Best corrected visual acuity
low luminance visual acuity
low luminance deficit

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EMRN workshop on Geographic Atrophy endpoints – 29 April 2026

Disclosure Statement

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Disclosures

Rufino Silva MD, PhD: Member of Advisory Board for Bayer, Roche, THEA
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Regulatory Compliance

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Agenda - EMRN Workshop on GA Endpoints

- Introduction and context
- 1- The feasibility and importance of VA- based outcomes in GA development programs: BCVA, LLVA, LLD
- 2- The minimal clinically important differences (MCID) for these outcomes in GA populations
- 3- The most appropriate time for assessment of stage/location and progression pattern of disease on trial design
- 4- Enrichment with fast-progressors; feasibility of extrapolation from fast-progressors to the broad GA-population
- 5- Relationship between endpoints, any potential for composite endpoints

Introduction & Context: : Current evidence - Natural History of GA

n=496 | 24 months

Anatomical Progression

GA lesion growth over 24 months

GA Area Change **3.87 mm²** Proxima A (bilateral)	Square Root **0.62 mm** Consistent growth
Subfoveal **48.1%** at baseline	Multifocal **78.7%** lesion type

- Faster progression in nonsubfoveal lesions

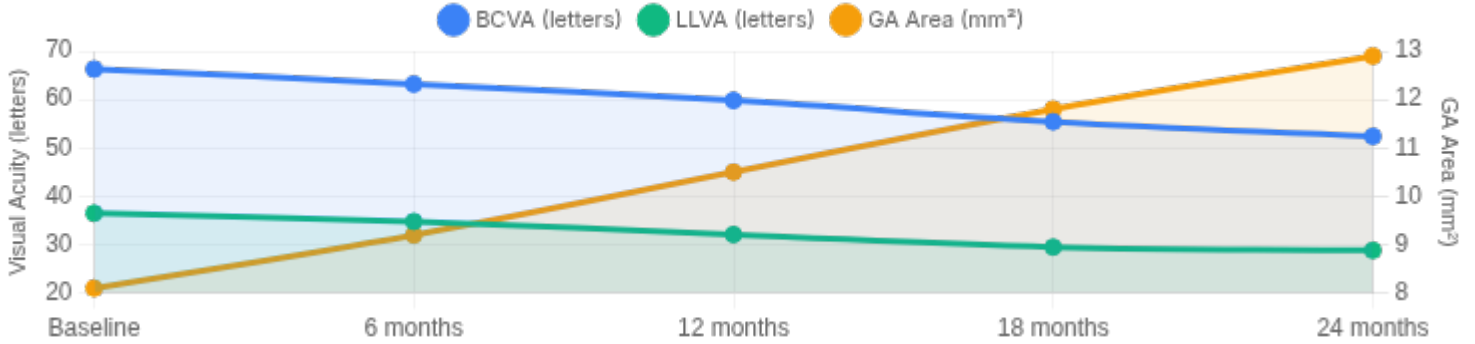
Key Predictors

Risk factors for progression

Factor	Impact
Multifocal lesions	+45% faster
Baseline LLD	+32% faster
Fellow eye CNV	+28% faster

Functional Progression (Visual function decline)

Primary Endpoint



-13.88 BCVA loss (letters) ↓ **20.8% from baseline**	**-7.65** LLVA loss (letters) ↓ **21.0% from baseline**	**34.6%** Moderate vision loss **≥15 letters**	**10.3%** Severe vision loss **≥30 letters**

Visual function deteriorates across all cohorts, with 34.6% experiencing moderate vision loss by 24 months, **with marked inter-individual variability driven by phenotypic heterogeneity and baseline disease characteristics (including lesion size, location, and progression pattern).**

Despite relatively preserved BCVA in early stages, patients with foveal sparing experience significant functional decline in low-light conditions.

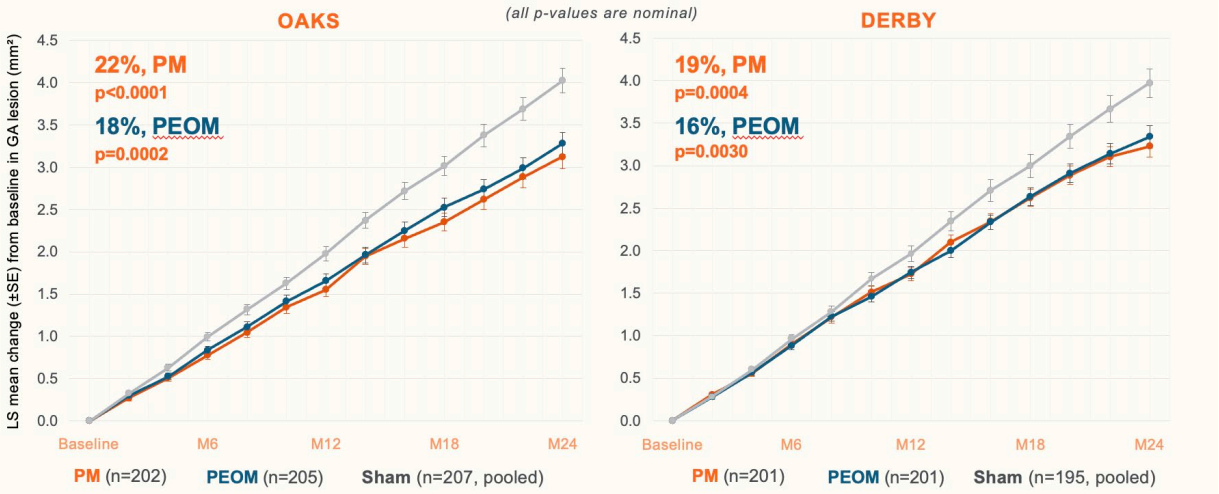
Holekamp, N. et al. Results from the Prospective Proxima A and B Clinical Trials. *Ophthalmology* 127, 769-783 (2020).

