



Patient-reported outcomes, quality of life measures, safety outcomes

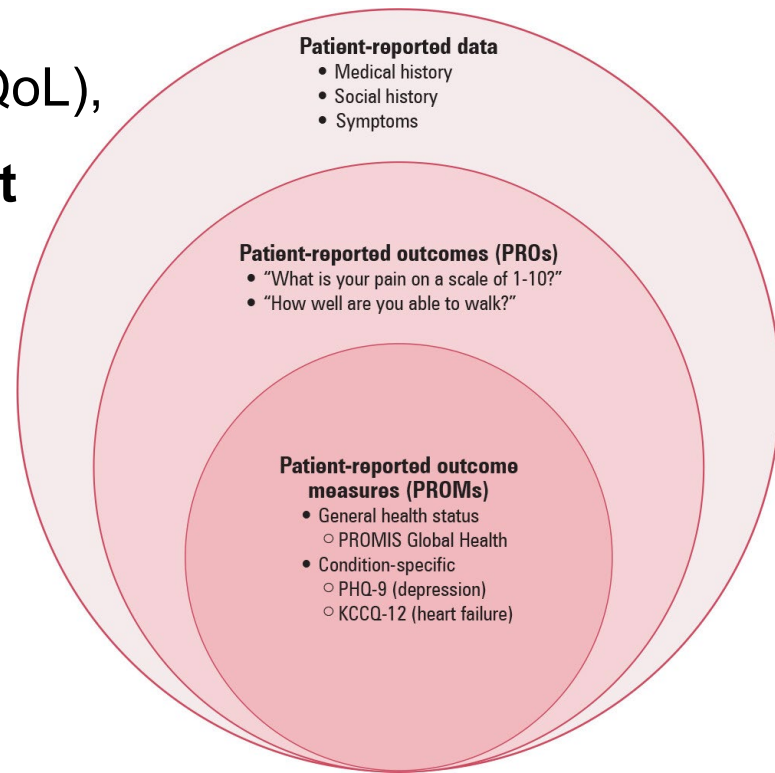
Jan H. Terheyden, MD, FEBO

European Medicines Regulatory Network (EMRN) Workshop on Geographic Atrophy Endpoints

April 29, 2026

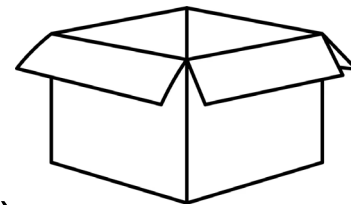
The concept of patient-reported outcomes (PROs)

- » Reports of health status, quality of life (QoL), and symptoms **directly from the patient**
- » PRO measures (PROMs): Validated **questionnaire instruments**
 - use of psychometric methodology
 - transform health status into scores
- » Measures of treatment benefit or risk in medical product clinical trials



Conceptual framework of PROs

- » Concept of a PRO = the *thing* being measured (FDA 2009)
 - e.g., symptom, groups of symptoms, effects on function(s)
- » Includes intended population, application (type of scores, mode of administration)
- » Foundation of content validity of PRO instrument („extent to which the instrument measures the concept of interest“) (FDA 2009)



EMA reflection on PROs

- » Successful medical treatment based on
 1. understanding of the disorder
 2. comprehensive patient data
 3. consideration of the **patient's expectations, preferences and values**
- » Directly reflect the experience of a patient, without input by a third party
- » Can include: health and functional status, disease symptoms, disease course, treatment preferences, QoL, factors impacting treatment adherence, treatment outcomes and side effects



PROs and QoL outcomes in GA trials

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☒ Any word

Syfovre

INN or common name: pegcetacoplan

Therapeutic area (MeSH): Macular Degeneration; Geographic Atrophy

Refusal of marketing authorisation: 16 December 2024 **Last updated:** 30 October 2025

Medicine

Human

Refused

Izelvay

INN or common name: avacincaptad pegol

Therapeutic area (MeSH): Macular Degeneration; Geographic Atrophy

Withdrawal of application: 24 October 2024 **Last updated:** 4 February 2025

Medicine

Human

Application withdrawn

NIH ClinicalTrials.gov Secondary outcome measure		
LS Mean Change From Baseline in Mean Functional Reading Independence (FRI) Index Score at Month 24	The FRI was an interviewer-administered questionnaire with 7 items on functional reading activities most relevant to GA AMD subjects. It had 1 total index score. For each FRI Index reading activity performed in the past 7 days, subjects were asked about the extent to which they required assistance beyond eyeglasses/contact lenses, including the use of low-vision aids, adjustments in the activity, or help from another subject. Mean FRI Index scores ranged from 1 (unable to do independently) to 4 (totally independent), with higher scores indicating higher functional reading independence. A negative change from baseline indicated a decrease in the FRI; disease worsening. LS mean was calculated using a MMRM model. Baseline was defined as the last available, non-missing observation prior to first study drug administration.	Baseline (screening) and Month 24

