Combination Therapy with Intravitreal Nesvacumab+Aflibercept in Diabetic Macular Edema: The Phase 2 RUBY Trial

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Financial Disclosures

Ang-1 & Ang-2 Discovery

Cell, Vol. 87, 1161–1169, December 27, 1996, Copyright ©1996 by Cell Press

Isolation of Angiopoietin-1, a Ligand for the TIE2 Receptor, by Secretion-Trap Expression Cloning

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Summary

TIE2 is a receptor-like tyrosine kinase expressed almost exclusively in endothelial cells and early hemopoietic cells and required for the normal development of vascular structures during embryogenesis. We report the identification of a secreted ligand for TIE2, termed Angiopoietin-1, using a novel expression cloning technique that involves intracellular trapping and detection of the ligand in COS cells. The structure of Angiopoietin-1 differs from that of known angiogenic factors or other ligands for receptor tyrosine kinases. Although Angiopoietin-1 binds and induces the tyrosine phosphorylation of TIE2, it does not directly promote the growth of cultured endothelial cells. However, its expression in close proximity with developing blood vessels implicates Angiopoietin-1 in endothelial developmental processes.

Introduction

Embryonic vascular development involves a complex series of events during which endothelial cells differentiate, proliferate, migrate, and undergo morphologic organization in the context of their surrounding tissues (Risau, 1991, 1995). Vascular development is generally classified into two successive phases. The first, known as vasculogenesis, refers to the process whereby newly differentiated endothelial cells spontaneously coassemble into tubules that fuse to form a rather homogeneous primary vasculature in the embryo. Subsequent remodeling of this primary vascular network into large and small vessels brings into play a different process, termed angiogenesis. Angiogenesis in the embryo also leads to the sprouting of vessels into initially avascular organs, such as the brain. In the adult, angiogenesis accounts for neovascularization that accompanies the normal processes of ovulation, placental development, and wound healing, as well as various clinically significant pathologic processes such as tumor growth and diabetic retinopathy (Ferrara, 1995; Folkman, 1995; Hanahan and Folkman, 1996).

Intercellular signaling mechanisms that govern the formation of blood vessels have only recently begun to be studied at the molecular level. Two families of receptor tyrosine kinases have been identified whose expression is largely restricted to endothelial cells and which are essential for normal development of blood vessels (Mustonen and Alitalo, 1995). One family includes Flt-1, Flk-4, and Flk-1/KDR, all of which are members of the vascular endothelial growth factor (VEGF) receptor family. The requisite roles of Flt-1 and Flk-1 during vascular development, as well as that of VEGF, have been confirmed by analysis of genetically engineered mice lacking these proteins (Fong et al., 1995; Shalaby et al., 1995; Carmeliet et al., 1996; Ferrara et al., 1996). The more recently discovered TIE receptor family (Dumont et al., 1992; Partanen et al., 1992; Iwama et al., 1993; Maisonpierre et al., 1993; Sato et al., 1993; Schnurch and Risau, 1993; Ziegler et al., 1993), consisting of TIE1 and TIE2 (also termed Tek), also have been found to be critically involved in the formation of vasculature (Dumont et al., 1994; Puri et al., 1995; Sato et al., 1995). Mice deficient in TIE1 die between embryonic day 13.5 (E13.5) and birth and display edema and hemmorhage resulting from poor structural integrity of the endothelial cells (Puri et al., 1995; Sato et al., 1995). In contrast, mice deficient in TIE2 have an earlier lethal phenotype and die by E10.5 (Dumont et al., 1994; Sato et al., 1995). The most prominent defects observed in these mice include the failure of the endothelial lining of the heart to develop properly, the failure of remodelling of the primary capillary plexus into large and small vessels, and the lack of capillary sprouts into the neuroectoderm. In addition to their expression by endothelial cells, the TIEs are also specifically expressed in early hemopoietic stem cells (Iwama et al., 1993; Batard et al., 1996; Hashiyama et al., 1996), perhaps reflecting the origin of both lineages from a common hemangioblast precursor (Shalaby et al., 1995); however, the early death of mice lacking the TIEs has limited the use of these mice in elucidating the precise roles of the TIEs in hemopoiesis (Rodewald and Sato, 1996). Because the TIE receptor family is critically involved in angiogenesis and may play a role in hemopoiesis as well, we initiated a search for ligands that may activate these receptors. Here we describe the use of a novel expression cloning strategy to identify a secreted ligand for the TIE2 receptor, which we designate Angiopoietin-1 to reflect not only its requisite role in angiogenesis (Suri et al., 1996 [this issue of *Cell*]) but also its potential actions during hemopoiesis.

Searches for the ligands for orphan receptors have traditionally proceeded by several routes, depending on the type of ligand that is sought. In the case of secreted ligands, two major approaches have been used. The first uses soluble forms of the receptors to effect affinity purification of the ligands, followed by protein sequencing and cloning of cDNAs containing the desired peptides (e.g., Stitt et al., 1995). Alternatively, expression cloning strategies involve the construction and screening of "pooled expression libraries" (e.g., Lok et al., 1994). In these strategies, many small pools of cDNAs are individually transfected into cells, and conditioned media from the individual transfections are then separately assayed for their ability to produce activities that stimulate receptor-bearing reporter cells. A sensitive and simple assay must be available, since tens of thousands of pools often must be screened, particularly if the desired cDNA is present only at low abundance.

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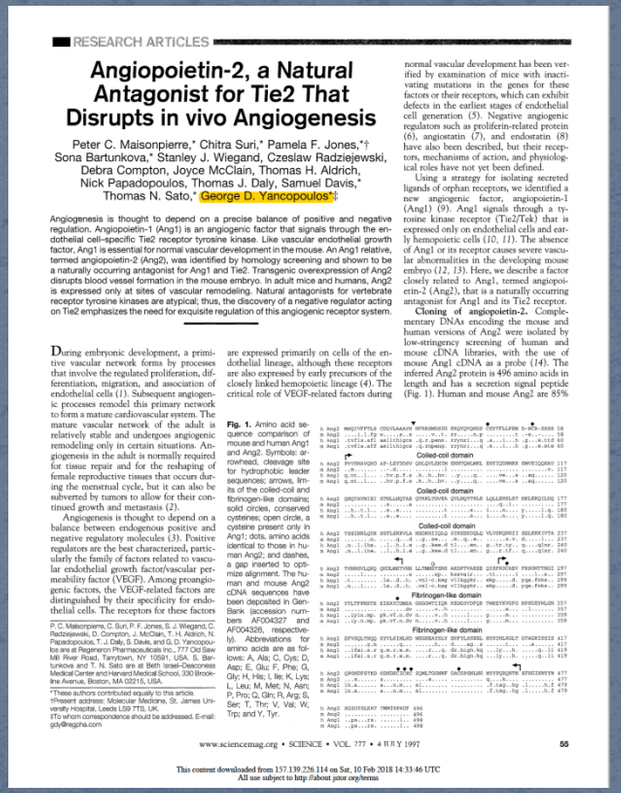

RESEARCH ARTICLES

Angiopoietin-2, a Natural Antagonist for Tie2 That Disrupts in vivo Angiogenesis

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Angiogenesis is thought to depend on a precise balance of positive and negative regulation. Angiopoietin-1 (Ang1) is an angiogenic factor that signals through the endothelial cell–specific Tie2 receptor tyrosine kinase. Like vascular endothelial growth factor, Ang1 is essential for normal vascular development in the mouse. An Ang1 relative, termed angiopoietin-2 (Ang2), was identified by homology screening and shown to be a naturally occurring antagonist for Ang1 and Tie2. Transgenic overexpression of Ang2 disrupts blood vessel formation in the mouse embryo. In adult mice and humans, Ang2 is expressed only at sites of vascular remodeling. Natural antagonists for vertebrate receptor tyrosine kinases are atypical; thus, the discovery of a negative regulator acting on Tie2 emphasizes the need for exquisite regulation of this angiogenic receptor system.

During embryonic development, a primitive vascular network forms by processes that involve the regulated proliferation, differentiation, migration, and association of endothelial cells (*1*). Subsequent angiogenic processes remodel this primary network to form a mature cardiovascular system. The mature vascular network of the adult is relatively stable and undergoes angiogenic remodeling only in certain situations. Angiogenesis in the adult is normally required for tissue repair and for the reshaping of female reproductive tissues that occurs during the menstrual cycle, but it can also be subverted by tumors to allow for their continued growth and metastasis (*2*).

Angiogenesis is thought to depend on a balance between endogenous positive and negative regulatory molecules (*3*). Positive regulators are the best characterized, particularly the family of factors related to vascular endothelial growth factor/vascular permeability factor (VEGF). Among proangiogenic factors, the VEGF-related factors are distinguished by their specificity for endothelial cells. The receptors for these factors are expressed primarily on cells of the endothelial lineage, although these receptors are also expressed by early precursors of the closely linked hemopoietic lineage (*4*). The critical role of VEGF-related factors during normal vascular development has been verified by examination of mice with inactivating mutations in the genes for these factors or their receptors, which can exhibit defects in the earliest stages of endothelial cell generation (*5*). Negative angiogenic regulators such as proliferin-related protein (*6*), angiostatin (*7*), and endostatin (*8*) have also been described, but their receptors, mechanisms of action, and physiological roles have not yet been defined.

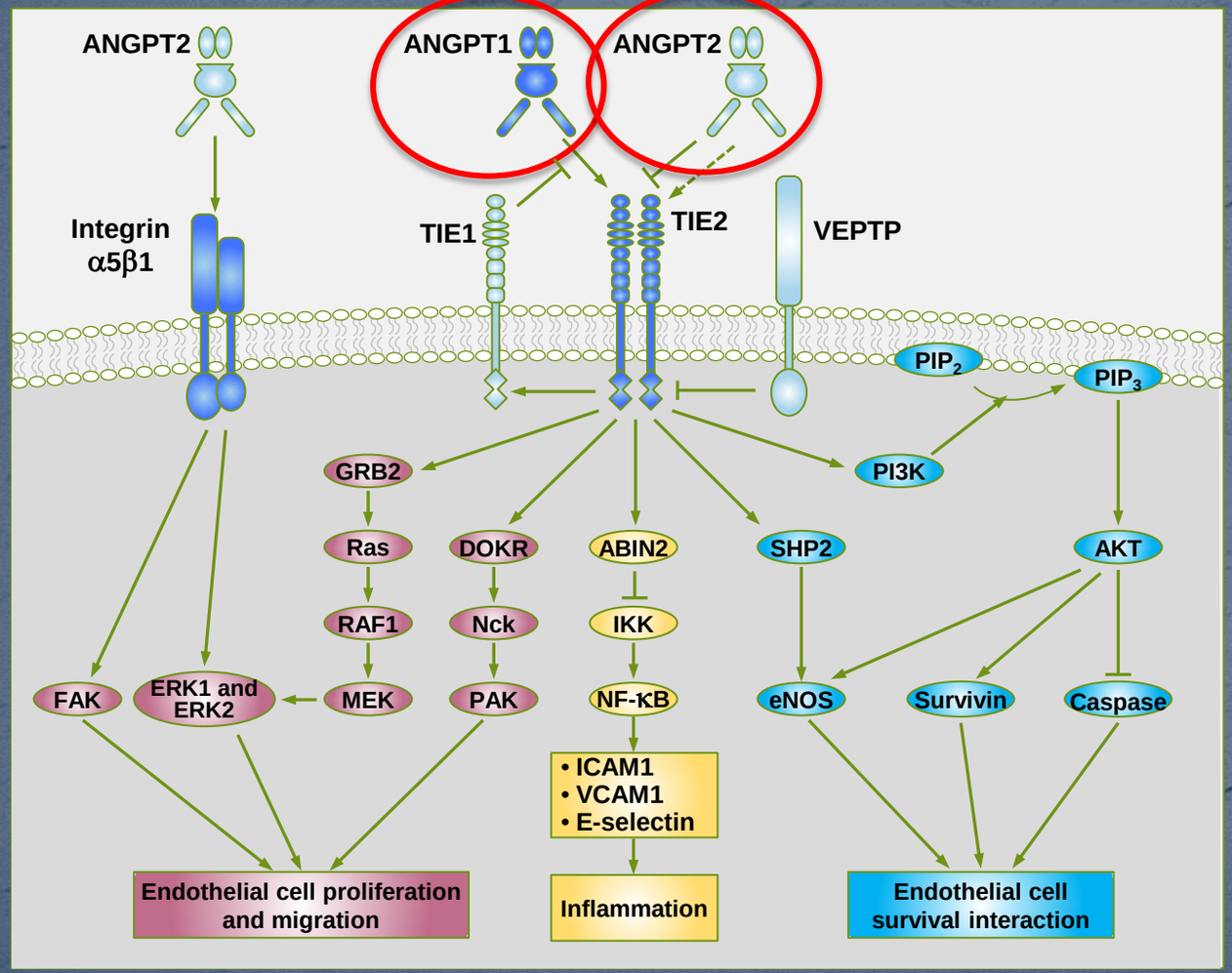
Using a strategy for isolating secreted ligands of orphan receptors, we identified a new angiogenic factor, angiopoietin-1 (Ang1) (*9*). Ang1 signals through a tyrosine kinase receptor (Tie2/Tek) that is expressed only on endothelial cells and early hemopoietic cells (*10*, *11*). The absence of Ang1 or its receptor causes severe vascular abnormalities in the developing mouse embryo (*12*, *13*). Here, we describe a factor closely related to Ang1, termed angiopoietin-2 (Ang2), that is a naturally occurring antagonist for Ang1 and its Tie2 receptor.