Introduction & Context: C3/C5 Inhibitors: reductions in GA growth but do not alter rate of vision loss

Oaks and Derby phase 3 trials reveal reductions in GA growth during Month 24 in pegcetacoplan treated eyes

SLIDES COURTESY OF APELLIS

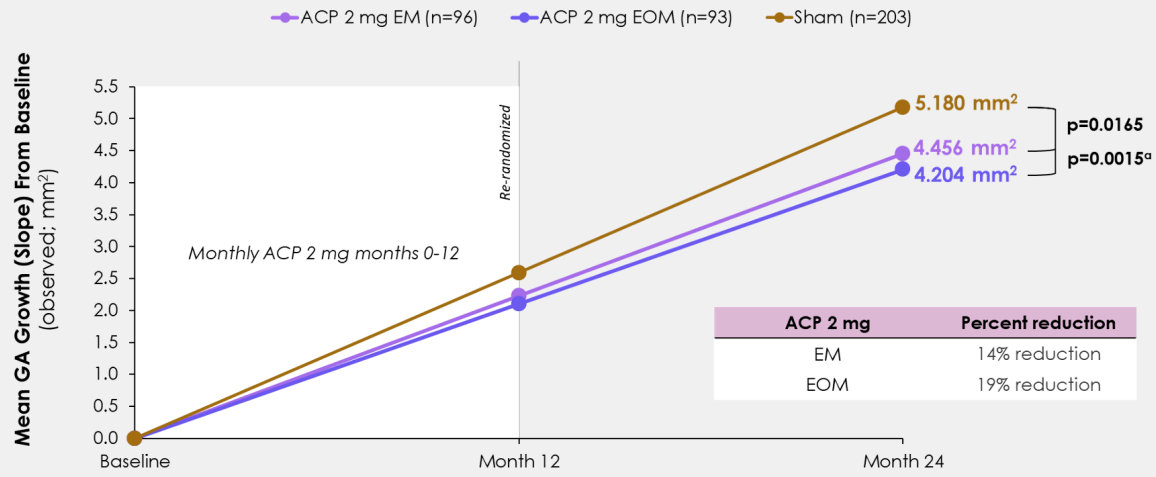
OAKS DERBY



Avacincaptad pegol (Zimura) treated eyes in the GATHER trials also experienced significant reductions in GA growth rate (presented at AAO 2023)

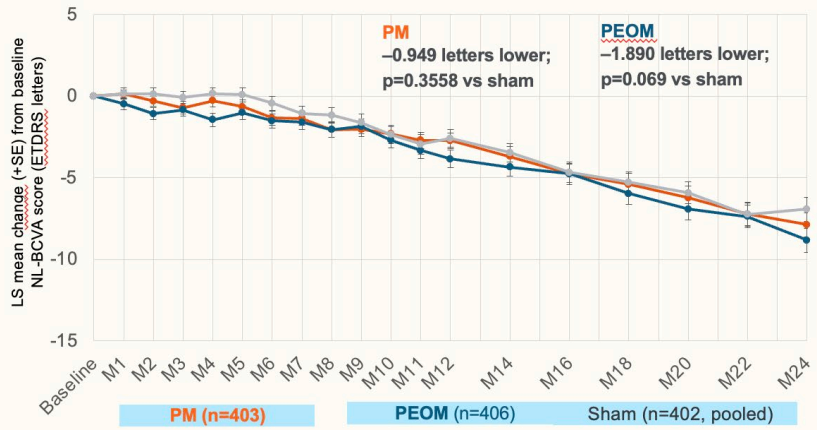
GATHER2

The mean BCVA change from baseline at month 24 was -10.5 L for ACP and -9.1 for sham



Change in BCVA in the study eye during the 24 months of follow up

OAKS DERBY



Visual function endpoints:

No statistically significant differences across study arms on key secondary endpoints at 24 months

- BCVA
- Maximum reading speed
- Functional Reading Independence Index
- Microperimetry: Mean threshold sensitivity (OAKS only)

In nonsubfoveal subgroup, lesion distance to foveal center at baseline was larger in sham pooled (370 microns) than in PM (337 microns) and PEOM (340 microns)

2 different modifiers of the complement pathway.

