

Impact of Retinal Neurodegenerative Changes in Patients with Diabetic Macular Edema from the VISTA Study

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Presented at the Macula Society Annual Meeting, February 7–10, 2024

Disclosures

- Dilraj S Grewal is a consultant for EyePoint, Priovent, IvericBio, Regeneron Pharmaceuticals, Inc., and Unity
- This analysis was funded by Regeneron Pharmaceuticals, Inc. (Tarrytown, New York), who is the sponsor and participated in the design and conduct of the study, analysis of the data, and preparation of this presentation
- Medical writing support was provided by India Wright, MSc, of Core Medica (a division of Prime, London, UK), in accordance with Good Publication Practice guidelines, and funded by Regeneron Pharmaceuticals, Inc.

Background and Objectives

- Retinal thickness measured by OCT has limited predictive value for visual acuity in patients with DR and DME^{1,2}
- DRIL represents a potential structural biomarker for loss of visual function in DR, and has been associated with worse visual acuity, increased RNP, disease severity, and risk of PDR³⁻⁵
- Presence of DRIL is also associated with loss of integrity in the ELM and EZ, which has been shown to correlate with loss of visual acuity^{3,6}

This study evaluated the impact of retinal neurodegenerative changes in patients with DME from the VISTA study

DME, diabetic macular edema; DR, diabetic retinopathy; DRIL, disorganization of retinal inner layers; ELM, external limiting membrane; EZ, ellipsoid zone; OCT, optical coherence tomography; PDR, proliferative diabetic retinopathy; RNP, retinal nonperfusion.

1. Nanegrungsunk O et al. *J Vitreoretin Dis.* 2022;6:284-289; 2. Bressler SM et al. *JAMA Ophthalmol.* 2019;137:977-985; 3. Nair A and Modi Y. *Retinal Physician.* 2020;17:16-19; 4. Sun JK et al. *JAMA Ophthalmol.* 2014;132:1309-1316; 5. Joltikof KA et al. *Invest Ophthalmol Vis Sci.* 2018; 59: 5481-5486; 6. Uji A et al. *Am J Ophthalmol.* 2012;153(4):710-717.

VISTA Study Design

Randomized, multicenter, double-masked trial in patients with clinically significant DME, central involvement and ETDRS BCVA 20/40 to 20/320
Randomized and treated: N=466

Patients randomized
1:1:1

IAI 2q4

IAI 2q8^a

Laser control

Primary endpoint:
mean change in BCVA

Primary endpoint:
Week 52

Key secondary endpoints:
mean change in OCT
% with ≥ 2 -step DRSS
improvement

Continued treatment through Year 3

^aAfter 5 initial monthly doses.

2q4, 2 mg every 4 weeks; 2q8, 2 mg every 8 weeks. BCVA, best-corrected visual acuity; DRSS, Diabetic Retinopathy Severity Scale; ETDRS, Early Treatment Diabetic Retinopathy Study; IAI, intravitreal aflibercept injection; OCT, optical coherence tomography.

Brown DM et al. *Ophthalmology*. 2015;122(10):2044-2052.

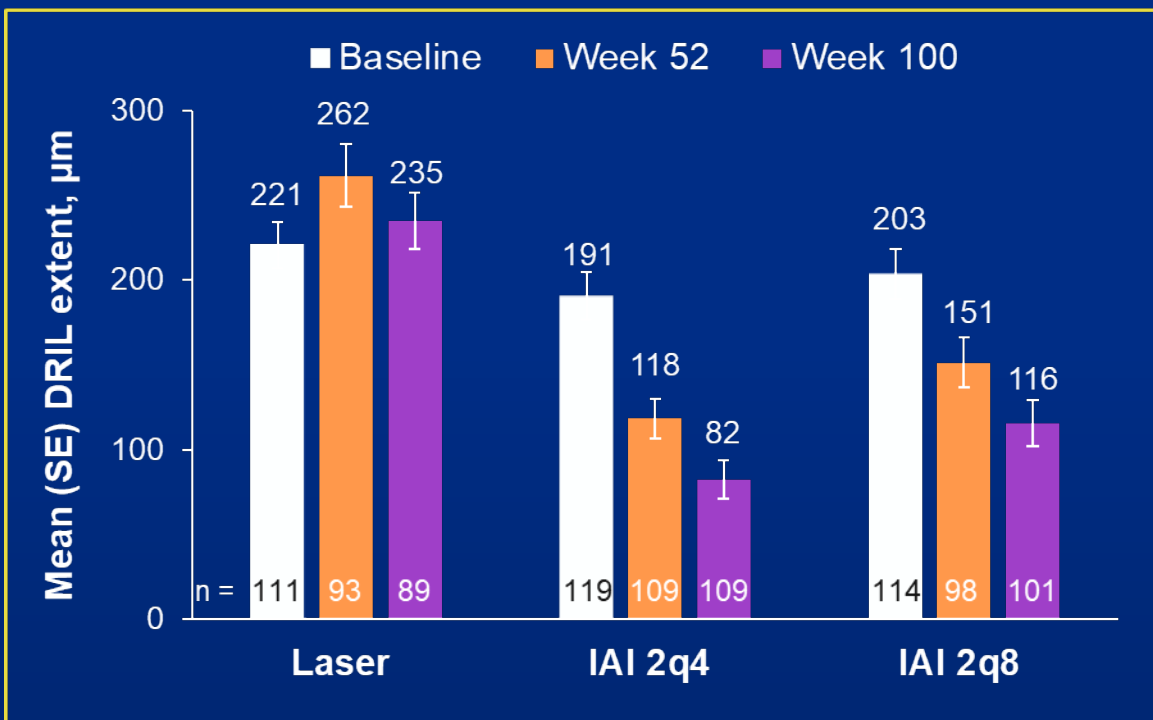
Methods

- Extent of DRIL, ELM loss, and EZ loss were quantified as microns in the central 1000- μ m macular area based on OCT images at baseline and Weeks 52 and 100 by Duke Reading Center
- Outcomes evaluated at Weeks 52 and 100:
 1. Changes in markers of retinal neurodegeneration over time
 2. Correlation between markers of retinal neurodegeneration and visual and anatomic parameters
 3. Changes in retinal neurodegeneration markers by baseline BCVA $\geq 20/40$ versus $\leq 20/50$
 4. DRIL, ELM loss, and EZ loss by their respective baseline extent
- RNP was assessed on fluorescein angiography; DRSS score was assessed on fundus photography
- Only gradable images were used in this analysis
- Statistical analyses included Pearson correlation and ANCOVA; *P*-values < 0.05 were considered nominally significant; observed case values were used in the analysis