Cloning of angiopoietin-2. Complementary DNAs encoding the mouse and human versions of Ang2 were isolated by low-stringency screening of human and mouse cDNA libraries, with the use of mouse Ang1 cDNA as a probe (*14*). The inferred Ang2 protein is 496 amino acids in length and has a secretion signal peptide (Fig. 1). Human and mouse Ang2 are 85% identical to those in human Ang2; and dashes, a gap inserted to optimize alignment. The human and mouse Ang2 cDNA sequences have been deposited in GenBank (accession numbers AF004327 and AF004328), respectively). Abbreviations for amino acids are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

Fig. 1. Amino acid sequence comparison of mouse and human Ang1 and Ang2. Symbols: arrowhead, cleavage site for hydrophobic leader sequences; arrows, limits of the coiled-coil and fibrinogen-like domains; solid circles, conserved cysteines; open circle, a cysteine present only in Ang1; dots, amino acids identical to those in human Ang2; and dashes, a gap inserted to optimize alignment. The human and mouse Ang2 cDNA sequences have been deposited in GenBank (accession numbers AF004327 and AF004328), respectively). Abbreviations for amino acids are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

[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.

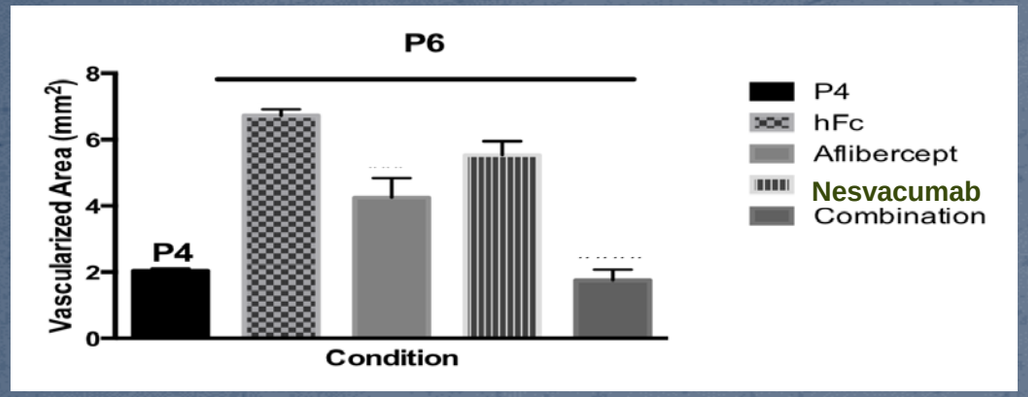
ANGIOPOIETIN/TIE2 SIGNALING PATHWAY



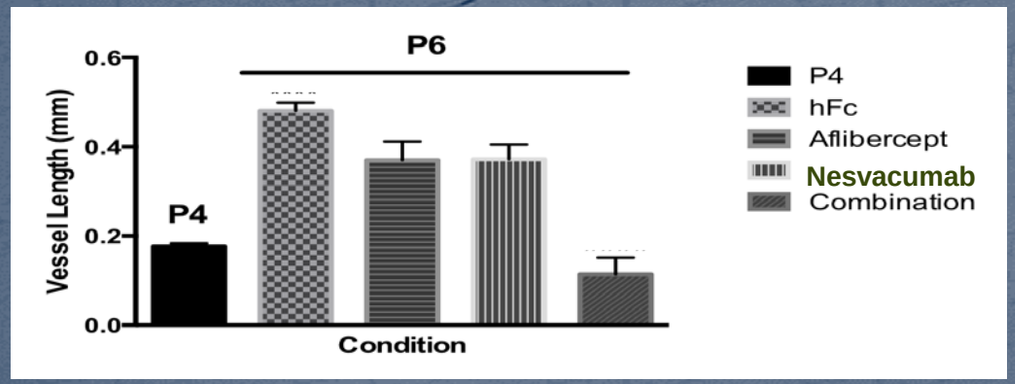
- Tie2 is an endothelial cell-specific tyrosine kinase receptor to which two ligands bind
  - **Ang1 –**
    - Expressed in normal adult tissues to help maintain vascular integrity
  - **Ang2 –**
    - Secreted by endothelial cells
    - Required for post-natal vascular remodeling and is ***only expressed under pathological conditions***
    - Expressed in endothelial cells at
      - very low levels in quiescent blood vessels
      - high levels in ‘angiogenic’ vessels

Thurston and Daly. Cold Spring Harb Perspect Med 2012;2:a006650
Jones et al. Nature Reviews Molecular Cell Biology 2, 257-267 (April 2001)
Eklund, Lauri et al. "Angiopoietin signaling in the vasculature." Experimental cell research 319.9 (2013): 1271-1280

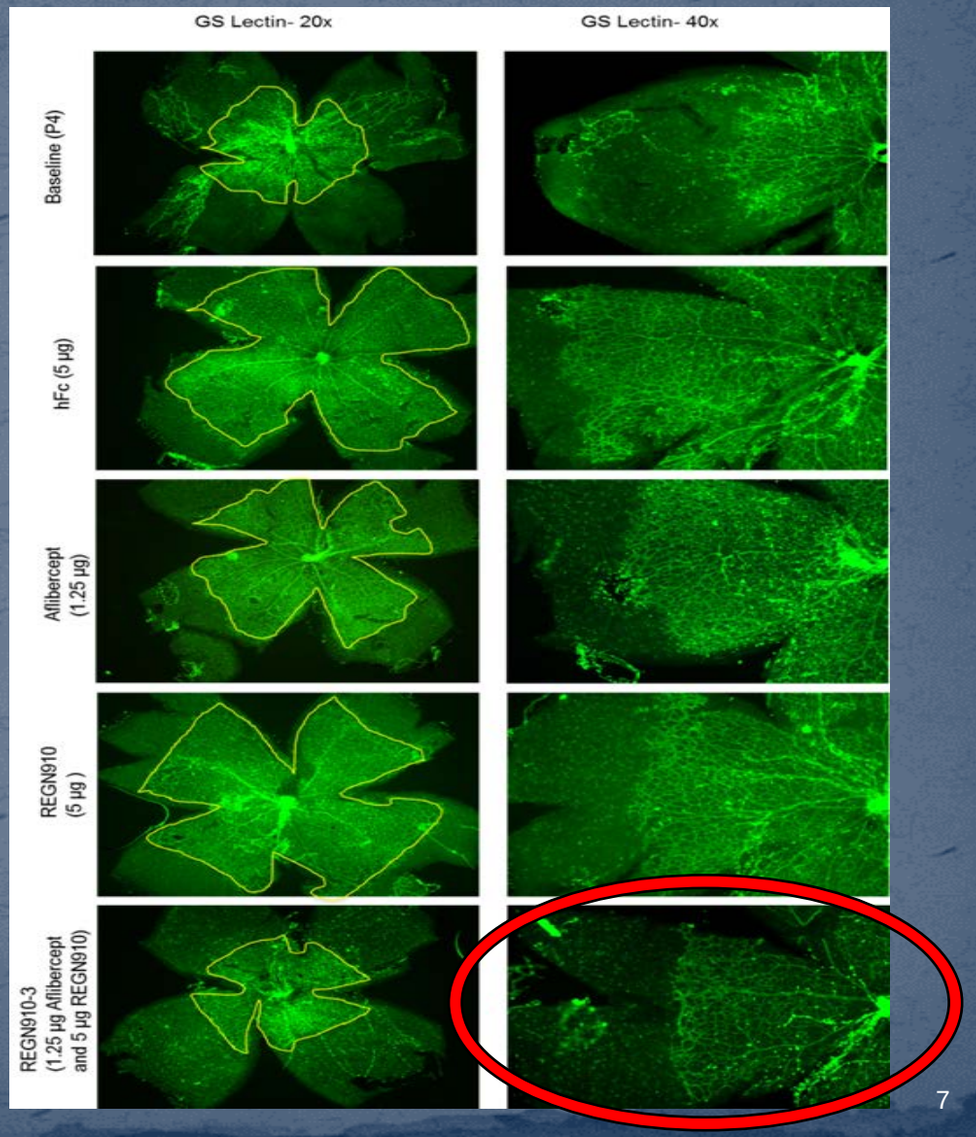
Effect of IVT Administration of Nesvacumab, Alone or in Combination with Aflibercept in a Retinal Vascular Development Model



Area of the superficial retinal plexus



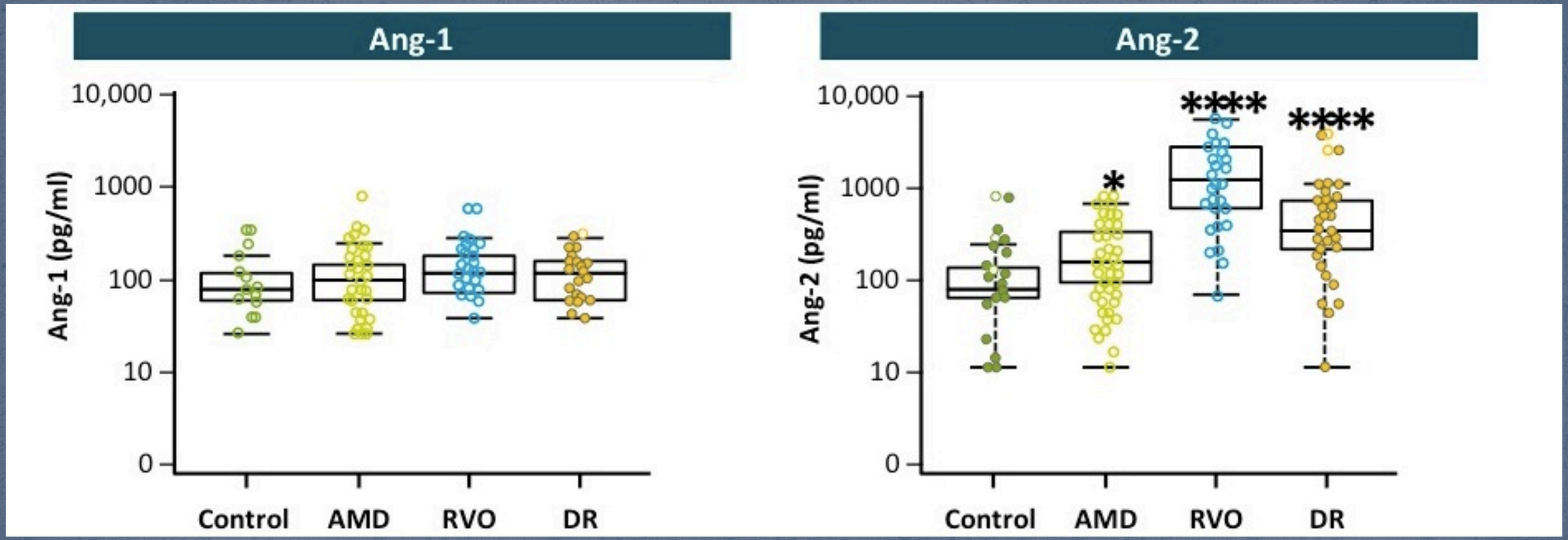
Total vessel length superficial retinal plexus



P4 (post natal day 4); P6 (post natal day 6)