NIH ClinicalTrials.gov Secondary outcome measures		
Change From Baseline in Visual Function Questionnaire (VFQ-25) Composite Scores at 24 Months +6, 12, 18 months	The National Eye Institute Visual Function Questionnaire-25 (VFQ-25) measured the influence of visual disability and visual symptoms on general health domains. The VFQ-25 consisted of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. A higher score represented better visual functioning. Each item was then converted to a 0 to 100 scale so that the lowest and highest possible scores were set at 0 and 100 points, respectively. Each subscale score had a range of 0 to 100 inclusive and were calculated from the re-scaled raw data. A composite score was derived based on the average of the 11 vision-related subscales.	Baseline and month 24
Number of Participants With Categorical One-level Loss in VFQ-25 Subscale	were set at 0 and 100 points, respectively.Categorical one-level loss in each item was defined as decline of one or more levels at Month 24 on the original scale from Baseline (equivalently 20 points for general vision and 25 points for other vision items in a 0 to 100 scale).	Baseline up to month 24

PROs and QoL outcomes in GA trials

Consideration of three PRO and QoL outcomes at particular interest

- » **NEI VFQ-25** (National Eye Institute Visual Functioning Questionnaire)
- » **FRI index** (Functional Reading Independence index)
- » **VILL-33** (Vision Impairment in Low Luminance questionnaire)
- ✓ Fulfillment of ***regulatory use criteria*** (incl. concept elicitation, qualitative development steps)
- ✓ ***Familiarity to the European Medicines Agency*** from previous interactions

NEI VFQ-25

*National Eye Institute Visual Functioning Questionnaire

EPIDEMIOLOGY AND BIostatISTICS

Identifying the Content Area for the 51-Item National Eye Institute Visual Function Questionnaire

Results From Focus Groups With Visually Impaired Persons

Carol M. Mangione, MD, MSPH; Paul P. Lee, MD, JD; Peter R. Gutierrez, MA; Karen Spritzer, BA; Sandra Berry, MS; Ronald Klein, MD, MPH; Cynthia Owsley, PhD; Paul P. Lee, MD, JD

EPIDEMIOLOGY AND BIostatISTICS

Development of the 25-Item National Eye Institute Visual Function Questionnaire

Carol M. Mangione, MD, MSPH; Paul P. Lee, MD, JD; Peter R. Gutierrez, MA; Karen Spritzer, BA; Sandra Berry, MS; Ron D. Hays, PhD; for the National Eye Institute Visual Function Questionnaire Field Test Investigators

» Commonly used **vision-related QoL** measure

» Thirteen Subscales

General health, general vision, ocular pain, near vision, distance vision, vision-specific social functioning, vision-specific mental health, expectations for visual function, vision-specific role functioning, dependency due to vision, driving, peripheral vision, color vision

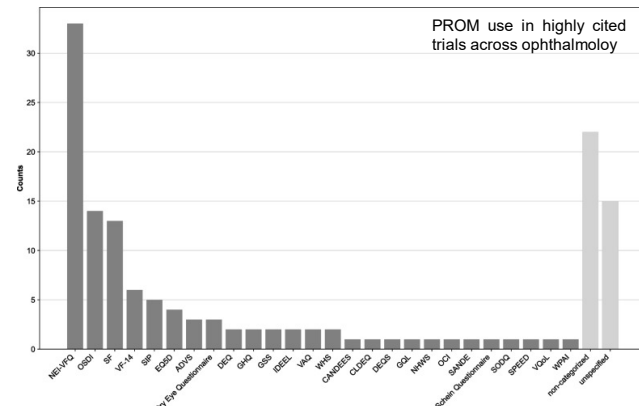
» Developed with patients (AMD, DR, glaucoma, cataract, CMV retinitis, low vision)

» Conventional sum scoring, Rasch model scorings

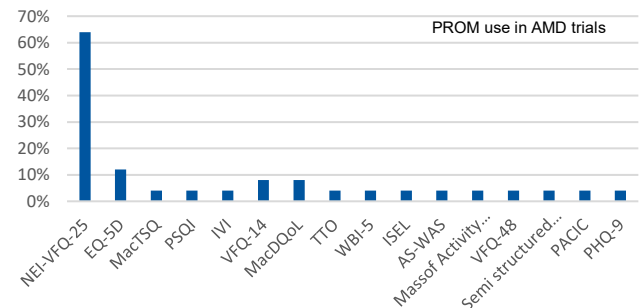
» 61 language versions

ePROVIDE™
By Mapi Research Trust

self-administration or interviewer administration



Terheyden JH et al, Health Qual Life Outcomes 2024



Krezel AK et al, BrJ Ophthalmol 2015

NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

Responsiveness

» Analysis of two samples (n=262 and 597)

recruited for a pilot study of the 51-item questionnaire and a field test

(AMD, DR, glaucoma, cataract, CMV retinitis, low vision, no underlying eye disease)