Independent trials conducted by different sponsors

Oaks & Derby: Pegecetacoplan acting on C3

Gather trials: Acincaptad Pegol acting on C5

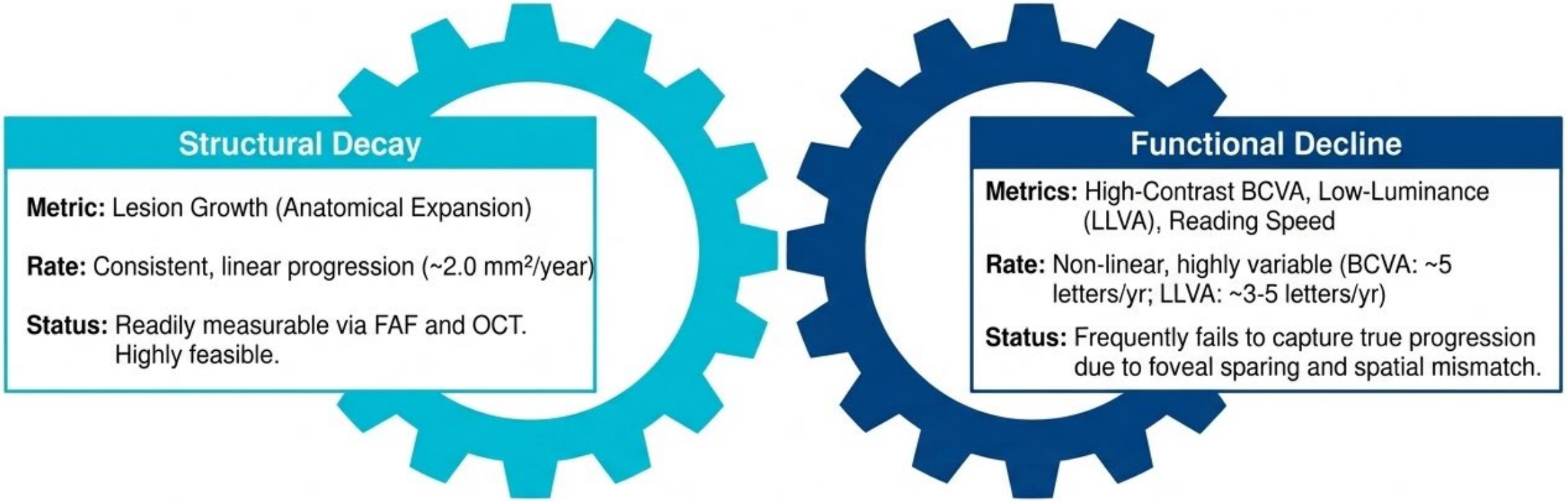
Khanani AM et al; GATHER2 trial investigators. Lancet 21;402(10411):1449-1458 (2023). Heier JS et al; OAKS and DERBY study investigators. 21;402(10411):1434-1448 (2023). Khanani AM et l, the GATHER2 Phase 3 Trial. Ophthalmology. Apr;133(4):451-465. (2026).

Why functional endpoints matter

- GA therapies show structural benefit without consistent functional improvement
- Functional measures remain central to patient relevance and regulatory value.
- Key challenge: aligning morphologic slowing with functional preservation.

The Measurement Paradox in Clinical Trials

The disconnect between linear structural decay and highly variable functional decline.



Key Takeaway: Relying solely on raw functional means without phenotypic screening risks severe false-negative efficacy readouts in development programs.

Heier JS et al., Ophthalmol Retina 2020;4:673-688
Shen LL et al., Ophthalmol Retina 2021;5:868-878

Question 1: The feasibility and importance of VA- based outcomes in GA development programs: BCVA, LLVA, LLD

BCVA relevance in specific subgroups:

- Baseline **BCVA <40 letters or GA >1 mm** from the foveal center did **not experience significant BCVA loss over 4 years**.
- GA involving or **within 1 mm of the foveal center** and baseline **BCVA ≥40 letters** significant vision loss over 4 years

BCVA limitations:

- **Limited dynamic range:** Ceiling and floor effects create a **narrow window where BCVA change is detectable**
- **Limited sensitivity to treatment effect:** substantial anatomic progression and minimal BCVA change
- **Subjective** measure dependent on refraction and testing conditions

Anegondi N, et al.: Learnings from the Lampalizumab Trials. Ophthalmology. Apr;132(4):420-430. (2025); Dinah C. et al, Progress in Retinal and Eye Research. Jan:110:101421(2026); Shen LL,et al. Ophthalmology. Jul;132(7):785-798 (2025). . Danzig CJ et al. Nov;8(11):1052-1060 (2024); Guymer RH et al, Lancet. Apr 29;401(10386):1459-1472 (2023).

Question 1: The feasibility and importance of VA- based outcomes in GA development programs: BCVA, LLVA, LLD

LLVA advantages:

- LLVA is **inexpensive and simple** to implement using readily available equipment.
- **Better reflects everyday visual** function (patients commonly report difficulty in dim lighting conditions)
- Standard ETDRS charts with a 2.0 log unit neutral density filter (1% transmission)
- **Earlier** clinical marker of central retinal function change **than standard VA**
- Baseline **LLD predicts subsequent visual acuity loss**

- **LLVA limitations:**
- **lack of standardization**, **weak structure-function** correlation, failure to demonstrate treatment effects in pivotal trials,
- **Limited dynamic range**, high test-retest **variability,** and regulatory uncertainty.

Dinah C. et al, Progress in Retinal and Eye Research. Jan:110:101421(2026) ; Fleckenstein M, et al; Ophthalmology. Mar;125(3):369-390. (2018), Li Y, et al. Clinical & Experimental Ophthalmology. Mar;54(2):260-274 (2026).

