (14.03)	55.6 (12.92)	56.7 (13.41)
Mean Lesion Size, mm^2 (SD)	6.8 (4.75)*	8.6 (6.51)	8.6 (6.42)	8.9 (6.04)	8.4 (5.14)	8.8 (5.27)
Patients with lesion size >4 DA, n (%)	13 (22.4%)	16 (28.1%)	21 (33.9%)	17 (28.3%)	18 (29.0%)	21 (36.2%)
Mean CRT, um (SD)	480.0 (178.11)	537.8 (232.36)	512.7 (147.50)	489.3 (148.10)	509.6 (142.77)	497.6 (193.25)
CNV Subtype, n (%)						
Occult	29 (50.0%)	28 (49.1%)	33 (53.2%)	34 (56.7%)	34 (54.8%)	35 (60.3%)
Minimally Classic	22 (37.9%)	20 (35.1%)	23 (37.1%)	18 (30.0%)	21 (33.9%)	18 (31.0%)
Predominantly Classic	7 (12.1%)	9 (15.8%)	6 (9.7%)	8 (13.3%)	7 (11.3%)	5 (8.6%)

*p=0.0417 vs. IAI

FAS -Secondary randomization set

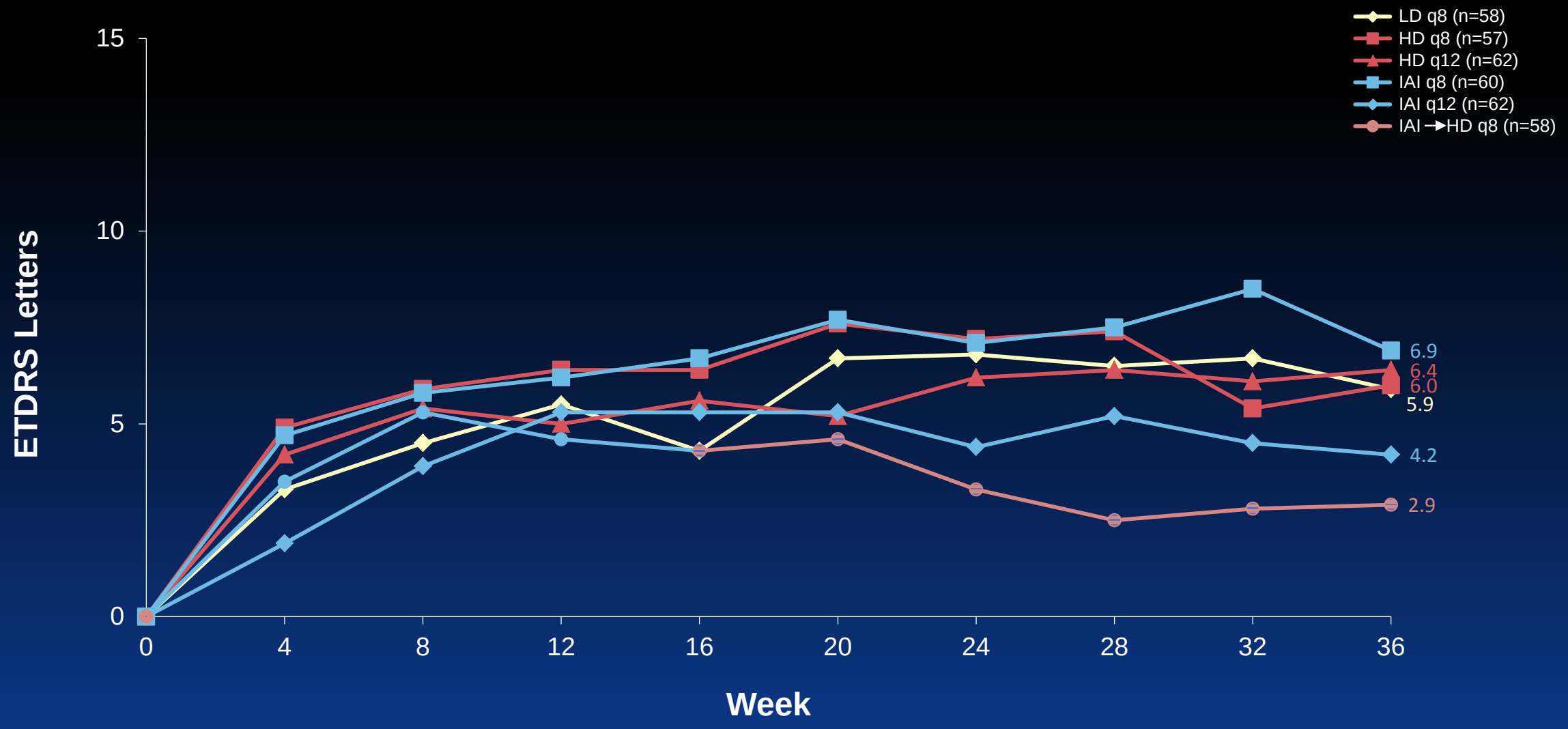
Dose Exposure Through Week 36

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=58)	*(n=57)*	*(n=62)*	*(n=60)*	*(n=62)*	*(n=58)*
Number of Planned Injections, n	6	6	5	6	5	6
Mean Number of Injections, n (SD)	6.6* (0.93)	5.9 (0.44)	5.1* (0.45)	5.9 (0.35)	4.9 (0.27)	5.9 (0.40)

**~50% and 75% of patients received per protocol dosing in the LD q8 and HD q12 groups, respectively.*

SAF-Secondary randomization set

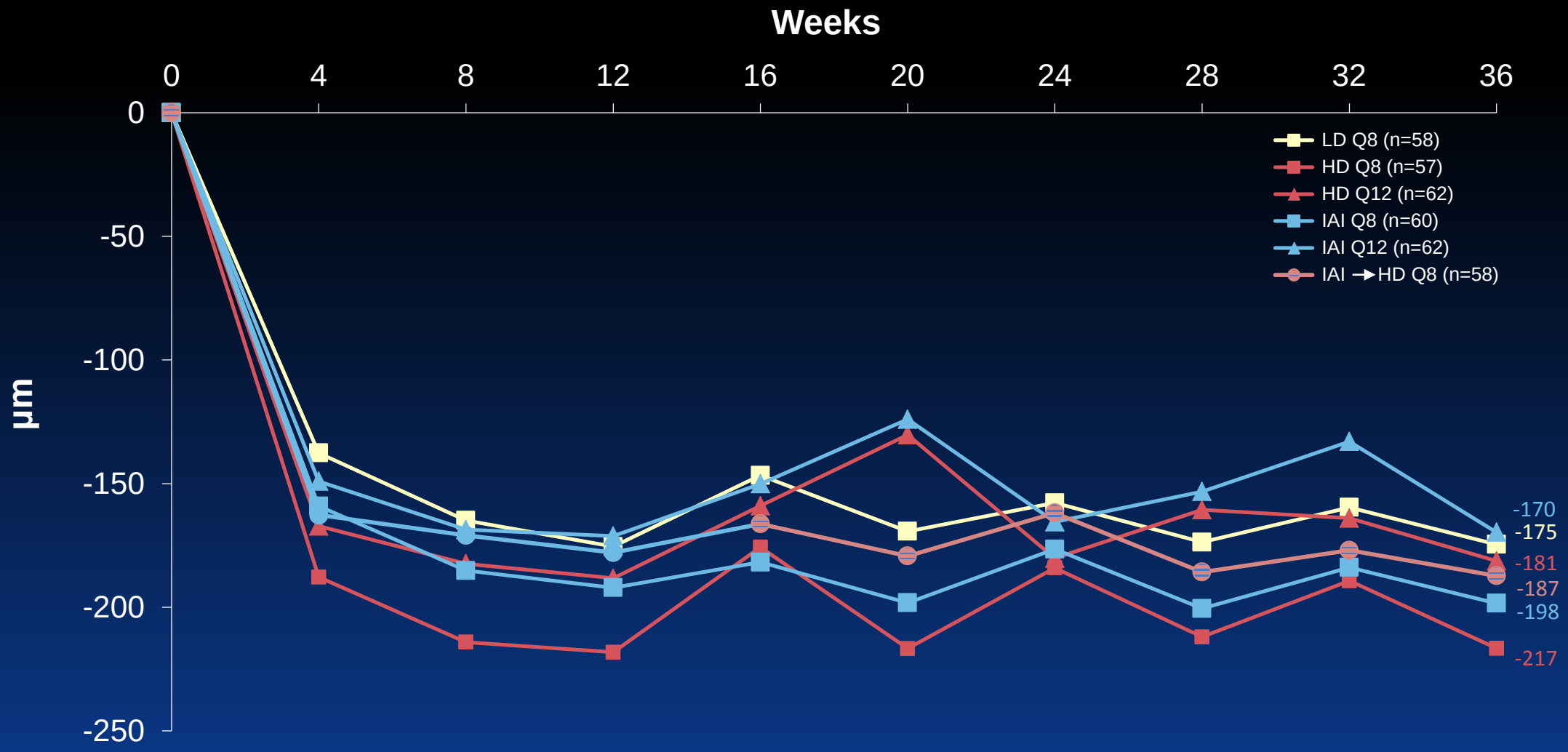
Mean Change in Best-Corrected Visual Acuity
Baseline – Week 36