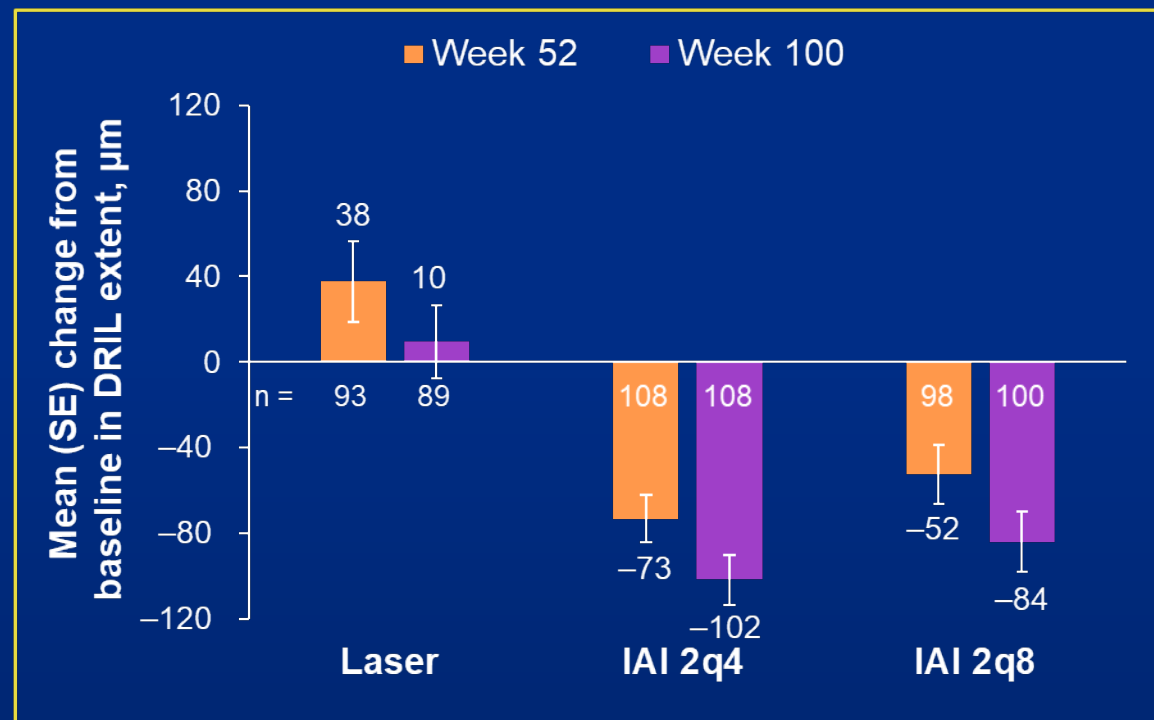
1. Changes in Markers of Retinal Neurodegeneration Over Time

DRIL Extent Through Week 100

Mean DRIL Extent



Mean Change in DRIL Extent from Baseline



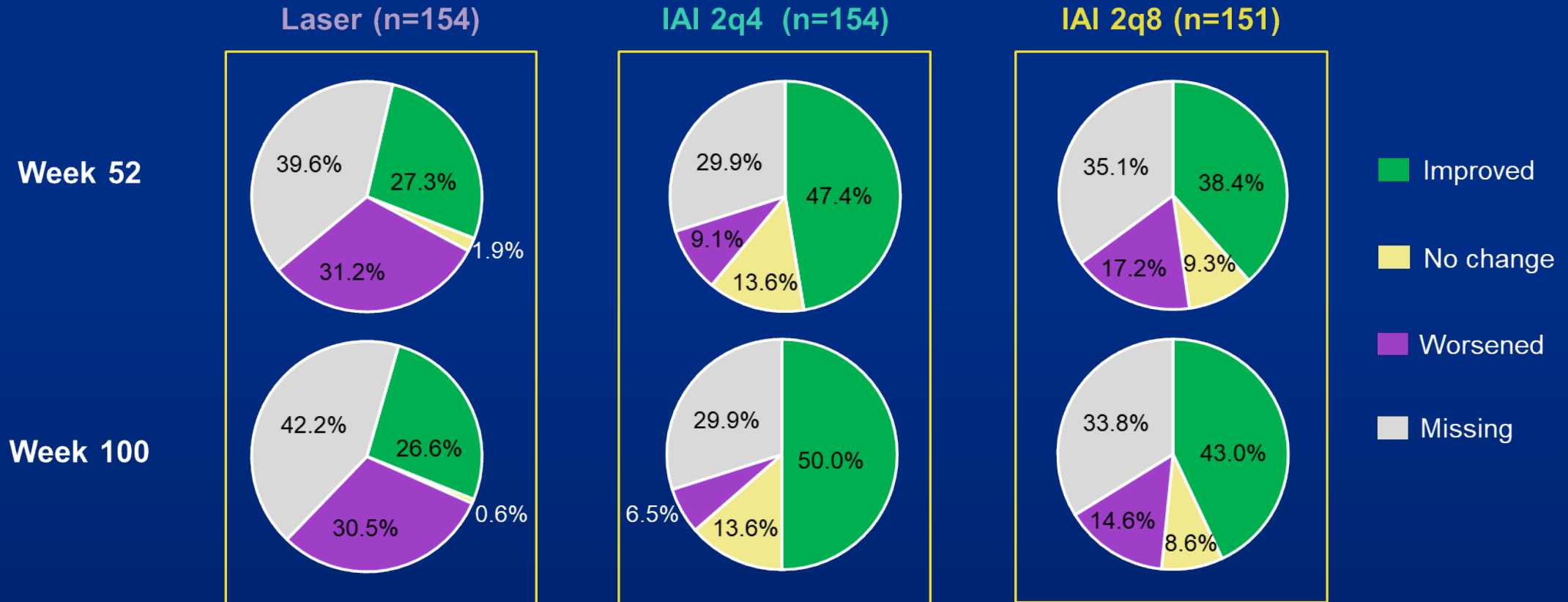
DRIL extent continued to improve from baseline with IAI treatment through Week 100

FAS, OC.

The number of patients with missing data with laser, IAI 2q4, and IAI 2q8 at baseline was 43, 35, and 37, respectively, at Week 52 was 61, 45, and 53, respectively, and at Week 100 was 65, 45, and 50, respectively.

FAS, full analysis set; OC, observed cases; SE, standard error.

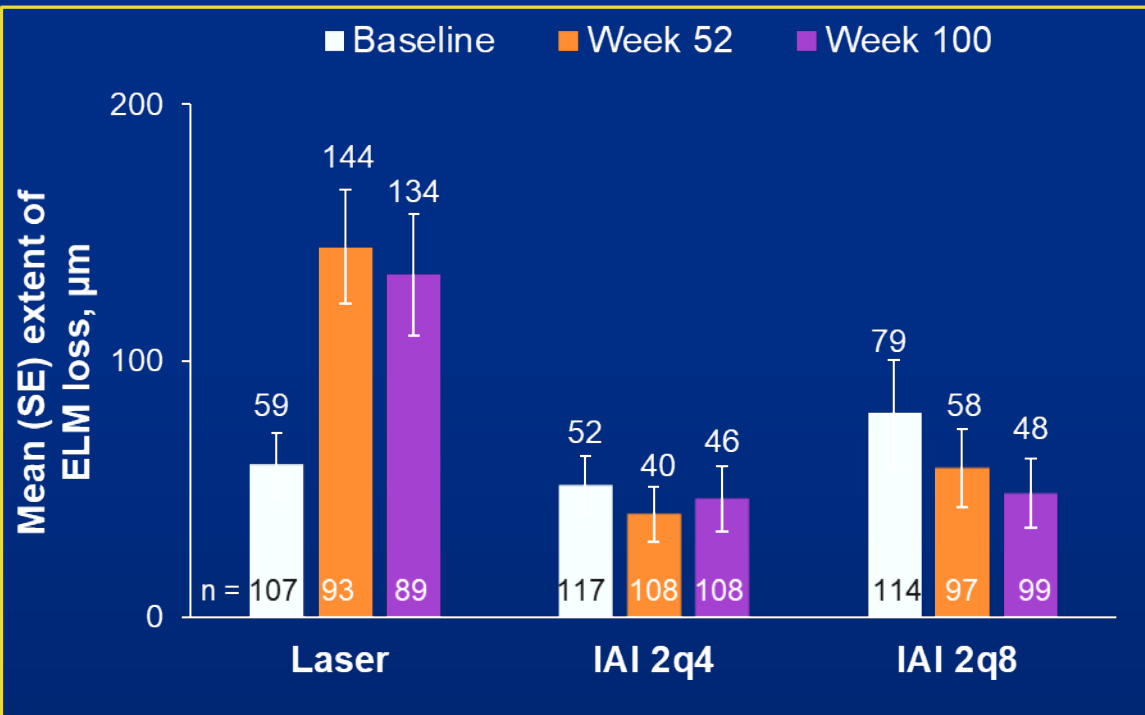
Proportion of Eyes with Changes in DRIL from Baseline Through Week 100