Question 1: - Low-Luminance Deficit (LLD) - Prognostic Value & Predictive Utility

BCVA vs LLVA vs LLD

Analysis

LLD Definition & Measurement

- LLD = BCVA - LLVA
- Probes macular cone function under dim light conditions
- Predicts faster future BCVA decline in GA patients

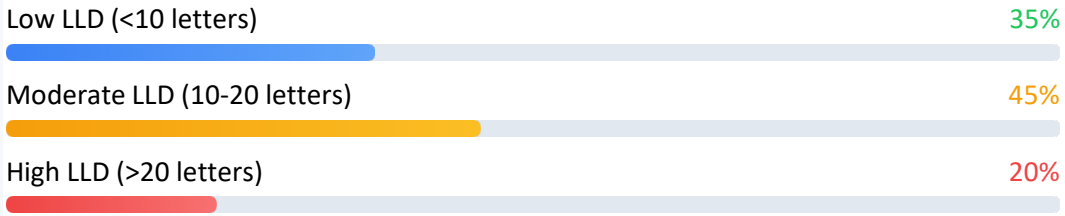
2.0	15-20	3yr
Log units filter	Letter difference	Predictive window

Prognostic Value & Clinical Utility

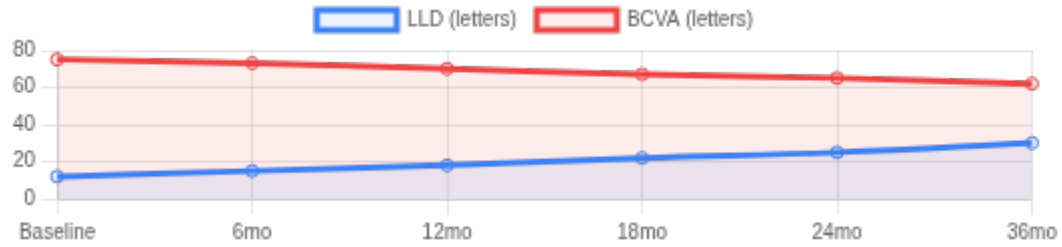
- Larger baseline LLD associated with faster VA loss
- LLD >15 letters predicts 2x faster progression
- Early functional deficit before structural changes visible

2x	15L	85%
Faster progression	Threshold	Sensitivity

Patient Stratification by LLD



LLD Trajectory Over Time



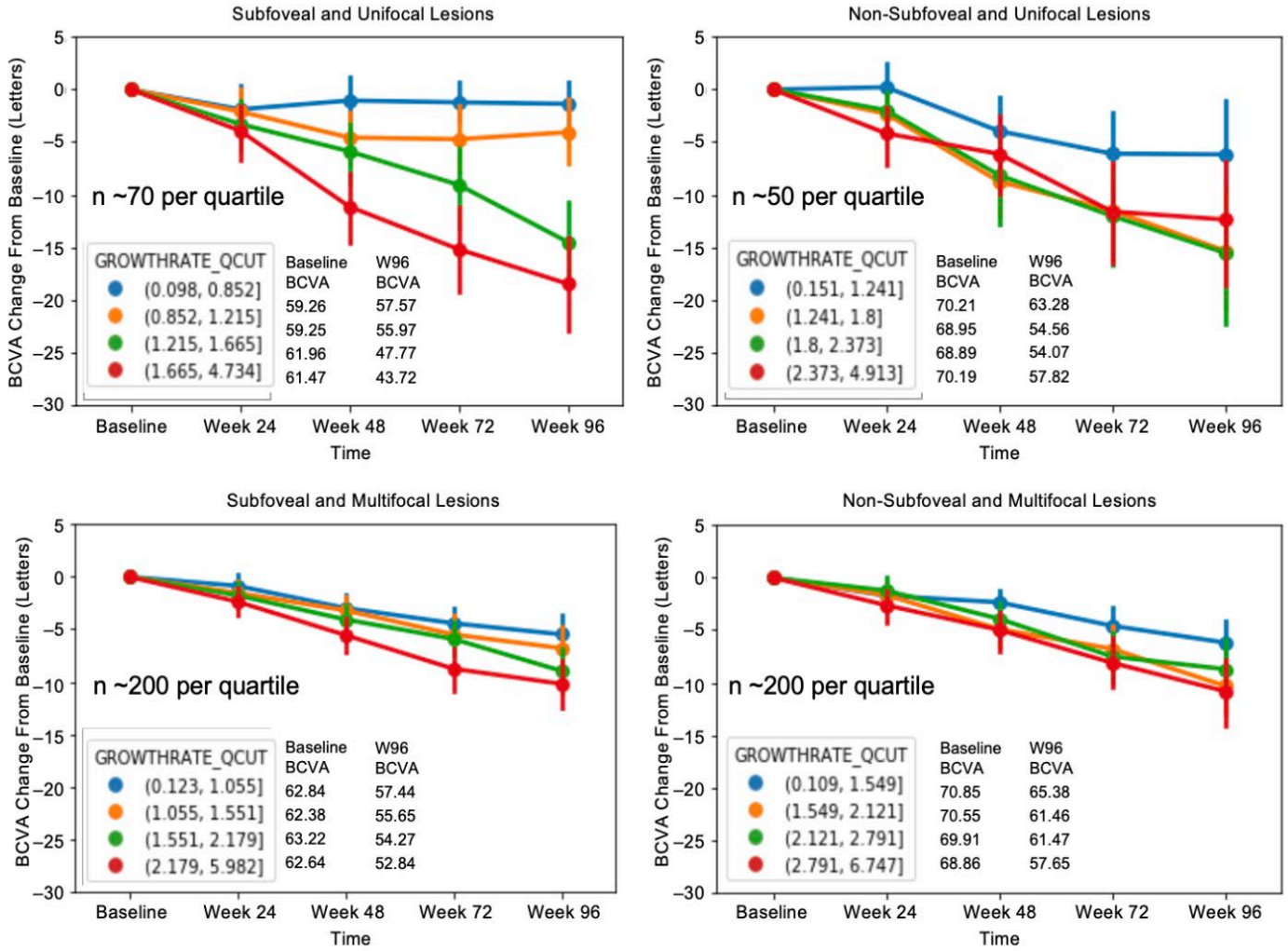
Data source: Chroma/Spectri trials, n=1519 patients