FAS -Secondary randomization set
LOCF

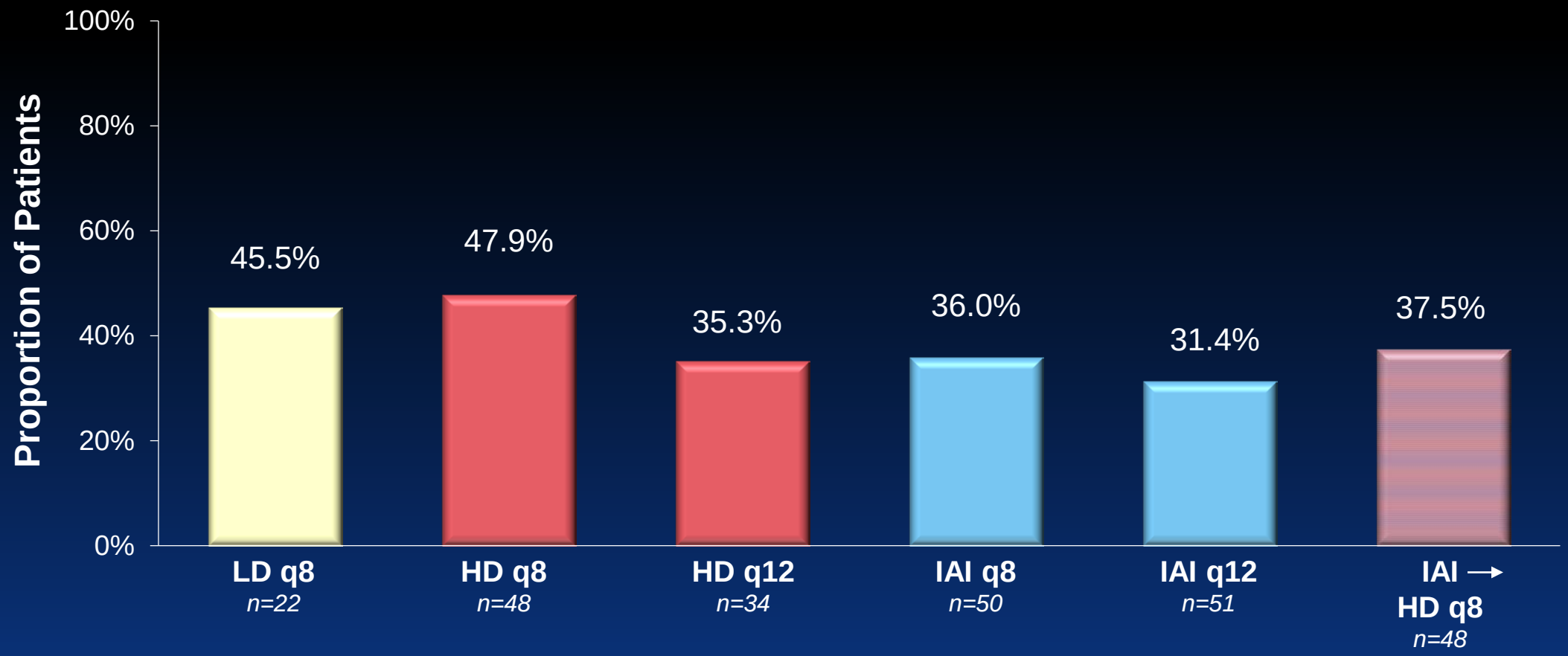
Mean Change in Central Retinal Thickness

