

Structure-Function Association Between Ellipsoid Zone and External Limiting Membrane Status and Visual Acuity in Eyes with Dry AMD with Geographic Atrophy in the ARCHER Trial

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Relevant Disclosures

- Glenn Jaffe: *Advisory Board Member* - Eyepoint; Ocular Therapeutix; *Consultant* - Boehringer Ingelheim; Kriya; Regeneron; Roche/Genentech;
- Kevin Choy, Sina Farsiu: None
- Vladislav Volman, Scott Borland, Lori Taylor, Kimberly Reed, W. Lloyd Clark, Margot Goodkin, Erik Pulkstenis, Jamie Dananberg, Ted Yednock, Alessia Tassoni: Owners and Employees of Annexon Biosciences

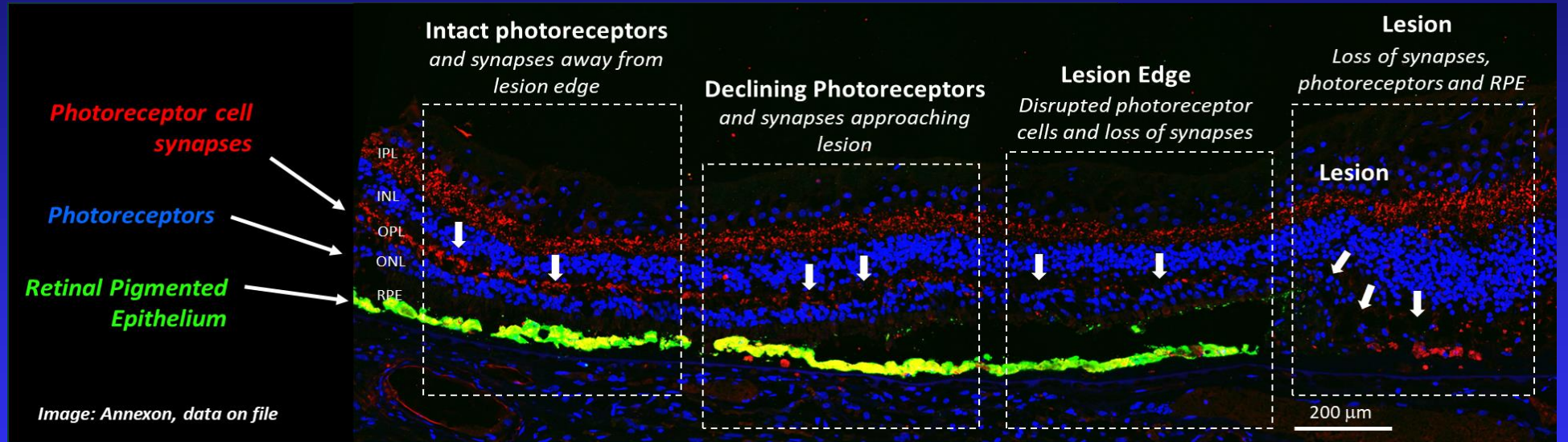
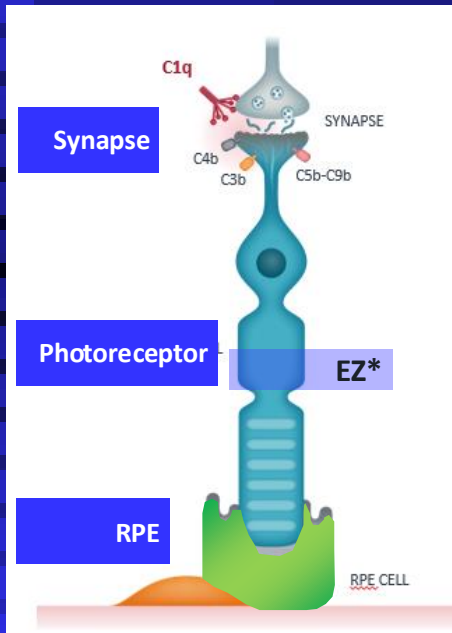
Key Take-Home Messages

- Integrity of both EZ and ELM in central subfields, and not outer subfields, correlates with BCVA, consistent with the importance of cones to fine vision
- Integrity of both EZ and ELM across the macula correlates LLVA, consistent with the importance of both rods and cones to fine vision in low light conditions
- The relationships between photoreceptor integrity and visual acuity are consistent with the results of the Phase 2 ARCHER trial
 - Vonaprumant inhibition of C1q protected photoreceptor integrity (EZ) and preserved visual acuity (both BCVA and LLVA)
 - Greatest EZ preservation near the foveal center

Anti-C1q: Neuroprotective Mechanism of Action

- Photoreceptors and RPE Cells provide bidirectional trophic support to each other
- In dry AMD with GA, Photoreceptor Loss Precedes RPE Loss (GA Lesion)
- Blocking C1q: Protects vulnerable synapses on stressed photoreceptors, thereby protecting vision

Retina from Human Donor with GA



Earlier-Stage Disease

Mid-Stage Disease: Reduced # of PR's and synapses; Likely reduced visual function; RPE Layer Present, but likely dysfunctional

Later-Stage Disease: Vision Loss Already Present
RPE & PR both missing

*The EZ represents the outer portion of PR inner segments where mitochondria are densely concentrated, creating a visible imaging layer on OCT

Disease Progression

Area At Lower Risk of vision loss over 1-2 years

Area At High Risk of **additional** vision loss over 1-2 years

Lower Risk of **additional** vision loss over 1-2 years

ARCHER: Phase 2 Trial of C1q Inhibitor Vonaprument in GA Patients

Randomized, double-masked
Included **foveal and non-foveal** lesions
Stratified for lesion location and lesion size
12 months (n=270)

Sham monthly or every other month
(n=89)

Vonaprument 5mg every other month (EOM)
(n=92)

Vonaprument 5mg monthly (EM)
(n=89)