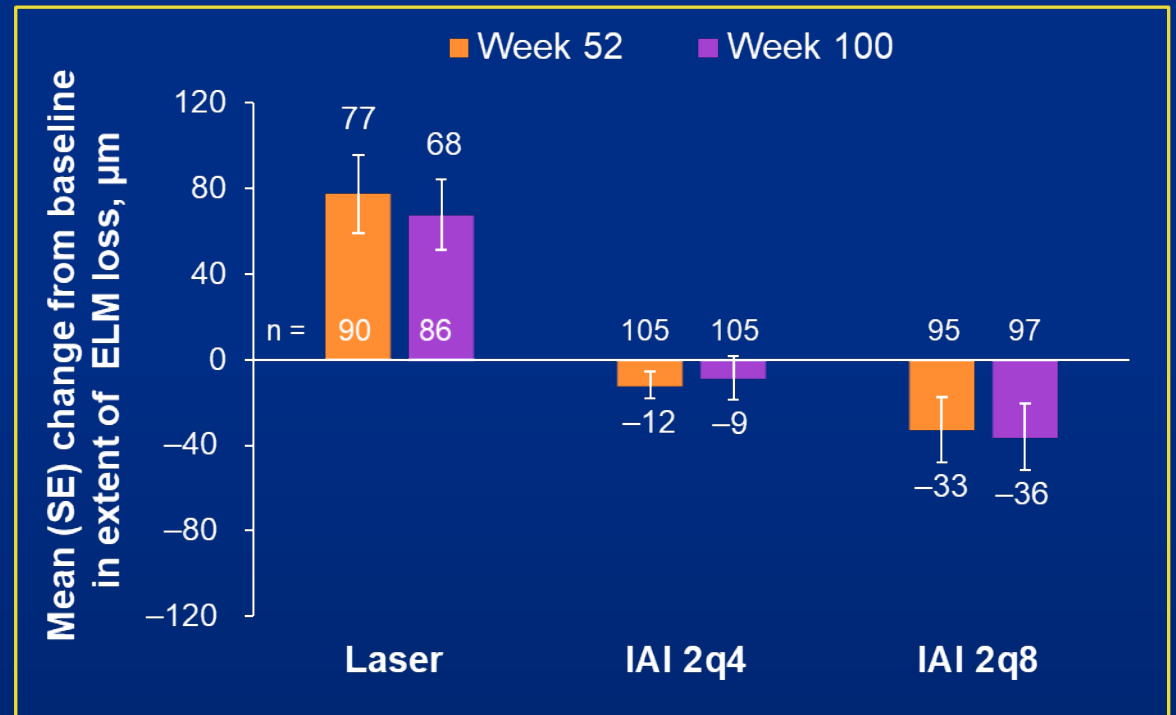
Among gradable eyes, DRIL more often improved in eyes treated with IAI than with laser through Week 100

Extent of ELM Loss Through Week 100

Mean Extent of ELM Loss



Mean Change in Extent of ELM Loss from Baseline

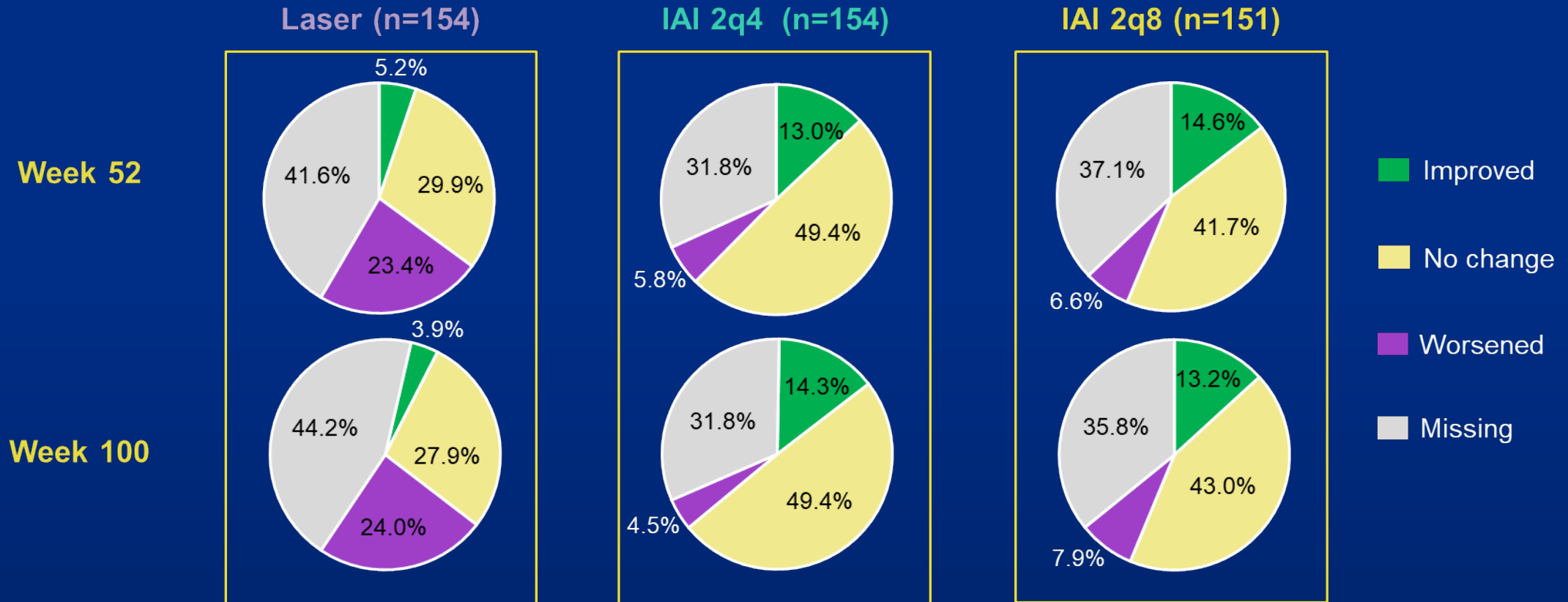


Extent of ELM loss was stabilized with continued IAI treatment compared to its progression with laser through Week 100

FAS, OC.

The number of patients with missing data with laser, IAI 2q4, and IAI 2q8 at baseline was 47, 37, and 37, respectively, at Week 52 was 61, 46, and 54, respectively, and at Week 100 was 65, 46, and 52, respectively.

