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Seventh Annual Pipeline Report

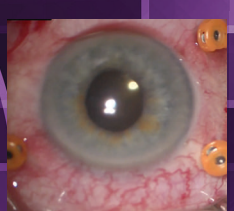
Breaking the century mark:

100 CANDIDATES AND COUNTING

Geographic atrophy continues to be the fastest growing area of interest, and new listings double the number of dropouts. **Page 18**

Also Inside

Online Video



Unique J-Code J-2403 Helps Facilitate Reimbursement

IHEEZO™
(chloroprocaine HCl ophthalmic gel) 3%

IHEEZO Gives You Nothing

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IHEEZO™ is the topical ocular anesthetic that compromises on nothing. Rapid onset and an established safety profile for your patients. No uncertainty with a sterile, single-use unit.

In a Phase III clinical trial of IHEEZO,

NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

HARROW®
Your patients. Our purpose.

References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

(chloroprocaine HCl ophthalmic gel) 3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

The safety and effectiveness of IHEEZO have not been established in pediatric patients.

8.5 Geriatric Use

No overall differences in safety or effectiveness of IHEEZO have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

For Full Prescribing Information, please visit www.iheezo.com/prescribinginformation.

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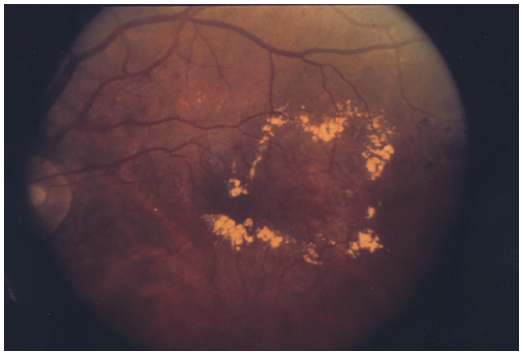
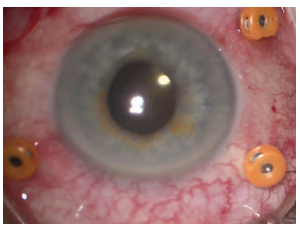
FEATURES

SEVENTH ANNUAL PIPELINE REPORT



DEPARTMENTS



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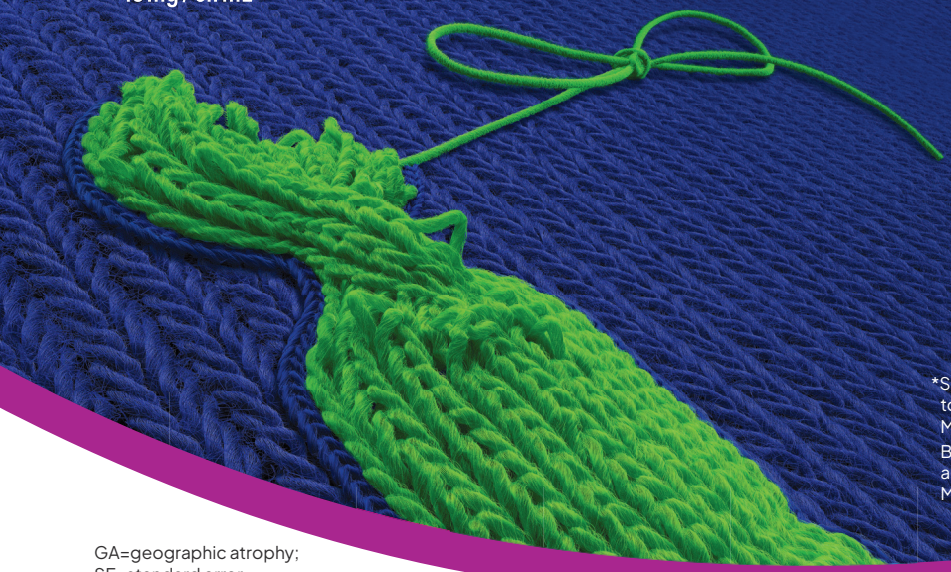
SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



GA unravels so much
SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24[1,4]

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23[1]

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis

SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections
SYFOVRE is contraindicated in patients with ocular or periocular infections.
Active Intraocular Inflammation
SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
Neovascular AMD
In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
Intraocular Inflammation
In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.
Increased Intraocular Pressure
Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.
The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month
*The following reported terms were combined:
Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of SYFOVRE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.
Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.
In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.
Lactation
Risk Summary
It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.
Females and Males of Reproductive Potential
Contraception
Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.
Pediatric Use
The safety and effectiveness of SYFOVRE in pediatric patients have not been established.
Geriatric Use
In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

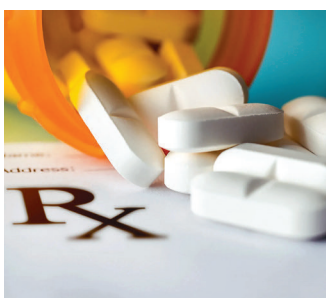
SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

Popular Alzheimer's Drug May Help Prevent AMD

While no cure exists for Alzheimer's disease, the use of acetylcholinesterase inhibitors (AChEIs) has been shown to help improve these patients' quality of life. Subsequently, this workhorse therapy has revealed secondary benefits, including lower mortality, myocardial infarction, stroke risk and even slowed progression of chronic kidney disease. Now, a recent observational study suggests acetylcholinesterase inhibitors may reduce the incidence of age-related macular degeneration in those with Alzheimer's.[1]

The retrospective cohort analysis, published in *JAMA Ophthalmology*, included health-care facilities within the U.S. Department of Veterans Affairs between 2000 and 2023. Participants were patients diagnosed with Alzheimer's between ages 55 and 80 with no preexisting AMD diagnosis, totaling 21,823 veterans. Those in the treatment group receiving AChEIs every additional year resulted in a 6 percent lower hazard of AMD, compared to untreated patients.



Some research has correlated Alzheimer's and AMD development based on drusen-producing peptides in these patients, theoretically triggering subsequent AMD. The study authors stated that their hypothesis was "based on the idea that AMD may be linked to neuroinflammatory processes in the macula. Preclinical studies have suggested that AChEIs may have the ability to mitigate neuroinflammation."

Study co-author Joseph Magagnoli, MS, says that, though the mechanism behind the drugs' potential protective effect is unknown, there are some theories. "While our study provides evidence of a potential association, the specific mechanism underlying acetylcholinesterase inhibitors' (AChEIs) protective effect against AMD remains unknown," he says. "Building on existing preclinical research and considering the anti-inflammatory properties of AChEIs, it's plausible that these medications could mitigate neuroinflammatory processes such as inflammasome activation in the macula, offering a protective effect against AMD. Further exploration through targeted investigations is needed to unravel the precise molecular mechanisms at play."

Randomized clinical trials would be necessary to truly evaluate any cause-and-effect relationship, according to the authors. They point out their treatment allocation wasn't randomized, therefore making selection bias and confounding factors possible. "Our study used as many variables in the propensity model as possible, including all diagnoses within a year prior to study index to minimize any systematic differences," they wrote. The use of data from the VA also potentially limits the generalizability of the findings to the broader population, according to the authors. "Lastly, this study does not account for genetic risk factors which could

(Continued on page 37)

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An atypical presentation of ocular toxoplasmosis

Diagnostic testing and multimodal imaging may help avoid a delay in treatment.

By Anthony Obeid, MD

Anthony Obeid, MD, MPH

A 49-year-old female with a past medical history of type 2 diabetes, hypertension and dyslipidemia was referred for evaluation. The patient had been complaining of blurred vision in the left eye for approximately one week. She had been taking topical prednisolone every two hours with a cycloplegic twice a day in the left eye. Review of systems was negative. Past ocular history was notable for anatomically narrow angles for which she underwent a laser peripheral iridotomy in both eyes.

Workup and imaging

Snellen visual acuity was 20/30 in the right eye and 20/70 in the left eye. Intraocular pressure was 20 and 16 mmHg in the right and left eye, respectively. Anterior segment evaluation of the right eye was within normal limits except for early nuclear sclerosis and a patent peripheral iridotomy. Anterior segment examination of the left eye revealed no injection of the conjunctiva/sclera, scattered fine keratic precipitates on the endothelium, a deep anterior chamber with trace cell, no frank iris nodules or posterior synechiae, and early nuclear sclerosis.

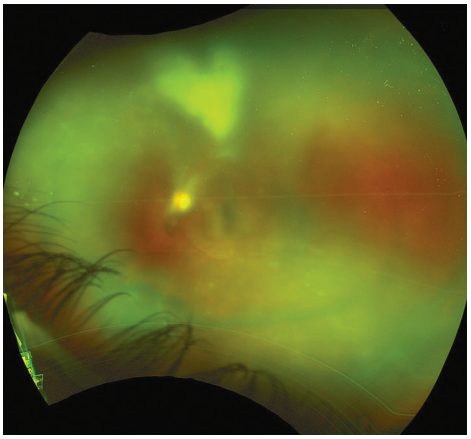

Figure 1. Ultra-widefield fundus photo of the left eye demonstrating dense vitritis with a large patch of retinal whitening and multiple white satellite lesions.

Dilated fundus exam of the right eye was normal. The dilated fundus exam of the left eye was notable for 2+ cells with 3+ vitreous haze. The nerve appeared flat with no frank disc edema. There was difficulty visualizing the retinal vessels and the macula. A large patch of retinal whitening, at least greater than three disc diameters in size, just sparing the macula was present. Abutting the inferior arcades were multiple white satellite lesions *(Figure 1)*.

Fluorescein angiography of the right eye was relatively unremarkable. Fluorescein angiography of the left eye revealed early blockage and late staining of the area of retinitis with peripheral vascular leakage *(Figure 2)*. Optical coherence tomography of the right eye revealed a clear hyaloid, intact retinal laminations and a normal choroid. OCT of the left eye was of poor signal owing to the dense vitritis, however, there did appear to be vitreous cell with a hyper-reflective foci overlying the internal limiting membrane *(Figure 3)*. Grossly, the retinal laminations appeared to be intact with no frank evidence of intraretinal or subretinal fluid.

Initial diagnosis

At this stage, the clinical picture was concerning for acute retinal necrosis secondary to a herpetic viral etiology. A diagnostic anterior chamber paracentesis was performed and an intravitreal injection of foscarnet was given in the left eye. A complete blood count, comprehensive metabolic profile, FTA-ABS/RPR, a QuantiFERON gold, angiotensin converting enzyme level, and a chest X-ray were ordered. The patient was initiated on Valtrex 1,000 mg /three times a day and instructed to follow up by the end of the week.

The differential diagnosis in such a presentation is broad but some of the common alternatives include acute retinal necrosis

BIO

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secondary to a herpetic virus, atypical toxoplasmosis, cytomegalovirus retinitis, syphilis, endogenous endophthalmitis and sarcoidosis.

Polymerase chain reaction testing of the anterior chamber fluid revealed 10,500 copies/ml of toxoplasmosis but was negative for HSV and CMV. The diagnosis of atypical acute retinitis secondary to toxoplasmosis was made and the patient was started on Bactrim DS b.i.d. orally until follow-up. On further questioning, the patient revealed she had been diagnosed with HIV "years ago" but didn't believe her initial diagnosis. She was instructed to follow up with an infectious disease specialist for testing along with a CD4 count. The patient followed up one week after initiating Bactrim DS. Her exam was notable for improvement in vitreous haze (1-2+), resolution of the satellite lesions and regression of the main superior lesion with borders now more clearly defined than in the prior fundus examination. She was continued on Bactrim DS with plans for close follow-up *(Figure 4.)*

Discussion

Toxoplasmosis is caused by the obligate intracellular protozoan parasite, *Toxoplasma gondii*. Transmission of the protozoan can be secondary to direct exposure to cats or the consumption of undercooked meat. The original infection is often asymptomatic.[1] Ocular toxoplasmosis is divided into congenital vs. postnatally acquired disease. If acquired while *in utero*, patients may have several systemic malformations, such as hydrocephalus, intracranial calcifications, myocarditis, hepatitis and cataracts.[2]

The classical presentation of ocular toxoplasmosis is a posterior uveitis with a unilateral chorioretinal lesion with associated vitritis, producing a "headlight in the fog" appearance. These lesions are often found proximal to an old chorioretinal scar, signaling reactivation secondary to rupture of intraretinal cysts which in turn stimulates a localized immune response.[3] However, ocular toxoplasmosis can present in a variety of different manners which may obfuscate the clinical picture.[4] This leads to delays in diagnosis and treatment.