Key insight:
LLD as a predictor before significant vision loss occurs: a higher initial LLD predicts worse outcomes.
Useless for tracking progression in advanced diseases: floor effect and differential decline rates.

Sunness JS et al.*Ophthalmology*;115:1480-1488(2008); Rosenfeld PJ et al.*Ophthalmology*;125:1869-1877(2018)

Question 2: Minimal Clinically Important Differences (MCID)

Defining Meaningful Change for BCVA, LLVA, and LLD in GA Populations

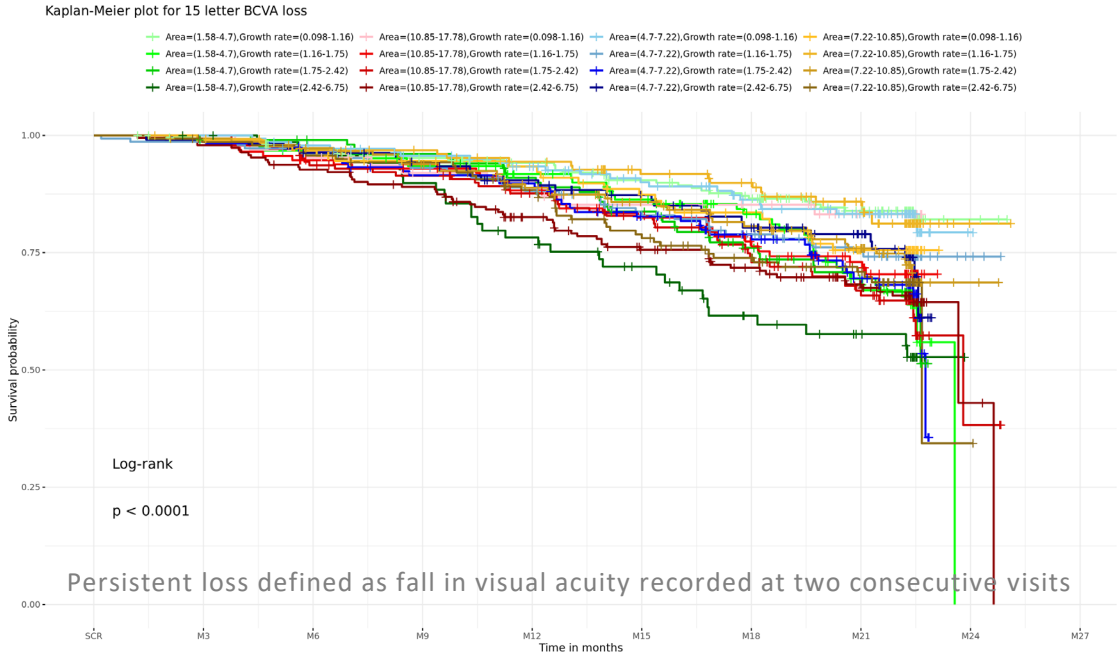


Visual Loss in Geographic Atrophy

Learnings from the Lampalizumab Trials

Neha Anegondi, MTech,[1] Verena Steffen, MSc,[1] Srinivas R. Sadda, MD,[2,3] Steffen Schmitz-Valckenberg, MD,[4,5] Adnan Tufail, MD,[6,7] Karl Csaky, MD, PhD,[8] Eleonora M. Lad, MD, PhD,[9] Peter K. Kaiser, MD, FASRS,[10] Daniela Ferrara, MD, PhD,[1] Usha Chakravarthy, FRCOphth, PhD[11]

Persistent 15 L loss event rates by baseline GA area and growth rate quartiles



Classification by location and focality of GA lesions and by annualized GA growth rates reveal differences in BCVA trajectories

Anegondi N, et al.: Learnings from the Lampalizumab Trials. Ophthalmology. Apr;132(4):420-430. (2025)

The 15-Letter MCID: Timelines & Quality of Life

Anchoring severe visual impairment to real-world disease trajectories.

Gap: LLVA/LLD thresholds require normative data and age-stratified values for regulatory acceptance.

Sunness JS et al.*Ophthalmology*;115:1480-1488(2008). Pfau M,et al. JAMA Ophthalmol. Oct 1;138(10):1026-1034 ((2026).

Question 2: Minimal Clinically Important Differences (MCID)

Defining Meaningful Change for BCVA, LLVA, and LLD in GA Populations

- **No formally validated, GA-specific MCIDs exist for BCVA, LLVA, or LLD.**

- **BCVA: ≥15 letters (3 lines)**:The FDA standard for clinically meaningful BCVA change

  0.2 logMAR (10 letters): can be reliably distinguished from no change with both sensitivity and specificity >95%

- **LLVA: D**istribution-based MCID estimate for LLVA would be 15 letters for late GA

  This is a statistical boundaries for detecting real change rather than patient-centered MCIDs.