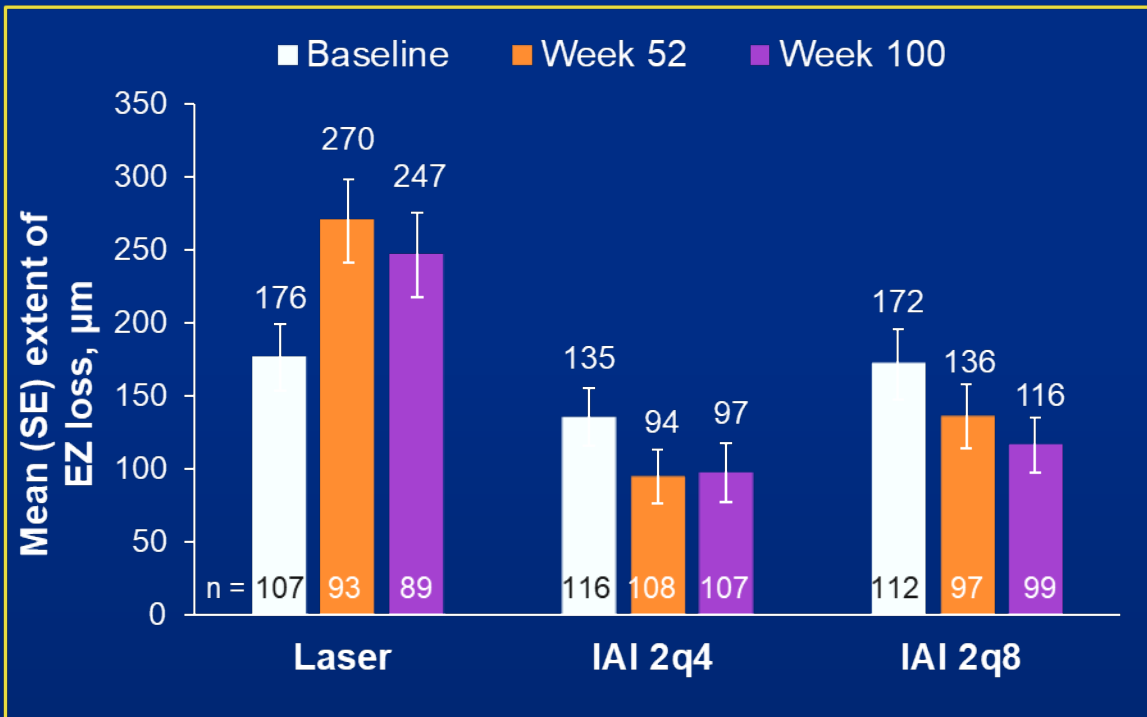
Proportion of Eyes with Changes in ELM Loss from Baseline Through Week 100



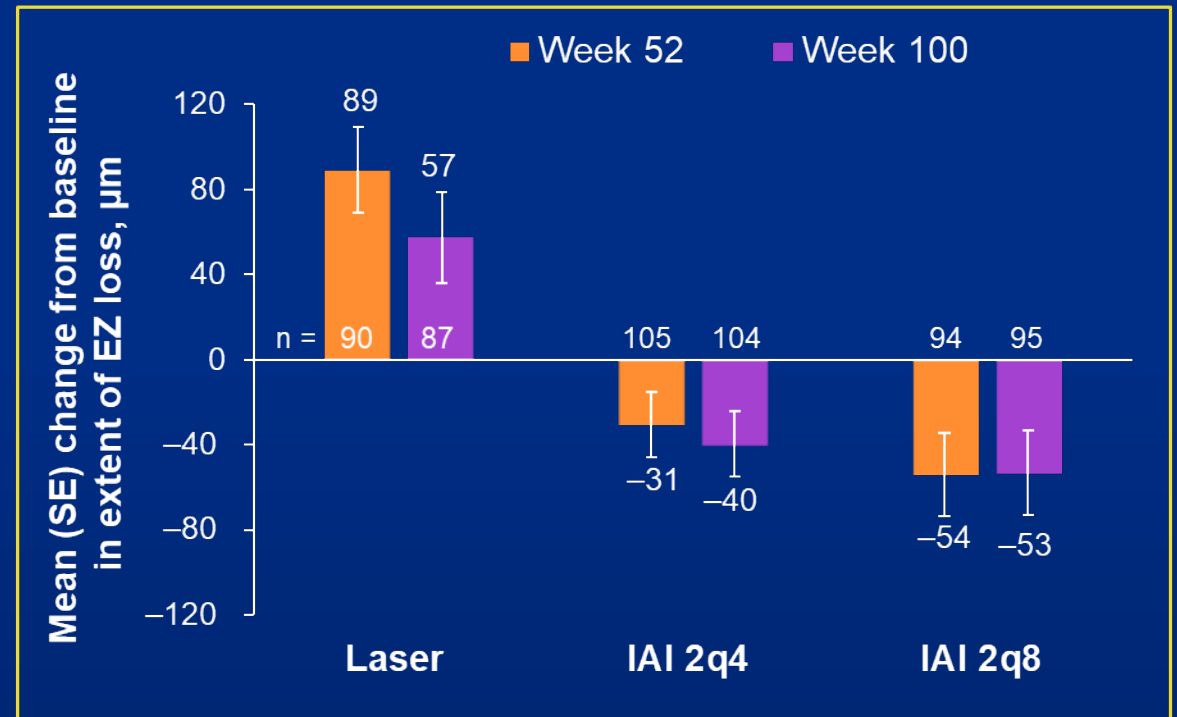
Among gradable eyes, ELM loss was stabilized in more eyes treated with IAI than with laser through Week 100