One atypical presentation, seen more frequently in immunocompromised patients, is a severe aggressive retinochoroiditis.[4] In these presentations, lesions are large, multiple and can be bilateral.[4] Pre-existing retinal scars may be absent owing to the parasite either being newly acquired or disseminated.[5] Satellite lesions may also be present. The area involved may progressively worsen rather than "burn out" and relapse on discontinuation of medication. In fact, some cases may even progress into a panophthalmitis.[6] Additionally, these patients may have concomitant cerebral toxoplasmosis.[7] Distinguishing such a presentation from other etiologies like cytomegalovirus retinitis may be difficult, although there are some clues which may increase suspicion for toxoplasmosis; these include a more prominent vitreous inflammation, a smoother edge with few satellite lesions, and a lack of intraretinal hemorrhages.[3] There appears to be no reliable method to distinguish this presentation from acute retinal necrosis secondary to a herpetic virus.

In these situations, diagnostic testing becomes essential.[8] Testing includes PCR,

(Continued on page 13)

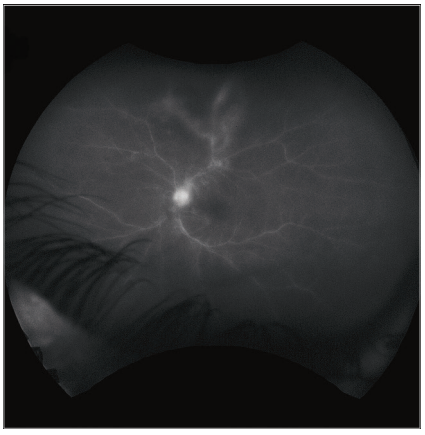

Figure 2. Fluorescein angiography of the left eye demonstrating hyperfluorescence of the disc as well as blockage and staining by the area of retinitis with some leakage from adjacent vessels.

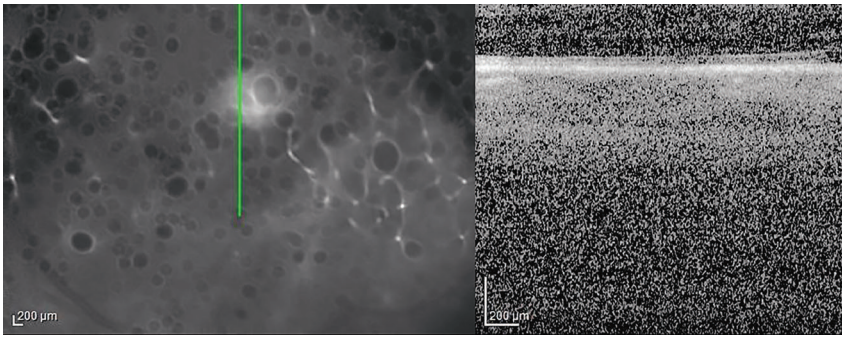

Figure 3. Optical coherence tomography of the left eye. There is a poor signal owing to the dense vitritis, however, there appears to be vitreous cell with a hyper-reflective foci overlying the internal limiting membrane.

THE FIRST AND ONLY FDA-APPROVED BIOSIMILAR **INTERCHANGEABLE** WITH LUCENTIS® FOR ALL INDICATIONS[1]

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Expect the same efficacy and safety as Lucentis® (ranibizumab injection) with the comprehensive support and savings of CIMERLI®

CIMERLI® has attributes identical to Lucentis®[1,2]:

- **Same** FDA-approved indications
- **Same** dosage strengths (0.3 mg & 0.5 mg)
- **Same** formulation & excipients
- **Same** amino acid sequence

IMPORTANT SAFETY INFORMATION & INDICATIONS FOR CIMERLI® (ranibizumab-eqrn)

CIMERLI® (ranibizumab-eqrn) is interchangeable* to Lucentis® (ranibizumab injection)

CIMERLI® (ranibizumab-eqrn), a vascular endothelial growth factor (VEGF) inhibitor, is indicated for the treatment of patients with:

- Neovascular (Wet) Age-Related Macular Degeneration (AMD)
- Macular Edema Following Retinal Vein Occlusion (RVO)
- Diabetic Macular Edema (DME)
- Diabetic Retinopathy (DR)
- Myopic Choroidal Neovascularization (mCNV)

CONTRAINDICATIONS

- CIMERLI® is contraindicated in patients with ocular or periocular infections or known hypersensitivity to ranibizumab products or any of the excipients in CIMERLI®. Hypersensitivity reactions may manifest as severe intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments:** Intravitreal injections, including those with ranibizumab products, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be utilized when administering CIMERLI®. Patients should be monitored following the injection to permit early treatment, should an infection occur
- **Increases in Intraocular Pressure:** Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with ranibizumab products. Monitor intraocular pressure prior to and following intravitreal injection with CIMERLI® and manage appropriately
- **Thromboembolic Events:** Although there was a low rate of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause)

Neovascular (wet) age-related macular degeneration

- The ATE rate in the 3 controlled neovascular AMD studies during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% (5 of 441) in patients from the control arms. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of ranibizumab-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3
- In a pooled analysis of 2-year controlled studies (AMD-1, AMD-2, and a study of ranibizumab used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg ranibizumab compared to 1.1% (5 of 435) in patients in the control arms (odds ratio 2.2 [95% confidence interval (0.8-7.1)])

Macular edema following retinal vein occlusion

- The ATE rate in the 2 controlled RVO studies during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab and 2 of 260 in the control arms). The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared to 0.4% (1 of 260) in the control arms

Diabetic macular edema and Diabetic Retinopathy

- In a pooled analysis of Studies D-1 and D-2, the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg ranibizumab, 5.6% (14 of 250) with 0.3 mg ranibizumab, and 5.2% (13 of 250) with control. The stroke

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rate at 2 years was 3.2% (8 of 250) with 0.5 mg ranibizumab, 1.2% (3 of 250) with 0.3 mg ranibizumab, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg ranibizumab and 10.8% (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8% (12 of 249) with 0.5 mg ranibizumab and 2.0% (5 of 250) with 0.3 mg ranibizumab

- **Fatal events in patients with diabetic macular edema and diabetic retinopathy at baseline:** A pooled analysis of Studies D-1 and D-2 showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg ranibizumab, in 2.8% (7 of 250) of patients treated with 0.3 mg ranibizumab, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4% (11 of 250) of patients treated with 0.3 mg ranibizumab. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded

ADVERSE REACTIONS

- Serious adverse events related to the injection procedure have occurred in <0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract
- In ranibizumab-treated patients compared with the control group, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and intraocular pressure. The most common non-ocular side effects included nasopharyngitis, anemia, nausea, and cough
- As with all therapeutic proteins, there is the potential for an immune response in patients treated with ranibizumab products. The clinical significance of immunoreactivity to ranibizumab products is unclear at this time

Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products:

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

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*An interchangeable product (IP) is a biological product that is approved based on data demonstrating that it is highly similar to an FDA-approved reference product (RP) and that there are no clinically meaningful differences between the products; it can be expected to produce the same clinical result as the RP in any given patient; and if administered more than once to a patient, the risk in terms of safety or diminished efficacy from alternating or switching between use of the RP and IP is not greater than that from the RP without such alternation or switch. Interchangeability of CIMERLI® has been demonstrated for the condition(s) of use, strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information

References: 1. CIMERLI® (ranibizumab-eqrn) prescribing information. Redwood City, CA: Coherus BioSciences, Inc. **2.** Data on file. Coherus BioSciences, Inc.

To report SUSPECTED ADVERSE REACTIONS, contact Coherus BioSciences at 1-800-483-3692 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of Full Prescribing Information on the following page.

CIMERLI®
(ranibizumab-eqrn) injection

CIMERLI® (ranibizumab-eqrn) injection, for intravitreal use

CIMERLI®
(ranibizumab-eqrn) injection

BRIEF SUMMARY—please review the full Prescribing Information prior to prescribing CIMERLI®. CIMERLI® is interchangeable with LUCENTIS® (ranibizumab injection).

1 INDICATIONS AND USAGE

CIMERLI is indicated for the treatment of patients with:

1.1 Neovascular (Wet) Age-Related Macular Degeneration (AMD)

1.2 Macular Edema Following Retinal Vein Occlusion (RVO)

1.3 Diabetic Macular Edema (DME)

1.4 Diabetic Retinopathy (DR)

1.5 Myopic Choroidal Neovascularization (mCNV)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

CIMERLI is contraindicated in patients with ocular or periocular infections.

4.2 Hypersensitivity

CIMERLI is contraindicated in patients with known hypersensitivity to ranibizumab products or any of the excipients in CIMERLI. Hypersensitivity reactions may manifest as severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with ranibizumab products, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique should always be used when administering CIMERLI. In addition, patients should be monitored following the injection to permit early treatment should an infection occur [*see Dosage and Administration (2.6, 2.7) in the Full Prescribing Information*].

5.2 Increases in Intraocular Pressure

Increases in intraocular pressure have been noted both pre-injection and post-injection (at 60 minutes) while being treated with ranibizumab products. Monitor intraocular pressure prior to and following intravitreal injection with CIMERLI and manage appropriately [*see Dosage and Administration (2.7) in the Full Prescribing Information*].

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the ranibizumab clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

Neovascular (Wet) Age-Related Macular Degeneration

The ATE rate in the three controlled neovascular AMD studies (AMD-1, AMD-2, AMD-3) during the first year was 1.9% (17 of 874) in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab compared with 1.1% (5 of 441) in patients from the control arms [*see Clinical Studies (14.1)*]. In the second year of Studies AMD-1 and AMD-2, the ATE rate was 2.6% (19 of 721) in the combined group of ranibizumab-treated patients compared with 2.9% (10 of 344) in patients from the control arms. In Study AMD-4, the ATE rates observed in the 0.5 mg arms during the first and second year were similar to rates observed in Studies AMD-1, AMD-2, and AMD-3.

In a pooled analysis of 2-year controlled studies [AMD-1, AMD-2, and a study of ranibizumab used adjunctively with verteporfin photodynamic therapy (PDT)], the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg ranibizumab compared to 1.1% (5 of 435) in patients in the control arms [odds ratio 2.2 (95% confidence interval (0.8-7.1)].

Macular Edema Following Retinal Vein Occlusion

The ATE rate in the two controlled RVO studies during the first 6 months was 0.8% in both the ranibizumab and control arms of the studies (4 of 525 in the combined group of patients treated with 0.3 mg or 0.5 mg ranibizumab and 2 of 260 in the control arms) [*see Clinical Studies (14.2)*]. The stroke rate was 0.2% (1 of 525) in the combined group of ranibizumab-treated patients compared to 0.4% (1 of 260) in the control arms.

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

In a pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], the ATE rate at 2 years was 7.2% (18 of 250) with 0.5 mg ranibizumab, 5.6% (14 of 250) with 0.3 mg ranibizumab, and 5.2% (13 of 250) with control. The stroke rate at 2 years was 3.2% (8 of 250) with 0.5 mg ranibizumab, 1.2% (3 of 250) with 0.3 mg ranibizumab, and 1.6% (4 of 250) with control. At 3 years, the ATE rate was 10.4% (26 of 249) with 0.5 mg ranibizumab and 10.8% (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8% (12 of 249) with 0.5 mg ranibizumab and 2.0% (5 of 250) with 0.3 mg ranibizumab.

5.4 Fatal Events in Patients with Diabetic Macular Edema and Diabetic Retinopathy at Baseline

Diabetic Macular Edema and Diabetic Retinopathy

Safety data are derived from studies D-1 and D-2. All enrolled patients had DME and DR at baseline [*see Clinical Studies (14.3, 14.4)*].

A pooled analysis of Studies D-1 and D-2 [*see Clinical Studies (14.3)*], showed that fatalities in the first 2 years occurred in 4.4% (11 of 250) of patients treated with 0.5 mg ranibizumab, in 2.8% (7 of 250) of patients treated with 0.3 mg ranibizumab, and in 1.2% (3 of 250) of control patients. Over 3 years, fatalities occurred in 6.4% (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4% (11 of 250) of patients treated with 0.3 mg ranibizumab. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Endophthalmitis and Retinal Detachments [*see Warnings and Precautions (5.1)*]
- Increases in Intraocular Pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic Events [*see Warnings and Precautions (5.3)*]
- Fatal Events in patients with DME and DR at baseline [*see Warnings and Precautions (5.4)*]

6.1 Injection Procedure

Serious adverse reactions related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis [*see Warnings and Precautions (5.1)*], rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

6.2 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data below reflect exposure to 0.5 mg ranibizumab in 440 patients with neovascular AMD in Studies AMD-1, AMD-2, and AMD-3; in 259 patients with macular edema following RVO. The data also reflect exposure to 0.3 mg ranibizumab in 250 patients with DME and DR at baseline [*see Clinical Studies (14)*].