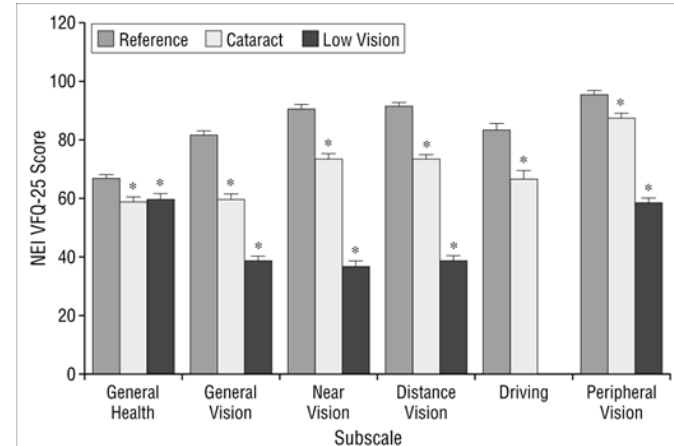
» Reliability: Cronbach's $\alpha = 0.71$ to 0.85
across subscales

» **Known-groups validity:** Significantly
poorer NEI VFQ-25 scores in cataract and
low vision patients than reference patients

EPIDEMIOLOGY AND BIOSTATISTICS

Development of the 25-Item National Eye Institute Visual Function Questionnaire

Carol M. Mangione, MD, MSPH; Paul P. Lee, MD, JD; Peter R. Gutierrez, MA; Karen Spritzer, BA; Sandra Berry, MS; Ron D. Hays, PhD; for the National Eye Institute Visual Function Questionnaire Field Test Investigators



NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

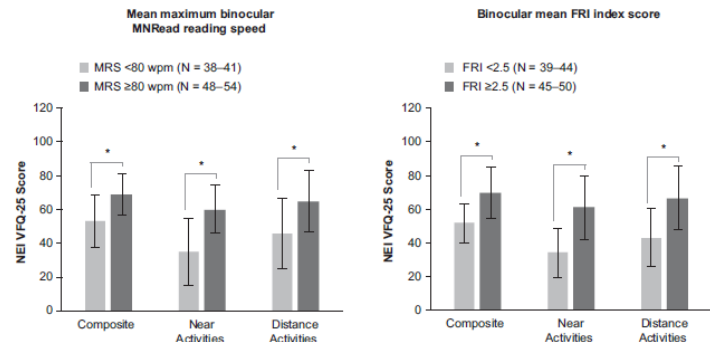
Responsiveness

- » Analysis of 100 participants with **geographic atrophy** of the phase 2 Lampalizumab trial Mahalo at baseline
- » Reliability: **Cronbach's $\alpha = 0.95$, test-retest (M6) ICC = 0.86** (composite score)
- » Convergent validity: **Pearson $r = 0.61$ (MNRad)** and $r = 0.69$ (FRI index) (composite score)
- » Known-groups validity: MNRad and FRI index

Reliability and Construct Validity of the NEI VFQ-25 in a Subset of Patients With Geographic Atrophy From the Phase 2 Mahalo Study



SOBHA SIVAPRASAD, ELIZABETH TSCHOSIK, AUDREY KAPRE, ROHIT VARMA, NEIL M. BRESSLER, MIRIAM KIMEL, CHANTAL DOLAN, AND DAVID SILVERMAN



NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

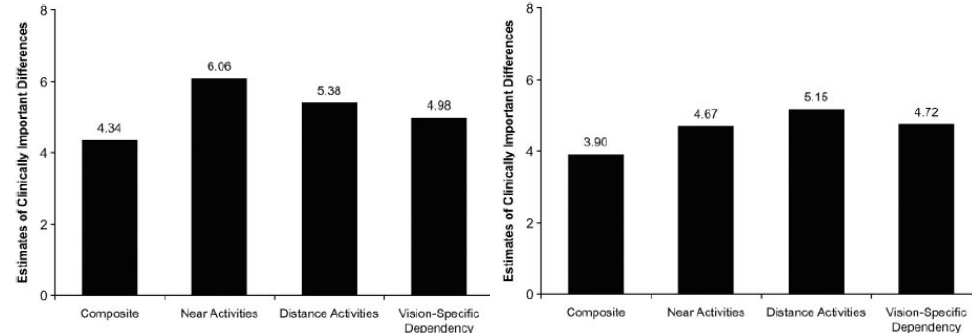
Validity

Responsiveness

Responsiveness of NEI VFQ-25 to Changes in Visual Acuity in Neovascular AMD: Validation Studies from Two Phase 3 Clinical Trials