Extent of EZ Loss Through Week 100

Mean Extent of EZ Loss



Mean Change in Extent of EZ Loss from Baseline

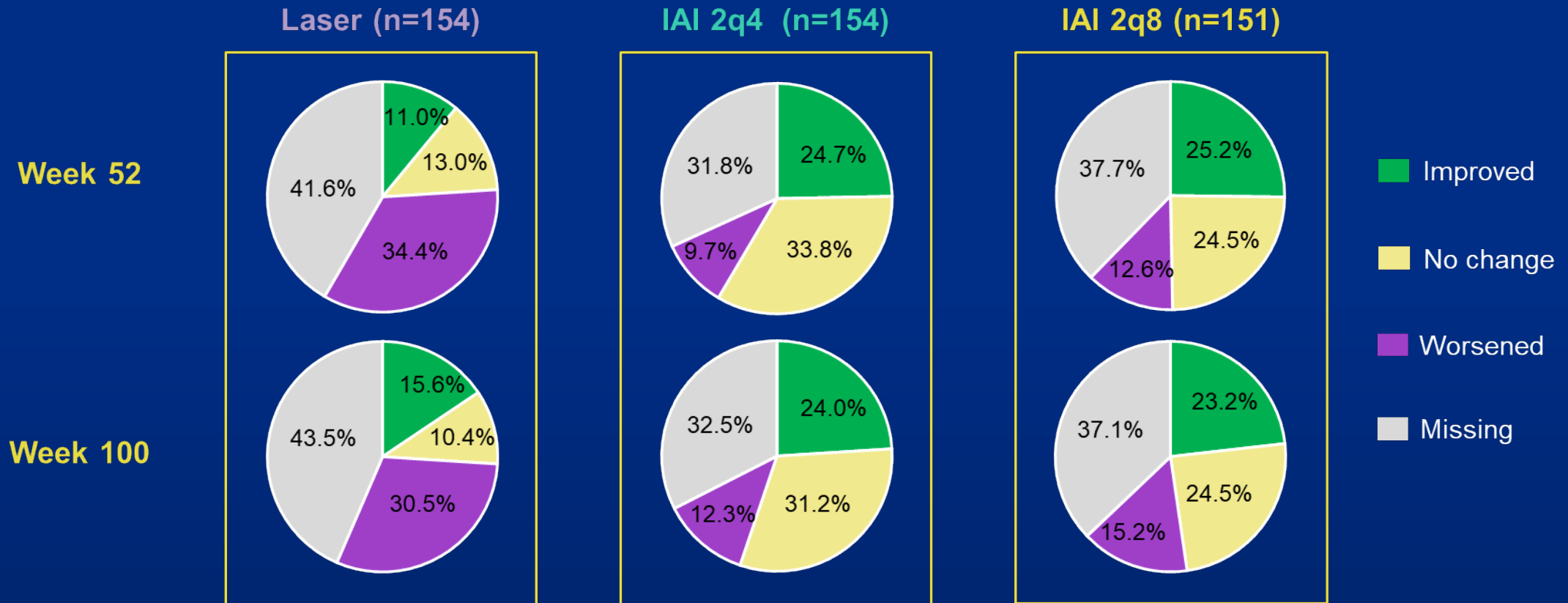


Extent of EZ loss was stabilized with continued IAI treatment compared to its progression with laser through Week 100

FAS, OC.

The number of patients with missing data with laser, IAI 2q4, and IAI 2q8 at baseline was 47, 38, and 39, respectively, at Week 52 was 61, 46, and 54, respectively, and at Week 100 was 65, 47, and 52, respectively.

Proportion of Eyes with Changes in EZ Loss from Baseline Through Week 100



Among gradable eyes, EZ loss was improved or stabilized in more eyes treated with IAI than with laser through Week 100

2. Correlation Between Markers of Retinal Neurodegeneration and Visual and Anatomic Parameters

Correlations between Markers of Retinal Neurodegeneration and BCVA, CST, DRSS score, and RNP at Baseline: All Treatment Groups Combined

Strength of correlation:

Weak ($r \leq 0.39$)

Moderate ($r = 0.4-0.69$)

Strong ($r > 0.7$)

DRIL	1		
ELM Loss	0.32 (n=335)	1	
EZ Loss	0.35 (n=332)	0.65 (n=334)	1
BCVA	-0.16 (n=344)	-0.40 (n=338)	-0.44 (n=335)
DRSS	-0.004 (n=343)	0.06 (n=337)	0.04 (n=334)
RNP	-0.005 (n=159)	0.11 (n=157)	0.21 (n=155)
	DRIL	ELM Loss	EZ Loss

At baseline, there was a moderate positive correlation between ELM and EZ loss and a moderate negative correlation between these 2 parameters and BCVA

FAS, OC.

Correlation between extent of DRIL, ELM loss, and EZ loss and BCVA, DRSS, and RNP, were determined, adjusted for CST at baseline.

n = number of patients with non-missing data from variables being tested in the correlation.

CST, central subfield thickness.

Correlations Between Markers of Retinal Neurodegeneration and BCVA, DRSS Score and RNP Through Week 100

Strength of correlation:

Weak ($r \leq 0.39$)

Moderate ($r = 0.4-0.69$)

Strong ($r > 0.7$)

Week 52

Laser

DRIL	1		
ELM Loss	0.34 (n=58)	1	
EZ Loss	0.56 (n=58)	0.85 (n=58)	1
BCVA	-0.32 (n=58)	-0.54 (n=58)	-0.60 (n=58)
DRSS	0.07 (n=57)	0.25 (n=57)	0.26 (n=57)
RNP	0.54 (n=30)	0.04 (n=30)	0.33 (n=30)
	DRIL	ELM Loss	EZ Loss

IAI 2q4

DRIL	1		
ELM Loss	0.50 (n=97)	1	
EZ Loss	0.51 (n=97)	0.89 (n=97)	1
BCVA	-0.52 (n=98)	-0.51 (n=97)	-0.52 (n=97)
DRSS	-0.01 (n=97)	-0.07 (n=96)	-0.07 (n=96)
RNP	-0.04 (n=38)	-0.07 (n=37)	-0.11 (n=37)
	DRIL	ELM Loss	EZ Loss

IAI 2q8

DRIL	1		
ELM Loss	0.66 (n=89)	1	
EZ Loss	0.71 (n=89)	0.75 (n=89)	1
BCVA	-0.50 (n=90)	-0.48 (n=89)	-0.60 (n=89)
DRSS	0.24 (n=89)	0.26 (n=88)	0.15 (n=89)
RNP	0.47 (n=30)	-0.03 (n=30)	0.32 (n=30)
	DRIL	ELM Loss	EZ Loss

Week 100

DRIL	1		
ELM Loss	0.49 (n=47)	1	
EZ Loss	0.50 (n=47)	0.87 (n=47)	1
BCVA	-0.50 (n=47)	-0.46 (n=47)	-0.56 (n=47)
DRSS	-0.04 (n=45)	0.18 (n=45)	0.03 (n=45)
RNP	0.38 (n=25)	-0.10 (n=25)	0.04 (n=25)
	DRIL	ELM Loss	EZ Loss

DRIL	1		
ELM Loss	0.55 (n=88)	1	
EZ Loss	0.51 (n=88)	0.94 (n=88)	1
BCVA	-0.49 (n=89)	-0.47 (n=88)	-0.49 (n=88)
DRSS	-0.02 (n=86)	0.04 (n=85)	0.03 (n=85)
RNP	-0.06 (n=31)	-0.21 (n=30)	-0.31 (n=30)
	DRIL	ELM Loss	EZ Loss