Safety data observed in 224 patients with mCNV, as well as Studies AMD-4 and D-3, were consistent with these results. On average, the rates and types of adverse reactions in patients were not significantly affected by dosing regimen.

Ocular Reactions

Table 1 shows frequently reported ocular adverse reactions in ranibizumab-treated patients compared with the control group.

Table 1

Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Conjunctival hemorrhage	47%	32%	74%	60%	64%	50%	48%	37%
Eye pain	17%	13%	35%	30%	26%	20%	17%	12%
Vitreous floaters	10%	4%	27%	8%	19%	5%	7%	2%
Intraocular pressure increased	18%	7%	24%	7%	17%	5%	7%	2%
Vitreous detachment	11%	15%	21%	19%	15%	15%	4%	2%
Intraocular inflammation	4%	3%	18%	8%	13%	7%	1%	3%
Cataract	28%	32%	17%	14%	11%	9%	2%	2%
Foreign body sensation in eyes	10%	5%	16%	14%	13%	10%	7%	5%
Eye irritation	8%	5%	15%	15%	13%	12%	7%	6%
Lacrimation increased	5%	4%	14%	12%	8%	8%	2%	3%
Blepharitis	3%	2%	12%	8%	8%	5%	0%	1%
Dry eye	5%	3%	12%	7%	7%	7%	3%	3%
Visual disturbance or vision blurred	8%	4%	18%	15%	13%	10%	5%	3%
Eye pruritis	4%	4%	12%	11%	9%	7%	1%	2%
Ocular hyperemia	9%	9%	11%	8%	7%	4%	5%	3%
Retinal disorder	2%	2%	10%	7%	8%	4%	2%	1%
Maculopathy	5%	7%	9%	9%	6%	6%	11%	7%
Retinal degeneration	1%	0%	8%	6%	5%	3%	1%	0%
Ocular discomfort	2%	1%	7%	4%	5%	2%	2%	2%
Conjunctival hyperemia	1%	2%	7%	6%	5%	4%	0%	0%
Posterior capsule opacification	4%	3%	7%	4%	2%	2%	0%	1%
Injection site hemorrhage	1%	0%	5%	2%	3%	1%	0%	0%

Non-Ocular Reactions

Non-ocular adverse reactions with an incidence of ≥ 5% in patients receiving ranibizumab for DR, DME, AMD, and/or RVO and which occurred at a ≥ 1% higher frequency in patients treated with ranibizumab compared to control are shown in Table 2. Though less common, wound healing complications were also observed in some studies.

Table 2

Non-Ocular Reactions in the DME and DR, AMD, and RVO Studies

Adverse Reaction	DME and DR 2-year		AMD 2-year		AMD 1-year		RVO 6-month	
	Ranibizumab 0.3 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control	Ranibizumab 0.5 mg	Control
	n=250	n=250	n=379	n=379	n=440	n=441	n=259	n=260
Nasopharyngitis	12%	6%	16%	13%	8%	9%	5%	4%
Anemia	11%	10%	8%	7%	4%	3%	1%	1%
Nausea	10%	9%	9%	6%	5%	5%	1%	2%
Cough	9%	4%	9%	8%	5%	4%	1%	2%
Constipation	8%	4%	5%	7%	3%	4%	0%	1%
Seasonal allergy	8%	4%	4%	4%	2%	2%	0%	2%
Hypercholesterolemia	7%	5%	5%	5%	3%	2%	1%	1%
Influenza	7%	3%	7%	5%	3%	2%	3%	2%
Renal failure	7%	6%	1%	1%	0%	0%	0%	0%
Upper respiratory tract infection	7%	7%	9%	8%	5%	5%	2%	2%
Gastroesophageal reflux disease	6%	4%	4%	6%	3%	4%	1%	0%
Headache	6%	8%	12%	9%	6%	5%	3%	3%
Edema peripheral	6%	4%	3%	5%	2%	3%	0%	1%
Renal failure chronic	6%	2%	0%	1%	0%	0%	0%	0%
Neuropathy peripheral	5%	3%	1%	1%	1%	0%	0%	0%
Sinusitis	5%	8%	8%	7%	5%	5%	3%	2%
Bronchitis	4%	4%	11%	9%	6%	5%	0%	2%
Atrial fibrillation	3%	3%	5%	4%	2%	2%	1%	0%
Arthralgia	3%	3%	11%	9%	5%	5%	2%	1%
Chronic obstructive pulmonary disease	1%	1%	6%	3%	3%	1%	0%	0%
Wound healing complications	1%	0%	1%	1%	1%	0%	0%	0%

6.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other ranibizumab products may be misleading.

The pre-treatment incidence of immunoreactivity to ranibizumab was 0%-5% across treatment groups. After monthly dosing with ranibizumab for 6 to 24 months, antibodies to ranibizumab were detected in approximately 1%-9% of patients.

The clinical significance of immunoreactivity to ranibizumab products are unclear at this time. Among neovascular AMD patients with the highest levels of immunoreactivity, some were noted to have iritis or vitritis. Intraocular inflammation was not observed in patients with DME and DR at baseline, or RVO patients with the highest levels of immunoreactivity.

6.4 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ranibizumab products. Because this reaction was reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

- Ocular: Tear of retinal pigment epithelium among patients with neovascular AMD

7 DRUG INTERACTIONS

Drug interaction studies have not been conducted with ranibizumab products.

Ranibizumab intravitreal injection has been used adjunctively with PDT. Twelve of 105 (11%) patients with neovascular AMD developed serious intraocular inflammation; in 10 of the 12 patients, this occurred when ranibizumab was administered 7 days (± 2 days) after PDT.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ranibizumab products administered in pregnant women.

Administration of ranibizumab to pregnant monkeys throughout the period of organogenesis resulted in a low incidence of skeletal abnormalities at intravitreal doses 13-times the predicted human exposure (based on maximal serum trough levels [C_{max}]) after a single eye treatment at the recommended clinical dose. No skeletal abnormalities were observed at serum trough levels equivalent to the predicted human exposure after a single eye treatment at the recommended clinical dose [*see Animal Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether ranibizumab products can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for ranibizumab products [*see Clinical Pharmacology (12.1)*], treatment with ranibizumab products may pose a risk to human embryofetal development.

CIMERLI should be given to a pregnant woman only if clearly needed.

Data

Animal Data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received intravitreal injections of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0, 0.125, and 1 mg/eye. Skeletal abnormalities including incomplete and/or irregular ossification of bones in the skull, vertebral column, and hindlimbs and shortened supernumerary ribs were seen at a low incidence in fetuses from animals treated with 1 mg/eye of ranibizumab. The 1 mg/eye dose resulted in trough serum ranibizumab levels up to 13 times higher than predicted C_{max} levels with single eye treatment in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/eye, a dose which resulted in trough exposures equivalent to single eye treatment in humans. No effect on the weight or structure of the placenta, maternal toxicity, or embryotoxicity was observed.

8.2 Lactation

Risk Summary

There are no data available on the presence of ranibizumab products in human milk, the effects of ranibizumab products on the breastfed infant or the effects of ranibizumab products on milk production/excretion.

Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when CIMERLI is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIMERLI and any potential adverse effects on the breastfed child from CIMERLI.

8.3 Females and Males of Reproductive Potential

Infertility

No studies on the effects of ranibizumab products on fertility have been conducted and it is not known whether ranibizumab products can affect reproduction capacity. Based on the anti-VEGF mechanism of action for ranibizumab products, treatment with ranibizumab products may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and effectiveness of ranibizumab products in pediatric patients have not been established.

8.5 Geriatric Use

In the clinical studies, approximately 76% (2449 of 3227) of patients randomized to treatment with ranibizumab were ≥ 65 years of age and approximately 51% (1644 of 3227) were ≥ 75 years of age [*see Clinical Studies (14)*]. No notable differences in efficacy or safety were seen with increasing age in these studies. Age did not have a significant effect on systemic exposure.

10 OVERDOSAGE

More concentrated doses as high as 2 mg ranibizumab in 0.05 mL have been administered to patients. No additional unexpected adverse reactions were seen.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following CIMERLI administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

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(Continued from page 9)

serology and immunohistochemical identification of the parasite.[3] PCR testing of intraocular fluid is of great value, although the sensitivity with ocular fluid may be dependent on the PCR protocol. Sensitivity may also be dependent on immunocompetence, as PCR testing in immunocompetent patients is often less sensitive as a result of the robust immune response.[9] Serological methods can also help determine if an infection was recently acquired or is chronic.

Imaging in ocular toxoplasmosis may also aid in the diagnosis and monitoring of the disease. OCT helps with monitoring the retinal lesions for resolution and scarring. Fluorescein angiography can be helpful in detecting small active lesions with hyperfluorescence emanating from the periphery and migrating toward the center.[3] Additionally, it can detect segmental vasculitis and papillitis. Ultrasound can be useful in cases with dense vitritis and a poor view on dilated fundus exam. Ultimately, a combination of clinical presentation, diagnostic testing and multimodal imaging will help in raising suspicion and diagnosing such atypical ocular toxoplasmosis cases.[3]

There are no clear guidelines when it comes to the treatment of ocular toxoplasmosis. Small peripheral lesions in immunocompetent patients who aren't very symptomatic could be observed closely without systemic therapy and are expected to improve over one to two months. Factors which may prompt the physician to treat include the patient's immunocompetence, location of the lesion, visual acuity, involvement of the nerve and other clinical parameters.[3] The classic therapy for ocular toxoplasmosis is a combination of pyrimethamine, sulfadiazine and prednisone (to be started 48 hours after initiation of antiparasitic agents). Initiation of prednisone may be omitted in immunocompromised patients.[3] Alternative regimens to the pyrimethamine/sulfadiazine combination include trimethoprim-sulfamethoxazole and clindamycin. Another alternative involves an intravitreal injection of clindamycin with or without dexamethasone.[3]

Both intravitreal and systemic therapy seem to demonstrate equal efficacy, although there's some evidence to suggest that patients who are IgM positive would benefit from systemic therapy and patients who are IgM negative would benefit from local therapy.[10] The rationale is that IgM-positive patients have a systemic infection which is more readily targeted by systemic therapy. Benefits of local therapy include fewer side effects and the avoidance of major adverse effects encountered with systemic therapy.

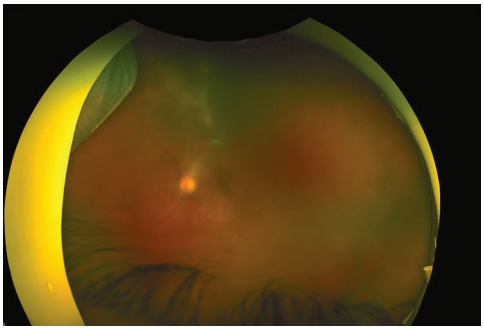

Figure 4. Follow-up ultra-widefield fundus photo of the left eye one week after initiating systemic Bactrim DS. There's improvement in vitreous haze (1-2+), resolution of the satellite lesions and regression of the main superior lesion with borders now more clearly defined than in the prior fundus photo.

In conclusion, although ocular toxoplasmosis often has a familiar appearance, some atypical presentations may cause a delay in diagnosis and treatment. Therefore, a clinician should always have a high index of suspicion and send for relevant testing to rule out this vision-threatening disease, particularly in susceptible populations.

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Managing acute retinal necrosis

This rare disease requires diagnostic vigilance and prompt, effective and—in many cases—long-term treatment in order to be managed properly.

By Dilraj Grewal, MD, FASRS

Dilraj Grewal, MD, FASRS

BIOS

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DISCLOSURES: Dr. Grewal is a consultant to Iveric Bio, Regeneron, DORC, Alimera and Apellis.

Dr. Thomas is a consultant to Allergan/AbbVie, Alimera Sciences, Avesis, EyePoint Pharmaceuticals, Genentech/Roche and Novartis.