Ivan J. Suñer,¹ Gregg T. Kokame,² Elaine Yu,³ James Ward,³ Chantal Dolan,³ and Neil M. Bressler⁴

- » Analysis of participants from the phase 3 ranibizumab trials Marina / Anchor in neovascular AMD (n=716 / 423)
- » A **4- to 6-point difference** in NEI VFQ-25 composite scores correspond to a patient-relevant 3-line BCVA change



NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

Responsiveness

» Analysis of 87 participants with **geographic atrophy** in a prospective, non-interventional cohort study

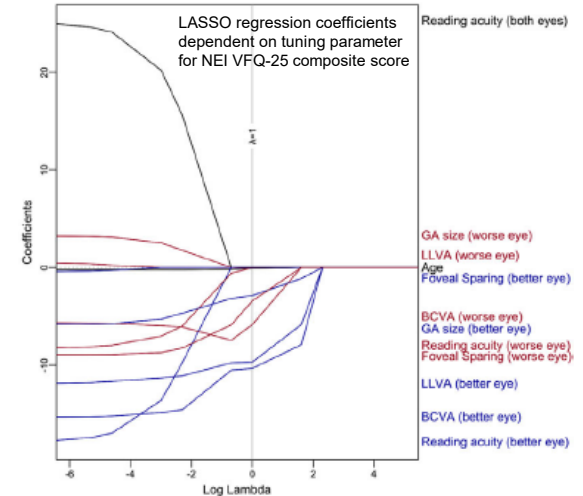
(subset of n=66 participants followed-up for 1 year)

» Low-luminance visual acuity (better eye) and best-corrected visual acuity (worse eye) were key determinants of NEI VFQ-25 scores

Low Vision

Determinants of Quality of Life in Geographic Atrophy Secondary to Age-Related Macular Degeneration

Sandrine H. Künzel,¹ Philipp T. Möller,^{1,2} Moritz Lindner,³ Lukas Goerdts,¹ Jennifer Nadal,⁴ Matthias Schmid,⁴ Steffen Schmitz-Valckenberg,^{1,2,5} Frank G. Holz,^{1,2} Monika Fleckenstein,^{1,2,5} and Maximilian Pfau^{1,2,6}



NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

Responsiveness

- » Secondary analysis of 298 participants (358 eyes) from the age-related eye disease study
- » **No significant decline** in Rasch model-calibrated over scores before vs. **after progression** to geographic atrophy ($p \geq 0.1$)
- » Faster decline in non-central GA ($p=0.03$) when considering visual functioning subscale

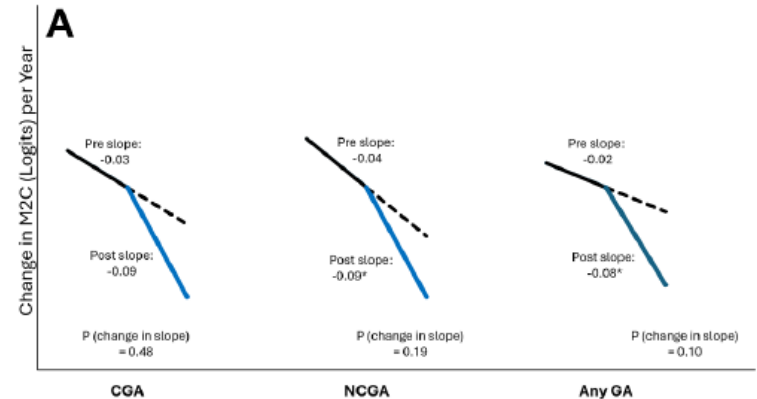


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Changes in Vision-Related Quality of Life before and after Geographic Atrophy Development in Age-Related Eye Disease Study Participants

Minali Prasad, BA, Susan Vitale, PhD, Elvira Agrón, MA, Thilaka Arunachalam, MD, Emily Y. Chew, MD



NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

Responsiveness

- » Secondary analysis of 856 participants with geographic atrophy from the Lampalizumab phase 3 trials Chroma / Spectri
- » Significant association between minimum atrophy extent and NEI VFQ-25 data
- » Subgroup analysis across different regions: **Central 2.5 mm diameter** region explains structure-PRO association ($R^2 = 0.11$)

FULL LENGTH ARTICLE · Articles in Press, April 22, 2026

Vision-Related Quality of Life in Geographic Atrophy: Association with Topographic Lesion Distribution

Neha Anegondi, MTech ^{1,2} · Diana Lam, PhD ^{1,2} · Robyn H. Guymer, MBBS, PhD ^{2,3} · Verena Steffen, MSc ¹ · Catherine A. Cukras, MD, PhD ⁴ · Daniela Ferrara, MD, PhD ⁵ · Zhichao Wu, BAppSc(Optom), PhD ^{2,3}   Show less

Table 2: Multivariable analyses of the associations between eye-level geographic atrophy (GA) extent within an individual, with estimates of vision-related quality of life.