Ang-2 Levels Elevated in Human Vitreous
RVO > DR > AMD

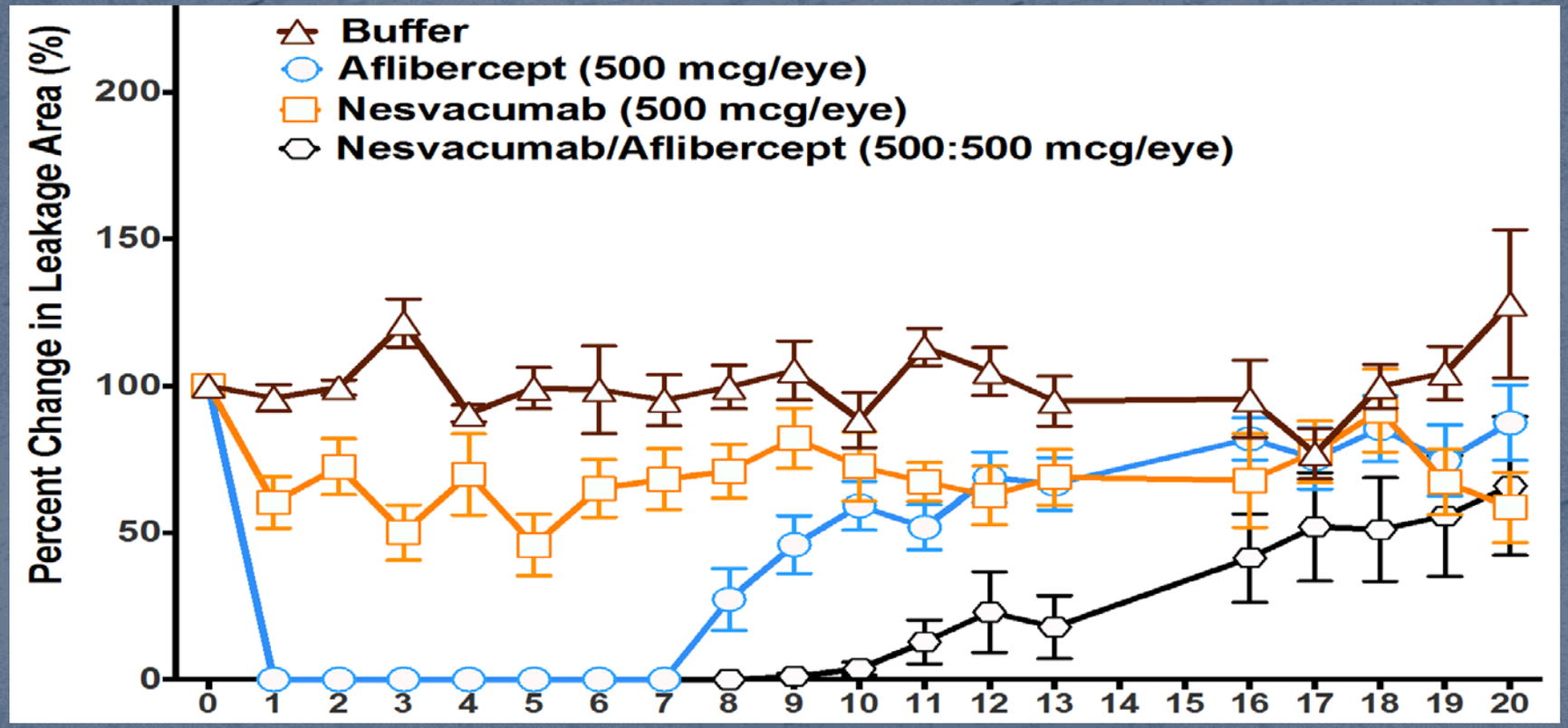
Vitreous levels in newly diagnosed patients



Data courtesy of Roche US Medical Affairs

Nesvacumab Increased Duration Of Anti-leak Action Of Aflibercept In Preclinical Model Of Chronic Vascular Leak

Single IVT injection of aflibercept or nesvacumab or both co-formulated



NESVACUMAB/AFLIBERCEPT (CO-FORMULATED ANTI-ANG2 + ANTI-VEGF)

- Nesvacumab/aflibercept is a co-formulated drug product consisting of the fully human mAb, REGN910, and the fusion protein, aflibercept

Study Design
Baseline - Week 12

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

Key Eligibility Criteria

- Clinically significant DME with central involvement
- BCVA ETDRS letter score equivalent to 20/40 to 20/320
- Intravitreal anti-VEGF ≥ 3 months from screening
- Panretinal laser photocoagulation or macular laser photocoagulation ≥ 3 months from screening
- Intraocular or periocular corticosteroids in the study eye ≥ 4 months from screening

LD Combo
Nesvacumab (3 mg) + aflibercept (2 mg) q4 weeks
(n=50)

HD Combo
Nesvacumab (6 mg) + aflibercept (2 mg) q4 weeks
(n=100)

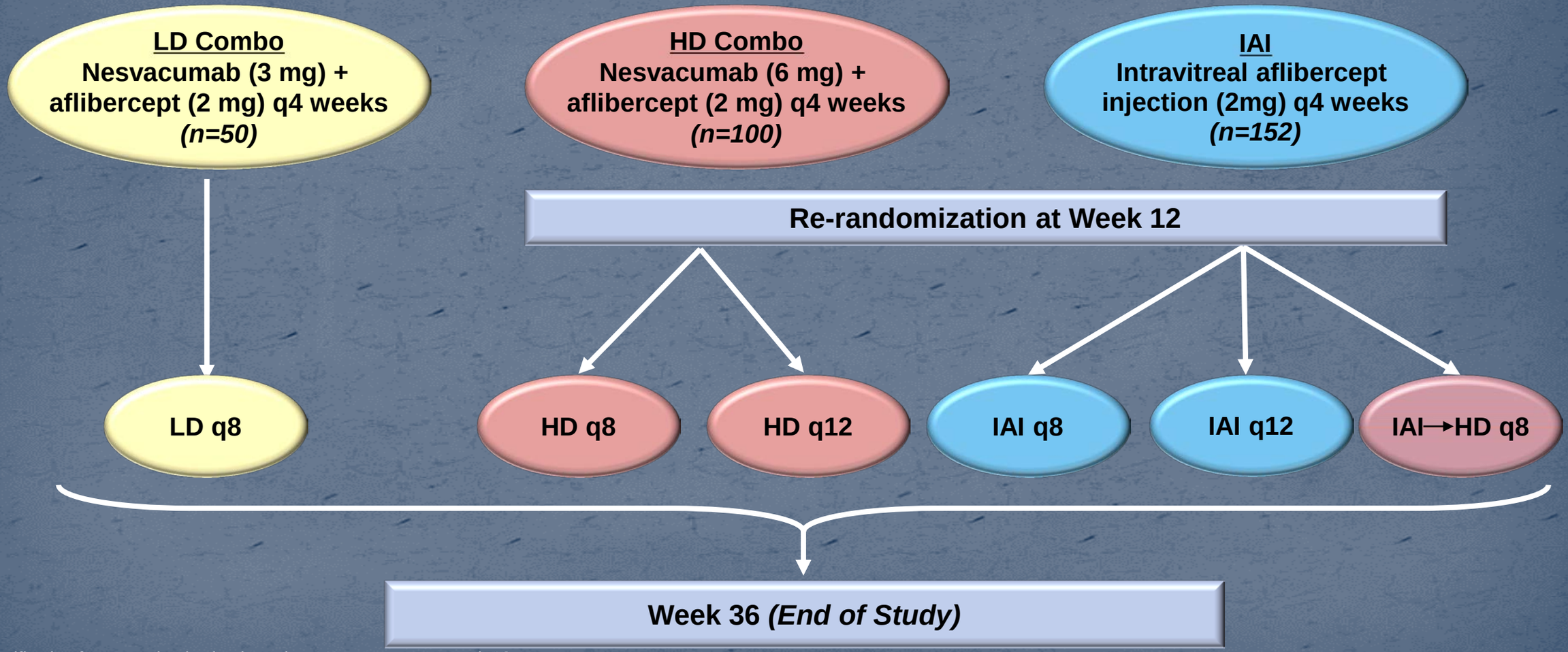
IAI
Intravitreal aflibercept injection (2 mg) q4 weeks
(n=152)

Week 12

Week 36 *(End of Study)*

LD: Low Dose; HD: High Dose

Study Design
Week 12 – Week 36



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

Patients Disposition and Demographics

	LD	HD	IAI	Total
	(n=50)	*(n=100)*	*(n=152)*	*(N=302)*
Patients completing Week 12 , n (%)	46 (92.0%)	97 (97.0%)	148 (97.4%)	291 (96.4%)
Mean Age, years (SD)	62.1 (8.90)	62.4 (10.37)	59.5 (10.24)	60.9 (10.15)
Female, n (%)	21 (42.0%)	49 (49.0%)	68 (44.7%)	138 (45.7%)
Race, n (%)				
White	37 (74.0%)	87 (87.0%)	121 (79.6%)	245 (81.1%)
Black or African American	11 (22.0%)	8 (8.0%)	19 (12.5%)	38 (12.6%)
Asian	1 (2.0%)	2 (2.0%)	4 (2.6%)	7 (2.3%)
American Indian or Alaska Native	1 (2.0%)	0	3 (2.0%)	4 (1.3%)
Native Hawaiian or Other Pacific Islander	0	1 (1.0%)	0	1 (0.3%)
Other	0	0	3 (2.0%)	3 (1.0%)
Not Reported	0	2 (2.0%)	2 (1.3%)	4 (1.3%)

SAF
LD: Low Dose; HD: High Dose

Baseline Disease Characteristics

	LD	HD	IAI	Total
	(n=47)	*(n=99)*	*(n=150)*	*(N=296)*
Mean Baseline Hemoglobin A1C (SD)	8.5 (1.86)	7.8 (1.61)	8.1 (1.86)	8.0 (1.79)
Mean Diabetes Duration, years (SD)	17.6 (10.93)	17.5 (11.22)	15.8 (10.69)	16.7 (10.90)
Diabetes Type, n (%)				
Type 1	2 (4.3%)	5 (5.1%)	11 (7.3%)	18 (6.1%)
Type 2	45 (95.7%)	94 (94.9%)	139 (92.7%)	278 (93.9%)
Prior Treatment for DME/DR*, Study Eye, n %	27 (57.4%)	40 (40.4%)	58 (38.7%)	125 (42.2%)
Prior Focal or Grid Laser	19 (40.4%)	27 (27.3%)	36 (24.0%)	82 (27.7%)
Prior Intravitreal Anti-VEGF	12 (25.5%)	28 (28.3%)	27 (18%)	67 (22.6%)
Prior Intravitreal Steroids	4 (8.5%)	7 (7.1%)	7 (4.7%)	18 (6.1%)

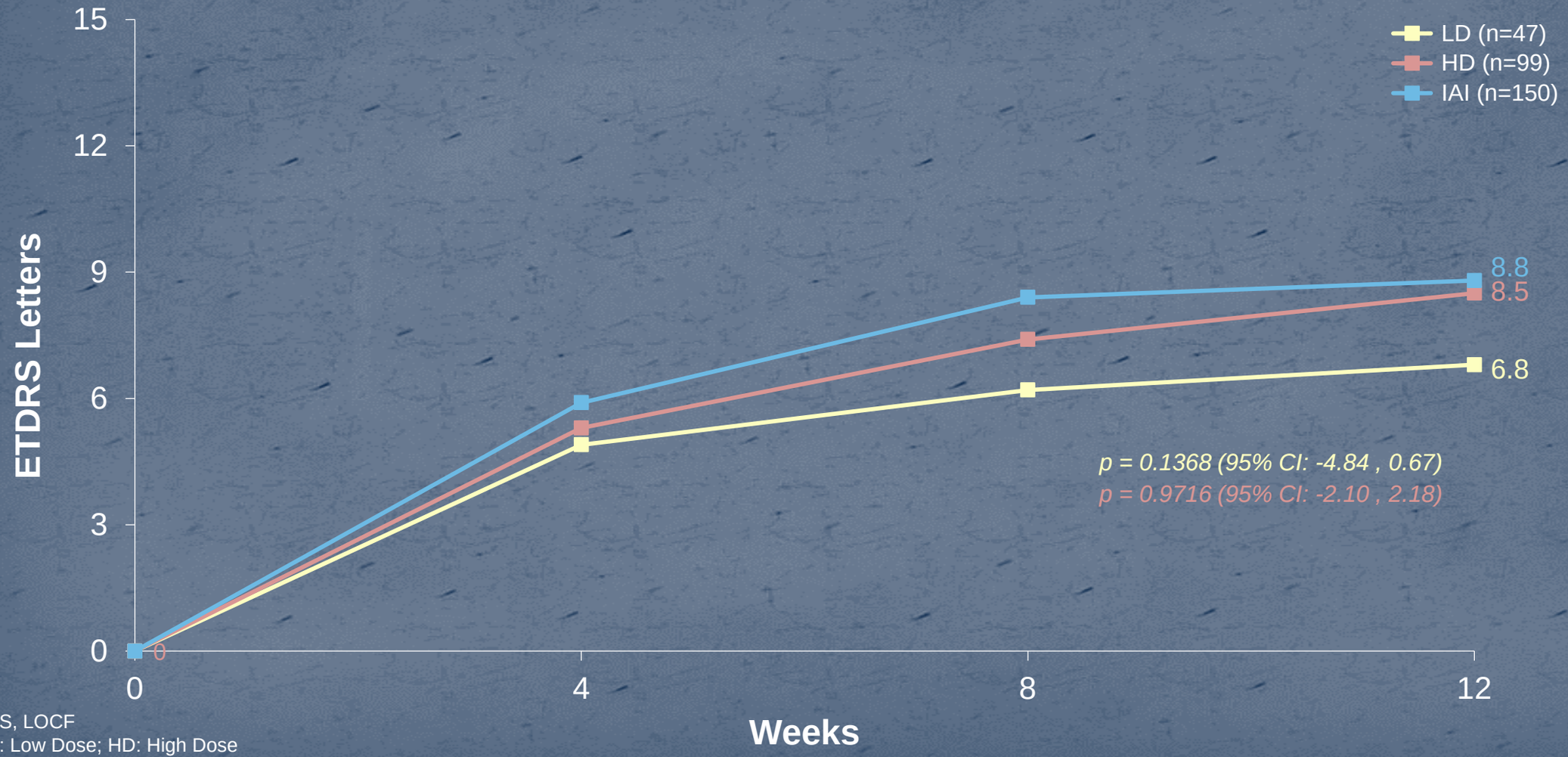
FAS
*Patients could have had more than one treatment
LD: Low Dose; HD: High Dose