Acute retinal necrosis (ARN), first described in 1971,[1] is a progressive inflammatory syndrome now defined by the American Uveitis Society on the basis of clinical appearance of (1) one or more foci of retinal necrosis located in the peripheral retina with distinct borders, (2) rapid progression with no antiviral therapy, (3) circumferential spread, (4) evidence of occlusive vasculopathy with arterial involvement and (5) significant inflammatory reaction in the vitreous and anterior chamber.[2]

ARN usually results from viral infections, primarily caused by the varicella-zoster virus (VZV), herpes simplex virus type 1 and 2 (HSV-1 and HSV-2) and less commonly cytomegalovirus (CMV). Toxoplasma chorioretinitis and syphilitic retinitis can also mimic retinal necrosis, among other manifestations, and are included in the differential and workup.

Presenting symptoms often include redness, photophobia, floaters and blurred vision.

On fundus examination there are multifocal areas of whitening in the peripheral retina corresponding to active retinal necrosis, which may become confluent and circumferentially progress to involve the posterior pole without prompt treatment. Vascular sheathing, perivascular hemorrhages, vascular occlusion and obliteration of arterioles may be present. Dense vitreous inflammation may develop as the disease progresses. Retinal breaks often develop within the peripheral necrotic retinal lesions. It's helpful to capture fundus photographs at presentation in order to monitor response to treatment. Features on OCT can sometimes be helpful to distinguish herpetic retinitis from toxoplasma chorioretinitis where there's often choroidal thickening and from syphilitic retinitis where there's typically involvement of the outer retina.[3] Fluorescein angiography may demonstrate signs of occlusive arteritis and areas of ischemia.

In immunodeficient patients, a variant—progressive outer retinal necrosis syndrome—can occur, most often caused by VZV and with early posterior pole involvement, absence of vitreous reactivity and relative sparing of the retinal vessels.[4]

Diagnosis

Polymerase chain reaction testing of ocular samples for HSV and VZV has a very high sensitivity and aqueous and vitreous sampling have similar yields.[5] It's important that immediate treatment for ARN should be initiated without waiting for the PCR results due to the risk of rapid progression. Additional infectious etiologies including human immunodeficiency virus, tuberculosis and syphilis should be tested for. Serum testing for herpesvirus antibodies doesn't add any value in the diagnosis of ARN.

Epstein-Barr Virus (EBV) as an etiologic agent for ARN hasn't yet been confirmed in retinal or vitreous specimens.

Antiviral Treatment

Early administration of antivirals is critical in the treatment of ARN. This includes intravenous acyclovir or oral valacyclovir. Oral and intravenous therapy have comparable outcomes and either is effective for induction therapy. Oral antiviral medications with greater bioavailability (valacyclovir, famciclovir) and increased use of adjunct intravitreal antivirals have led to more frequently initiating treatment with oral antivirals. This treatment algorithm can avoid the need for a hospital admission and intravenous medication.[6] There's level II and III evidence suggesting that the combination of intravitreal and systemic antiviral therapy may have greater therapeutic efficacy than systemic therapy alone.[5,7]

Intravitreal monotherapy is inadequate as involvement of the fellow eye has been reported in up to 70 percent of patients without

systemic treatment. Combination of systemic and intravitreal treatment is typically used in more severe or progressive cases, immunodeficient individuals or in those with more posterior zone involvement of the retinitis.

Intravitreal foscarnet (2.4 mg/0.1 mL) or ganciclovir (2 mg/0.1 mL) may be given as adjuvant intravitreal therapy. There's animal data to suggest that intravitreal ganciclovir has better retinal pharmacokinetics than intravitreal foscarnet.[8] Ganciclovir concentration remains at a higher therapeutic level than foscarnet for 72 hours post injection and its concentration in the retina remains higher. Ganciclovir has activity against CMV and HSV, and can be administered intravenously, orally or intravitreally.

Valacyclovir is an orally administered prodrug that's converted to acyclovir and has a much higher bioavailability vs. oral acyclovir. Oral valacyclovir (2 g three times a day) can reach concentrations in the vitreous in the inhibitory ranges for HSV-1, HSV-2 and VZV,[9] similar to intravenous acyclovir 10 mg/kg t.i.d. Following initiation of therapy, there can still be progression of retinitis, particularly in the first 24 hours before consolidation of retinitis starts to occur. The duration of induction therapy should be titrated based on response of retinitis and it may take longer than two to three weeks before the retinitis adequately consolidates.

Acyclovir and valacyclovir are well tolerated in the oral form but intravenously administered can cause neurotoxicity and renal toxicity.[10] Ganciclovir, when given intravenously, may cause bone marrow suppression, anemia, granulocytopenia and thrombocytopenia and renal toxicity.[10] Renal function should be tested prior to initiation of antiviral therapy to monitor for drug toxicity and subsequent dose adjustments, particularly those with impaired renal function.

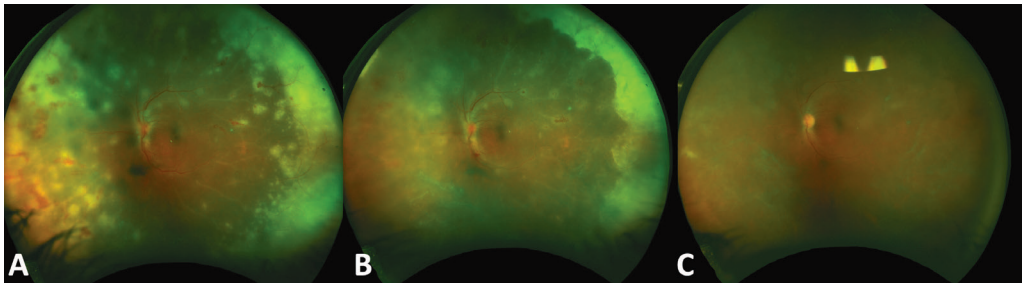
Depending on the severity of inflammation, topical and systemic corticosteroids are frequently administered alongside antivirals. While topical steroids can be initiated immediately, oral steroids are added 24 to 48 hours after observing the initial response to anti-viral treatment. Avoid local steroids.

Resistance to Therapy

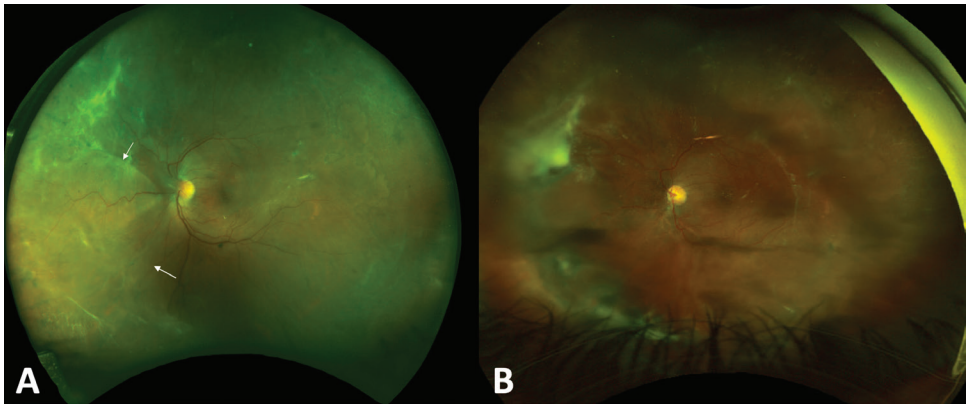
Acyclovir-resistant HSV has been reported to be caused by a mutation of the thymidine kinase gene A156V.[11] Acyclovir-resistant HSV almost triples the time to achieve a viral load reduction with acyclovir treatment[12] and in such cases, famciclovir can be considered. CMV resistance can occur due to mutations in the viral UL97 kinase and UL54 DNA polymerase genes. Resistance can sometimes be overcome by intravitreal dosing. Letermovir is a novel antiviral recently approved for CMV prophylaxis following hematopoietic cell transplantation and has been shown to be effective as salvage treatment for ganciclovir-resistant CMV retinitis.[13]

Role of Long Term Anti-viral Prophylaxis

Herpes viruses can remain latent for a lifetime and may undergo episodic reactivation triggered by various stimuli, including immu-



A 45-year old immunocompetent male with acute retinal necrosis secondary to varicella zoster virus (VZV). On presentation (A), there were multiple near-confluent areas of whitening in the peripheral retina corresponding to active retinal necrosis, vasculitis, perivascular hemorrhages and vascular sheathing. Three days after initiation of combined oral and intravitreal treatment there was significant consolidation of the retinitis (B) and by two weeks (C) the retinitis was completely consolidated and vasculitis had improved following the initiation of oral steroids to control the inflammatory component.



Two months later, the same patient from Figure 1 developed a nasal rhegmatogenous retinal detachment (A) requiring surgery with a scleral buckle and pars plana vitrectomy with silicone oil for retinal re-attachment (B).

nosuppression. Contralateral ocular involvement or encephalitis can occur, anywhere from within a few months to several years later, underscoring the importance of long term antiviral prophylaxis, often for a lifetime in immunosuppressed individuals.[14]

Visual Outcomes

Visual outcomes are limited due to complications such retinal detachment, chronic vitreous inflammation, epiretinal membrane, macular ischemia, macular edema and optic neuropathy.[15]

Nearly half of affected eyes have a visual acuity of ≤20/200, six months after the onset of ARN.

The role of prophylactic laser and/or pars plana vitrectomy to reduce risk of retinal detachment in ARN remains unclear. The rationale behind vitrectomy is to remove inflammatory mediators, clear the media and perform endolaser. A recent meta-analysis found that prophylactic pars plana vitrectomy could reduce the risk of retinal detachment compared to antiviral treatment alone, although the final vision of the vitrectomy group was worse.[16] Vitrectomy in younger patients with ARN is particularly challenging due to the difficulty in removing the posterior hyaloid and risk of causing breaks over the thin necrotic retina.

In conclusion, ARN, while rare, can result in severe ocular morbidity if not accurately diagnosed and immediately treated. It's important to manage the concurrent inflammatory response, and long-term prophylaxis therapy—potentially for life—is critical to reduce the risk of fellow-eye involvement.

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WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA[1]

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data[1]

Over 60% of wet AMD "fellow eyes" lose too much vision[1]– even with frequent treatment visits

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ForeseeHOME™
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Introduce your patients to ForeseeHome during an injection visit and offer them an extra level of protection.

Our Monitoring Center works with your staff to easily implement an "inject and protect" protocol into your practice workflow that requires minimal effort or additional time.

The Key to Successful Home Monitoring

NOTAL VISION MONITORING CENTER

- Engagement & Education
- Benefits Verification & Authorization
- Continuous Monitoring

NOTAL VISION™
Monitoring Center

- Practice Workflow Implementation
- Remote Patient Management
- Vision Alert Management

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Seventh Annual Pipeline Report

Hitting the century mark: 100 candidates and counting

Geographic atrophy continues to be the fastest-growing area of interest, and new entries double the number of dropouts.

By Richard Mark Kirkner, Editor

Richard Mark Kirkner

How we compiled this listing

This listing was compiled from company press releases and regulatory filings, published reports in the literature, searches on ClinicalTrials.gov and the European Union Clinical Trials Register (EudraCT), presentations at the American Academy of Ophthalmology Retina Subspecialty Day, American Society of Retina Specialists, Retina Society, Association for Research in Vision and Ophthalmology, EURETINA 2023, Eyecelerator and OIS Retina, supplemented with conversations with a multitude of clinical investigators and representatives of trial sponsors.

Take-home points

- This year's listing includes 100 investigative programs, including 29 new listings.
- Three high-profile programs from last year exited the list: pegcetacoplan; avacincaptad pegol; and aflibercept 8 mg.
- Geographic atrophy continues to be a robust area of interest, increasing from 12 to 16 programs despite the exits of two high-profile candidates.
- Overall, 14 programs from last year's list don't appear on this year's.

The Year of Geographic Atrophy lived up to its billing. This year's list of investigative treatments for retinal disease is notable for three high-profile exits, two of which are for GA. The U.S. Food and Drug Administration last year approved pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Iveric Bio/Astellas Pharma).

Another high-profile FDA approval was aflibercept 8 mg (Eylea HD, Regeneron Pharmaceuticals) for neovascular age-related macular degeneration, diabetic retinopathy and diabetic macular edema.

GA continues to be a robust area for innovation. This year's listing of GA candidates has grown to 16 from 12 last year, with seven new programs joining the list.