PRIMARY BIOMARKER ENDPOINT

Change in GA lesion area as assessed by fundus autofluorescence at Month 12

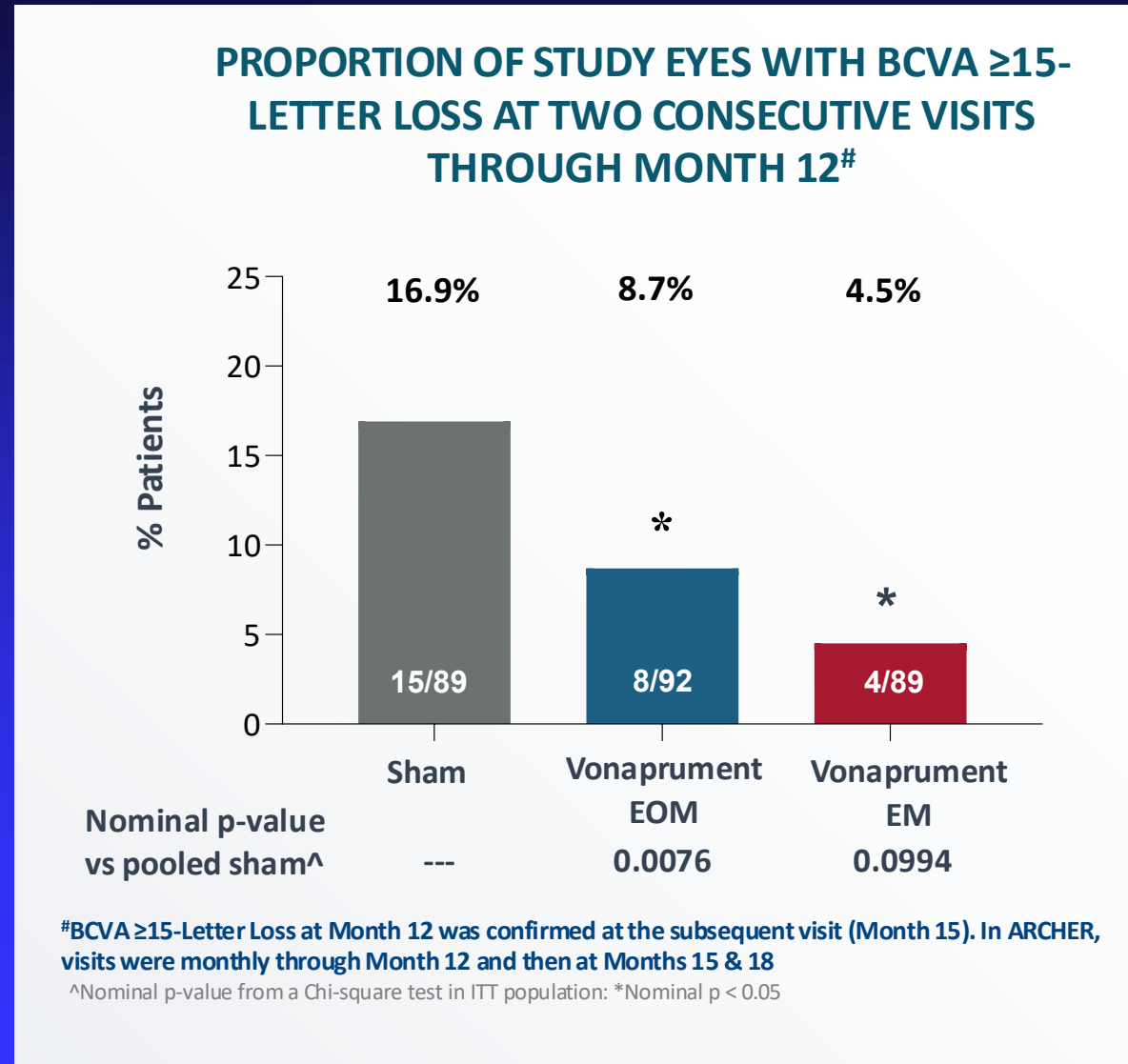
PRESPECIFIED SECONDARY FUNCTIONAL ENDPOINTS

Best Corrected Visual Acuity (BCVA)
Low Luminance Visual Acuity (LLVA) & Deficit (LLVD)

Off-treatment
(6 months)

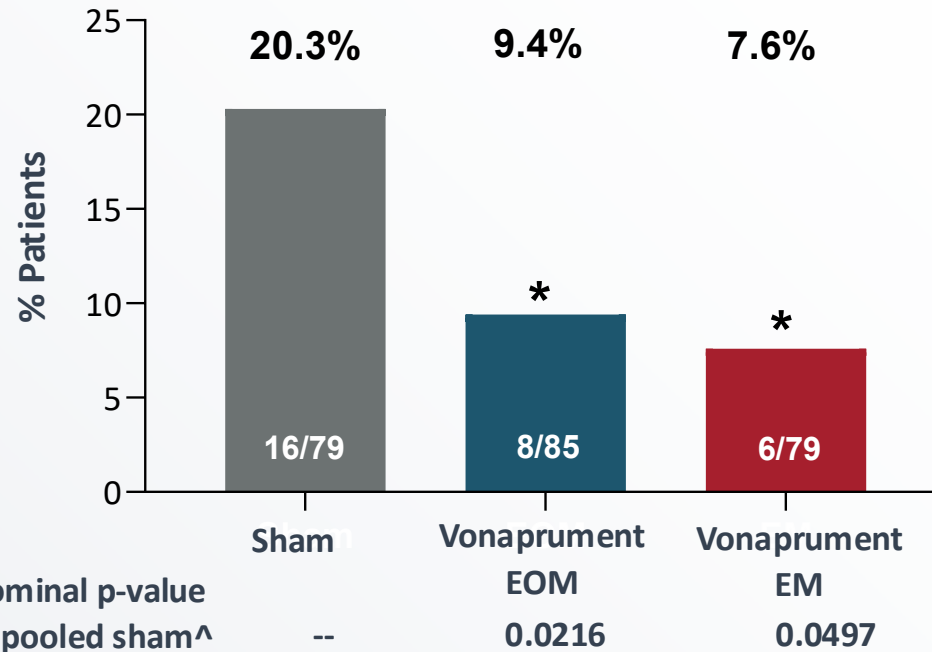
END OF STUDY
Month 18

Fewer Vonaprument-Treated Eyes Experienced BCVA \geq 15-Letter Loss Compared to Sham



Fewer Vonaprument-Treated Eyes Experienced LLVA \geq 15-Letter Loss Compared to Sham

PROPORTION OF EYES WITH LLVA \geq 15-LETTER LOSS AT TWO CONSECUTIVE VISITS, OR AT THE LAST VISIT, THROUGH MONTH 12[#]



