

Macular Research on the Move



Phase 1 and 2 studies are exploring novel targets in the treatment of AMD and DME.

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Early clinical studies are under way assessing the safety and tolerability of several novel molecules that may potentially show efficacy in the treatment of macular edema or macular degeneration. The studies outlined in this article are expected to yield insights into new treatment targets to improve the management of both wet and dry age-related macular degeneration (AMD) and diabetic macular edema (DME). The Retina Research Center has experience with all of these drugs through participation in these clinical trials (Figures 1 to 3).

ONE-TWO PUNCH

BI 836880 (Boehringer Ingelheim) is a bispecific nanobody drug. Administered via intravitreal injection, it targets VEGF and angiopoietin-2 (Ang-2) by incorporating antigen-binding areas that are present in antibodies of VEGF and Ang-2. By inhibiting VEGF and Ang-2 receptors, the compound is thought to block signaling pathways for neovascularization and address the effects of wet AMD.¹

Study Design

An open-label, nonrandomized, uncontrolled phase 1 study (NCT03861234) with projected enrollment of 42 patients was initiated last year. The purpose of the study, which will include a single rising dose phase followed by a multiple rising dose phase, is to evaluate the safety, tolerability, and pharmacodynamics of BI 836880 in intravitreal injections.

The primary endpoint in the single rising dose portion is to measure ocular dose-limiting events within 43 days of administration. Secondary endpoints include drug-related adverse events (AEs) or any ocular AEs in the study eyes.

The primary endpoint in the multiple rising dosage portion is drug-related AEs occurring from administration up to 169 days. Secondary measures include changes from baseline in central subfield thickness and BCVA at 12 weeks for each dose administration, time to recurrence after last treatment, and number of patients with ocular AEs in the study eye.¹

Looking Forward

The study began in June 2019, and completion is projected for October 2021.

AT A GLANCE

- ▶ Multiple compounds that address novel targets in AMD and DME are undergoing early clinical evaluation.
- ▶ Mechanisms beyond the well-known anti-VEGF include inhibition of Ang-2, the complement pathway, the HtrA1 enzyme, and plasma kallikrein.
- ▶ Results of some phase 2 studies may be available next year.

Image courtesy of Yong Ren

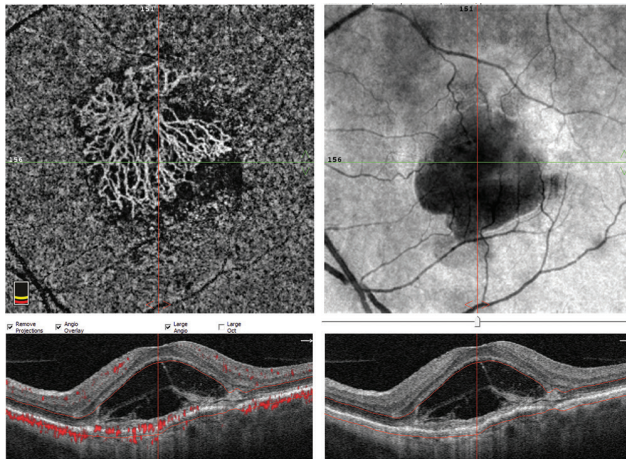


Figure 1. This OCT angiography image demonstrates a neovascular AMD lesion with type 1 (below RPE) and type 2 (above RPE) mixed choroidal neovascularization at the outer retina and choriocapillaris segmentations.

EASE THE STRESS

Mitochondria-mediated oxidative stress is considered a likely contributing factor to the underlying pathologic processes of AMD, as reactive oxygen species (ROS) cause injury to the photoreceptors, the retinal pigment epithelium (RPE), and the choriocapillaris. Elamipretide (MTP-131 and SS-31, Stealth BioTherapeutics) is an aromatic-cationic tetrapeptide that penetrates cell membranes and transiently localizes to the inner mitochondrial membrane.

Elamipretide has been shown to improve cellular adenosine triphosphate levels in dysfunctional mitochondria and prevent pathologic ROS formation and opening of the mitochondrial permeability transition pore, which can reduce the extent of apoptosis and necrosis. The drug is administered with a novel delivery system as a subcutaneous injection.

Study and Results

The ReCLAIM study was a phase 1, single-site, open-label clinical trial to evaluate the safety and tolerability of subcutaneous elamipretide in individuals with dry AMD. Patients were placed into one of two groups: those with noncentral geographic atrophy (GA) or those with high-risk drusen (HRD) without GA.

Noncentral GA was defined as an area greater than 1.27 mm² and less than 10.16 mm² as determined by fundus autofluorescence, with sparing of the fovea. HRD was defined as the presence of either at least one large ($\geq 125 \mu\text{m}$) druse or multiple medium-sized (63–124 μm) drusen.