- **LLD**: No MCID for LLD change has been established.

  Has been used primarily as a **prognostic biomarker** rather than a change-based outcome.

Vance E, Ophthalmol Retina.. Mar;10(3):231-240 (2026); Hou J, *JAMA Ophthalmol.* ;144(3):238–246(2026). Dunbar HMP et al, A MACUSTAR Study Report. *JAMA Ophthalmol.* ;140(8):780–789(2022); Vemulakonda GA et al. *Ophthalmology* ;132(4):P1-P74(2025): Tzoumas N, et al. *The Cochrane Database of Systematic Reviews* ;6:CD009300 (2023).

Question 3- Assessment timing and disease stage impact on trial design:

Disease Stage	BCVA Sensitivity	Recommended Primary Endpoints	Recommended secondary Functional Endpoints	Assessment Intervals
Extrafoveal GA (>1 mm from fovea)	Insensitive; no significant change over 4 years	GA area growth (FAF/OCT)	Microperimetry, LLVA, reading speed, dark adaptation	Structural: 6–12 months; Microperimetry: 6 months
Junctional GA (within 1 mm of fovea)	Highest sensitivity window; mean −11.33 letters over 4 years	Combined structure + function; junctional zone scotomatous points	LLVA, microperimetry, reading speed	Structural: 6 months; BCVA/functional: 3–6 months
Subfoveal GA (foveal involvement)	Responsive but floor effect if BCVA 40 letters	Event-driven BCVA loss (≥15 letters); time-to-event	Limited utility of functional outcomes	BCVA: every visit (monthly); Structural: 6 months

Heier JS, et al. Ophthalmol Retina. Jul;4(7):673-688 (2020). Anegondi, N., et al. *Ophthalmology* 132, 420–430 (2025); Heier JS, et al. Lancet. Oct 21;402(10411):1434-1448(2023); Shen LL, et al. Ophthalmology. Jul;132(7):785-798 (2025); Wu Z, et al. *JAMA Ophthalmol.* ;133(4):442–448(2015).; Vemulakonda G, et al. Ophthalmology,; 132, P1-P74 (2025)

Question 3- Assessment timing and disease stage impact on trial design

Patient Subgroup	Structural Assessment	Functional Assessment	Rationale
Junctional GA (≤1 mm from fovea) + BCVA ≥40 letters	6 months	3–6 months	Highest sensitivity for detecting meaningful BCVA change
Subfoveal unifocal GA	6 months	Every visit (monthly)	Strongest structure-function correlation; event-driven endpoints
Diffuse/diffuse-trickling FAF pattern	6 months	6 months	4× faster growth rate than "none" pattern
Multifocal GA	6 months	6–12 months	Faster structural progression; BCVA less sensitive
Bilateral GA	6 months	6 months	High concordance; high disability risk
Extrafoveal GA (>1 mm from fovea)	6–12 months	12 months (microperimetry preferred)	BCVA insensitive; structural endpoints primary

Shen LL et al. Ophthalmol Retina;4:899-910(2020); Sunness JS et al. Ophthalmology ;114:271-277(2007); Holz FG et al. Graefes Arch Clin Exp Ophthalmol;245:1-12(2007); Dinah C. et al, Progress in Retinal and Eye Research. Jan:110:101421(2026; Holekamp, N. et al. Ophthalmology 127, 769-783 (2020);). Anegondi, N., et al. *Ophthalmology* 132, 420–430 (2025); Schmitz-Valckenberg S, et al. Ophthalmology. 2016 Feb;123(2):361-368. Egger D, et al. Acta Ophthalmol. Jun;103(4):e204-e212(2025).

Question 4: Enrichment with Fast-Progressors - Feasibility and Extrapolation to Broad GA Population

Biomarker	Progression Rate Impact	Evidence Strength
FAF Diffuse/Diffuse-trickling	4× faster than "none" pattern	Strong (meta-analysis)
Multifocal lesions	Significantly faster than unifocal (P 0.001)	Strong (multiple cohorts)
Larger baseline lesion size	Upper 50th percentile	Strong
Extrafoveal lesion location	Faster structural progression than subfoveal	Strong
Fellow eye with GA	Highest progression rate vs. fellow eye early/interme. AMD	Strong
Hyperreflective foci (HRF)	Significant interaction with FAF patterns (P = 0.01)	Moderate
Genetic factors	ARMS2 risk, C3 non-risk, APOE non-risk associated with faster enlargement	Moderate
SDD/RPD	Associated with faster growth (P = 0.005)	Moderate
Higher PR-RPE loss ratio	Correlated with faster progression (ρ = 0.35, P = 0.001)	Moderate

Fleckenstein M, et al. Ophthalmology. Mar;125(3):369-390(2018); Borchert GA et al; Graefes Arch Clin Exp Ophthalmol. May;264(5):1201-1216(2026); . Khanani AM, et al; Lancet. Oct 21;402(10411):1449-1458 (2023); Schmitz-Valckenberg S, et al. Ophthalmology. Feb;123(2):361-368 (2016).; Egger D, et al. Acta Ophthalmol. Jun;103(4):e204-e212 (2025); Vemulakonda G, et al; Ophthalmology,; 132, P1-P74 (2025).

Question 4: Enrichment with Fast-Progressors - Feasibility and Extrapolation to Broad GA Population

Enrichment criteria should be matched to the trial's primary endpoint and disease stage.