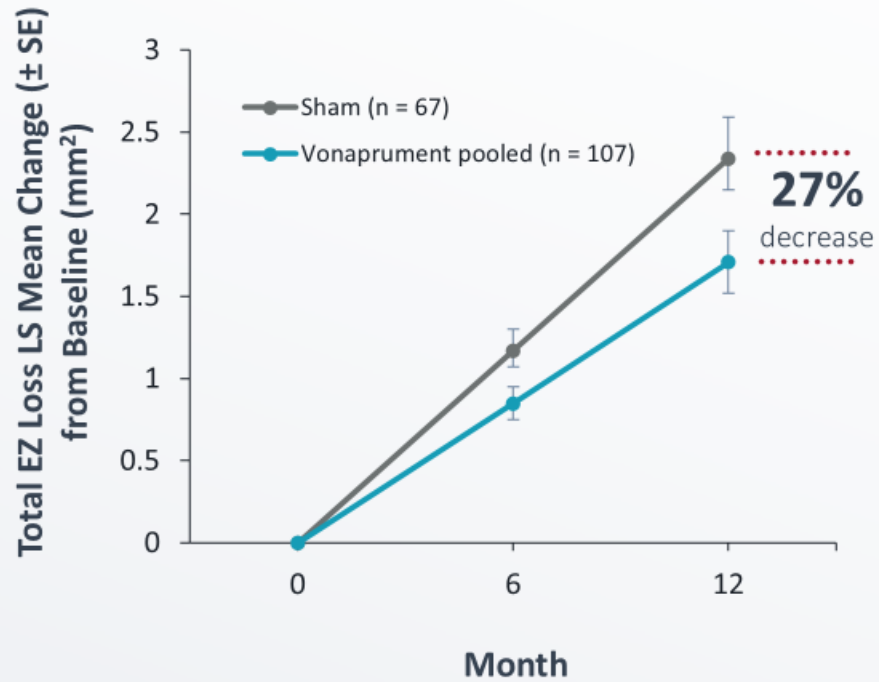
[#]Patients with at least one post-baseline LLVA measurement and two consecutive or last visit 15-letter loss events; final data

[^]Nominal p-value from a Chi-Square test; *nominal p<0.05

Numerically Greater Photoreceptor Protection in Central Macula with Vonaprument

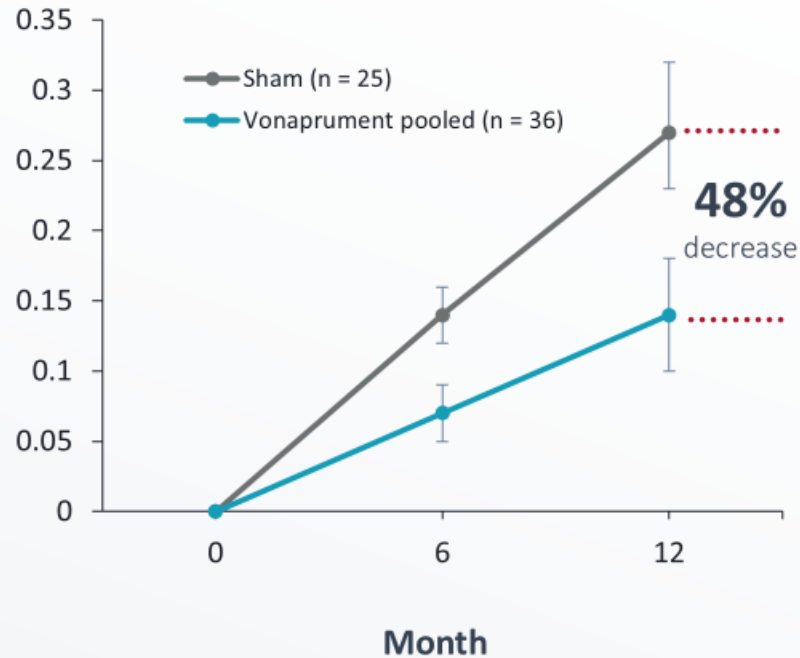
Comparison of Vonaprument effect on Ellipsoid Zone (EZ) across macula and in central subdomains through 12 months

PAN-MACULA



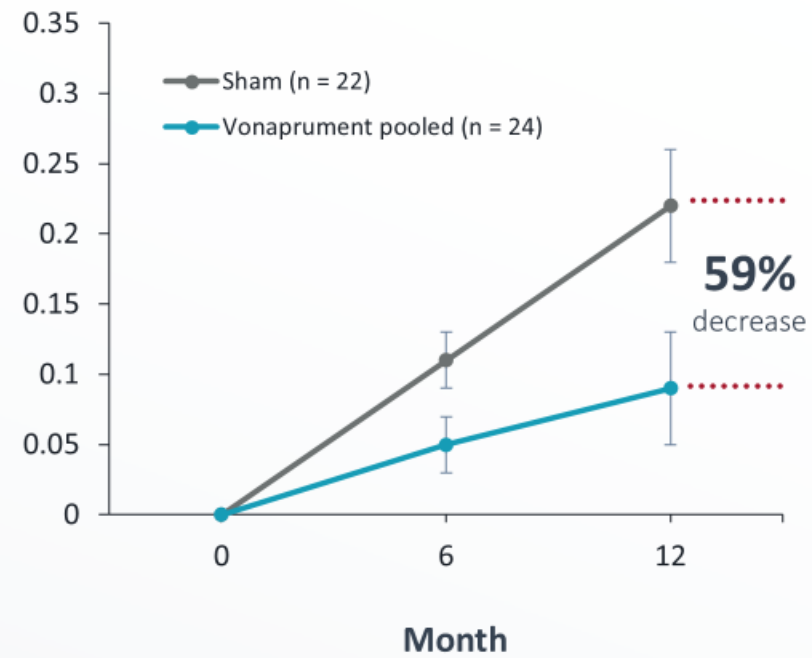
Nominal p-value[^] **Vonaprument Pooled vs Sham 0.0457**