While any number of programs drop from one year to the next, new entries inevitably more than make up for those exits. This year's list includes 100 entries in total, 29 of which are new. Last year's list consisted of 87 entries, 21 of which hadn't appeared previously.

A number of candidates carried over from last year's list appear under new names this year. For example, Xipere (Clearside Biomedical) is now listed as Arcatus/ARVN001 (Arctic Vision). Xiflam (InflammX) last year is Tonabersat this year. On the primary list, four preexisting listings have added new names.

A number of listings from last year didn't make this year's list. One is Conbercept (Chengdu Kanghong Biotechnology),

List of tables

an anti-VEGF agent long approved in China. All of its trials on ClinicalTrial.gov are either listed as "Unknown Status" or haven't posted updates for more than a year.

Programs that have either been terminated or haven't posted updates for more than a year, and their sponsors didn't reply to queries by press time, include:

- GB-102 (Graybug Vision).
- ISTH0036 (Isarna Therapeutics).
- PAN-90806 (PanOptica).
- THR-149 and THR-687 (Oxurion).
- GT005 (Gyroscope Therapeutics).
- AGTC-402 and rAAV2tYF-PR.7-hCNGB3 (Applied Genetics Technologies Corp.).
- Visomitin/SkQ1 (Mitotech).
- Retilux (PhotoOpTx).

This list consists of programs in human clinical trials.

Investigative agents for nAMD, DME, DR and RVO

NEW: AG-73305 (Allgenesis Biotherapeutics)

This intravitreal humanized, bispecific Fc-fusion protein is designed to simultaneously block vascular endothelial growth factors and integrins. Preliminary Phase IIa data (n=22, NCT05301751) in DME reported no dose-limiting toxicities and no serious adverse events. Study completion is set for this year.

NEW: AIV007 (AiViva BioPharma)

Described as an injectable, broad-spectrum tyrosine kinase inhibitor (TKI), AIV007 is the focus of a Phase I trial initiated last year (n=24, NCT05698329). Subjects with DME and nAMD receive one periocular injection with monthly evaluation for up to six months. AIV007 uses a proprietary technology that transitions to a biodissolvable gel depot at body temperature for prolonged drug release. Study completion is set for 2025.

AKST4290 (Alkahest)

AKST4290 is an oral inhibitor of the chemokine C-C motif receptor 3 (CCR3) that blocks eotaxin, an immunomodulatory protein that increases as humans age and contributes to age-related diseases. The sponsor last year halted a Phase II trial in patients with diabetic retinopathy after enrolling just three patients (NCT04499235). A second Phase II trial in nAMD (n=107, NCT04331730), completed in 2021, evaluated oral AKST4290 daily in combination with aflibercept injections. Results were posted in 2022. Alkahest didn't respond to a query for updated information.

APX3330 (Ocuphire Pharma)

This small-molecule, oral inhibitor blocks the downstream pathways regulated by the transcription factor regulator Ref-1 (reduction-oxidation effector factor-1), which involve VEGF and inflammation.

The Phase II ZETA-1 trial (n=103, NCT04692688) in moderately severe-to-severe nonproliferative DR or mild proliferative DR failed to meet its primary endpoint, but the U.S. Food and Drug Administration accepted a revised endpoint: the percentage of patients with greater than three-step worsening on a binocular Diabetic Retinopathy Severity Scale, which more placebo patients than APX3330-treated patients demonstrated. The FDA has green-lighted Phase III studies.

AR-1105, AR-13503 (Aerie Pharmaceuticals/Alcon)

AR-1105 is a dexamethasone implant platform for DME and retinal vein occlusion. Aerie reported last year that an open-label six-month study (n=49, NCT03739593) in patients with RVO-related macular edema demonstrated improvements in best-corrected visual acuity. Plans for Phase III trials in DME are underway.

AR-13503 is a rho-kinase inhibitor implant that's an active metabolite of netarsudil that demonstrated efficacy as a monotherapy and anti-VEGF adjunct in preclinical studies. It's the subject of a Phase I study in nAMD and DME (n=18, NCT03835884).

Arcatus/ARVN001 (Arctic Vision; Xipere, Clearside Biomedical)

This suprachoroidal triamcinolone acetonide suspension is already FDA approved for uveitic macular edema. Arctic Vision is pursuing the DME indication for its rebranded iteration in Australia, New Zealand and Asia. Arctic, meanwhile, has completed enrollment in a Phase III randomized, double-blind, placebo-controlled clinical trial in China in uveitic macular edema. No clinical trials are listed on ClinicalTrials.gov or the European Union Clinical Trials Register (EudraCT).

AXT107 (AsclepiX Therapeutics)

AXT107 is a microparticulate suspension for intraocular injection. It targets VEGF receptor 2 and activates the vessel-stabilizing receptor tyrosine kinase (Tie2). The sponsor is recruiting for a Phase I/IIa trial in nAMD (n=15, NCT05859776) that's evaluating 40-week outcomes of three dose levels of a single injection. A Phase I/IIa trial

in DME (n=6, NCT04697758) was completed in 2022, but no results have been posted.

NEW: AVD-104 (Aviceda Therapeutics)

Aviceda describes AVD-104 as an engineered glycan (sialic acid) nanoparticle that targets the self-pattern recognition receptors on overly activated retinal neutrophils, macrophages and microglia, and repolarizes them to their resolution state. Enrollment opened in the GLYCO Phase II U.S. trial (n=30, NCT06181227) in DME. Study completion is anticipated in the second quarter this year. Aviceda is also pursuing a Phase I trial in geographic atrophy.

CLS-AX (Clearside Biomedical)

CLS-AX is a suprachoroidal suspension of the TKI axitinib. Clearside completed enrollment in the Phase IIb ODYSSEY trial (n=60, NCT05891548), which random-

Table. Investigative agents for nAMD, DME, DR and RVO

Drug name (manufacturer)	Description/active agent
NEW: **AG-73305** (Allgenesis Biotherapeutics)	Humanized, bispecific Fc-fusion protein that blocks vascular endothelial growth factors and integrins
NEW: **AIV007** (AiViva BioPharma)	Broad-spectrum tyrosine kinase inhibitor (TKI) delivered biodissolvable gel depot
AKST4290 (Alkahest)	Oral small-molecule chemokine C-C motif receptor 3
APX3330 (Ocuphire Pharma)	Twice-daily oral treatment targeting Ref-1 protein
AR-1105 (Aerie Pharmaceuticals/Alcon)	Bioerodable dexamethasone implant
AR-13503 (Aerie Pharmaceuticals/Alcon)	Bioerodable netarsudil implant
Arcatus/ARVN001 (Arctic Vision; Xipere, Clearside Biomedical)	Triamcinolone acetonide 40 mg/mL suspension for suprachoroidal injection
AXT107 (AsclepiX Therapeutics)	Intravitreal self-forming gel depot peptide
CLS-AX (Clearside Biomedical)	Suprachoroidal axitinib injection
NEW: **D-4517.2** (Ashvattha Therapeutics)	Subcutaneously administered anti-angiogenic nanomedicine hydroxyl dendrimer VEGFR TKI
NEW: **Danegaptide** (Breye Therapeutics)	Oral therapy targeting cell-cell uncoupling, vascular cell apoptosis and vascular leakage
NEW: **EXN407** (Exonate)	Topical SRPK1 kinase inhibitor
EYP-1901 (EyePoint Pharmaceuticals)	Bioerodable vorolanib implant
IBE-814 (Ripple Therapeutics)	Bioerodable intravitreal dexamethasone implant
IBI302 (Innovent Biologics)	Bispecific anti-VEGF and anti-complement recombinant fully human fusion protein
NEW: **IBI324** (Innovent Biologics)	Intravitreal, bispecific recombinant fully humanized antibody targeting VEGF-A and angiopoietin-2
NEW: **IBI333** (Innovent Biologics)	Recombinant bispecific antibody targets VEGF-A and C
OCS-01 (Oculis)	Topical formulation of high-concentration, preservative-free dexamethasone
NEW: **OCU200** (Ocugen)	Fusion protein consisting of human transferrin linked to human tumstatin
ONS-5010/Lytenava (bevacizumab-vikg, Outlook Therapeutics)	Ophthalmic formulation of intravitreal bevacizumab-vikg
OPL-0401 (Valo Health)	Oral small molecule rho-kinase 1/2 inhibitor
OPT-302/Sozinibercept (Opthea)	Anti-VEGF-C and -D
OTT166/Nesvategrast (OcuTerra Therapeutics)	Small-molecule selective integrin inhibitor eye drop
OTX-TKI/Axpaxli (Ocular Therapeutix)	Hydrogel-based sustained-release intravitreal axitinib implant
NEW:**Restoret** (Eyebiotech)	Intravitreal, tri-specific Wnt agonist antibody
NEW: **RX-402** (Rezolute)	Oral selective and plasma kallikrein inhibitor
RO7250284/Zifibancimig (Genentech/Roche)	Bispecific human antigen-binding fragment (Fab) form of faricimab delivered via port delivery system
Tarcocimab tedromer (formerly KSI-301, Kodiak Sciences)	Anti-VEGF biopolymer conjugate
Tonabersat (formerly Xiflam, InflammX)	Oral small-molecule Connexin43 hemichannel blocker
UBX1325/Fuselotoclax (Unity Biotechnology)	Small-molecule B-cell lymphoma-extra large (Bcl-xL) inhibitor
Umedaptanib pegol (formerly RBM-007, Ribomic)	Oligonucleotide-based aptamer with anti-fibroblast growth factor 2 activity

ized nAMD patients 2:1 to CLS-AX and aflibercept. Meanwhile, in the Phase I/IIa OASIS trial (n=27, NCT04626128) in nAMD, 83 percent of patients in the two highest dose cohorts (n=12) demonstrated reduction in treatment burden at four months. Completion of the ODYSSEY trial is due this year.[1]

NEW: D-4517.2 (Ashvattha Therapeutics)

D-4517.2 (hydroxyl dendrimer VEGF-R TKI) is a subcutaneously administered anti-angiogenic nanomedicine that selectively targets activated microglia, macrophages and hypertrophic retinal pigment epithelial cells. Enrollment started last year in a Phase II trial (n=30, NCT05387837) evaluating chronic dosing of D-4517.2 in nAMD and DME. The company expects to report preliminary results in the first half of the year.

NEW: Danegaptide (Breye Therapeutics)

This oral treatment for DR and

	Indication	Status
	Diabetic macular edema	Preliminary Phase IIa data (n=22) demonstrated safety and tolerability.
	DME, neovascular age-related macular degeneration	Phase I trial (n=24) launched in spring 2023.
	nAMD, diabetic retinopathy	Phase II trial in DR halted early. No update available on Phase II trial in nAMD (n=107).
	Nonproliferative and proliferative DR	Phase IIb trial (n=103) failed to meet endpoint, but revised endpoint accepted. Phase III pending.
	DME, macular edema associated with retinal vein occlusion	Phase II trial in RVO (n=49) demonstrated vision improvement. Phase III trial in DME planned.
	nAMD, DME	Phase I trial (n=18) ongoing.
	DME, uveitic macular edema	Phase I trial in DME underway in Australasia. Phase III trial in uveitic macular edema in China completed enrollment.
	DME, nAMD	Phase I/IIa trial in nAMD (n=15) recruiting. Phase I/IIa trial in DME completed but no results posted.
	nAMD	Phase IIb trial (n=60) completed enrollment. Phase I/IIa trial (n=27) demonstrated reduced treatment burden.
	nAMD, DME	Phase II trial (n=30) initiated enrollment. Preliminary results due later in year.
	DME, DR, nAMD	Phase I/IIa DME trial commenced enrollment.
	DME	Phase Ib/IIa trial (n=48) demonstrated safety in patients. Phase II trial planned.
	nAMD, NPDR	Phase II nAMD trial (n=160) met primary endpoint. Phase III in nAMD planned. Phase II in NPDR (n=105) results due this year. Phase II trial in DME to start this year.
	RVO, DME	Phase II trial (n=50) ongoing. Completion expected later in year.
	nAMD	Phase II trial (n=231) showed noninferiority vs. aflibercept. Phase III nAMD (n=600) initiated in 2023. Phase I/II trial in nAMD and DME suspended.
	DME	Phase I trial (n=24) demonstrated safety and efficacy.
	nAMD	Phase I trial (n=24) initiated enrollment last year.
	DME	Phase III trial (n=497) demonstrated vision improvement. Phase III trial planned.
	DME	Phase I trial (n=28) filed in 2023.
	AMD, DME, branch RVO	Food and Drug Administration rejected Biologics License Application. FDA reviewing application for second trial.
	NPDR	Phase II trial (n=90) continuing recruitment.
	nAMD, DME	Two Phase III trials in nAMD (n=1,980) ongoing. Completion expected in 2024 and 2025..
	NPDR, mild PDR, nAMD	Phase II trial (n=225) completed enrollment. Phase I/II results in nAMD (n=44) showed modest visual acuity gain.
	nAMD; DR	Interim Phase Ib data in severe NPDR (n=21) due in 2024. Phase III trial in DR planned. Topline Phase I nAMD data (n=21) showed reduced treatment burden. Phase III trial in nAMD (n=300) started recruitment.
	nAMD, DME	Phase Ib/II trial in nAMD, DME (n=90) initiated recruitment.
	DME	Phase II trial (n=100) completed enrollment. Topline results expected in 2024.
	nAMD	Phase I trial (n251) recruiting. Completion due in 2027.
	nAMD, DME, RVO, NPDR	Mixed results from Phase III trials in DME (n=1,172 combined). Phase III RVO trial (n=568) showed BCVA improvement. Phase III nAMD trial (n=557) met primary endpoint.
	DME	Phase II trial (n=128) ongoing.
	nAMD, DME	Proof-of-concept Phase II trial in DME (n=65) demonstrated efficacy. Second Phase II DME trial (n=40) underway. nAMD trial (n=51) demonstrated vision gains with combined aflibercept therapy vs. aflibercept monotherapy.
	nAMD	Four trials (n=148) failed to show added benefit in monotherapy or in combination with aflibercept.