For trials with anatomic primary endpoints (GA area growth):

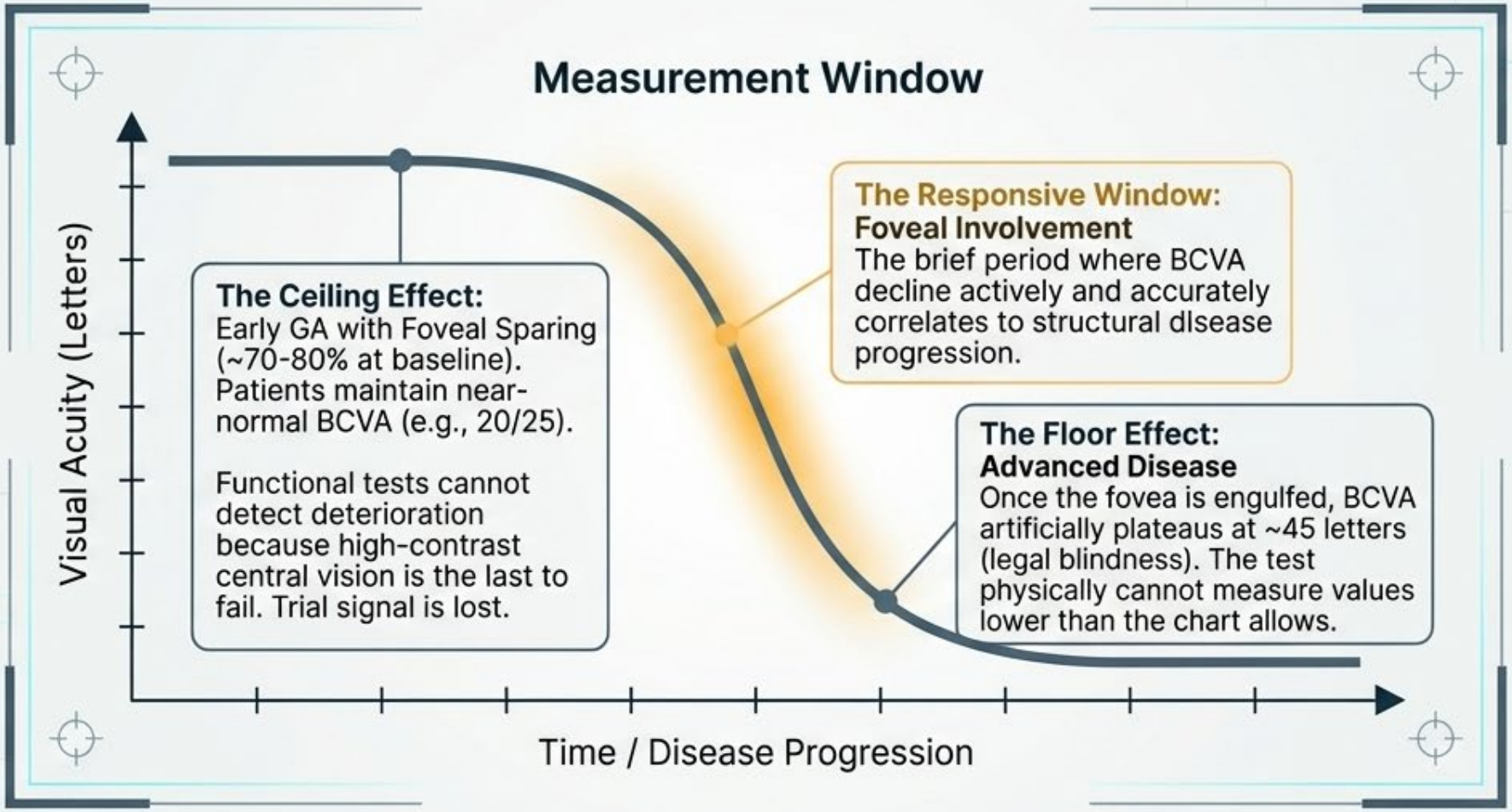
- Lesion size 2.5–17.5 mm^2 (standard)
- Stratify by FAF pattern, lesion focality, and baseline GA area
- Consider RPD status as a stratification factor
- Bilateral GA designs can dramatically reduce sample size

For trials with functional co-primary/key secondary endpoints:

- Non-center-point-involving GA within 1500 µm of fovea (GATHER2 model)
- BCVA ≥40 and ≤ 75 letters to maximize functional signal
- Baseline LLD as a prognostic enrichment biomarker

Fleckenstein M, et al. Ophthalmology. Mar;125(3):369-390(2018); .Shen LL et al. Ophthalmology ;132:785-798(2025).;). Anegondi, N., et al. Learnings from the lampalizumab trials. *Ophthalmology* 132, 420–430 (2025); Heier JS, et al. Lancet. Oct 21;402(10411):1434-1448(2023 ; Heier JS et al. Ophthalmol Retina;4:673-688(2020); Shen LL et al. Ophthalmol Retina;9:412-420 (2021); Emde L , et al. JAMA Ophthalmol; 143;(12):1014-1023 (2025).