	NEI VFQ-VF		NEI VFQ-SE	
	Coefficient*	P-Value	Coefficient*	P-Value
Multivariable Analysis 1 – Minimum GA Extent* within Different Regions				
Central 2.50-mm diameter region ("inside")	-0.18 (-0.23 to -0.14)	< 0.001	-0.12 (-0.17 to -0.07)	< 0.001
2.50- to 6.00-mm diameter annulus ("outside")	-0.03 (-0.12 to 0.06)	0.541	-0.05 (-0.15 to 0.05)	0.324

NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

Responsiveness

- » Secondary endpoint analysis of the phase 3 Pegcetacoplan trials Derby/Oaks in patients with **geographic atrophy**
- » **No significant difference** after 24-month period between treatment and sham



Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials

Jeffrey S Heier, Eleonora M Lad*, Frank G Holz, Philip J Rosenfeld, Robyn H Guymer, David Boyer, Federico Grossi, Caroline R Baumal, Jean-Francois Korobelnik, Jason S Slakter, Nadia K Waheed, Ravi Metlapally, Ian Pearce, Nathan Steinle, Anibal A Francone, Allen Hu, David R Lally, Pascal Deschatelets, Cedric Francois, Caleb Bliss, Giovanni Staurenghi, Jordi Monés, Rishi P Singh, Ramiro Ribeiro, Charles C Wykoff, on behalf of the OAKS and DERBY study investigators†*

	Pegcetacoplan monthly	Pegcetacoplan every other month	Sham
National Eye Institute Visual Functioning Questionnaire 25 distance activity subscale score			
Patients included in the model†	375/403 (93%)	380/406 (94%)	377/402 (94%)
Least-squares mean change (SE), score	-10.98 (1.35)	-10.10 (1.26)	-9.93 (1.19)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, score	-1.05 (-4.35 to 2.25)	-0.17 (-3.35 to 3.00)	NA
p value pegcetacoplan vs sham	0.53	0.92	NA

NEI VFQ-25 Psychometrics

*National Eye Institute Visual Functioning Questionnaire

Reliability

Validity

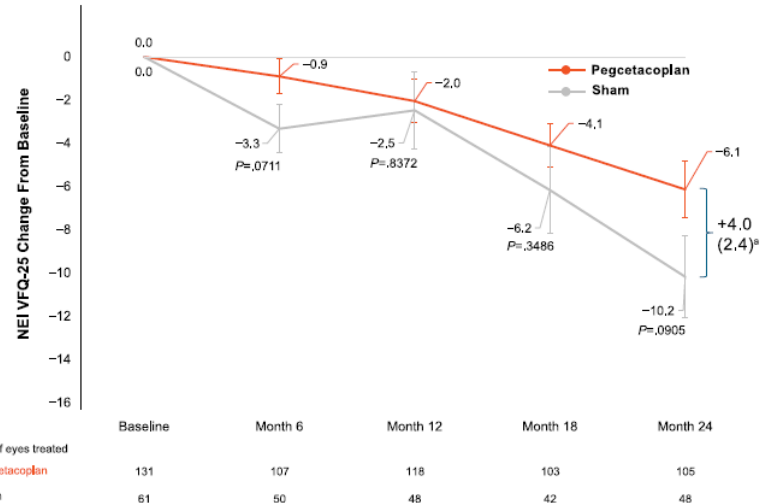
Responsiveness

- » Post-hoc analysis of the phase 3 Pegcetacoplan trials Derby/Oaks in patients with **geographic atrophy**
- » Slower decline in NEI VFQ-25 in treated eyes with geographic atrophy lesion margins $\geq 250 \mu\text{m}$ from the fovea (mean + 4.0 [SE 2.4]) over 24M

Visual Acuity and Quality of Life Outcomes With Pegcetacoplan Treatment: A Post Hoc Analysis From the OAKS and DERBY Trials



ALLEN CHIANG, MATTHEW DAVIS, WARREN STEVENS, SUNIR GARG, TOM SHEIDOW, DANIEL L. JONES, MICHELE INTORCIA[‡], ALEX MCKEOWN[‡], URSULA M. SCHMIDT-ERFURTH, SUJATA P. SARDA[‡], AND CAROLINE R. BAUMAL



FRI index

*Functional Reading Independence

Retina

Functional Reading Independence (FRI) Index: A New Patient-Reported Outcome Measure for Patients With Geographic Atrophy

Miriam Kimel,¹ Nancy Kline Leidy,¹ Elizabeth Tschosik,² Chantal Dolan,³ Eric H. Souied,⁴
Rohit Varma,⁵ and Neil M. Bressler⁶