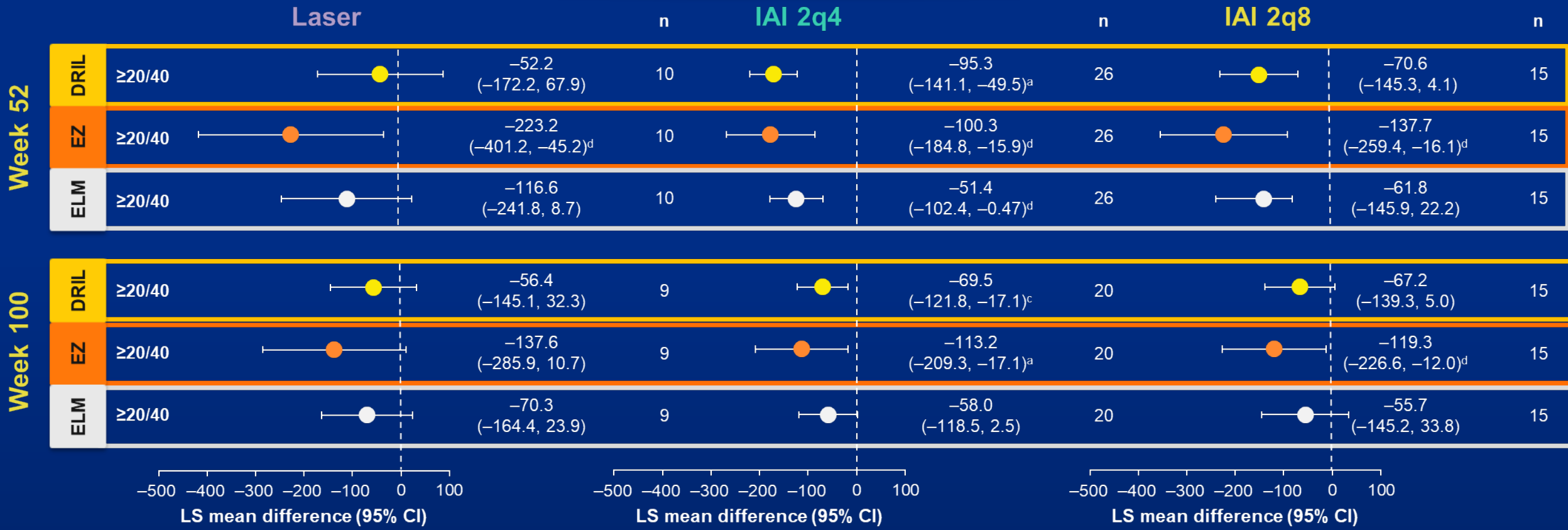
DRIL	1		
ELM Loss	0.75 (n=77)	1	
EZ Loss	0.79 (n=77)	0.81 (n=77)	1
BCVA	-0.60 (n=77)	-0.53 (n=77)	-0.65 (n=77)
DRSS	0.06 (n=73)	0.08 (n=73)	0.03 (n=73)
RNP	0.27 (n=26)	0.25 (n=26)	0.33 (n=26)
	DRIL	ELM Loss	EZ Loss

FAS, OC.

Correlation between extent of DRIL, ELM loss, and EZ loss and BCVA, DRSS, and RNP, were determined, adjusted for CST at Weeks 52 and 100. n = number of patients with non-missing data from variables being tested in the correlation.

3. Changes in Retinal Neurodegeneration Markers by Baseline BCVA $\geq 20/40$ Versus $\leq 20/50$

Magnitude of Difference in Retinal Neurodegeneration in Eyes with Baseline BCVA $\geq 20/40$ Versus $\leq 20/50$



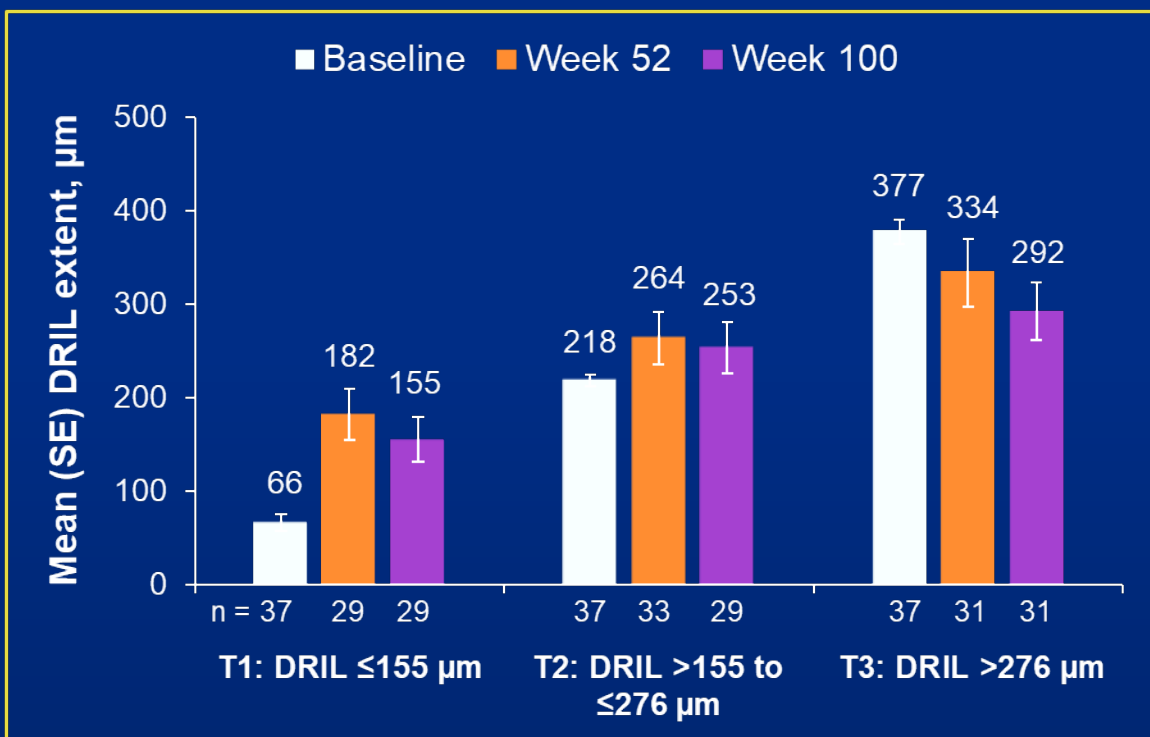
At Weeks 52 and 100, there was a trend towards less DRIL, EZ loss, and ELM loss in eyes with BCVA $\geq 20/40$ versus those with BCVA $\leq 20/50$

FAS, OC.
 LS mean difference was determined using ANCOVA model with CST at Weeks 52 and 100 as covariates. N = number of patients with non-missing DRIL, ELM or EZ loss, non-missing baseline BCVA, and non-missing CST at Weeks 52 and 100.
^a $P < 0.0001$; ^b $P < 0.001$; ^c $P < 0.01$; ^d $P < 0.05$ vs reference (BCVA $\leq 20/50$ group).
 CI, confidence interval; LS, least squares.

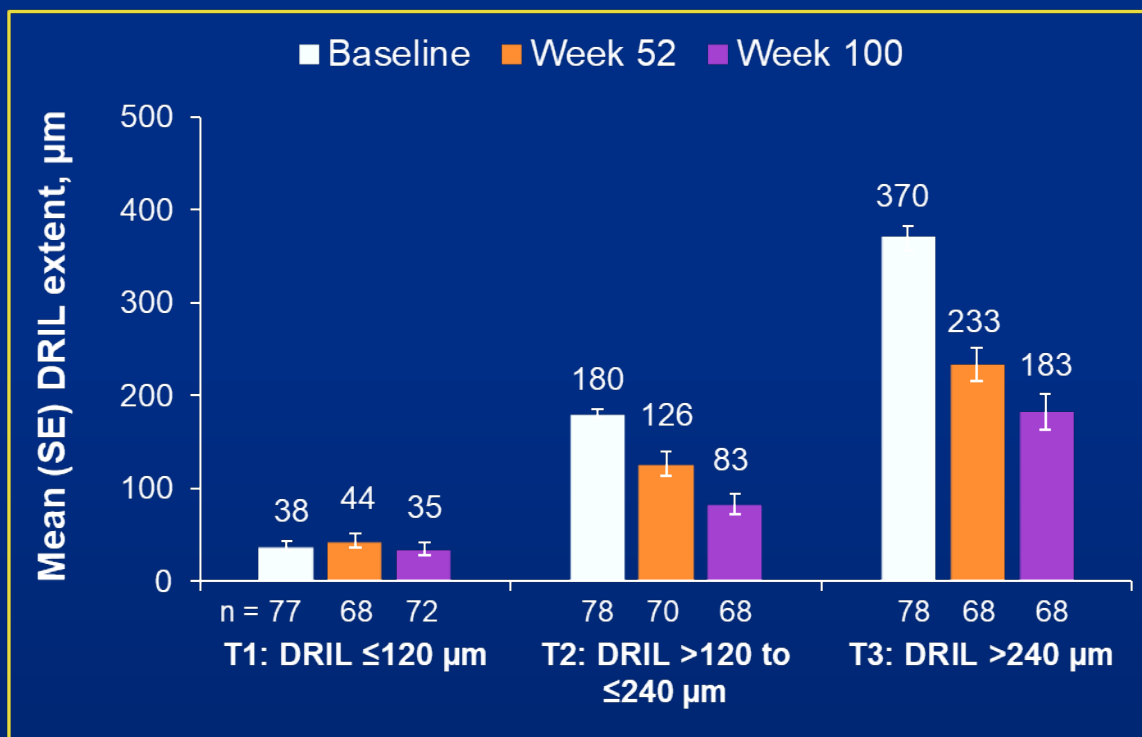
4. DRIL, ELM Loss, and EZ Loss by Their Respective Baseline Extent