Baseline Disease Characteristics

	LD	HD	IAI	Total
	(n=47)	*(n=99)*	*(n=150)*	*(N=296)*
Mean ETDRS BCVA, letters (SD)	57.7 (11.13)	60.6 (11.11)	58.7 (10.78)	59.2 (10.96)
Mean CRT, um (SD)	484.2 (152.78)	497.8 (151.77)	520.1 (151.27)	507.0 (151.80)
Diabetic Retinopathy Severity Score, n (%)				
10, 20	0	3 (3.0%)	1 (0.7%)	4 (1.4%)
35	10 (21.3%)	14 (14.1%)	17 (11.3%)	41 (13.9%)
43	10 (21.3%)	15 (15.2%)	37 (24.7%)	62 (20.9%)
47	9 (19.1%)	34 (34.3%)	46 (30.7%)	89 (30.1%)
53	13 (27.7%)	19 (19.2%)	35 (23.3%)	67 (22.6%)
61	1 (2.1%)	2 (2.0%)	4 (2.7%)	7 (2.4%)
65	1 (2.1%)	7 (7.1%)	3 (2.0%)	11 (3.7%)
71	1 (2.1%)	4 (4.0%)	5 (3.3%)	10 (3.4%)
75	1 (2.1%)	0	1 (0.7%)	2 (0.7%)

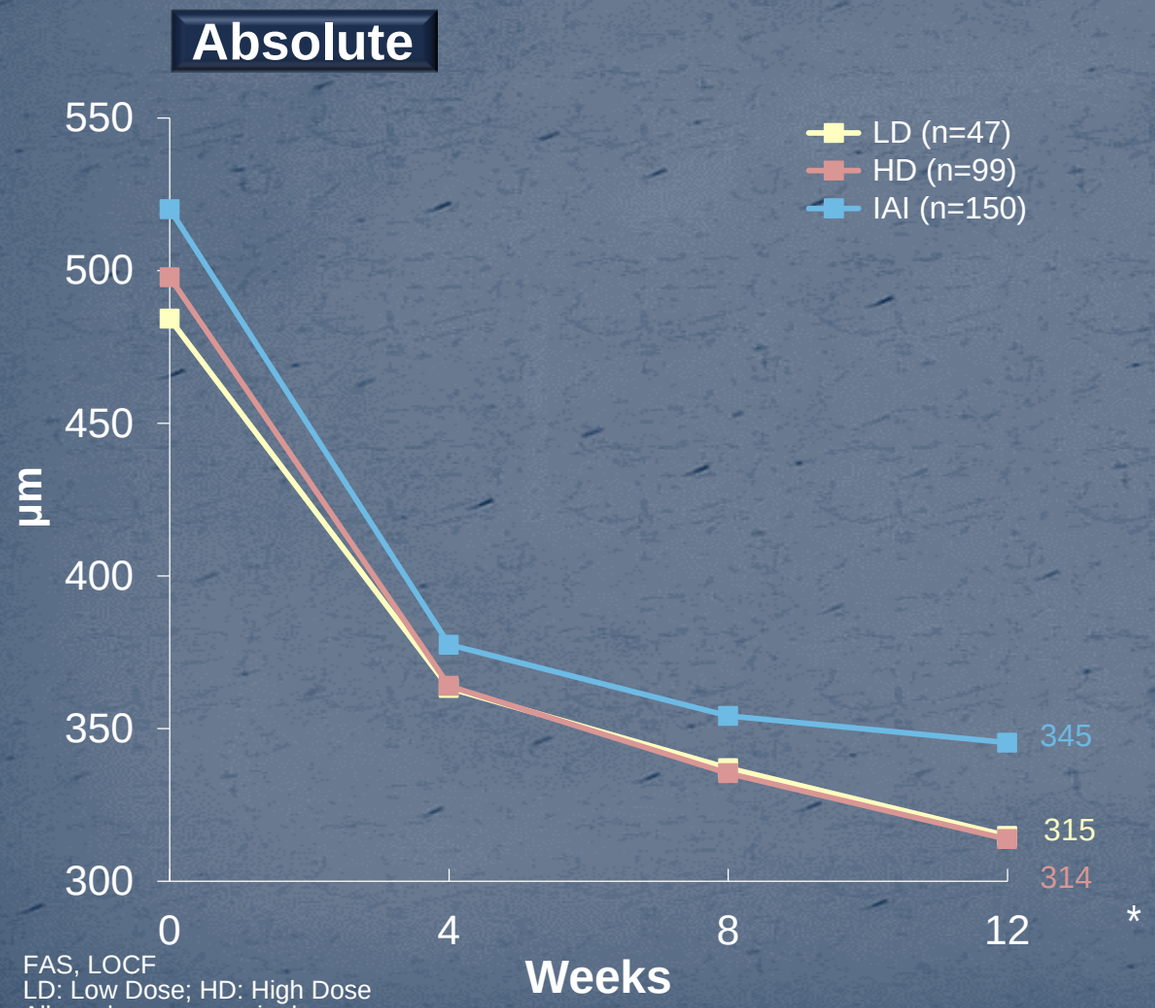
FAS, 3 patients (1 in each group) were ungradable for DRSS and are not included
LD: Low Dose; HD: High Dose

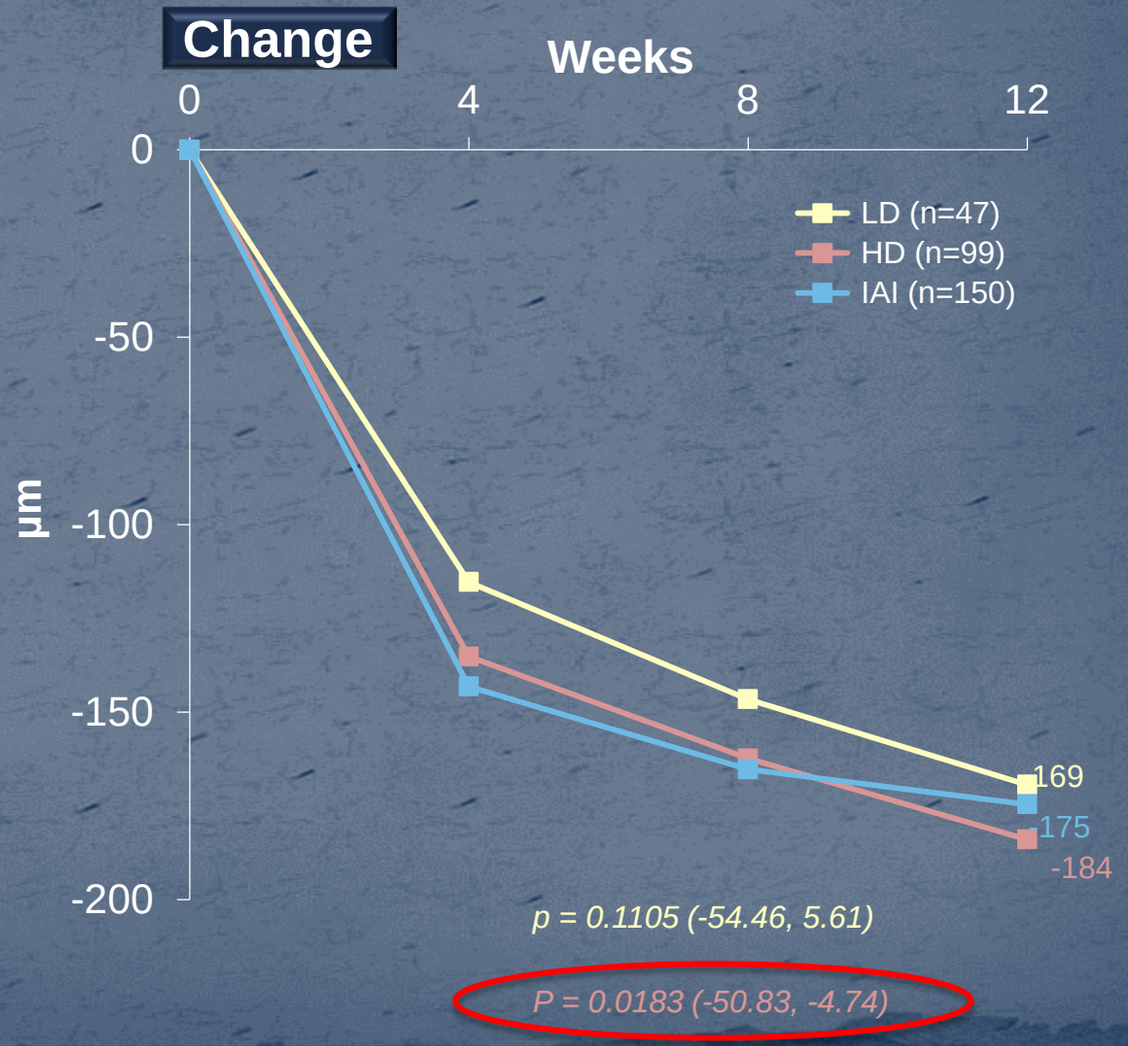
Mean Change in Best-Corrected Visual Acuity
Baseline - Week 12



FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal

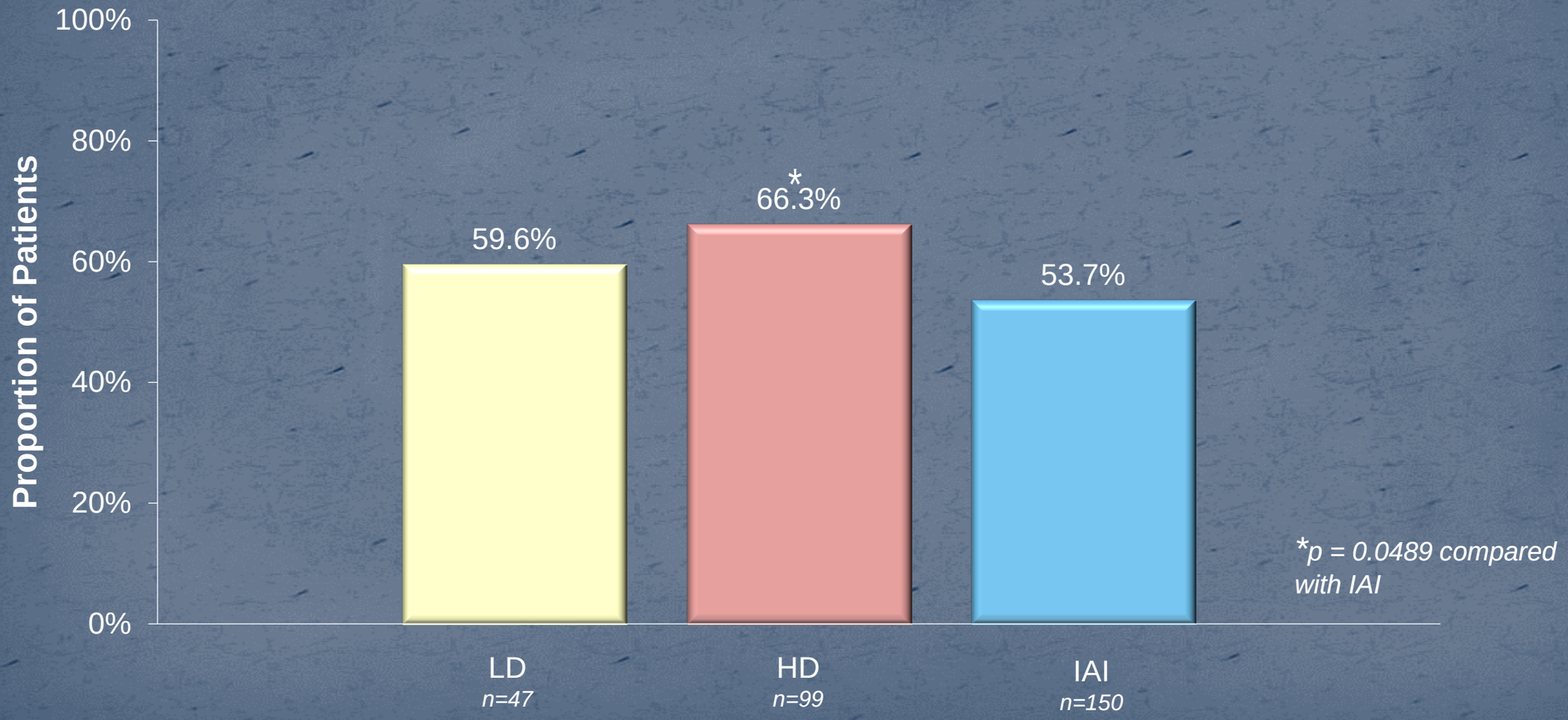
Mean Central Retinal Thickness
Baseline - Week 12