- » 7-item unidimensional measure of visual functioning
 - specifically focuses on reading activities
 - » Developed specifically with geographic atrophy patients
 - » Scoring uses conventional means or levels
 - » 24 language versions
- interviewer administration

FRI index Psychometrics

*Functional Reading Independence

Retina

Functional Reading Independence (FRI) Index: A New Patient-Reported Outcome Measure for Patients With Geographic Atrophy

Miriam Kimel,¹ Nancy Kline Leidy,¹ Elizabeth Tschosik,² Chantal Dolan,³ Eric H. Souied,⁴ Rohit Varma,⁵ and Neil M. Bressler⁶

- » Analysis of 100 participants with **geographic atrophy** of the phase 2 Lampalizumab trial Mahalo at baseline
- » Reliability: IRT marginal reliability = 0.90, test-retest (M6) **ICC = 0.86** (27 stable NEI VFQ)
- » Convergent validity: Pearson $r = -0.26$ (GA lesion size), $r = 0.66$ (NEI VFQ) but **BCVA $r = 0.16$** ($p=0.11$)
- » Internal responsiveness: Worsening scores with GA growth $\geq 0.94\text{mm}^2$ (FRI: -0.3) vs. $<0.94\text{mm}^2$ (FRI: -0.1; $p=0.02$)

FRI index Psychometrics

*Functional Reading Independence

Reliability

Validity

Responsiveness

- » Secondary endpoint analysis of the phase 3 Pegcetacoplan trials Derby/Oaks in patients with **geographic atrophy**
- » **No significant differences** after 24-month period between treatment and sham arm



Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials

Jeffrey S Heier, Eleonora M Lad*, Frank G Holz, Philip J Rosenfeld, Robyn H Guymer, David Boyer, Federico Grossi, Caroline R Baumal, Jean-Francois Korobelnik, Jason S Slakter, Nadia K Waheed, Ravi Metlapally, Ian Pearce, Nathan Steinle, Anibal A Francone, Allen Hu, David R Lally, Pascal Deschatelets, Cedric Francois, Caleb Bliss, Giovanni Staurenghi, Jordi Monés, Rishi P Singh, Ramiro Ribeiro, Charles C Wykoff, on behalf of the OAKS and DERBY study investigators†*

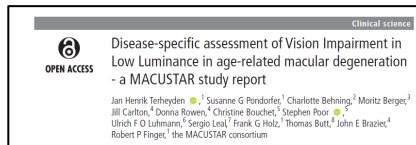
	Pegcetacoplan monthly	Pegcetacoplan every other month	Sham
Functional reading independence index score			
Patients included in the model†	371/403 (92%)	376/406 (93%)	373/402 (93%)
Least-squares mean change (SE), score	-0.35 (0.04)	-0.37 (0.04)	-0.32 (0.04)
Difference (95% CI) in least-squares mean pegcetacoplan vs sham, score	-0.03 (-0.14 to 0.08)	-0.06 (-0.16 to 0.05)	NA
p value pegcetacoplan vs sham	0.58	0.30	NA

FRI index Regulatory Use

*Functional Reading Independence

“The **further use and development of the FRI index** and reading speed in patients with GA, both to provide information on the relationship between GA lesion size and reading function, and to explore the potential effect of treatment on reading function is **supported**”





- » **Vision-related QoL** measure with a focus on **low-luminance and reduced contrast**
- » Specifically developed with AMD patients (early, intermediate late AMD)
- » **Three Subscales:** Reading/accessing information, mobility incl. driving and safety, socio-emotional well-being
- » Rasch model scoring
- » 52 language versions
- » Interviewer- or self-administration

VILL-33 psychometrics

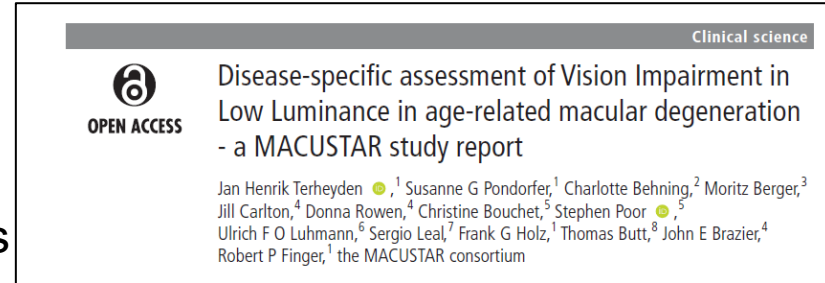
*Vision Impairment in Low Luminance Questionnaire

