Innovations in eDREAM, a Phase 2 Clinical Trial in Geographic Atrophy

A double-masked, randomized, multicenter, placebo-controlled study to investigate the efficacy and safety of GAL-101 2 % ophthalmic solution in patients with non-foveal geographic atrophy secondary to non-neovascular age-related macular degeneration (NCT06659549)

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eDREAM

- 12 sites in US, Georgia, Armenia, Ireland and Israel
- Target enrollment 100 subjects, split 50:50 active and placebo
- Treatment between 12-24 months; patients recruited consecutively but complete study simultaneously
- **Primary endpoint:** Δ rate of ↑ GA area by FAF
- **Secondary endpoint:** Δ rate of ↑ area of photoreceptor degeneration (PRD) by OCT
- **Secondary endpoint:** Δ rate of ↓ sensitivity of grid points on mesopic microperimetry
- **3-month visual function improvement endpoint:** Δ in sensitivity of grid points on mesopic microperimetry

INNOVATION 1: Targeting amyloid beta

- Oligomers of misfolded amyloid beta (Aβ) are highly neurotoxic. They play a fundamental role in the pathophysiology of neurodegenerative diseases, including Alzheimer's, AMD, and glaucoma[1]
- GAL-101 (previously MRZ-99030) has been shown both to reverse and prevent this toxicity in vitro and in animal models[2]
- GAL-101 is designed to bind only to abnormal, misfolded Aβ, not to Aβ monomers, which have important physiological functions
- Phase 1 study with GAL-101 eye drops showed no safety issues

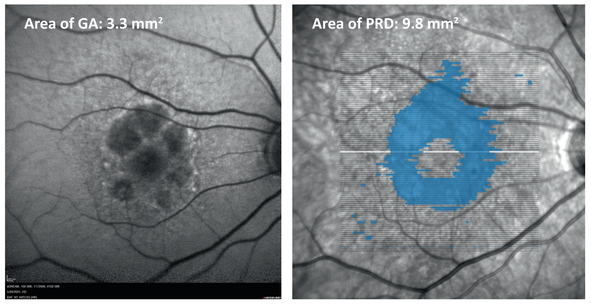
INNOVATION 2: Eye drop drug delivery to the retina

- Self-administration of eye drops at home would reduce the burden for GA patients and caregivers compared to approved intraocular injections
- Extensive animal PK studies including a large monkey ocular PK study confirm sufficient delivery of GAL-101 after eye drop application to the retina
- GAL-101 delivered from the conjunctiva to the retina in high concentration via sclera and choroid, not vitreous

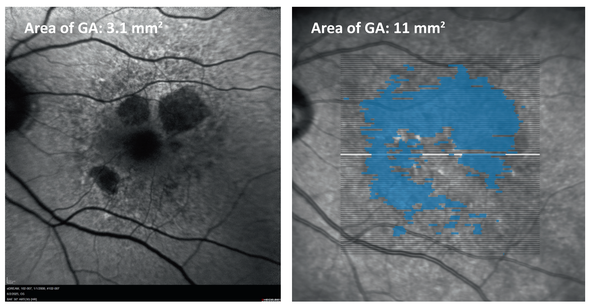
INNOVATION 3: Measuring area of photoreceptor degeneration (PRD)

- Utilized newly available AI-assisted software to measure individual retinal layers.[3,4] Moorfields Reading Centre measures area of PRD to be used both as enrollment criterion and as endpoint
- **PRD as enrollment criterion:** Early literature and Galimedix-Moorfields internal analysis suggests higher area of PRD around the GA → higher GA growth; this has the potential to improve recruitment of GA patients with optimal change in the primary efficacy endpoint
- **PRD as efficacy endpoint:** Provides another potential target to show effect of GAL-101 on photoreceptors, not only RPE cells
- Figures below demonstrate this for the first two eDREAM patients