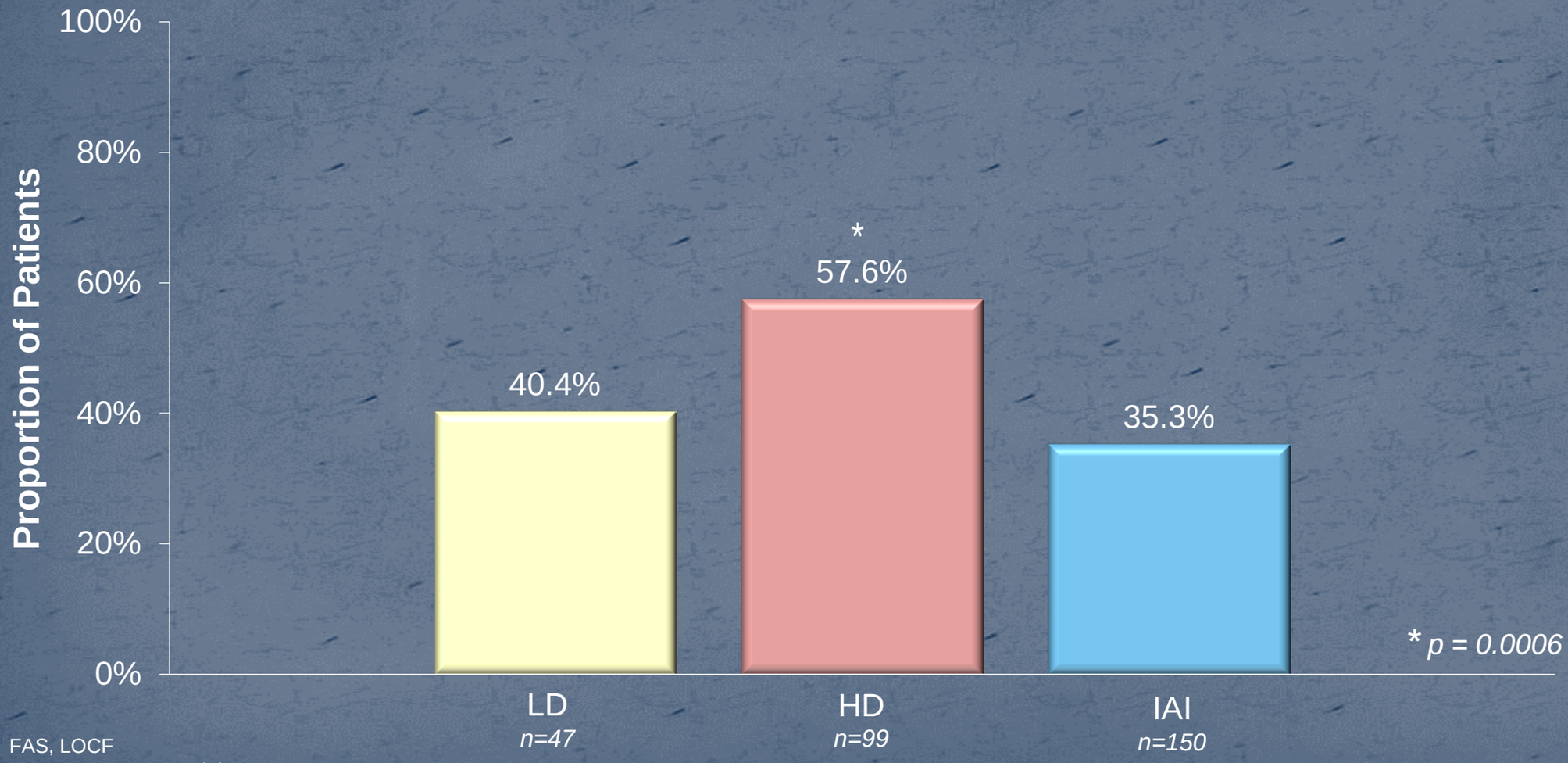
FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal

Proportion of Patients With Complete Resolution of Fluid at the Foveal Center at Week 12



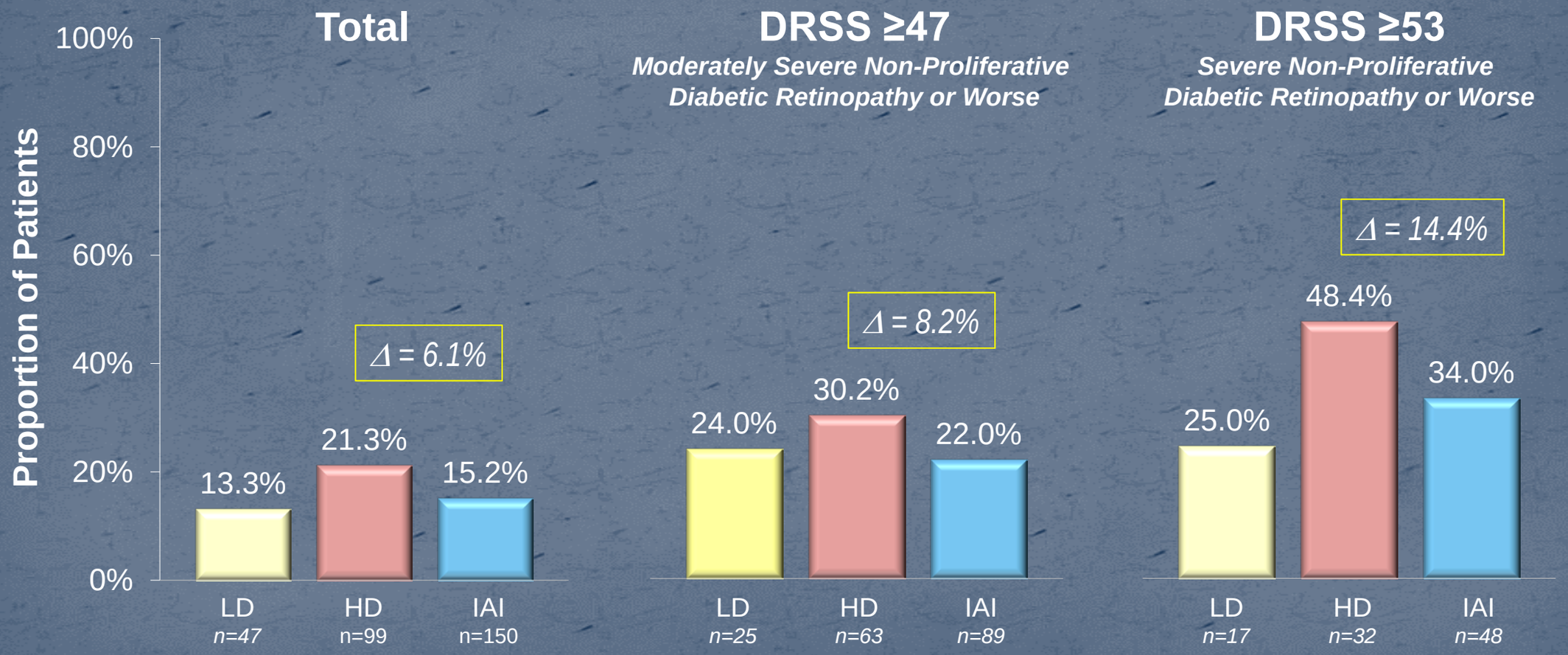
FAS, Patients with no intraretinal or subretinal fluid at the foveal center on SD-OCT, LOCF; LD: Low Dose; HD: High Dose; All p values are nominal

Proportion of Patients With Normalization of Macular Thickness (CRT ≤300 µm) at Week 12



FAS, LOCF
LD: Low Dose; HD: High Dose
All p values are nominal

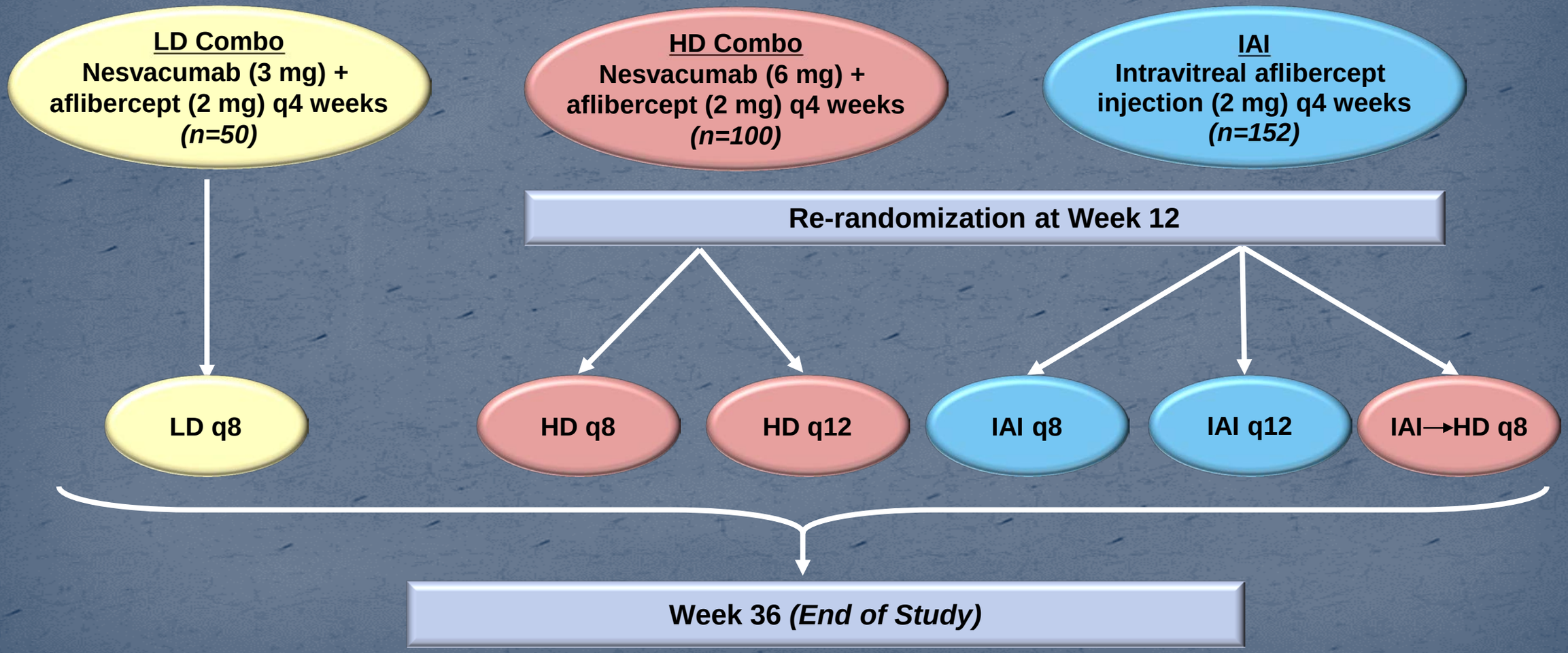
Proportion of Patients With ≥2 Step Improvement in DRSS at Week 12



FAS, LOCF
LD: Low Dose; HD: High Dose

Week 36 

Study Design
Week 12 – Week 36



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

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=45)*	*(n=44)*	*(n=52)*	*(n=46)*	*(n=48)*	*(n=49)*
Number of patients completing week 36, n (%)	44 (97.8%)	42 (95.5%)	50 (96.2%)	46 (100%)	43 (89.6%)	45 (91.8%)