All patients received daily subcutaneous 40 mg elamipretide, and outcomes were assessed at week 24. In the noncentral GA subgroup there was a mean increase in BCVA of 4.6 ± 5.1 letters from baseline ($P = .003$), and the mean change in square root area of GA was $0.13 \pm 0.14 \text{ mm}$ as measured on OCT. (The GA growth rate was less than

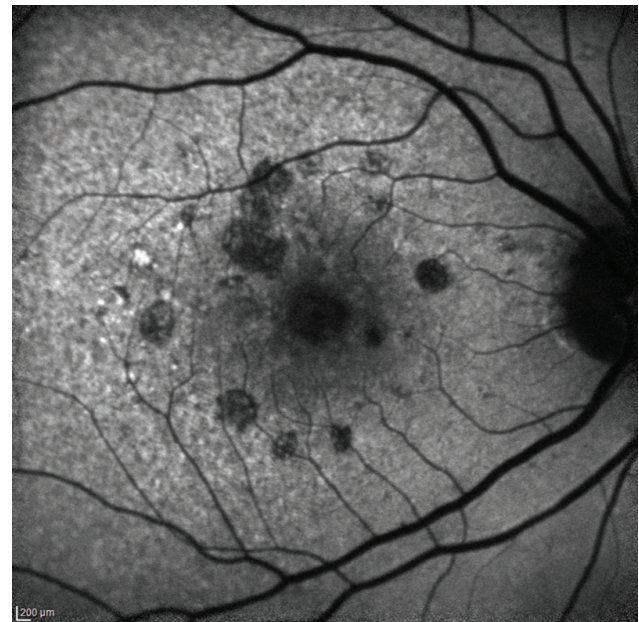


Figure 2. This fundus autofluorescence image from a dry AMD patient shows small size GA lesions in the macula away from the fovea.

Image courtesy of Yong Ren

the 24-week growth rate in the placebo control arms of other clinical trials.) At week 24 in the HRD group, there was a mean increase in BCVA of 3.6 ± 6.4 letters from baseline ($P = .025$). Most AEs were limited to injection site reactions.²

Looking Forward

ReCLAIM-2 (NCT03891875) is a phase 2 randomized, double-masked, placebo-controlled clinical trial, initiated last year, to evaluate the safety, efficacy, and pharmacokinetics of elamipretide in individuals with AMD with noncentral GA. About 180 patients will be enrolled and randomized in a 2:1 ratio to receive either elamipretide or placebo through the elamipretide delivery system. The participants will self-administer either elamipretide 40 mg or placebo via daily subcutaneous injections using the delivery system for 48 weeks, followed by a 4-week follow-up period.

The primary efficacy endpoint is the change in low-luminance BCVA. Secondary outcome measures include change in BCVA, reading acuity, and size of GA. Estimated completion date for ReCLAIM-2 is December 2021.

SLOW PRODUCTION

IONIS-FB-LRx (Ionis Pharmaceuticals) is an antisense oligonucleotide that reduces the production of complement factor B (FB). The FB protein is a primary fluid-phase regulator of the alternative complement pathway. Genetic association studies show that variants of the FB gene that provide modest increases in FB activity increase the incidence of GA. IONIS-FB-LRx is administered subcutaneously and is proposed to decrease the progression of GA.³

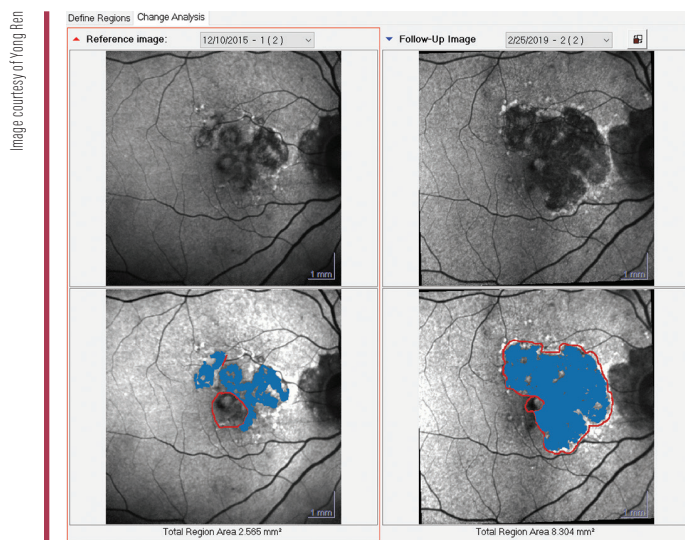


Figure 3. Fundus autofluorescence images of the same patient from two different visits (left, 2015; right, 2019) illustrates GA (secondary to dry AMD) increasing from a total region area of 2.565 mm² to 8.304 mm². The GA progression has not reached the foveal center.