DME targets cell-to-cell uncoupling, vascular cell apoptosis and vascular leakage at an early disease stage. Breye says it launched a Phase I/IIa trial in DME, but the only trials listed are in cardiovascular disease.

NEW: EXN407 (Exonate)

EXNP407 is a selective small-molecule drop designed to inhibit SRPK1 kinase to modulate VEGF splicing and rebalance VEGF isoforms to decrease angiogenic and pathogenic VEGF factors. A Phase Ib/IIa trial in mild NPDR (n=48, NCT0456756) demonstrated safety and a proclivity to reduce macular thickness and vascular leakage at 12 weeks compared with placebo, Exonate CEO Catherine Beech, MD, ChB, said at OIS Retina. The company plans to move forward to a Phase II trial.

EYP-1901 (EyePoint Pharmaceuticals)

This bioerodable sustained-release insert marries the Durasert platform with the TKI vorolanib. Topline data from the Phase II DAVIO 2 trial in nAMD (n=160, NCT05381948) showed noninferior BCVA improvement vs. aflibercept, along with no treatment-related serious adverse events. Patients in the 2- and 3-mg EYP-1901 dose groups demonstrated an 80-percent reduction in treatment burden.

A Phase III pivotal trial in nAMD should start enrollment in the second half of the year. Meanwhile, EyePoint says a topline data readout from the Phase II PAVIA trial in NPDR (n=105, NCT05381948) are expected in the second quarter, and the Phase II VERONA trial in DME should start recruitment in the first quarter this year.

IBE-814 (Ripple Therapeutics)

IBE-814 is a bioerodable, low-dose

Investigative programs in geographic atrophy, dry AMD

NEW: ADX-248 (Aldeyra Therapeutics). ADX-248 is an intravitreally administered reactive aldehyde species (RASP) modulator. RASP metabolites have been implicated in dark-adaptation compromise. ADX-248 is expected to initiate clinical testing in 2024. Aldeyra says it expects to file an investigational new drug application this year with the U.S. Food and Drug Administration for a Phase I/II clinical trial in dry AMD patients with dark-adaptation deficit.

ANX007 (Annexon Biosciences). ANX007 is a C1q and classical complement inhibitor. Annexon says it's prepared to move ahead with the ARCHER II Phase III registration program that includes using, for the first-time, the prevention of ≥15-letter loss of best corrected visual acuity as the primary endpoint. Annexon also notes that the FDA won't require evaluation of lesion growth, an anatomical endpoint used for other GA programs. ARCHER II would enroll around 400 GA patients randomized 1:1 to monthly ANX007 or sham.

ARROW, a second Phase III trial, would enroll about 500 GA patients and evaluate monthly ANX007 head-to-head with pegcetacoplan, using the same primary endpoint as ARCHER II. One-year results from the Phase II ARCHER trial (n=270, NCT04656561) showed 15.7 percent of patients treated monthly with ANX007 lost ≥10 letters vs. 25.8 percent of sham patients (p=0.096).[1] However, the study also showed ANX007 didn't significantly reduce lesion area.

NEW: ASP7317 (Astellas Pharma). ASP7317 is designed to replace retinal pigment epithelium cells lost in AMD with new cells generated from pluripotent stem cells. A Phase Ib trial (n=42, NCT031781149) is recruiting.

NEW: AVD-104 (Aviceda Therapeutics). Intravitreal AVD-104 is an engineered glycan (sialic acid) nanoparticle that targets the self-pattern recognition receptors on overly activated retinal macrophages and microglia. It aims to repolarize these immune cells to reduce inflammation while enhancing complement factor H activity.

Aviceda completed enrollment in the SIGLEC Phase II/III trial in GA (n=287, NCT05839041). Early results from the trial showed an acceptable safety profile for up to three months of treatment.[2]

NEW: BI 771716 (CDR-Life/Boehringer Ingelheim). Intravitreal BI 771716 is described as a highly specific antibody fragment of reduced size that enables penetration of all retina layers. The Phase I GA trial (n=24, NCT06006585) is set for midyear completion.

NEW: CT1812 (Cognition Therapeutics). CT1812 is a small-molecule oral agent designed to penetrate the blood-brain and blood-retina barriers and bind selectively to the sigma-2 receptor complex, which is thought to be involved in regulation of membrane trafficking and autophagy damage that can cause loss of RPE cell function. Cognition last year initiated the Phase II MAGNIFY trial in GA (n=246, NCT05893537).

Danicopan (Alexion Pharmaceuticals/AstraZeneca). Also known as ALXN2040, this oral factor D inhibitor is being developed as an add-on to C5-inhibition therapies for patients with paroxysmal nocturnal hemoglobinuria. Alexion is also evaluating danicopan as a monotherapy for GA in a Phase II trial (n=365, NCT05019521) that completed enrollment last year.

NEW: EA-2351 (Endogena Therapeutics). Endogena describes EA-2351 as a novel small-molecule compound that centers on RPE cells to regenerate and restore photoreceptor function and reduce GA lesion size. Its IND last year received FDA clearance and Endogena said it would launch the in-human study this year, but none has been filed with ClinicalTrials.gov.

Elamipretide (Stealth BioTherapeutics). This cell-permeating peptide has demonstrated properties to normalize mitochondrial structure. The Phase II ReCLAIM-2 study (n=176, NCT03891875) failed to meet its primary endpoints—change in low-luminance visual acuity (LLVA) and GA lesion size—but Stealth CEO Renee McCarthy said at OIS XIII last year that the company plans to move onto a Phase III trial based on a "positive" end-of-Phase II FDA meeting that confirmed ellipsoid zone attenuation as an appropriate clinical trial endpoint. The Phase III trial hasn't been registered with ClinicalTrials.gov.

IONIS-FB-LRx (Ionis Pharmaceuticals/Roche). Also known as RG6299, this is a ligand-conjugated investigational antisense inhibitor that targets complement factor B production and the alternative complement pathway. Ionis says it expects to report results this year from the Phase II GOLDEN study (n=332, NCT03815825).

NEW: QA102 (Smilebiotek Zhuhai). QA102 is an oral capsule. No further description is available. The sponsor doesn't have a website. A Phase II U.S. trial (n=145, NCT 05536752) last year completed enrollment.

RG6501/OpRegen (Lineage Cell Therapeutics). RG6501 is a suspension of human allogeneic RPE cells delivered subretinally. Imaging analyses demonstrated improvement in outer retinal structure in the Phase I/IIa trial (n=24, NCT02286089).[3] All five patients enrolled in cohort 4, who had extensive coverage of the GA lesion with the surgical bleb containing OpRegen in suspension, demonstrated improvement in outer retinal structure as assessed by optical coherence tomography within the first three months after treatment. A Phase IIa study is currently recruiting (n=60, NCT05626114).

Risuteganib/Luminate (Allegro Ophthalmics). Risuteganib is a small-peptide oxidative stress stabilizer. Allegro received FDA agreement under special protocol assessment for the design of its Phase IIb/III trial in intermediate dry AMD. Licensee AffaMed Therapeutics also received clearance for a Phase III trial in China for the same indication. Neither trial is registered yet.

RPESC-RPE-4Q (Luxa Biotechnology). RPESC-RPE-4W consists of allogeneic retinal pigment epithelium stem cell (RPESC)-derived RPE cells isolated from the RPE layer of human cadaveric eyes, transplanted under the macula. The Phase I/IIa trial (n=18, NCT04627428) is recruiting, with completion anticipated in 2025.

Tinlarebant/LBS-008 (Belite Bio). This oral therapy aims to reduce the accumulation of vitamin A-based toxins, or bisretinoids, thought to contribute to GA progression. The Phase III U.S. clinical trial (n=429, NCT05945993) last year opened recruitment. Phase III trials are also underway in China and Europe. A Phase III trial in Stargardt disease is ongoing.

Tonabersat (formerly Xiflam, InflammX). Tonabersat is an oral small molecule that targets the Connexin43(Cx43) hemichannel protein. The FDA approved an IND for a trial in early stage dry AMD. The trial hasn't been posted at ClinicalTrials.gov. The company says it plans to have the trial in the clinic by the second quarter.

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Product name (manufacturer)	Description	Status
NEW: **ADX-248** (Aldeyra Therapeutics)	Intravitreal reactive aldehyde species modulator	Investigational new drug (IND) application expected in 2024.
ANX007 (Annexon Biosciences)	Intravitreal antigen-binding fragment (Fab) to complement factor q1	One-year Phase II results (n=270) demonstrated efficacy vs. sham. Phase III trials (n=900) planned in 2024.
NEW: **ASP7317** (Astellas Pharma)	Pluripotent stem cell therapy	Phase Ib trial (n=42) recruiting. Completion due in 2025.
NEW: **AVD-104** (Aviceda Therapeutics)	Intravitreal sialic acid nanoparticle targeting complement factor H	Phase II/III trial (n=287) completed enrollment. Early results show acceptable safety profile.
NEW: **BI 771716** (CDR-Life/Boehringer Ingelheim)	Intravitreal highly specific antibody fragment	Phase I trial (n=24) initiated. Completion set for midyear.
NEW: **CT1812** (Cognition Therapeutics)	Oral small-molecule binding to sigma-2 receptor complex	Phase II trial (n-246) launched in 2024. Completion set for 2027.
Danicopan (Alexion Pharmaceuticals)	Oral factor D inhibitor	Phase II trial (n=365) completed enrollment. Completion due in 2025.
NEW: **EA-2351** (Endogena Therapeutics)	Small molecule targeting damaged retinal pigment epithelium cells	IND received clearance for in-human studies to start this year.
Elamipretide (Stealth BioTherapeutics)	Mitochondria-targeting, cell-permeable peptide for subcutaneous injection	Phase III trial planned despite failure of Phase II trial (n=176) to meet primary endpoints.
IONIS-FB-LRx (Ionis Pharmaceuticals)	Anti-sense oligonucleotide inhibiting complement factor B	Phase II trial (n=330) completed enrollment. Results expected in 2024.
NEW: **QA102** (Smilebioteck Zhuhai)	Oral capsule	Phase II U.S. trial (n=145) completed recruitment. Study completion expected in 2025.
RG6501/OpRegen (Lineage Cell Therapeutics)	Subretinally administered allogeneic retinal pigment epithelium cells	Phase I/IIa (n=24) demonstrated efficacy signal. Phase IIa trial (n=60) recruiting.
Risuteganib/Luminate (Allegro Ophthalmics)	Small-peptide oxidative stress stabilizer	Phase IIb/III trial cleared by FDA. Phase III trial pending in China.
RPESC-RP-4Q (Luxa Biotechnology)	Allogeneic RPE stem cell therapy	Phase I/IIa trial (n=18) ongoing. Completion due in 2025.
Tinlarebant/LBS-008 (Belite Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist	Phase III trial (n=429) launched, with completion due in 2027. Phase III trials in China, Europe underway.
Tonabersat (formerly Xiflam, InflammX)	Oral small-molecule connexin43 hemichannel blocker	FDA approved IND. Trial to begin in second quarter.

dexamethasone intravitreal implant that releases one-tenth the drug load of the corticosteroid dexamethasone. The Phase II trial in RVO and DME (n=60, NCT04576689) is continuing, with completion expected later in the year.