CENTRAL 2.0 MM



Nominal p-value[^] **Vonaprument Pooled vs Sham 0.0218**

CENTRAL 1.5 MM

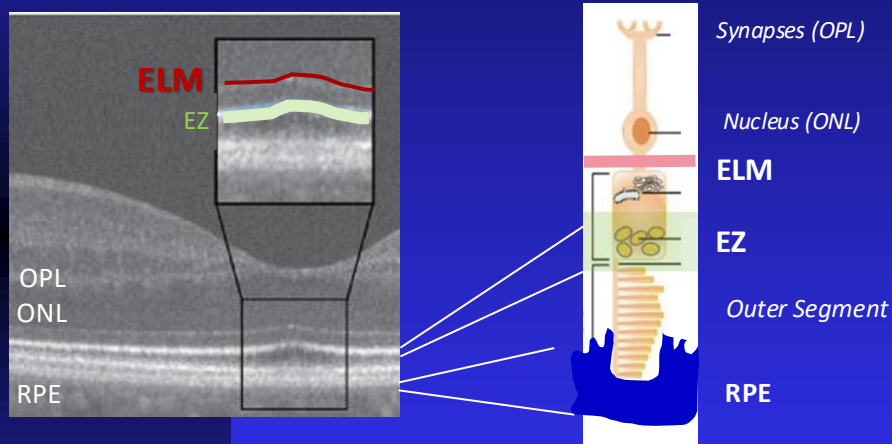


Nominal p-value[^] **Vonaprument Pooled vs Sham 0.0319**

[^]Nominal p-values from a linear mixed model for repeated measures model (slope) analysis; Heidelberg Spectralis OCT population with baseline OCT data, excludes patients with >98% atrophy/attenuation at baseline

ELM and EZ Are Biomarkers of Photoreceptor Integrity

Functional photoreceptors are required for vision



ARCHER ELM POPULATION

Sham	Vonaprument EM	Vonaprument EOM	Total
71	60	62	193

External Limiting Membrane (ELM)

- Exploratory structural endpoint
- An Imaging Biomarker of Outer Nuclear Layer Integrity
- In GA, the ELM disruption:
 - *delimits an area of near-total photoreceptor depletion*
 - *indicates irreversible tissue damage*

Christine Curcio, Retina 2018

Ellipsoid Zone (EZ)

- FDA approved structural endpoint
- In Dry AMD/GA, **EZ integrity is:**
 - *A surrogate measure of photoreceptor health*
 - *associated with visual outcomes*
 - *An indicator for predicting future functional outcomes*

Ehlers J. J Pers Med 2025 and ARVO 2025

- 192 patients with OCT scans from Heidelberg Spectralis and baseline EZ data were included in structure-function correlation assessments

Structure - Function Relationships in the ARCHER Trial

Objective

- Assess relationships between retinal structural integrity (EZ, ELM) and visual function (BCVA, LLVA) in the ARCHER Phase 2 trial at baseline

Methods

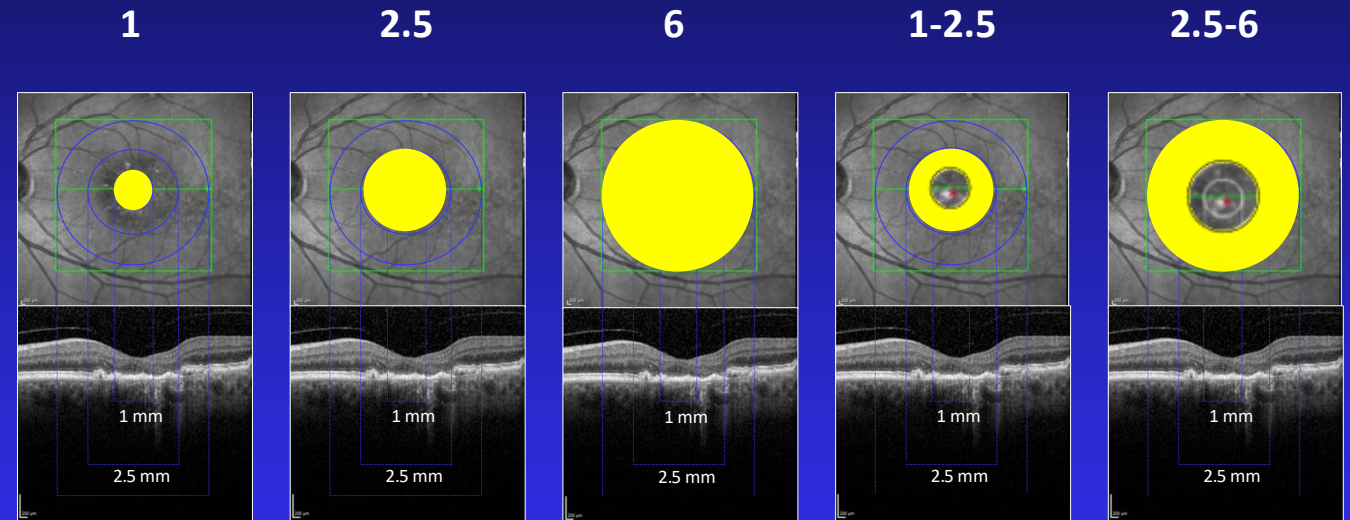
Analysis was performed across macular subfields* in the subset of eyes with Heidelberg OCT images (n=193)