Patient #1



Patient #2

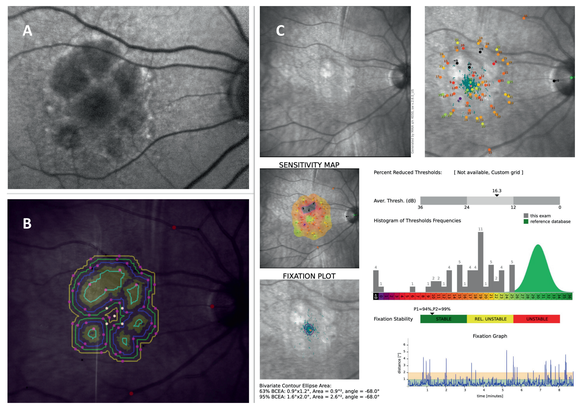


Left: Multifocal GA shown on fundus autofluorescence
Right: PRD segmentation (AI) from individual B-scans projected on an en-face fundus photograph

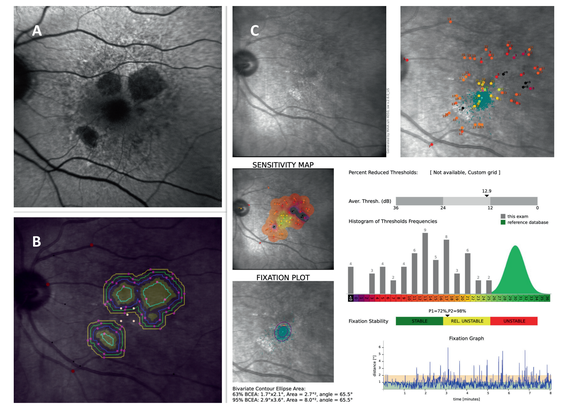
INNOVATION 4: Personalized peri-GA microperimetry grid

- Sensitivity is not expected to change on the whole macula during the study but rather near the GA border
- GRADE reading center prepares a customized grid of 60 points around the GA based on submitted OCT and FAF. This grid is sent to the site, uploaded on the Maia machine, and used for that subject during the entire trial[5]
- Figures below demonstrate this for the first two eDREAM patients

Patient #1



Patient #2



Figures show **A)** FAF **B)** schematic of programmed personalized microperimetry grid **C)** Actual microperimetry testing

INNOVATION 5: Functional improvement outcome measure

- Preclinical evidence suggests that removal of toxic Aβ oligomers from the tissue leads to improved function of neurons which are still viable[3]
- We expect to see improved sensitivity in microperimetric sensitivity after 3 months
- Grid points included in this analysis will be limited to those with "abnormal" sensitivity after baseline, as "normal" points likely cannot be expected to improve[6]
  - Grid points which are considered "doomed", such as < 4 dB, will also not be included

CONCLUSIONS

Our novel drug's MoA has the potential to prevent AMD by acting upstream in the pathophysiologic chain compared with e.g., complement inhibitors, thereby enabling probably a stronger treatment effect.
Topical delivery would be a game-changer for patients, providing self-administered, convenient, safer drug delivery at home. Robust analysis of photoreceptor degeneration paves the way for two opportunities to measure drug effects – on both photoreceptors and RPE cells – and may contribute to elucidating the location of primary pathophysiology in these two key cell types. Individually customized microperimetry grids will enable the detection of a functional effect (visual improvement) with optimized power, also in future studies.

References:
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2. Rammes G, Parsons CG. The Aβ aggregation modulator MRZ-99030 prevents and even reverses synaptotoxic effects of Aβ1-42 on LTP even following serial dilution to a 500:1 stoichiometric excess of Aβ1–42, suggesting a beneficial prion-like seeding mechanism. Neuropharmacology. 2020 Nov 15;179:108267
3. Zhang G, et. al. Clinically relevant deep learning for detection and quantification of geographic atrophy from optical coherence tomography: a model development and external validation study. Lancet Digit Health. 2021 Oct;3(10):e665–e675.
4. Fu DJ, et. Al. Pegcetacoplan Treatment and Consensus Features of Geographic Atrophy Over 24 Months. JAMA Ophthalmol. 2024 Jun 1;142(6):548–558.
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6. Barkana Y, et. Al. Improved sensitivity of microperimetric outcomes for clinical studies in age-related macular degeneration. Sci Rep. 2021 Feb 26;11(1):4764.

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