FAS -Secondary randomization set
LD: Low Dose; HD: High Dose

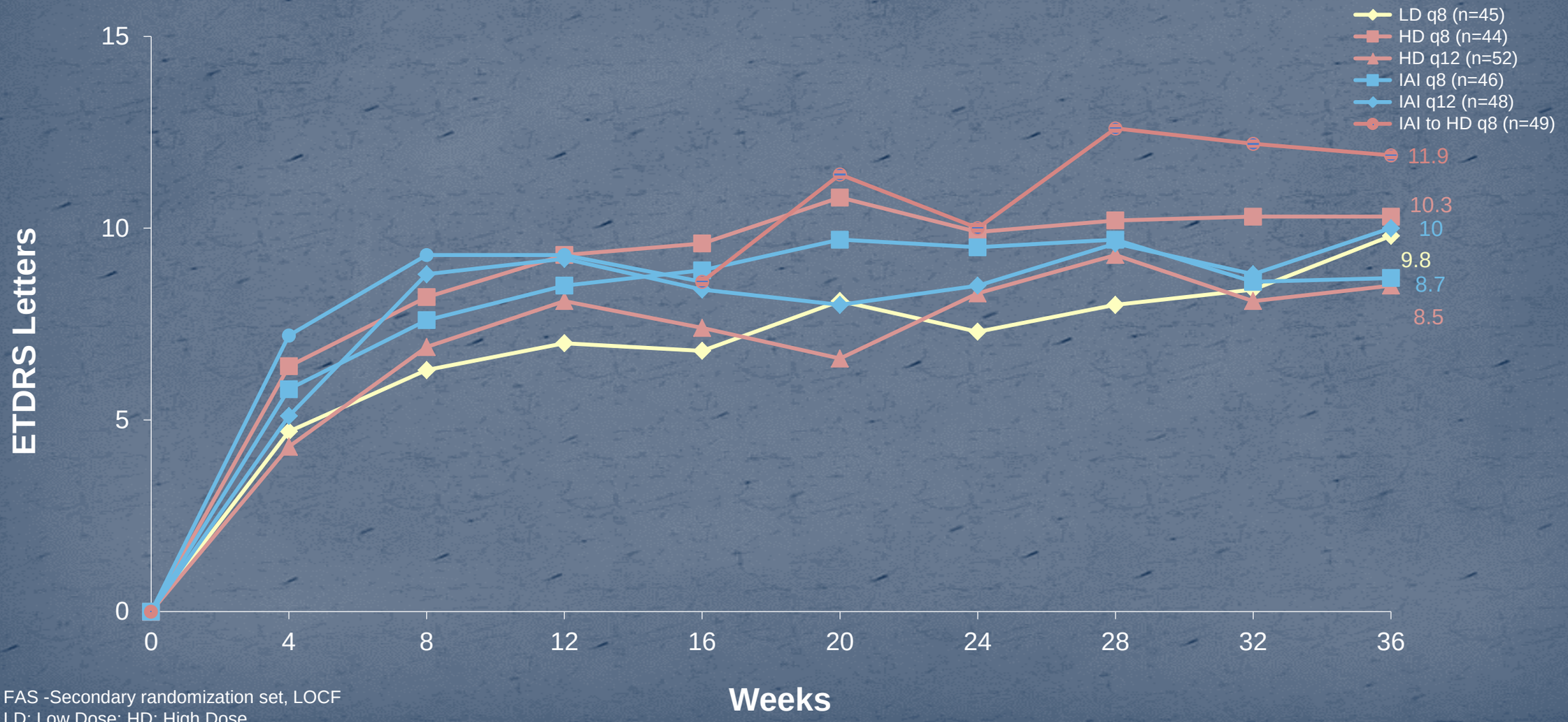
Dose Exposure Through Week 36

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=45)	*(n=44)*	*(n=52)*	*(n=46)*	*(n=48)*	*(n=49)*
Number of Planned Injections, n	6	6	5	6	5	6
Mean Number of Injections, n (SD)	7.2* (0.92)	5.9 (0.35)	5.1* (0.58)	5.9 (0.45)	4.8 (0.63)	5.8 (0.44)

**~10% and 50% of patients received per protocol dosing in the LD q8 and HD q12 groups, respectively.*

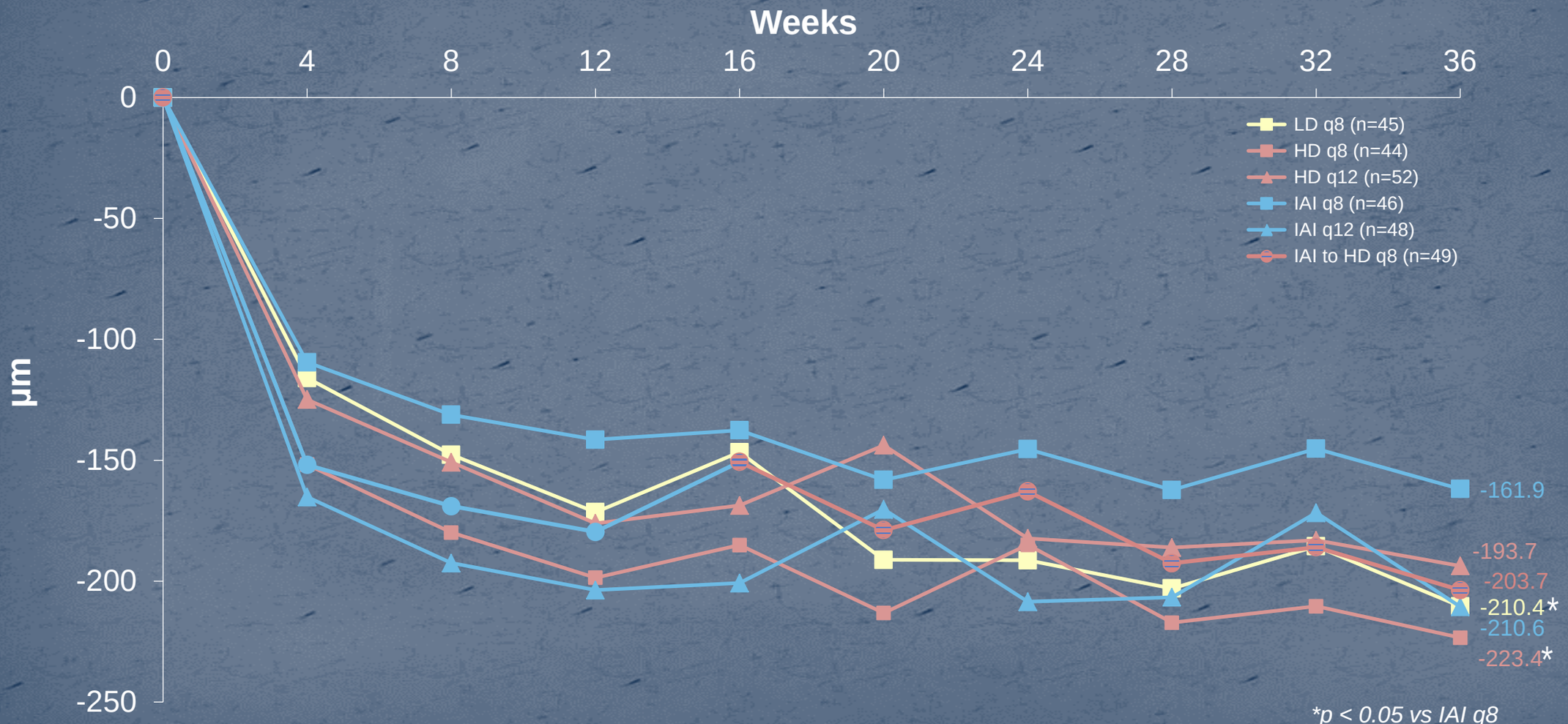
SAF-Secondary randomization set
LD: Low Dose; HD: High Dose

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



FAS -Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose

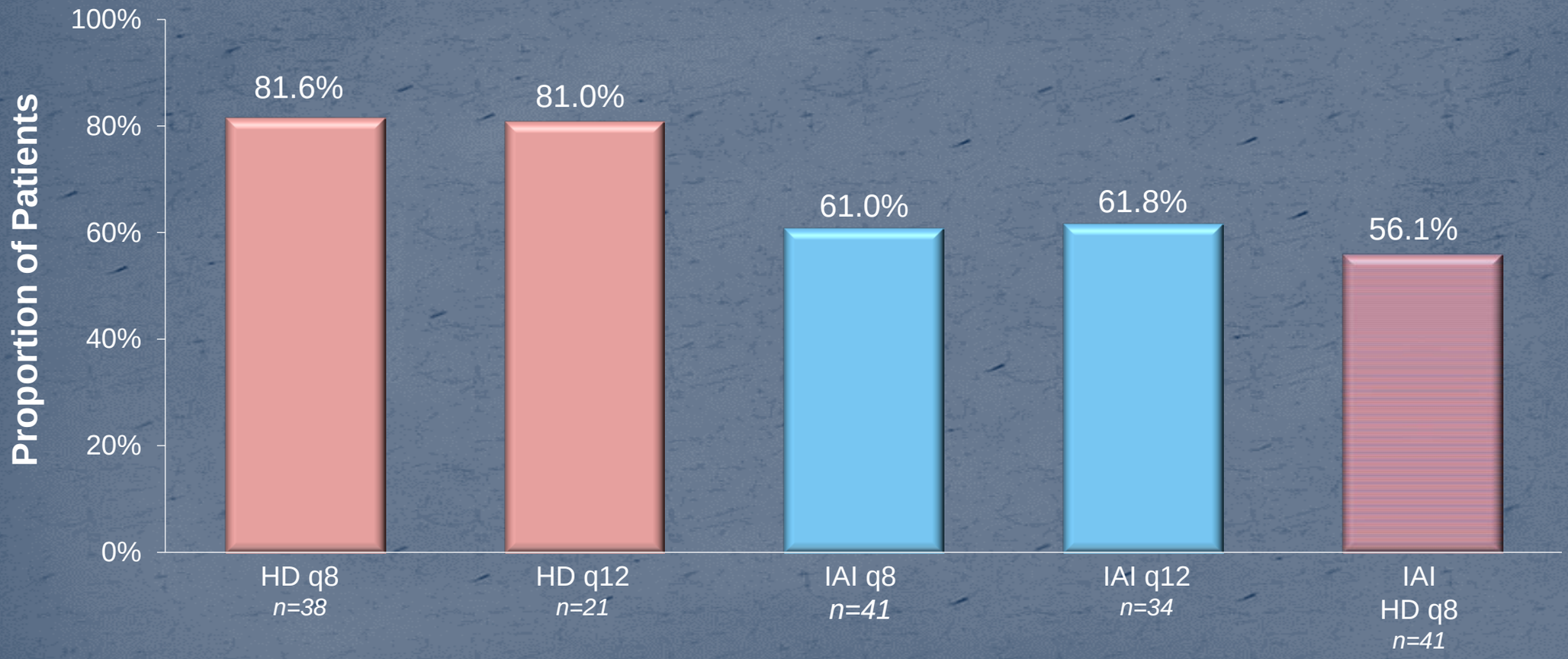
Mean Change in Central Retinal Thickness
Baseline – Week 36



**p < 0.05 vs IAI q8*

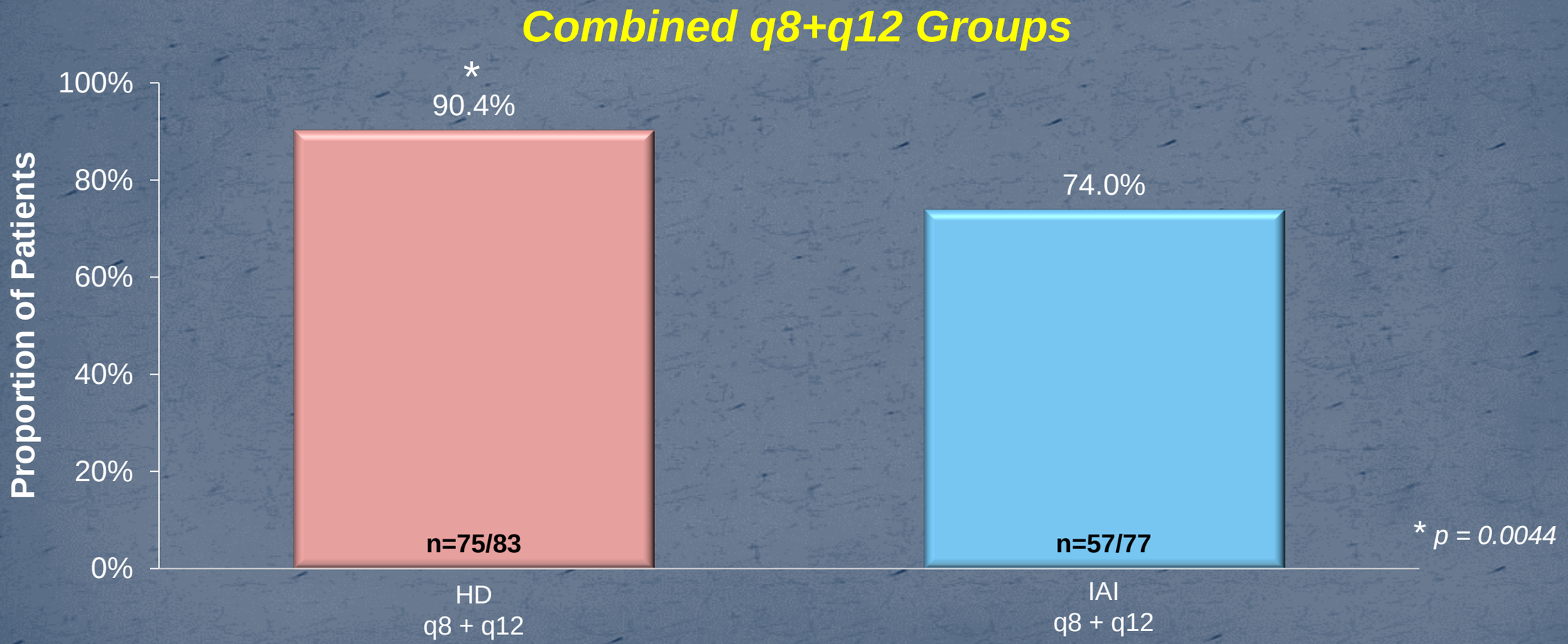
FAS -Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose. All p values are nominal