Structural Metrics

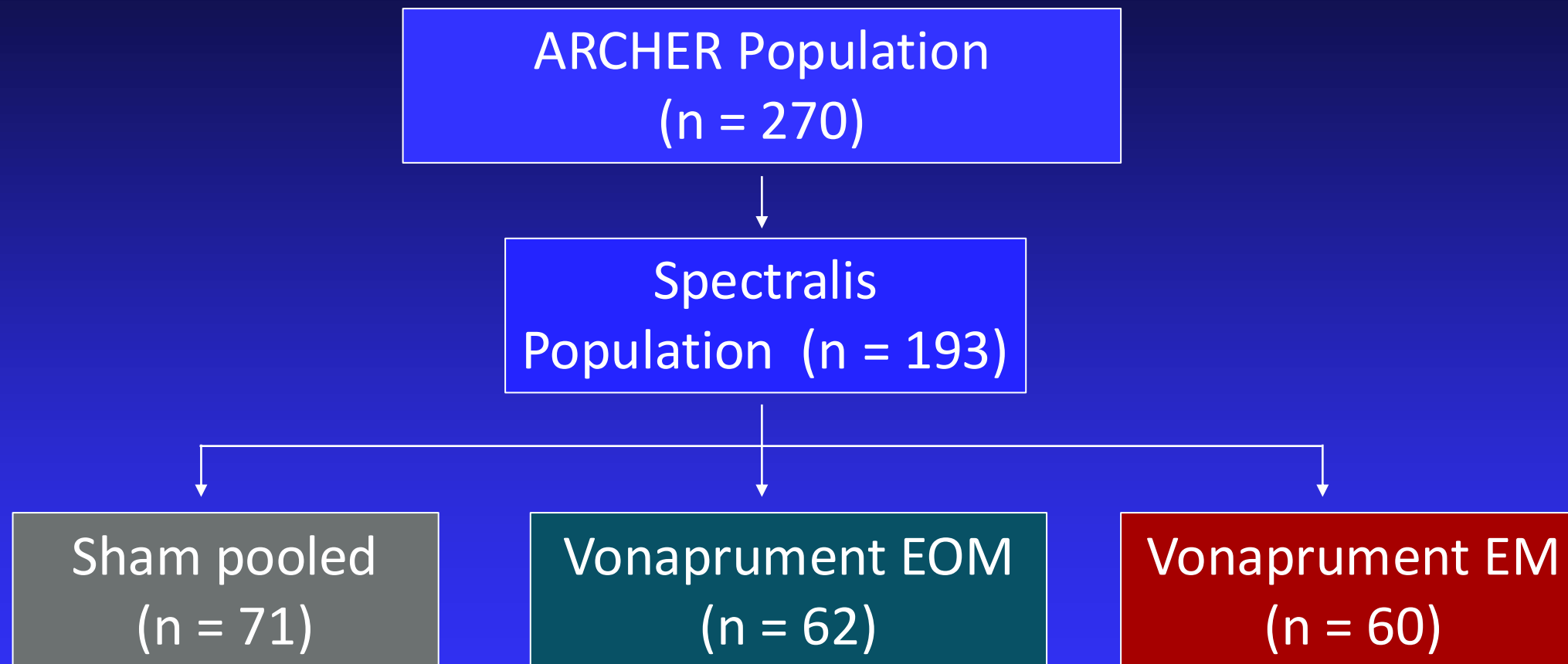
- Total EZ Loss = Proportion of the area where EZ thickness is 0
- Total ELM Loss = Proportion of the area where ELM thickness is 0

Functional Metrics

- Best Corrected Visual Acuity (BCVA)
- Low Luminance Visual Acuity (LLVA)



Spectralis OCT Population in ARCHER Closely Mirrors Overall Population



Patient demographics and study eye characteristics in the Spectralis population were generally well-balanced across groups and consistent with overall population

Patient Demographics and Study Eye Baseline Characteristics

ARCHER POPULATION (N=270)

Characteristic	Sham (N = 89)	Vonaprument EOM (N = 92)	Vonaprument EM (N = 89)
Age, mean (SD)	79.8 (7.49)	80.5 (8.53)	79.7 (8.64)
Female, n (%)	59 (66.3)	60 (65.2)	47 (52.8)
Mean BCVA (SD)	58.5 (16.2)	58.3 (15.0)	58.3 (17.2)
Foveal Lesion (%)	49.4	53.3	57.3
GA Lesion size (mm ²), mean (SD)	7.28 (3.99)	7.53 (4.10)	7.28 (3.96)
GA Lesion < 7.5mm ² (%)	61.8	57.6	58.4
Fellow Eye CNV (%)	22.5	17.4	24.7
Multifocality, n (%)	65 (73.0)	65 (73.0)	61 (68.5)

SPECTRALIS POPULATION (N=192)

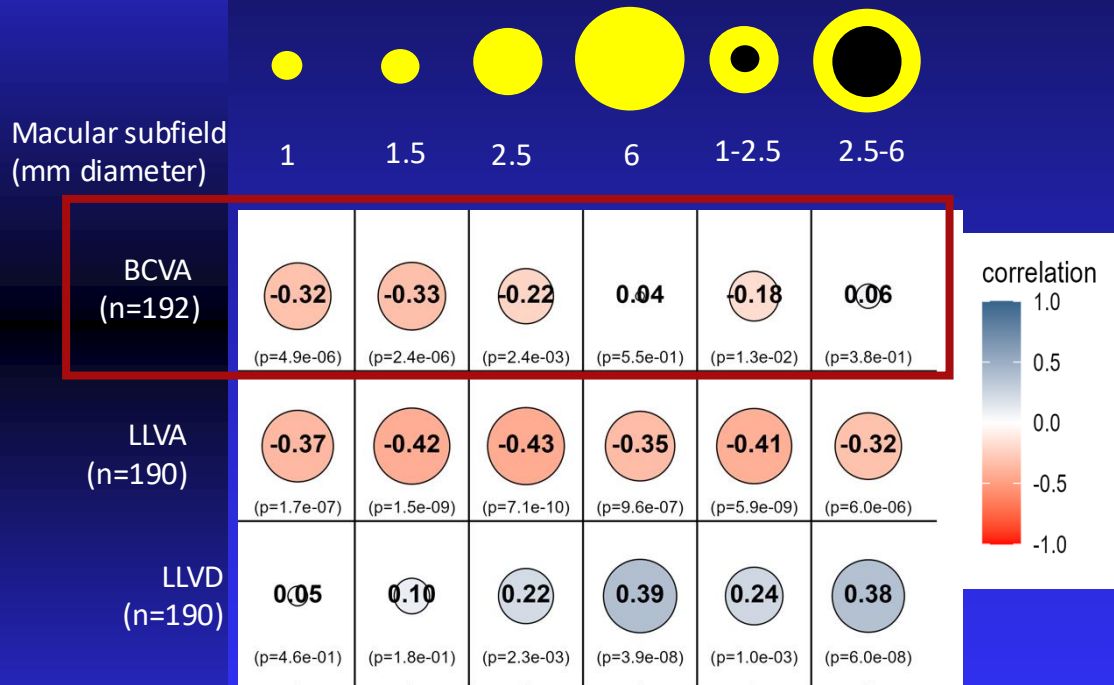
Characteristic	Sham (N = 71)	Vonaprument EOM (N = 61)	Vonaprument EM (N = 60)
Age, mean (SD)	79.4 (7.50)	81.5 (7.41)	79.7 (8.08)
Female, n (%)	46 (64.8)	36 (59.0)	32 (53.3)
Mean BCVA (SD)	57.7 (17.0)	58.7 (15.1)	58.1 (17.9)
Foveal Lesion (%)	53.5	62.3	61.7
GA Lesion size (mm ²), mean (SD)	7.50 (4.00)	7.42 (4.02)	7.74 (3.96)
GA Lesion < 7.5mm ² (%)	60.6	59.0	50.0
Fellow Eye CNV (%)	23.9	19.7	25.0
Multifocality, n (%)	50 (70.4)	40 (65.6)	43 (71.7)