The Limits of Psychophysics: Floor and Ceiling Effects



Heier JS et al. Ophthalmol Retina 2020;4:673-688; Shen, L. L. et al. Ophthalmol Retina 5, 868–78 (2021); Chakravarthy, U. et al. Ophthalmology 125, 842–49 (2018); Agrón, E. et al. Ophthalmology 130, 488–500 (2023); Lad et al., Annu Rev Vs Sc 2024. 10:455-476; Csaky, K. G. et al. Surv Ophthalmol 64, 353–364 (2019). Fleckenstein, M. et al. Ophthalmology 125, 369–90 (2018)., Agrón, E. et al. Ophthalmology 130, 488–500 (2023).

Question 5: Relationship Between Endpoints and Potential for Composite Endpoints

Composite Strategy	Components	Rationale	Regulatory Status
Weighted anatomic endpoint (GAWAIN)	GA area weighted by foveal proximity	Bridges structure-function gap; objective; correlates with BCVA	Not yet validated in trials
Combined anatomic + event-driven functional	GA area growth + time to ≥15-letter loss	Captures both slowing of progression and prevention of clinically meaningful vision loss	Exploratory in GATHER2
Junctional zone microperimetry	Scotomatous points in 250 µm border zone	Spatially aligned with treatment effect; strongest structure-function correlation	Post-hoc in OAKS
iRORA/cRORA progression	OCT-defined early atrophy markers	Enables earlier intervention trials; CAM consensus definitions	Under development
Multimodal composite	GA area + LLVA + reading speed + PRO	Captures multiple dimensions of disease impact	Proposed in COS

Chang DS, et al. Ophthalmol Sci. 3 Jun 12;4(1):100351 (202); Heier JS, et al. Lancet. Oct 21;402(10411):1434-1448(2023 ; Anegondi N, et al.,. Ophthalmology. Apr;132(4):420-430 (2025)

Question 5: Relationship Between Endpoints and Potential for Composite Endpoints

Disease Stage	Recommended Primary Endpoint	Recommended Secondary/Exploratory Endpoints	Rationale
Extrafoveal GA	GA area growth (FAF/OCT)	LLVA, reading speed, microperimetry (perilesional), GAWAIN	BCVA insensitive; functional outocomes capture perilesional dysfunction
Junctional/approaching fovea	GA area growth + junctional zone MP	Time to ≥15-letter loss, GAWAIN, reading speed	Highest sensitivity window; combine structure + function
Subfoveal GA	Time to ≥15-letter loss or BCVA change	GA area growth, PROs (NEI VFQ-25)	BCVA becomes responsive; event-driven endpoints capture meaningful change
Prevention (iAMD → GA)	Time to incident GA (cRORA)	iRORA progression, LLVA, dark adaptation	Early structural markers enable shorter trials

Agrón E, et al., Ophthalmology. Feb;131(2):208-218(2024); Keenan TDL. Ophthalmol Sci. Apr 10;3(3):100306(2023); Shen LL, et al.; Ophthalmology. Jul;132(7):785-798(2025); Dinah C, et al., Prog Retin Eye Res. 2026 Jan;110:101421; Vemulakonda G, et al.; Ophthalmology,; 132, P1-P74(2025).

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- **Patient/study eye criteria**
- Rapid growth: images available from prior visits and or abnormal peri lesional AF patterns
- Residual central visual function: BCVA > 50 L but less than 70 L (extent of foveal occupancy)
- Location of GA: juxtafoveal with posterior edge of lesion close to the FAZ or within FAZ
- **Criteria of lesser importance or exclusionary**
- Fellow eye with visual loss due to GA (logMAR 1.0 or worse) (choose better eye)
- Size of GA > 12 mm^2
- BCVA better than 75 L or worse than 35L

- **Potential primary outcome measure**
  - Proportions with persistent loss in BCVA (-5, -10, -15 L maintained over at least 2 visits)
  - Time to event categorical loss and time to reach a specified level of BCVA eg. 35 L
  - Mesopic MP. Progression from no scotoma or mild scotoma to persistent absolute scotoma within the central zone
- **Secondary outcome measures**
  - Mean changes in BCVA
  - Mean changes in near visual acuity
  - Vision related QOL in group when treatment is given to the better eye

** uncertainity on role of carriage of high risk alleles of CFH as potential to interact with therapeutic interventions

The Regulatory Extrapolation Challenge

Balancing precise trial engineering with real-world label scope.

Precision Trials

- **Cohort**: Fast-progressors (~15-25% of GA population).
- **Advantage**: Guarantees statistical success and proves biological mechanism.

Real-World Generalizability

- **Cohort**: All-comers population (100%), including slow progressors and floor-effect patients.
- **Regulatory Friction**: Does preserving foveal cells in an aggressive unifocal lesion guarantee efficacy in a massive, slow multifocal lesion?

Synthesis: Extrapolation is biologically plausible as the complement-mediated decay mechanism is uniform. However, broad labels demand post-market phase 4 surveillance to prove efficacy in non-enriched anatomical phenotypes.

Keenan TDL et al., Ophthalmology 2020;127:1598-1611
Grassmann F et al., Ophthalmology 2015;122:2516-2524

Synthesis: Summary of answers to 5 EMA questions and recommendations

Conclusions

Structure is consistent; function is stage-dependent.

Meaningful change varies by location and growth rate.

Junctional stage = highest sensitivity window.

Enrichment improves detection, but limits generalizability.

No linear extrapolation to the full GA population.

Composite, stage-specific endpoints are essential.

Take-home: Align **biology, timing, and endpoints** to show meaningful and generalizable benefit.