Proportion of Patients with Complete Resolution of Fluid at the Foveal Center at Week 32*



*8 or 12 weeks from the last study treatment
FAS -Secondary randomization set, OC
Per Protocol Set
LD: Low Dose; HD: High Dose

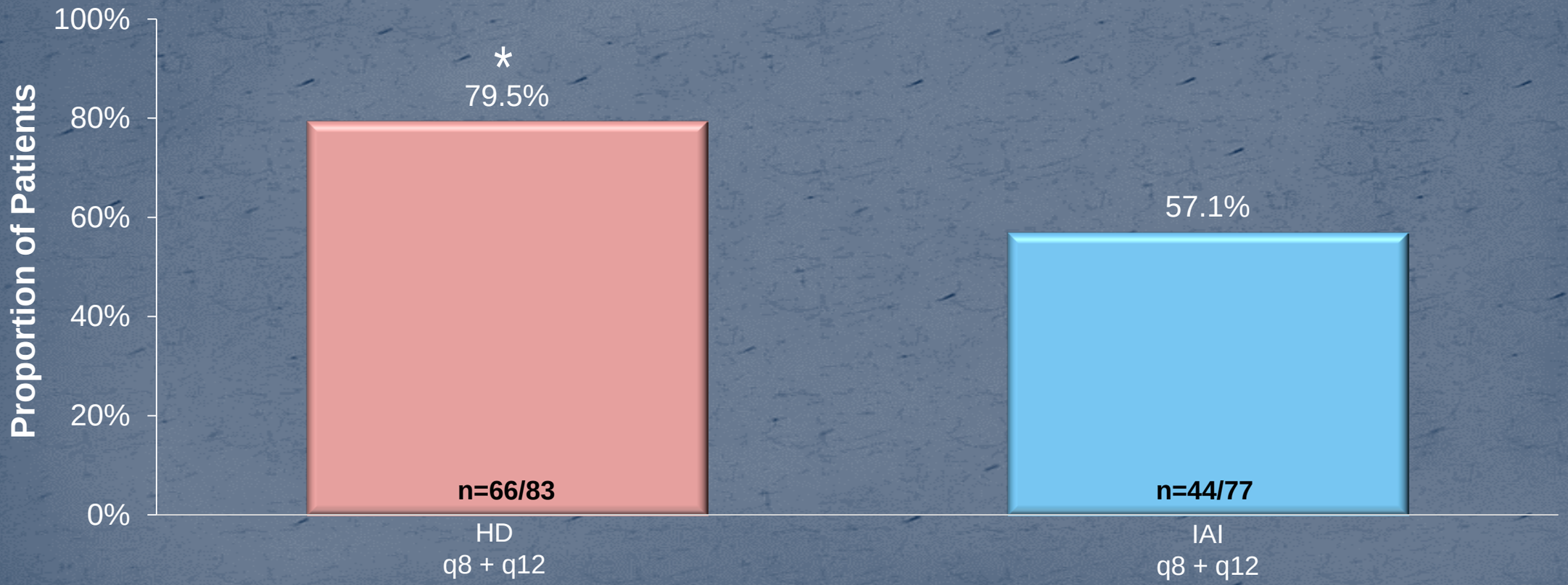
Proportion of Patients with Complete Resolution of Fluid at the Foveal Center at Week 36



FAS -Secondary randomization set, Patients with no intraretinal or subretinal fluid at the foveal center on SD=-OCT; OC
LD: Low Dose; HD: High Dose
All p values are nominal

Patients Maintaining* Complete Resolution of Fluid at the Foveal Center through Week 36

Combined q8+q12 Groups

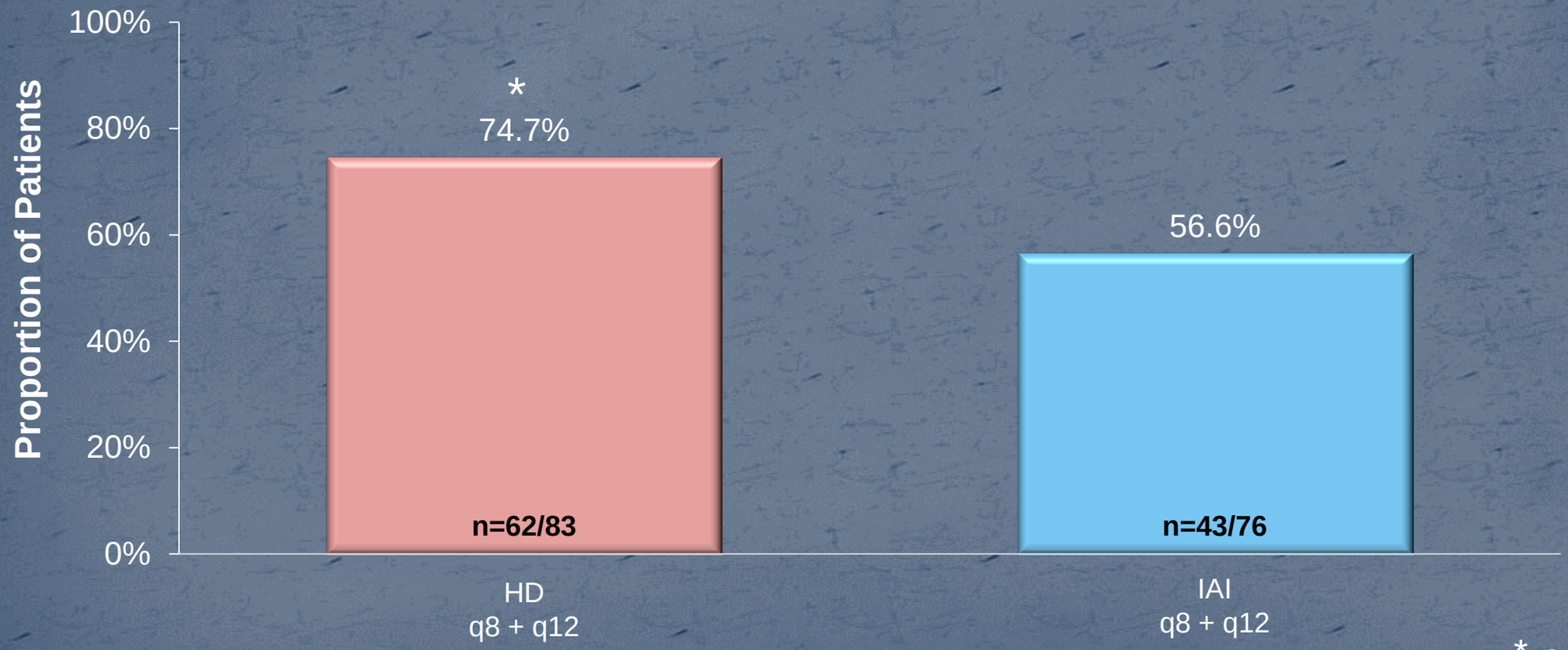


* Defined as reaching “No fluid at the foveal center” and maintaining that status for all subsequent study visits.
FAS -Secondary randomization Set, OC
LD: Low Dose; HD: High Dose
All p values are nominal

** p = 0.0025*

Proportion of Patients with Normalization of Macular Thickness (CRT ≤300 µm) at Week 36

Combined q8+q12 Groups

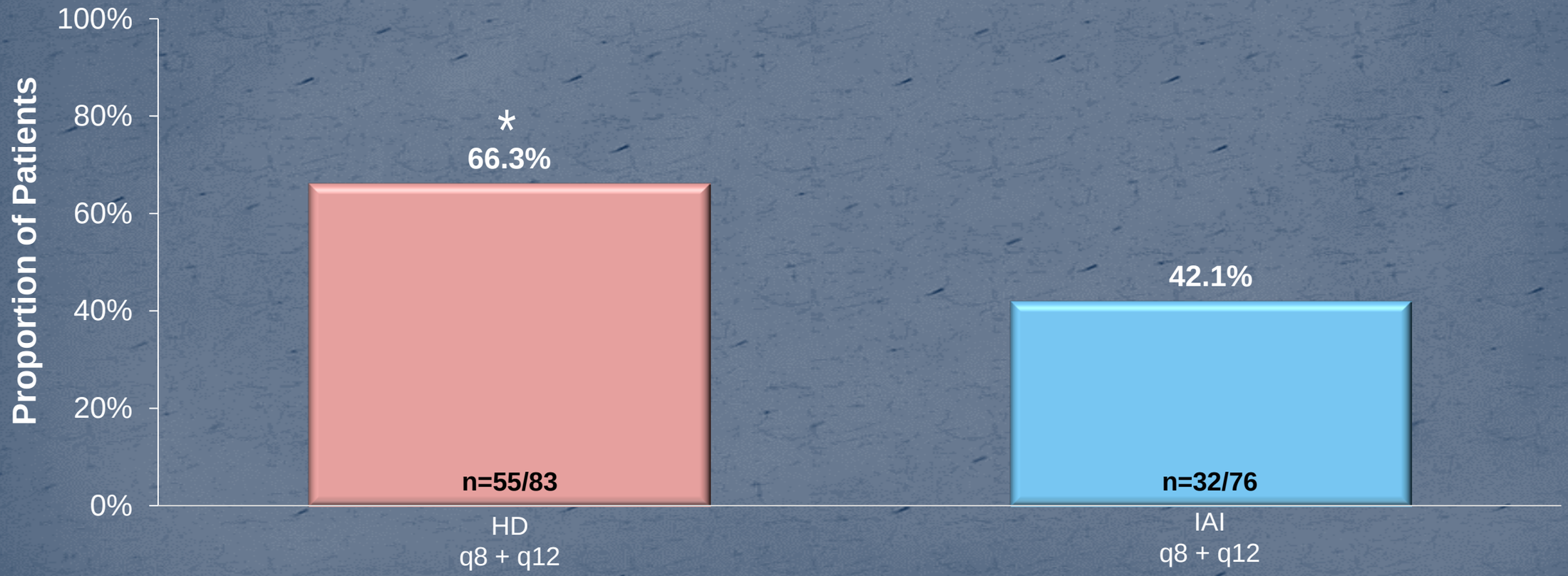


* *p = 0.0089*

FAS- Secondary randomization set; OC
LD: Low Dose; HD: High Dose
All p values are nominal

Patients Maintaining* Normalization of Macular Thickness (CRT ≤300 µm) through Week 36