Patient demographics and study eye characteristics in the Spectralis population were generally well-balanced across groups and consistent with overall population

Correlation Between EZ Loss and BCVA at Baseline in ARCHER

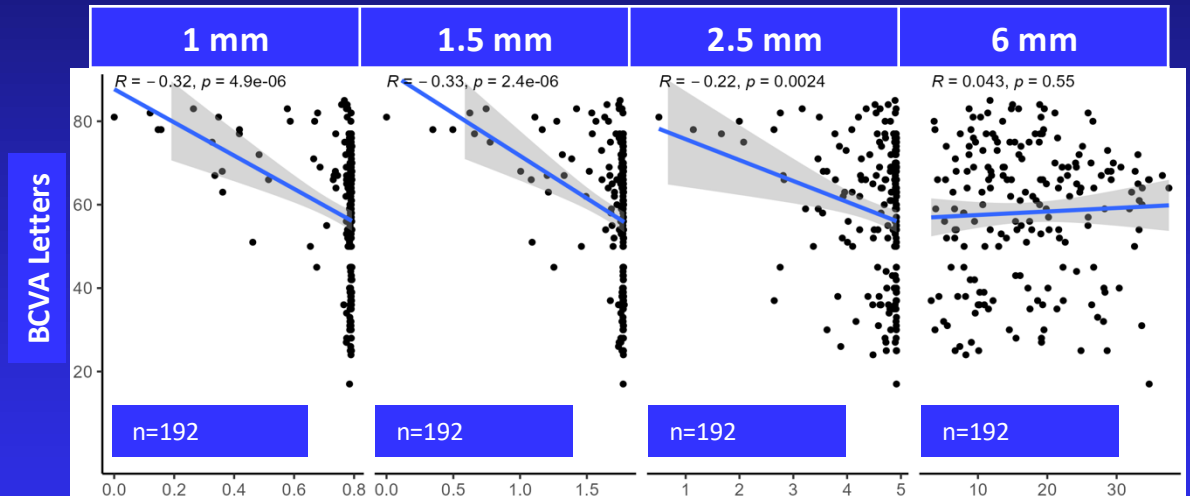
All eyes with Spectralis OCT images and baseline data (n=192)

Correlation Between BCVA and Area of Total EZ Loss at Baseline



Post-hoc analysis; all p-values are nominal

BCVA vs. Area of Total EZ Loss in each macular subfield



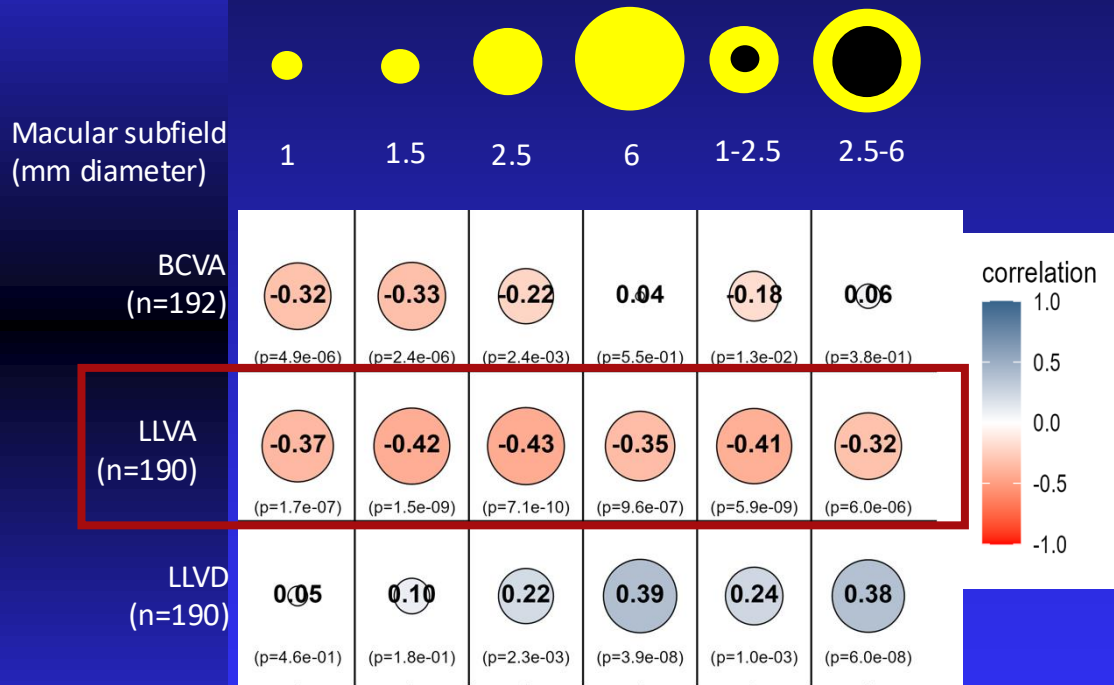
Post-hoc analysis; all p-values are nominal

BCVA (negative) correlation with EZ loss is stronger in the central subfields
Consistent with the relevance of central macula in visual acuity