DRIL Extent Through Week 100 by Baseline DRIL Tertile

Laser



Combined IAI

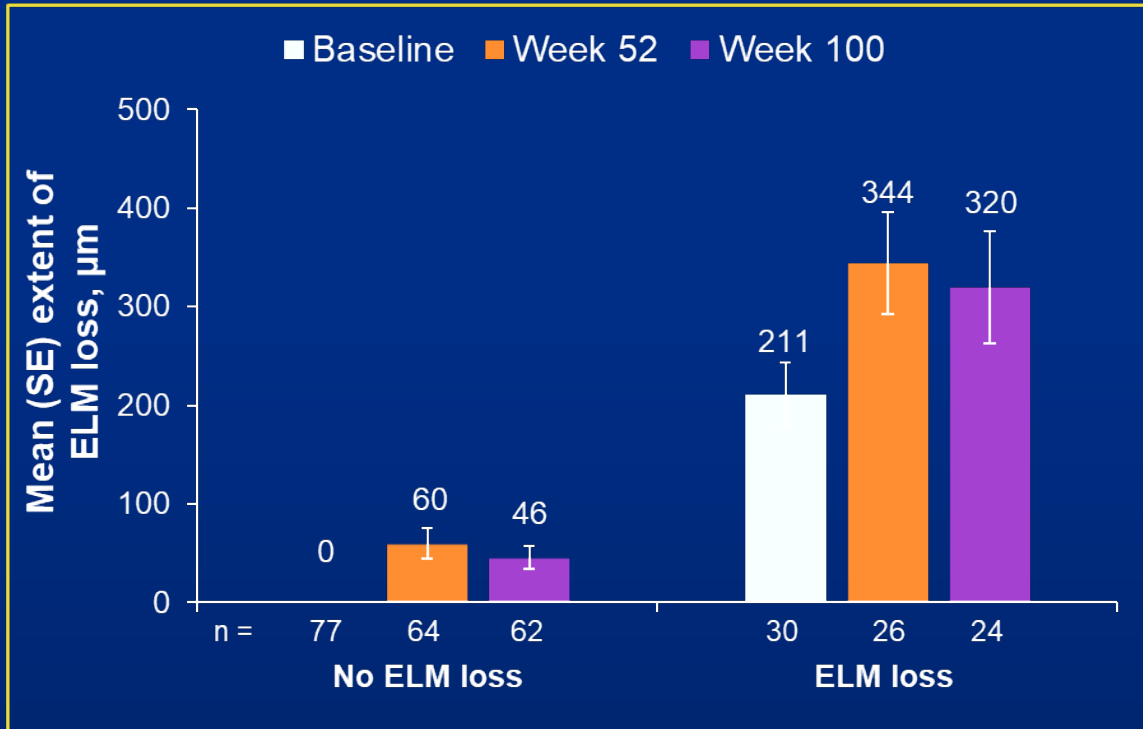


In eyes treated with IAI, magnitude of improvement in DRIL extent was greater in eyes in T3. However, eyes in T1 treated with IAI had greater preservation of anatomy at Week 100

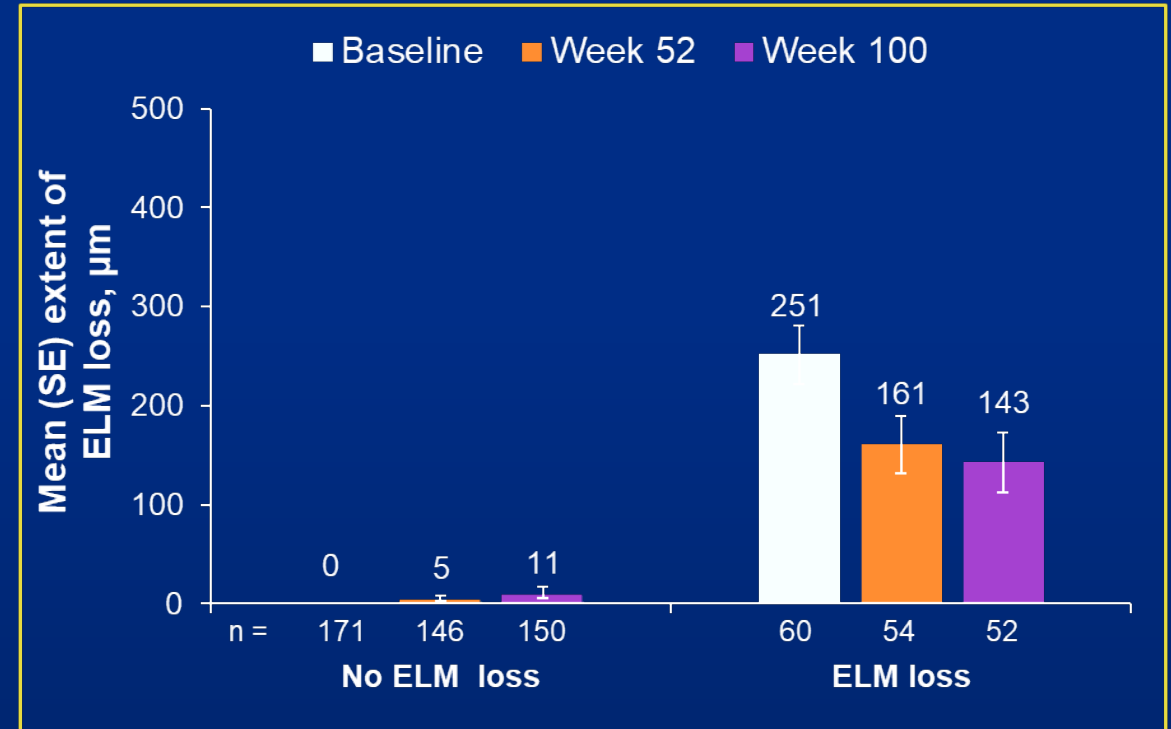
FAS, OC.
 No missing values at baseline with laser or combined IAI. The number of patients with missing values with laser at Week 52 for T1 was 8, for T2 was 4, for T3 was 6, and at Week 100 for T1 was 8, for T2 was 8, for T3 was 6; missing values with combined IAI at Week 52 for T1 was 9, for T2 was 8, for T3 was 10, and at Week 100 for T1 was 5, for T2 was 10, for T3 was 10.
 T, tertile.