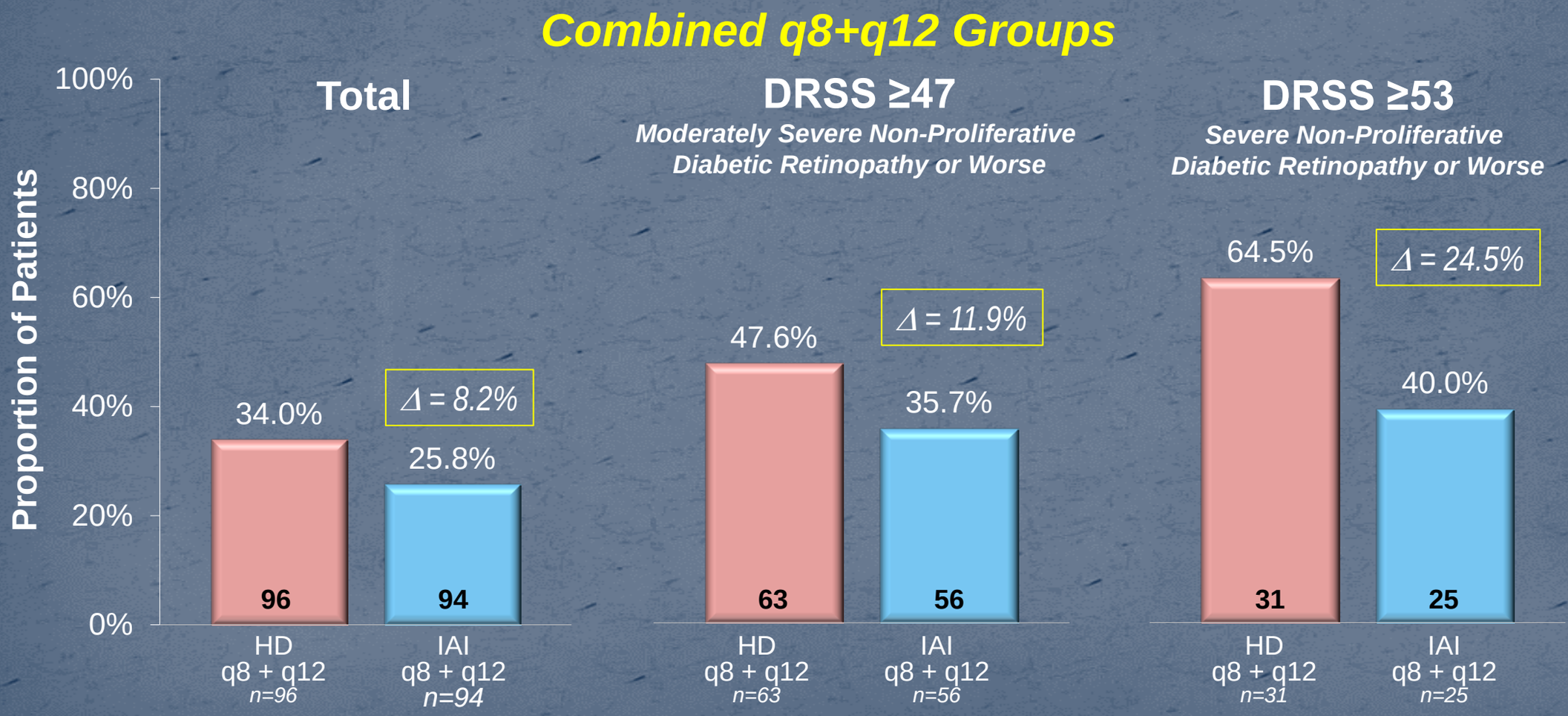
Combined q8+q12 Groups



* Defined as reaching CRT<=300 and maintaining <=300 for all subsequent study visits.
FAS -Secondary randomization Set, OC
LD: Low Dose; HD: High Dose
All p values are nominal

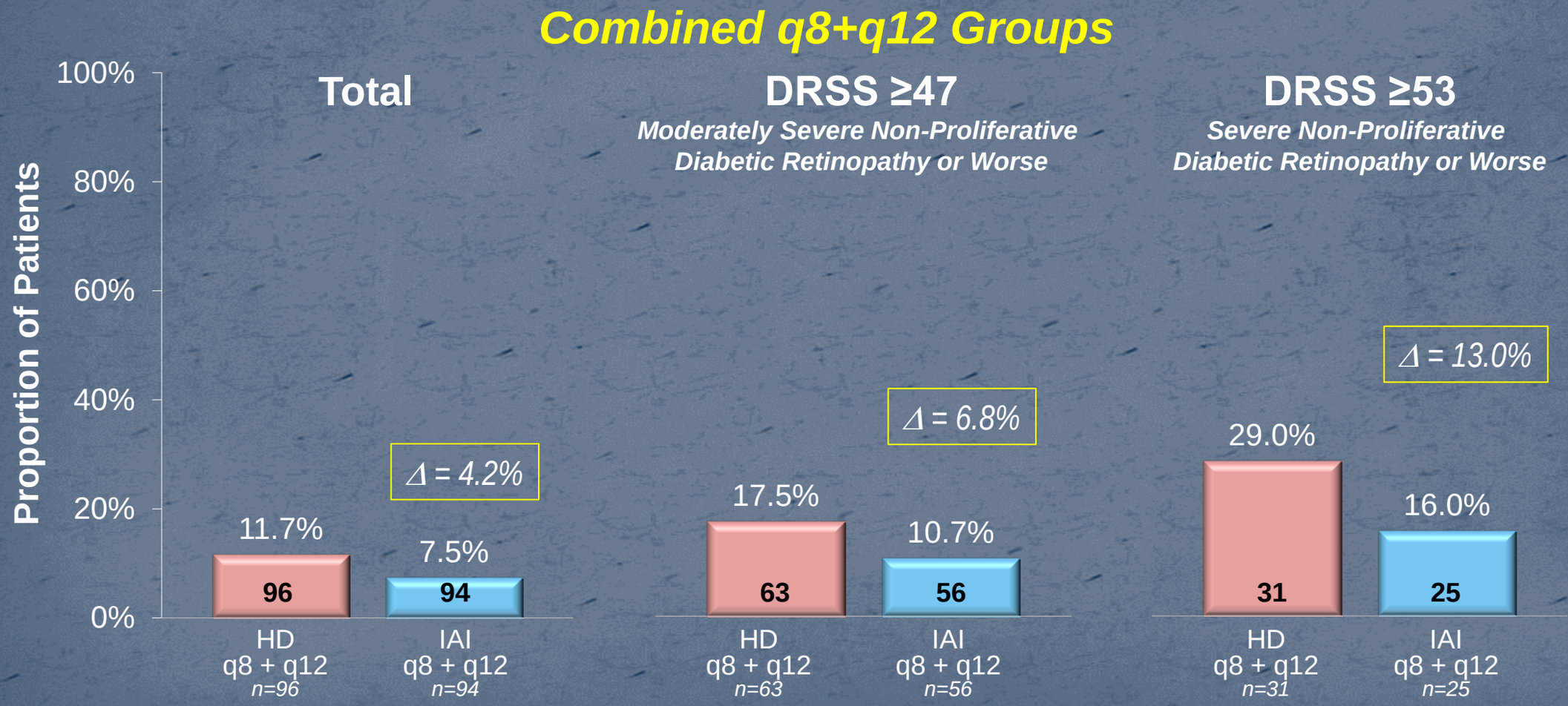
** p = 0.0005*

Proportion of Patients with ≥2 Step Improvement in DRSS at Week 36



FAS- Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose

Proportion of Patients with ≥3 Step Improvement in DRSS at Week 36



FAS- Secondary randomization set, LOCF
LD: Low Dose; HD: High Dose

Safety 

Most Frequent Ocular Adverse Events *Through Week 36*

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=46)	*(n=44)*	*(n=53)*	*(n=47)*	*(n=49)*	*(n=49)*
No. of patients with at least 1 AE, n (%)	14 (30.4%)	12 (27.3%)	19 (35.8%)	10 (21.3%)	11 (22.4%)	17 (34.7%)
Vitreous detachment	0	4 (9.1%)	3 (5.7%)	1 (2.1%)	0	4 (8.2%)
Conjunctival hemorrhage	4 (8.7%)	1 (2.3%)	1 (1.9%)	6 (12.8%)	2 (4.1%)	3 (6.1%)
Cataract	1 (2.2%)	0	0	2 (4.3%)	2 (4.1%)	2 (4.1%)
Eye pain	2 (4.3%)	1 (2.3%)	2 (3.8%)	0	2 (4.1%)	2 (4.1%)
Punctate keratitis	0	1 (2.3%)	0	0	0	2 (4.1%)
Visual acuity reduced	1 (2.2%)	1 (2.3%)	1 (1.9%)	0	1 (2.0%)	2 (4.1%)
Vitreous hemorrhage	0	1 (2.3%)	1 (1.9%)	0	0	2 (4.1%)
Vitreous floaters	1 (2.2%)	0	2 (3.8%)	1 (2.1%)	2 (4.1%)	1 (2.0%)
Dry eye	0	1 (2.3%)	4 (7.5%)	0	0	0
Retinal exudates	1 (2.2%)	0	3 (5.7%)	0	2 (4.1%)	0

SAF-Secondary randomization set; >4% in any treatment group.
LD: Low Dose; HD: High Dose

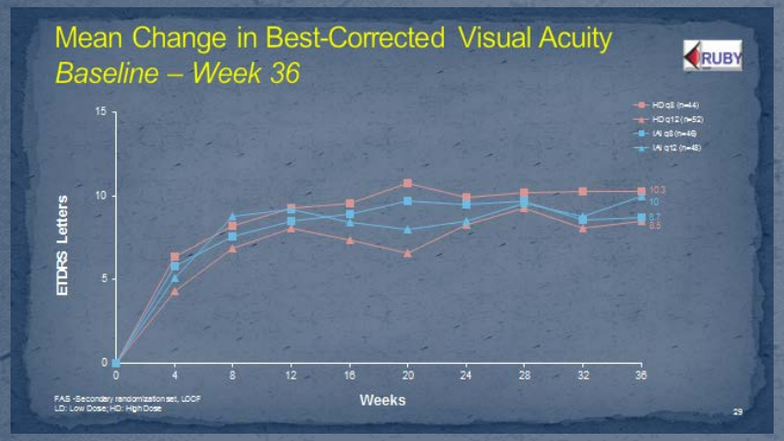
Anti-Platelet Trialists' Collaboration-Defined Arterial Thromboembolic Events Through Week 36

	LD q8	HD q8	HD q12	IAI q8	IAI q12	IAI → HD q8
	(n=46)	*(n=44)*	*(n=53)*	*(n=47)*	*(n=49)*	*(n=49)*
No. of patients **w/ at least 1 AE, n (%)**	3 (6.5%)	0	2 (3.8%)	2 (4.3%)	1 (2.0%)	0
Non-fatal MI	1 (2.2%)	0	1 (1.9%)	1 (2.1%)	1 (2.0%)	0
Non-fatal stroke	1 (2.2%)	0	1 (1.9%)	0	0	0
Vascular death	2 (4.3%)	0	0	1 (2.1%)	0	0

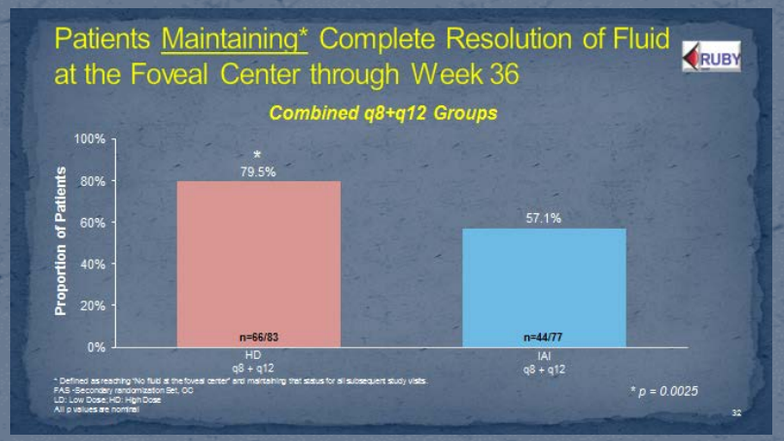
SAF-Secondary randomization set
LD: Low Dose; HD: High Dose

Conclusions

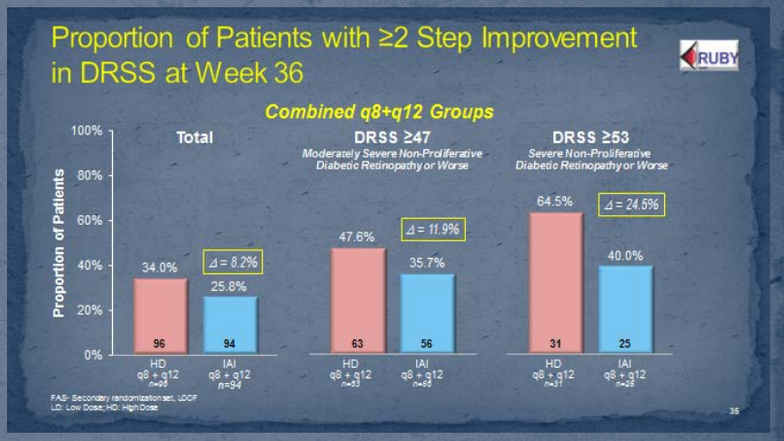
- **Ocular and systemic safety consistent with IAI monotherapy**



BCVA Equivalent



Combo Better Anatomy



Combo Improved DRS