Reliability

Validity

Responsiveness

- » Analysis of participants across AMD stages including with geographic atrophy from the multi-center study MACUSTAR (n=716)
- » Internal consistency: Subscale **person reliabilities 0.78 to 0.91**, subscale person separation indices 1.9 to 3.3 (across AMD stages) (comparable to AMD participants in development study (Pondorfer, Terheyden et al, Trans Vis Sci Tech 2021))
- » Test-retest reliability: subscale **ICCs = 0.77 to 0.93** (late AMD group)
- » Known-groups validity: Subscale scores lower in late AMD than iAMD ($p < 0.0001$)



VILL-33 psychometrics

*Vision Impairment in Low Luminance Questionnaire

Reliability

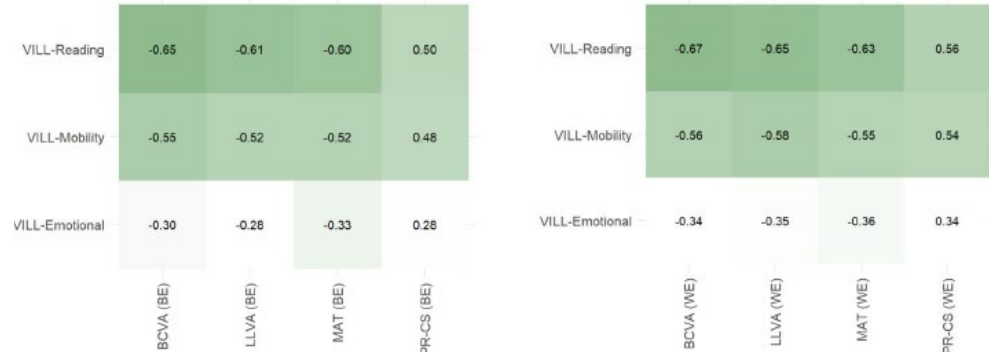
Validity

Responsiveness

- » Analysis of participants across AMD stages including with geographic atrophy from the cross-sectional part of the multi-center study MACUSTAR (n=245)
- » Correlation of VILL-33 scores with visual function assessments across AMD stages

Patient-reported vision impairment in low luminance relates to visual function in age-related macular degeneration: A MACUSTAR study report

Jan Henrik Terheyden¹, Charlotte Behning², Hannah M. P. Dunbar³, Stephen Poor⁴, Nadia Zakaria⁴, Alison M. Binns⁵, Marlene Saßmannshausen⁴, Sergio Leal⁶, Matthias Schmid², Frank G. Holz², David P. Crabb⁵, Ulrich F. O. Luhmann⁷, Robert P. Finger^{1,8} & MACUSTAR consortium^{*}



VILL-33 psychometrics

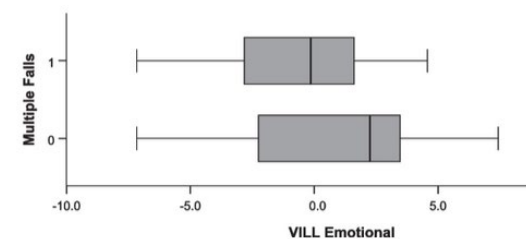
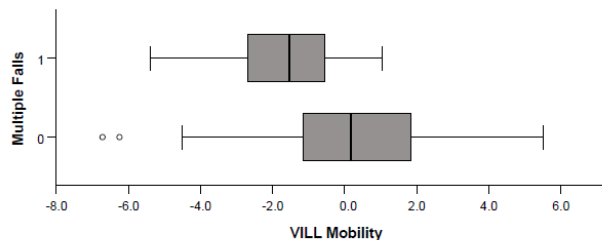
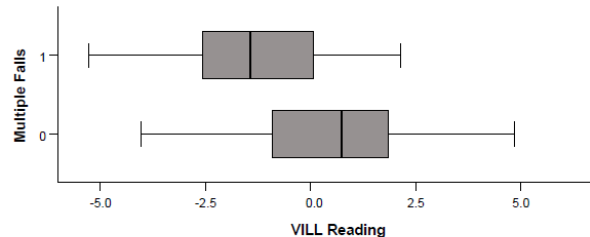
*Vision Impairment in Low Luminance Questionnaire

Reliability

Validity

Responsiveness

- » Analysis of participants including with geographic atrophy from a cohort study on risk of falling in individuals with varying degrees of visual impairment (n=112)
- » Significant association between lower vision-related QoL (VILL-33) and an increased risk of multiple falls at 12-month follow-up



Terheyden et al. *BMC Geriatrics* (2023) 23:583
<https://doi.org/10.1186/s12877-023-04317-y>

BMC Geriatrics

RESEARCH

Open Access

Patient-reported vision impairment in low luminance predicts multiple falls

Jan Henrik Terheyden^{1*}, Johanna Gerhards¹, Reglind A. D. Ost¹, Maximilian W. M. Wintergerst¹, Frank G. Holz¹ and Robert P. Finger^{1,2}