IBI302 (Innovent Biologics)

This intravitreal bispecific antibody targets both VEGF and C3b/C4b pathways. A Phase II comparator trial vs. aflibercept in nAMD (n=231, NCT04820452) reported comparable BCVA gains at 36 weeks.[2] The Phase III STAR trial in nAMD (n=600, NCT05972473) is comparing IBI302 8 mg and aflibercept 2 mg. Enrollment opened last fall, with completion anticipated in 2027. A Phase I/II trial in both nAMD and DME (n=234) was suspended last year.

NEW: IBI 324 (Innovent Biologics)

This intravitreal, dual-target specific recombinant fully humanized antibody targets VEGF-A and angiopoietin-2 (Ang-2). Phase I results in DME (n=24, NCT05489718) demonstrated 4 mg was the maximum tolerated dose. No ocular serious adverse events, intraocular inflammation or dose-limiting toxicities were reported. Both single- and multiple-dose groups demonstrated BCVA improvement.[3]

NEW: IBI333 (Innovent Biologics)

This recombinant bispecific antibody targets VEGF-A and C. Enrollment opened last year in a Phase I nAMD trial (n=24, NCT05639530). IBI333 targets the VEGF-A-mediated signaling pathway to inhibit vascular endothelial cell proliferation and reduce VEGF-C-induced epithelial cell window formation to further reduce vascular permeability and inhibit the binding of compensatory up-regulated VEGF-C to endogenous VEGF receptors. Study completion is due this year.

OCS-01 (Oculis)

OCS-01 is a topical formulation of a 15-mg/ml-concentration of preservative-free dexamethasone. Results from Stage 1 of the Phase II/III DIAMOND trial (n=497, NCT05066997) in DME showed that patients on OCS-01 (n=100) had an average 7.6-letter improvement in BCVA at 12 weeks vs. 3.7 letters for those on vehicle (n=48).[4] Patient enrollment has since started in the Phase III DIAMOND-1 trial, with completion expected in 2025.

NEW: OCU200 *(Ocugen)*

OCU200 is a novel fusion protein consisting of human transferrin linked to human tumstatin with antiproliferative, anti-inflammatory and antioxidative properties that selectively targets retinal and choroidal tissues. The formulation is designed to demonstrate better bioavailability and tissue penetration than tumstatin alone. Ocugen last year filed for a Phase I trial in DME (n=28, NCT05802329).

ONS-5010/Lytenava (bevacizumab-vikg, Outlook Therapeutics)

The FDA last year didn't approve the biologics license application (BLA) for this ophthalmic formulation of Avastin. In December, Outlook submitted a special protocol assessment request with the FDA seeking confirmation that the NORSE EIGHT trial would fulfill the FDA's requirement for a second clinical trial in nAMD. Outlook says it expects a response early this year. NORSE EIGHT would enroll about 400 patients and compare ONS-5010 1.25 mg with ranibizumab 0.5 mg. The previous NDA was based on Phase III NORSE TWO results (n=228, NCT03834753) in nAMD, which showed noninferiority vs. ranibizumab.

OPL-0401 (Valo Health)

OPL-0401 is an oral, small-molecule rho-kinase 1/2 inhibitor. The Phase II Spectra trial in mild, mod-

Gene therapy programs in AMD, DR, DME

4D-150 (4D Molecular Therapeutics). 4D-150 consists of the targeted and evolved intravitreal vector, R100, and a dual transgene payload that expresses aflibercept and a vascular endothelial growth factor-C RNA interference to inhibit VEGF A, B, C and placental growth factor (PLGF). It's designed for low-dose intravitreal delivery.

The first patients were enrolled last year in the dose-confirmation stage (n=18) of the Phase II SPECTRA trial (n=72, NCT05930561) in diabetic macular edema and in the population extension cohort of the Phase II PRISM trial (n=150, NCT05197270) in neovascular age-related macular degeneration. 4DMT says it expects to complete enrollment in SPECTRA and report interim 24-week data later in the year.

4D-150 also received regenerative medicine advanced therapy (RMAT) designation from the U.S. Food and Drug Administration for intravitreal treatment of nAMD. RMAT allows for accelerated review based on surrogate endpoints. Interim PRISM data demonstrated what 4DMT describes as "encouraging safety, tolerability and clinical activity" in nAMD. 4DMT this year expects to report interim PRISM data and update plans for the Phase III trial.

AABV-RGX-314 (RegenxBio/AbbVie). This adeno-associated virus-8 (AAV8) vector contains an anti-VEGF transgene delivered suprachoroidally. One-year results from the Phase II ALTITUDE trial in DME (n=100, NCT04567550) showed acceptable tolerance in 50 patients, with 70.8 percent of treated patients achieving improvement in Diabetic Retinopathy Severity Scale scores vs. 25 percent of controls.[1]

In nAMD, interim six-month results of 65 patients in the Phase II AAVIATE trial (n=115, NCT04514653) demonstrated an 85-percent reduction in the annualized injection rate in the highest-dose cohort, with 67 percent remaining injection free.[2] Both ALTITUDE and AAVIATE are due for completion this year.

RegenxBio is also evaluating a subretinal

erate and severe NPDR (n=90, NCT05393284) is continuing to recruit. Trial completion is set for this year.

OPT-302/Sozinibercept (Opthea)

OPT-302 targets VEGF-C and D. Opthea adopted sozinibercept as its nonproprietary drug name. Recruitment is continuing in two Phase III trials in nAMD: ShORe (n=990, NCT04757610) and COAST (n=990, NCT04757636). They're evaluating delivery platform. The Phase II/III ATMOSPHERE (n=300, NCT04704921) and ASCENT (n=465, NCT05407636) trials in nAMD are expected to support a biologics license application (BLA) in 2025 or 2026.

EXG102-031 (Exegenesis Bio). EXG102-031 is an injectable recombinant AAV-based gene therapy that aims to express a therapeutic fusion protein that binds or neutralizes all known subtypes of VEGF and angiopoietin-2 (ang-2). Two separate clinical trials in nAMD last year started recruiting patients: a Phase I U.S. trial (n=6) known as Everest; and a Phase I/II trial in China (n=42, NCT06183814).

FT-003 (Frontera Therapeutics). FT-003 is an AAV gene platform. The first patients were dosed last year in two Phase I trials in China: in nAMD (n=18, NCT05611424); and in central-involvement DME (n=18, NCT05916391).

Ixo-vec/ADVM-022 (Adverum Biotechnologies). The long name is isoberogene soroparvovec. Adverum completed enrollment last year in the Phase II Luna trial in nAMD (n=69, NCT05536973), randomizing patients to two different doses: a 2 x 10^{11} vector genes per eye (vg/eye) and a lower 6 x 10^{10} vg/eye dose. Patients are also randomized across four prophylactic regimens, with the goal to determine the utility of oral prophylaxis in future trials.

JNJ-81201887 (Janssen Pharmaceuticals). This candidate has also been known as JNJ-1887, HMR59, developed by Hemera Biosciences, and AAVCAGsCD59. The intravitreal vector aims to boost expression of soluble CD59, a protective protein found in the cellular plasma membrane. The Phase IIb trial in GA, known as PARASOL, (n=300, NCT05811351) initiated recruitment last year. A pooled analysis of the open-label Phase I trial (n=17, NCT03144999) demonstrated a single injection was well-tolerated with an acceptable safety and a manageable inflammatory profile in patients with both GA and nAMD.[3]

NEW: KH631 (Chengdu Origen Biotechnology/Vanotech). This recombinant AAV vector encodes a human VEGF receptor fusion protein. The first patient was dosed in the VAN-2201 Phase I trial in nAMD (n=25, NCT05657301). A second Phase I trial is registered in China (n=42, NCT05672121).

NEW: OCU410 (Ocugen). OCU410, also known as AAV-RORA, uses an AAV platform to deliver the *RORA* (RAR-related orphan receptor A) gene to the retina. The RORA protein is thought to reduce lipofuscin deposits and oxidative stress, and it has demonstrated anti-inflammatory properties in animal studies. Ocugen last year dosed the first patient in the Phase I/II ArMaDa trial in dry AMD (n=63, NCT06018558).

OLX10212 (Olix Pharmaceuticals). This agent uses an asymmetric small-interfering RNA (siRNA), gene-penetrating technology to target genetic origins of inflammation. A Phase I nAMD trial (n=42, NCT05643118) launched last year. Early results demonstrate no serious safety signals. The study also identified dose levels suitable for future trials. In the study, OLX10212 was administered at dose levels between 100 µg/eye/50 µL and 950 µg/eye/50 µL via a single intravitreal injection. Trial completion is anticipated by yearend.

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Product name (manufacturer)	Description/active agent	Indication	Status
4D-150 (4D Molecular Therapeutics)	Dual-transgene intravitreal therapy	Neovascular age-related macular degeneration, diabetic macular edema	Phase II trials in nAMD (n=15) and DME (n=18) ongoing. Interim DME data due in 2024.
AABV-RGX-314 (RegenxBio)	Adeno-associated virus (AAV) 8 vector with anti-VEGF fab transgene	DME, nAMD	Phase II DME trial (n=100) showed safety and efficacy. Phase II nAMD trial (n=115) showed efficacy. Trials of subretinal delivery in nAMD (n=765) ongoing.
EXG102-031 (Exegenesis Bio)	Recombinant AAV-based therapy targeting VEGF and angiopoietin-2 (Ang-2)	nAMD	In nAMD, Phase I U.S. trial (n=6) and Phase I/II China trial (n=42) launched. Completion due in 2025.
FT-003 (Frontera Therapeutics)	AAV gene expression platform	nAMD, DME	Phase I trials in nAMD (n=18) and DME (n=18) initiated.
IBI324 (Innovent Biologics)	Dual-target recombinant fully humanized antibody targeting VEGF-A and Ang-2	DME	Phase I trial (n=36) initiated.
Ixo-vec/ADVM-022 (Adverum Biotechnologies)	Intravitreal injection of ixoberogene soroparvovec (AAV vector 7m8 of aflibercept)	nAMD	Phase II trial (n=69) in previously treated nAMD patients ongoing.
JNJ-81201887 (Janssen Pharmaceuticals)	Intravitreal vector of soluble form of CD59 protein	GA secondary to dry AMD, nAMD	Phase IIb trial in GA (n=300) initiated. Phase I trial in GA and nAMD demonstrated safety.
NEW: KH631 (Chendu Origen Biotechnology/Vanotech)	Recombinant AAV vector that encodes human VEGF receptor fusion protein	nAMD	Phase I trial (n=25) initiated. Second Phase I trial in China (n=42) planned.
NEW: OCU410 (Ocugen)	AAV platform to deliver RAR-related orphan receptor A gene	dry AMD	Phase I/II trial (n=63) initiated.
OLX10212 (Olix Pharmaceuticals)	Asymmetric small-interfering RNA (siRNA), gene-penetrating platform	nAMD	Phase I trial (n=42) initiated.

intravitreal OPT-302 2 mg in combination with ranibizumab 0.5 mg or aflibercept 2 mg, respectively. The primary endpoint for both studies is superiority in visual acuity gains at 12 months for the combination therapy compared with monotherapy. Study completion is set for the end of this year in ShORe and next year for COAST. Phase IIb results demonstrated that combination OPT-302-ranibizumab for nAMD achieved a statistically superior gain in visual acuity at 24 weeks vs. ranibizumab alone.[5]

OTT166/Nesvategrast (OcuTerra Therapeutics)

Nesvategrast is the new name given this topical small-molecule, selective integrin inhibitor. OcuTerra completed patient enrollment in the Phase II DR:EAM trial (for Diabetic Retinopathy: Early Active Management) in adults with moderately severe-to-severe NPDR or mild PDR with minimal vision loss (n=225, NCT05409235). OcuTerra says it expects topline results in the first quarter this year. Results from the Phase I/II trial in nAMD (n=44, NCT02914639), posted last year, demonstrated good outcomes for safety and tolerability, but mixed outcomes for back-of-the-eye findings, along with modest improvement in BCVA improvement.