Study and Results

A phase 1 placebo-controlled masked study of IONIS-FB-LRx in 54 healthy volunteers demonstrated the ocular and systemic safety of the drug when given subcutaneously. The study demonstrated reduction of pharmacodynamic endpoints such as plasma FB levels and complement alternative pathway activity. An approximately 70% reduction in plasma FB was accompanied by an equivalent reduction of the FB split product, Bb. A long duration of action was observed, suggesting the potential for monthly administration.

Looking Forward

GOLDEN (NCT03815825) is a phase 2 randomized, placebo-controlled, double-masked study currently recruiting participants with GA secondary to AMD to assess safety and efficacy of multiple doses of IONIS-FB-LRx. Approximately 330 participants will be randomly assigned into one of two groups. The first group will receive IONIS-FB-LRx with random assignment to one of 3 dosage levels, administered subcutaneously every 4 weeks for 45 weeks.

A second stage will expand two of the three dosing cohorts in a new randomized group of participants. The second group will receive a matching placebo solution administered in the same manner. The primary outcome measure will be absolute change from baseline in GA area at week 49, as determined by imaging.³

STYMIE PROGRESSION

RG6147 (Genentech) is a potent inhibitor of high-temperature requirement A1 (HtrA1), an enzyme that causes the breakdown and elimination of extracellular matrix proteins,

resulting in atrophy of the photoreceptors, RPE, and Bruch membrane choroid. HtrA1 may affect the visual cycle as well as the stability of proteins required for photoreceptor and RPE cell survival.⁴ As an anti-HtrA1 antibody, RG6147 should theoretically target this novel pathway in GA secondary to AMD, potentially slowing the progression of lesion growth.

Study and Results

A phase 1 multicenter, open-label, single-dose, dose-escalation, and multiple-dose study assessed the safety, tolerability, pharmacokinetics, and immunogenicity of intravitreal injections of RG6147 in patients with GA secondary to AMD. The study found that RG6147 was well tolerated at doses up to 20 mg per eye, with no dose-limiting toxicities, serious ocular AEs, or treatment-related systemic or ocular AEs in all 28 patients. Furthermore, an enzyme activity-based pharmacodynamic assay suggested the potential for 8-week target inhibition at higher doses.

Looking Forward

GALLEGO (NCT03972709) is a phase 2 multicenter, randomized, single-masked, sham-controlled study that began enrolling last year. It will assess the safety, tolerability, and efficacy of intravitreal injections of RG6147 in patients with GA secondary to AMD. Approximately 285 patients will be randomly assigned into one of four study arms: RG6147 or sham injection dosed every 4 or 8 weeks. The primary outcome is the change in GA area at 18 months.

Secondary endpoints include the percentage of patients with ocular and nonocular AEs, serious AEs, and AEs of special interest.⁵ Completion of the trial is expected in 2022.

A STABLE TARGET

THR-149 (Oxurion) is a bicyclic peptide inhibitor targeting plasma kallikrein (PKal). Through the inhibition of the PKal-kinin system, THR-149 prevents induction of retinal vascular permeability, inflammation, and angiogenesis.⁶ Individuals with DME have elevated levels of PKal, and the vitreous level of PKal varies less than vitreous levels of VEGF. This may enable THR-149 to serve as a target in the treatment of DME more effectively than VEGF.

Study and Results

A phase 1 open-label, US multicenter, nonrandomized trial evaluated the safety of a single intravitreal injection of THR-149 at three ascending dose levels in 12 participants with visual impairment due to center-involved DME. The primary outcome measure was incidence of dose-limiting toxicities up to the day 14 visit.

Secondary outcome measures included incidence of systemic and ocular AEs, including serious AEs, and laboratory abnormalities detected up to the end of the study. No

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dose-limiting toxicities or drug-related serious AEs were reported. After a single injection, an increasing average improvement in BCVA of up to 7.5 letters was seen from day 1 to day 14. There was an average improvement in BCVA of 6.5 letters at day 90 following a single injection.⁷

Looking Forward

The phase 2 KALAHARI clinical trial (NCT03511898) began earlier this year and is recruiting approximately 122 patients with DME who are poor responders to anti-VEGF therapies. The first part of the study will assess the optimal dose from three dose levels of THR-149 injections. Part 2 will then evaluate the efficacy and safety of the selected optimal dose of THR-149 versus aflibercept (Eylea, Regeneron) for the treatment of DME.⁸ Study completion is expected in 2022.

CONCLUSION

Modern treatments for macular edema and macular degenerations continue to evolve as new pathways of progression are discovered. The novel drugs outlined here show promise to give patients additional options to help preserve their vision. ■

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