VILL-33 psychometrics

*Vision Impairment in Low Luminance Questionnaire

Preliminary, unpublished data

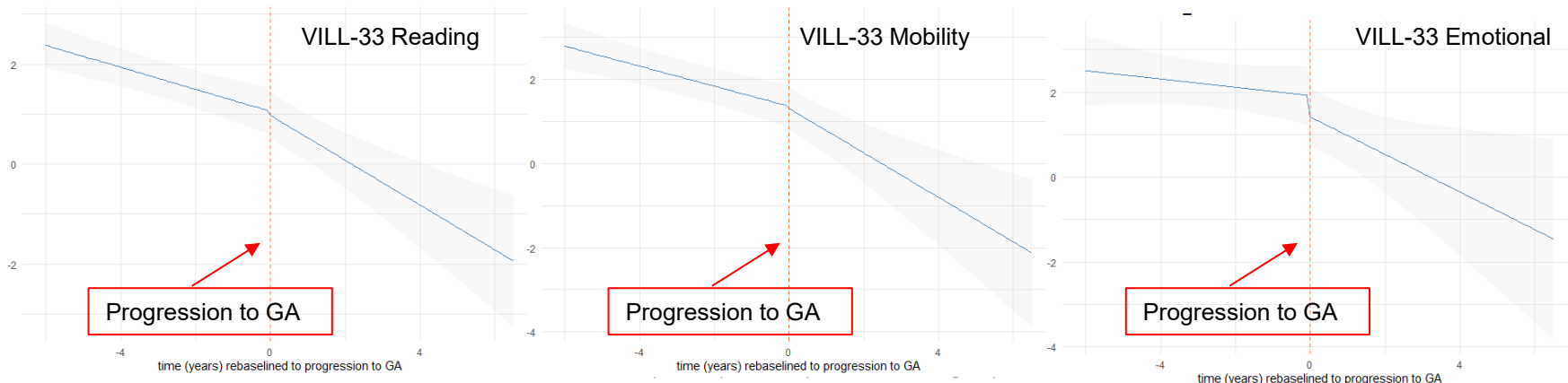
Reliability

Validity

Responsiveness

- » Analysis of participants who **progressed** from intermediate AMD to **geographic atrophy** from the multi-center study MACUSTAR (subgroup of n=86)
- » Significant increase in decline of VILL scores in geographic atrophy over iAMD ($p \leq 0.027$)

Mean observation times: 3.7 ± 1.6 years before progression, 1.4 ± 1.4 years after



VILL-33 regulatory use

*Vision Impairment in Low Luminance Questionnaire



“CHMP appreciated the development of a new patient related outcome measure, and the Vision Impairment in Low Luminance (VILL) as a promising measure for future trials”

PROs and QoL outcomes in GA trials

Consideration of three PRO and QoL outcomes at particular interest

- » **NEI VFQ-25** (National Eye Institute Visual Functioning Questionnaire)
- » **FRI index** (Functional Reading Independence index)
- » **VILL-33** (Vision Impairment in Low Luminance questionnaire)

- ✓ Fulfillment of ***regulatory use criteria*** (incl. concept elicitation, qualitative development steps)
- ✓ ***Familiarity to European Medicines Agency*** from previous interactions

Consideration of patient preference research

JAMA Ophthalmology | Original Investigation

Patient-Reported Importance of Functional Benefit in Geographic Atrophy

Christiana Dinah, BSc, MBBS, MRes; Jamie Enoch, PhD; Arevik Ghulakhshian, MBBS; Mandeep Sekhon, PhD; Serena Salvatore, MD; Gabriella DeSalvo, MD; Praveen Kumar, MD; Sanjiv Banerjee, PhD; Devaki Nayak, PhD; Winfried Amoaku, PhD; Marianne Shiew, MB, BS; Olayinka Osoba, MB, BS; David P. Crabb, PhD; Deanna J. Taylor, PhD

- » Cross-sectional survey study in 153 participants with geographic atrophy
- » 82% of participating patients indicate extreme, high or moderate acceptability of intravitreal treatment in geographic atrophy
- » **Potential of patient preference-related secondary endpoints** in addition to QoL secondary endpoints in future trials on geographic atrophy

Safety outcomes in GA trials

- » Ocular and systemic treatment-emergent **adverse events** (AE) / **severe adverse events** (SAE) consideration, including
 - endophthalmitis,
 - intraocular inflammation,
 - ischaemic optic neuropathy,
 - choroidal neovascularization (CNV),
 - intraocular pressure elevation,
 - injection-related ocular AEs
- » Additional safety outcomes, including vital signs, 12-lead ECG, laboratory metrics



Patient-reported outcomes, quality of life measures, safety outcomes

Jan H. Terheyden, MD, FEBO

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