Correlation Between EZ Loss and LLVA at Baseline in ARCHER

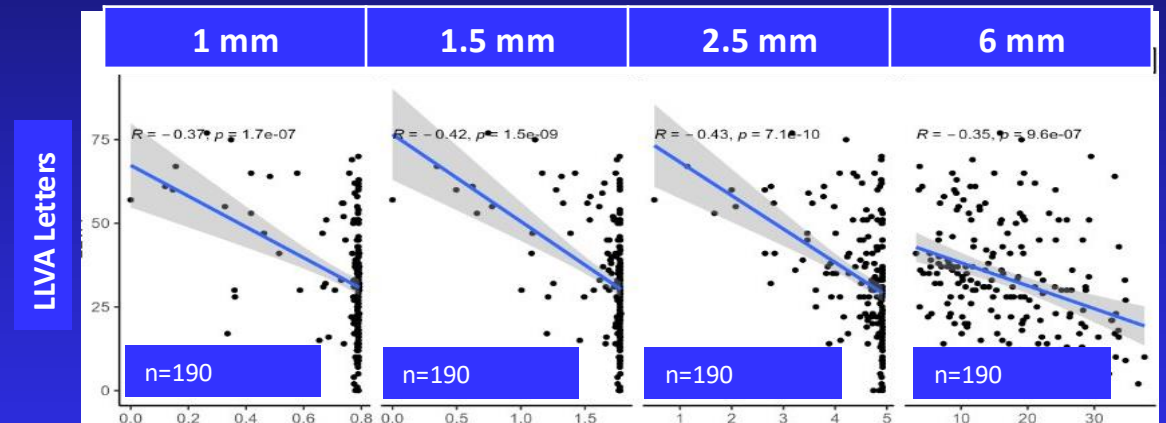
All eyes with Spectralis OCT images and baseline data (n=192)

Correlation Between BCVA and Area of Total EZ Loss at Baseline



Post-hoc analysis; all p-values are nominal

LLVA vs. Area of Total EZ Loss in each macular subfield



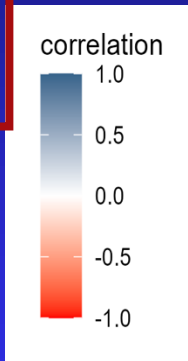
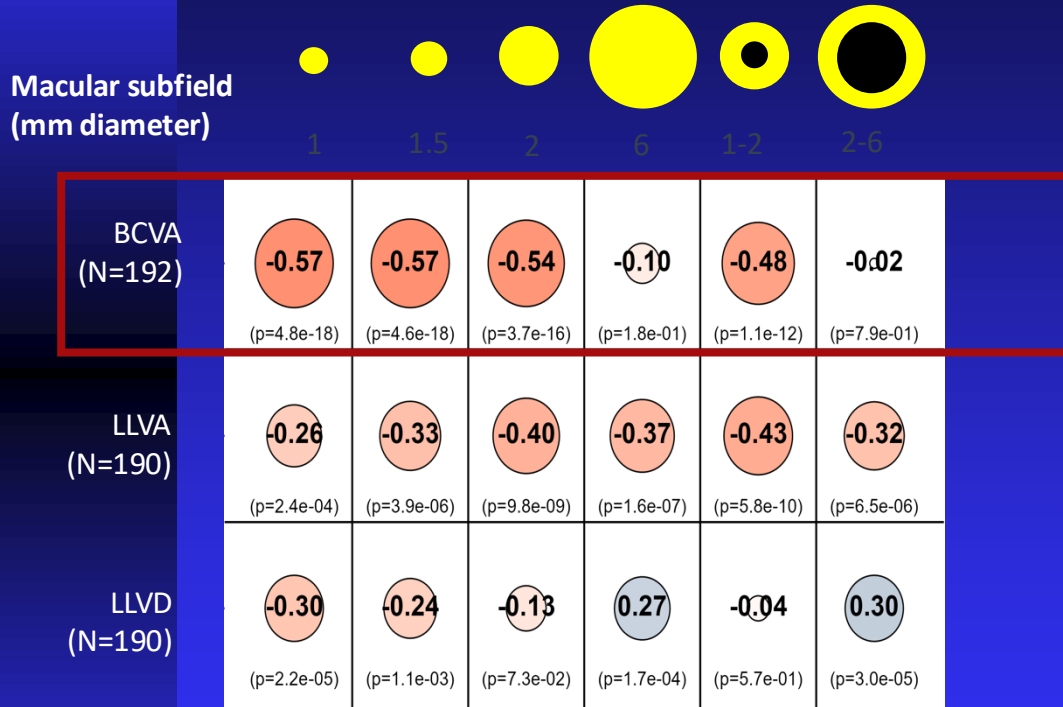
Area of Total EZ Loss (EZ=0 thickness (mm²))

Post-hoc analysis; all p-values are nominal

BCVA (negative) correlation with EZ loss is stronger in the central subfields
Consistent with the relevance of central macula in visual acuity

ELM Loss Correlates with BCVA in Central Subfields at Baseline in ARCHER

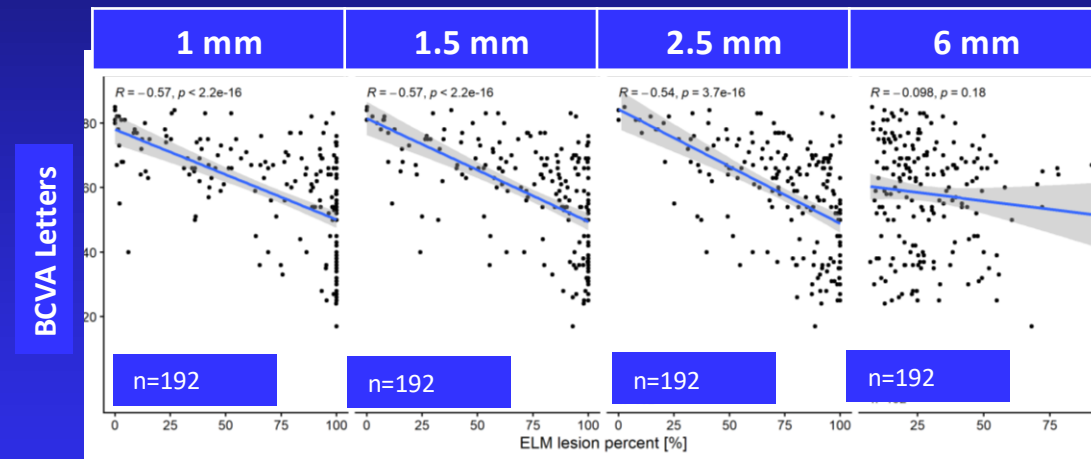
Correlation Between BCVA and Area of Total ELM Loss at Baseline



Data: ARCHER, eyes with Spectralis OCT images (n=192), Baseline

Post-hoc analysis; all p-values are nominal

BCVA vs. Area of Total ELM Loss in each macular subfield



ELM Loss percent (%)