Extent of ELM Loss Through Week 100 by Baseline ELM Loss Subgroup

Laser



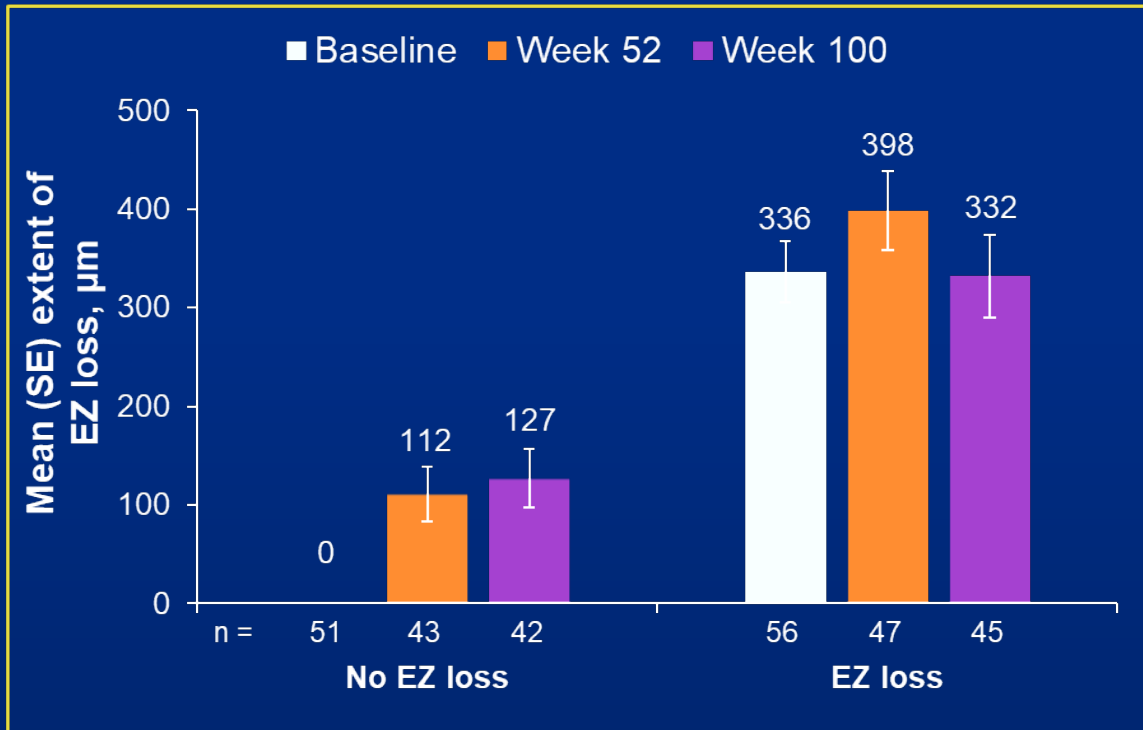
Combined IAI



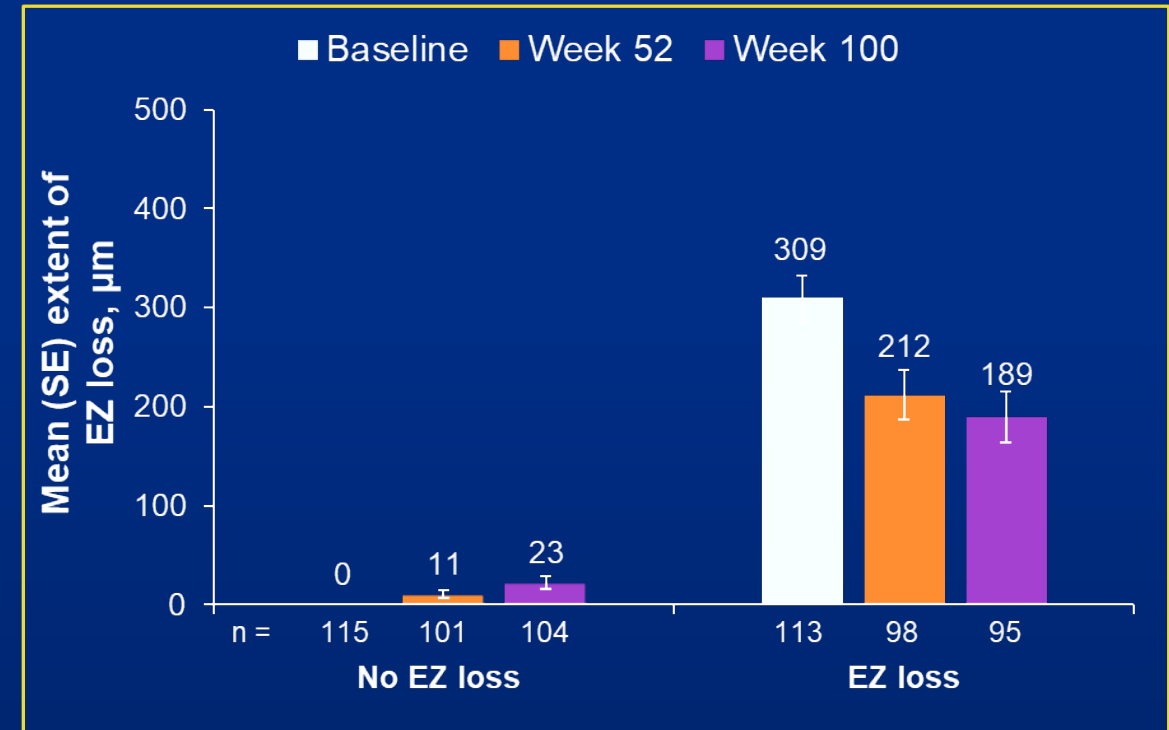
At Week 100, only partial ELM reconstitution was achieved in eyes with ELM loss at baseline, despite treatment with IAI. Eyes without ELM loss at baseline maintained ELM integrity with IAI treatment

Extent of EZ Loss Through Week 100 by Baseline EZ Loss Subgroup

Laser



Combined IAI



At Week 100, only partial EZ reconstitution was achieved in eyes with EZ loss at baseline, despite treatment with IAI. Eyes without EZ loss at baseline maintained EZ integrity with IAI treatment

Conclusion

- At Weeks 52 and 100, in patients with DME:
 - Those treated with IAI had greater improvement in DRIL and better preservation of EZ and ELM compared with laser
 - Across all treatment groups, DRIL, ELM loss, and EZ loss had a moderate negative correlation with BCVA, and weak correlations with DRSS score and RNP area
 - There was a trend towards less DRIL, EZ loss, and ELM loss in eyes with better baseline visual acuity
- In eyes treated with IAI, greater DRIL improvement at Week 100 was observed in eyes with larger baseline DRIL ($>240\ \mu\text{m}$). However, anatomy preservation at Week 100 was greater in eyes with lower baseline DRIL ($\leq 120\ \mu\text{m}$)
 - Similarly, ELM and EZ were only partially restored in eyes with ELM and EZ loss at baseline, despite treatment with IAI
- These data support the importance of early treatment with IAI for anatomy preservation, which may help to achieve better visual outcomes