Baseline – Week 36



FAS -Secondary randomization set
LOCF

Proportion of Patients with Complete Resolution of Fluid at Week 32*



*8 or 12 weeks from the last study treatment.
FAS -Secondary randomization set, OC. Patients with no intraretinal or subretinal fluid in the center subfield on SD-OCT.
Per Protocol Set

Safety

Most Frequent Ocular Adverse Events
Through Week 36

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=58)	*(n=57)*	*(n=62)*	*(n=60)*	*(n=62)*	*(n=58)*
No. of pts. with at least 1 AE, n (%)	18 (31.0%)	21 (36.8%)	28 (45.2%)	14 (23.3%)	24 (38.7%)	15 (25.9%)
Retinal haemorrhage	0	1 (1.8%)	1 (1.6%)	1 (1.7%)	3 (4.8%)	2 (3.4%)
Vitreous floaters	1 (1.7%)	1 (1.8%)	2 (3.2%)	1 (1.7%)	4 (6.5%)	2 (3.4%)
Conjunctival haemorrhage	2 (3.4%)	3 (5.3%)	3 (4.8%)	3 (5.0%)	1 (1.6%)	1 (1.7%)
Dry eye	0	0	4 (6.5%)	1 (1.7%)	2 (3.2%)	1 (1.7%)
Eye irritation	1 (1.7%)	1 (1.8%)	1 (1.6%)	2 (3.3%)	0	1 (1.7%)
Iridocyclitis	1 (1.7%)	2 (3.5%)	0	0	0	1 (1.7%)
Retinal pigment epithelial tear	0	2 (3.5%)	1 (1.6%)	1 (1.7%)	1 (1.6%)	1 (1.7%)
Visual acuity reduced	1 (1.7%)	2 (3.5%)	3 (4.8%)	1 (1.7%)	2 (3.2%)	1 (1.7%)
Eye pain	1 (1.7%)	2 (3.5%)	1 (1.6%)	1 (1.7%)	1 (1.6%)	0
Vitreous detachment	3 (5.2%)	1 (1.8%)	3 (4.8%)	2 (3.3%)	1 (1.6%)	0

SAF-Secondary randomization set; >2% in any treatment group

Anti-Platelet Trialists' Collaboration-Defined Arterial Thromboembolic Events Through Week 36

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=58)	*(n=57)*	*(n=62)*	*(n=60)*	*(n=62)*	*(n=58)*
No. of pts. **w/ at least 1 AE, n (%)**	0	1 (1.8%)	0	3 (5.0%)	2 (3.2%)	0
Non-Fatal Stroke	0	0	0	2 (3.3%)	1 (1.6%)	0
Non-Fatal Myocardial Infarction	0	0	0	1 (1.7%)	1 (1.6%)	0
Vascular Death	0	1 (1.8%)	0	0	0	0

SAF-Secondary randomization set

Conclusions

- No significant differences in mean change in BCVA between combination of nesvacumab+aflibercept vs. IAI monotherapy
- No significant differences in mean change in CRT between combination of nesvacumab+aflibercept vs. IAI monotherapy
  - Trend towards greater proportion of patients achieving complete fluid resolution with HD combination
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THANK YOU