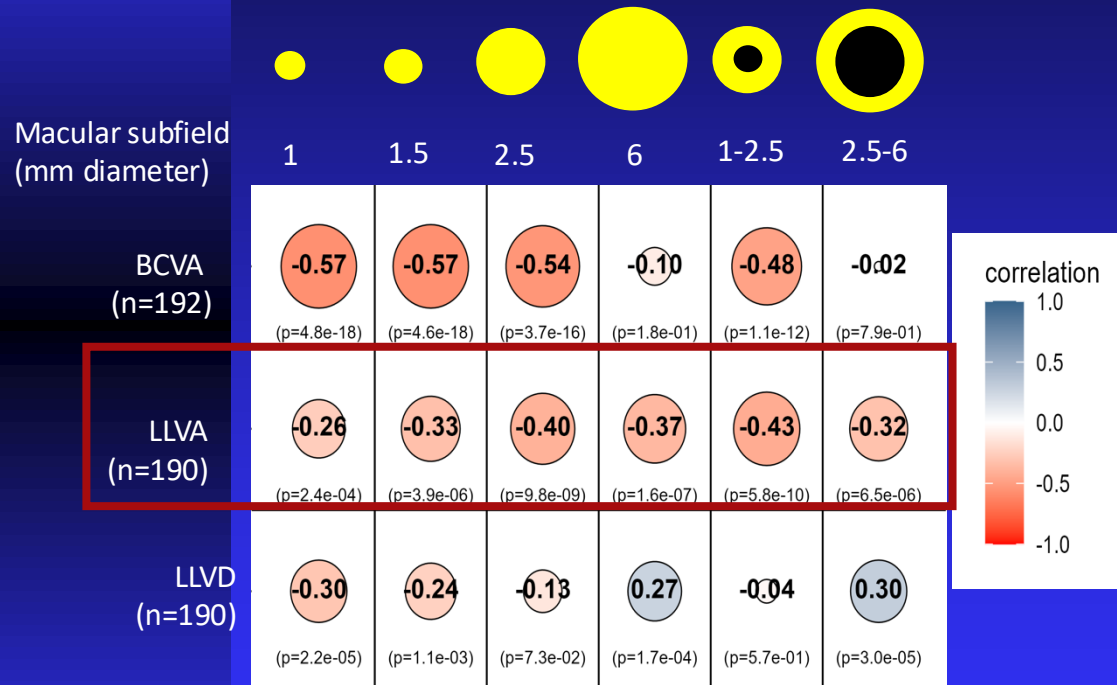
Post-hoc analysis; all p-values are nominal

BCVA (negative) correlation with ELM Loss is stronger in central subdomains
Consistent with the relevance of central macula to visual acuity

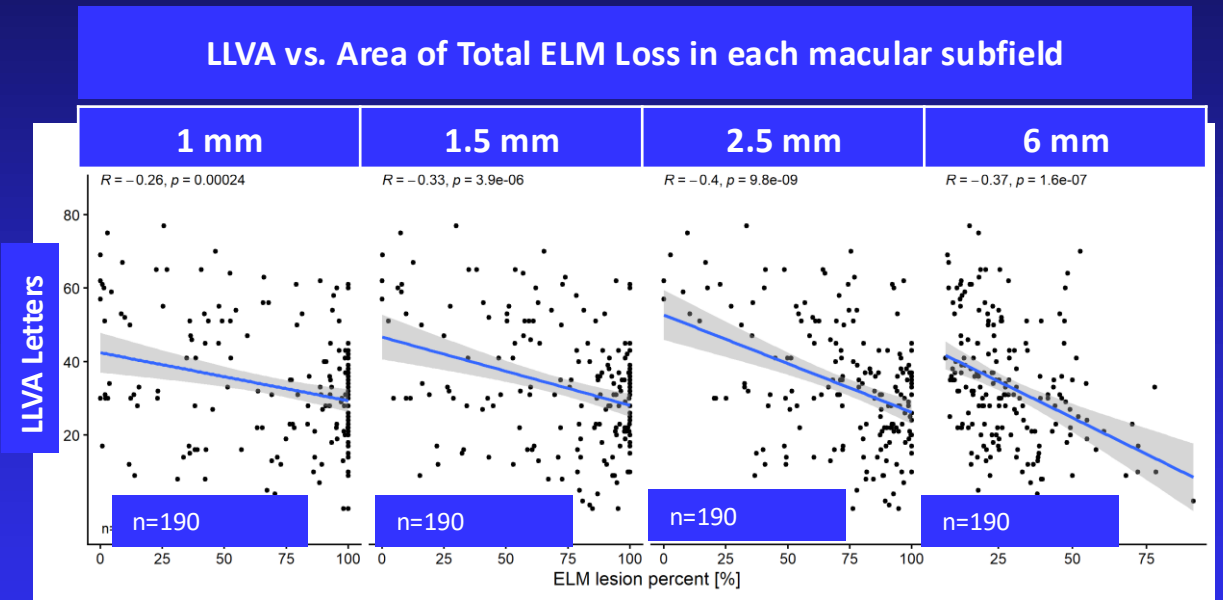
Correlation Between ELM Loss and LLVA at Baseline in ARCHER

All eyes with Spectralis OCT images and baseline data (n=192)

Correlation Between LLVA and Area of Total ELM Loss at Baseline



Post-hoc analysis; all p-values are nominal



Area of Total ELM Loss (ELM=0 thickness (mm²))

Post-hoc analysis; all p-values are nominal

LLVA (negative) correlation with ELM loss is stronger in the central subfields
Consistent with the relevance of central macula in visual acuity

Structure Function Association in ARCHER: EZ/ELM and Visual Acuity Conclusions

- **Central subfields are important for BCVA**
 - EZ integrity in central subfields correlates with BCVA
 - ELM integrity in central subfields correlates with BCVA
- **The full macula is important for LLVA**
 - EZ integrity across all macular subfields correlates with LLVA
 - ELM integrity across all macular subfields correlates with LLVA
- **These relationships between photoreceptor integrity and visual acuity are consistent with the results seen with vonaprunent in the Phase 2 ARCHER trial**
- **ELM may be used as an alternative measure of photoreceptor integrity**