OTX-TKI/Axpaxli (Ocular Therapeutix)

This axitinib intravitreal implant also has a new name. Ocular reported completing enrollment in the Phase Ib trial in moderately severe-to-severe NPDR (n=21, NCT05695417). Interim six-month data are expected in the first quarter, when, Ocular says, it plans to also prepare a Phase III trial in DR. Twelve-month topline data from the Phase I nAMD trial (n=21, NCT04989699) demonstrated an overall 89-percent reduction in treatment burden in OTX-TKI patients.[6] Ocular last year initiated the pivotal Phase III trial in nAMD (n=300, NCT06223958), for which the FDA this year granted a special protocol assessment agreement modification to include treatment-naive patients with VA of 20/80 or better.

NEW: Restoret (Eyebiotech)

This intravitreal, tri-specific agonist antibody targets the Wnt signaling pathway to halt vascular leakage and restore and maintain the blood-retinal barrier. The Phase Ib/II AMARONE trial (for Anti-permeability Mechanism and Age Related Ocular Neovascularization Evaluation) last year started enrolling patients with DME

Table. Investigative therapies for inherited retinal disease

Product name (manufacturer)	Description
NEW: **4D-110** (4D Molecular Therapeutics)	Intravitreal CHM transgene insert and proprietary 4D-R100 vector 4D
4D-125 (4D Molecular Therapeutics)	Subretinal delivery of functional copies of RPGR gene
NEW: **ACDN-01** (Ascician Therapeutics)	RNA exon editor
AGTC-501/rAAV2tYF-GRK1-RPGR (Beacon Therapeutics)	Recombinant adeno-associated virus vector-based gene therapy
ATSN-101/SAR439483 (Atsena Therapeutics)	Functional copy of *GUCY2D* gene delivered subretinally
NEW: **ATSN-201** (Atsena Therapeutics)	AAV.SPR capsid to deliver *RS1* to photoreceptors
Botaretigene sparoparvovec/AAV-RPGR (MeiraGTx/Janssen Pharmaceutical Cos.)	Delivers functional copy of *RPGR* gene
EA-2353 (Endogena Therapeutics)	Selective small-molecule activator of endogenous retinal stem and progenitor cells
Emixustat (Kubota Vision)	*RPE65* inhibitor
FT-001 (Frontera Therapeutics)	AAV vector to deliver functional copy of RPGR gene
NEW: **FT-002** (Frontera Therapeutics)	Intraocular recombinant AAV virus
Glideuretinol (formerly ALK-001, Alkeus Pharmaceuticals)	Oral modified vitamin A
jCell (jCyte, Santen)	Intravitreal human retinal progenitor cells
Lumevoq/GS010 (GenSight)	Single intravitreal injection of rAAV2/s-ND4
MCO-10 (Nanoscope Therapeutics)	Ambient light activatable optogenetic therapy
OCU400 (Ocugen)	AAV to deliver functional *NR2E3* gene
NEW: **OCU410** (Ocugen)	AAV delivery platform for RORA (ROR Related Orphan Receptor A) gene
OPGx-001 (Opus Genetics)	AAV-8 vector to deliver functional *LCA5* gene
Sepofarsen/QR-110 (Laboratoires Théa)	RNA therapy targeting c.2991+1655A>G mutation in *CEP290* gene
Tinlarebant/LBS-008 (Belite Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist
NEW: **SPVN06** (SparingVision)	Mutation-agnostic AAV vector

and nAMD. The trial isn't yet listed.

NEW: RZ-402 (Rezolute)

RZ402 is an oral selective and plasma kallikrein inhibitor (PKI). Rezolute last year reported completing enrollment in the Phase II trial in DME (n=100, NCT05712720). The proof-of-concept study is evaluating RZ402 administered once daily as monotherapy over 12 weeks plus a four-week follow-up in treatment-naive patients or those who have had limited anti-VEGF injections. Topline results are expected in the second quarter this year.

RO7250284/zifibancimig (Genentech/Roche)

And yet another new name, this one for this bispecific human Fab form of faricimab delivered via the port-delivery implant used with Susvimo. The three-part Phase I BURGUNDY trial in nAMD (n=251, NCT04567303) is still recruiting patients. Study completion is set for 2027.

Tarcocimab (formerly KSI-301, Kodiak Sciences)

This anti-VEGF biopolymer conjugate has had quite the up-and-down year. Last summer, Kodiak said it would drop the program after the GLEAM (n=460, NCT04611152) and GLIMMER (n=459, NCT04603937) DME trials failed to show noninferiority vs. aflibercept. Kodiak pulled an about-face after first-time results from the GLOW Phase III trial (n=253, NCT05066230) showed 41 percent of treated patients had a greater-than-two-step improvement in DRSS score at 48 weeks vs. 1.4 percent of sham patients (p<0.0001).[7] Tarcocimab patients received 3.8 injections a year on average.

Updated one-year results from the BEACON Phase III trial in RVO (n=568, NCT04592419) demonstrated tarcocimab met the primary endpoint of noninferiority vs. aflibercept for BCVA change at 24 weeks. Enrollment was also completed in the Phase III GLOW trial in NPDR (n=253, NCT05066230), but then the study was terminated because the primary endpoint wasn't met.

The Phase III DAYLIGHT trial evaluating monthly tarcocimab in nAMD (n=557, NCT04964089) met its primary endpoint of noninferior VA outcomes vs. aflibercept.

Tonabersat (formerly Xiflam, InflammX)

This oral, small-molecule NLRP3 inflammasome inhibitor targets the Connexin43 protein and blocks the formation of hemichannels. A Phase II

	Indication	Status
	Choroideremia	Phase I trial (n=13) ongoing. Completion due in 2027.
	X-linked retinitis pigmentosa (XLRP)	Enrollment in Phase I/II trial (n=21) halved. Completion due in 2029.
	Stargardt disease, ABC4A retinopathies	Fast track designation granted. Phase I/II trial in to begin enrollment this year.
	XLRP	Phase I/II (n=42) trial ongoing. Phase II/III (n=63) planned.
	GUCY2D-associated Leber congenital amaurosis 1	Phase I/II trial (n=15) data showed no safety or tolerability issues. High-dose treatment (1E11 vg/eye) yielded vision improvements.
	RS1-associated XLRP	Phase I/II trial (n=18) initiated.
	RPGR-associated XLRP	Phase III trial (n=97) enrolling patients.
	Retinitis pigmentosa	Enrollment completed in Phase I/II trial (n=14).
	Stargardt disease	Phase III trial (n=194) demonstrated no clinically change in atrophy area vs. placebo.
	LCA2	Phase II trial in China (n=9) initiated.
	XLRP	Phase I trial (n=18) initiated.
	Stargardt disease	Phase II trial (n=140) demonstrated slowing of lesion growth. Early extension trial results (n=140) demonstrated safety and efficacy.
	RP	Phase II trial (n=30) evaluating repeat injections in adults reported half of patients had treatment-related adverse events.
	Leber hereditary optic neuropathy	Real-world study (n=63) showed efficacy and safety after one year or more of treatment. Phase III trial planned.
	RP, Stargardt disease	Phase IIb RP trial (n=27) due for completion this year. One-year Phase II Stargardt trial data (n=6) showed efficacy signal.
	RP, LCA	Phase I/II trial (n=124) recruiting patients. Phase III trial pending. Regenerative medicine advanced therapy designation granted.
	Stargardt, *ABCA4*-associated retinopathies	Orphan drug designation granted.
	LCA from biallelic mutations.	Phase I/II trial (n=9) initiated.
	LCA10	Phase II/III trial (n=36) failed to meet primary endpoint. Phase II/III (n=15) listed as recruiting.
	Stargardt disease	Two-year Phase Ib/II trial (n=13) demonstrated positive results. Phase III trial (n=104) completed enrollment.
	RP	Early Phase I/II trial (n=33) data showed tolerability and safety.

Anti-VEGF biosimilars in clinical trials

AFLIBERCEPT BIOSIMILARS

ABP 938 (Amgen). The U.S. Food and Drug Administration accepted the biologics license application (BLA) for ABP 938. Final analysis from a Phase III study in neovascular age-related macular degeneration (n=566, NCT04270747) confirmed no clinically meaningful differences in efficacy between the biosimilar and reference product. A separate Phase III trial (n=49, NCT05704725) is evaluating ABP 938 in chorioretinal vascular disease.

ALT-L9 (Alteogen). Alteogen last year completed enrollment in the Phase III comparator trial with aflibercept in nAMD (n=431, EudraCT: 2021-004530-11).

NEW: AVT06 (Alvotech). This Iceland-based company reported positive top-line results from a Phase III trial of AVT06 in nAMD (n=413, NCT05155293).

CT-P42 (Celltrion). Twenty-four week results from the Phase III trial in diabetic macular edema (n=348, NCT04739306) demonstrated equivalence to aflibercept for eight-week improvement in best-corrected visual acuity. Celltrion said last year it plans to complete the Phase III trial and file for licensure of CT-P42 in the United States and Europe, but no further update was available at press time.

FYB203 (Formycon/Klinge Biopharma). The FDA and European Medicines Agency (EMA) last year accepted the development partners' application. Results from the Phase III MAGELLAN-AMD trial in nAMD (n=434, NCT04522167) demonstrated equivalency with aflibercept.

LY9004 (Ocumension Therapeutics/Shandong Boan Biological Technology). China-based Ocumension reported last year that the Phase III clinical trial completed enrollment (n=416). The trial isn't registered at ClinicalTrials.gov or the European Union Clinical Trials Register (EudraCT). Boan holds licensing rights outside China.

M710/MYL-1701P (Viatris/Mylan Pharmaceuticals). Results from the Phase III trial in central DME (n=355, NCT03610646) demonstrated comparable vision and anatomical outcomes with the reference product. Eligible subjects from the study would be enrolled in the AFIL-IJZ-3002 extension study (n=52, NCT04674800). Results are still pending from the extension study.

SB15 (Samsung Bioepis)**.** A post-hoc analysis of data from a Phase III trial in patients with nAMD (n=449, NCT04450329) demonstrated those who switched from aflibercept to SB15 maintained comparable clinical efficacy and safety.[1]

NEW: SCD411 (Sam Chun Dang Pharmaceutical Co.). Sam Chun Dang last year completed a Phase III trial in nAMD (n=576, NCT04480463) that demonstrated equivalence with aflibercept in visual and safety outcomes.

SOK583A1 (Sandoz/Novartis). Sandoz, a division of Novartis, reported comparable efficacy and safety results between the biosimilar and reference product from the Phase III MYLIGHT trial (n=485, NCT04864834) in nAMD. Sandoz said last year it would file for regulatory approval for biosimilar aflibercept in the United States and European Union "in the coming months."

NEW: Yesafili (Biocon Biologics). The EMA last July issued a positive opinion recommending approval of Yesafili, but no update has been issued since.

Biosimilar name (manufacturer)	Indication	Status
Reference Product: Aflibercept		
ABP 938 (Amgen)	Neovascular age-related macular degeneration	Phase III trial (n=566) showed equivalence to aflibercept.
ALT-L9 (Alteogen)	nAMD	Phase III trial (n=431) completed enrollment.
NEW: AVT06 (Alvotech)	nAMD	Positive topline Phase III results (n=413).
CT-P42 (Celltrion Healthcare)	Diabetic macular edema	Phase III trial (n=348) showed equivalence.
FYB203 (Formycon/Klinge Biopharma)	nAMD	FDA and EMA accepted application. Phase III results (n=434) showed equivalence.
LY9004 (Ocumension Therapeutics/Shandong Boan Biological Technology)	nAMD	Phase III trial in China (n=416) completed enrollment.
M710/MYL-1701P (Viatris/Momenta)	DME	Phase III trial (n=355) showed equivalence. Extension study (n=52) results pending.
SB15 (Samsung Bioepis)	nAMD	Phase III trial (n=449) completed.
NEW: SCC411 (Sam Chung Dang Pharmaceutical Co.)	nAMD	Phase III trial (n=576) showed equivalence.
SOK583A1 (Sandoz)	nAMD	Phase III trial (n=485) showed equivalence. Filing for regulatory approval pending.
NEW: Yesafii (Biocon Biologics)	NA	EMA issues positive opinion. No further update available.
Reference Product: Bevacizumab		
HLX04-O (Shanghai Henlius Biotech)	nAMD	Phase III trial with ranibizumab as comparator (n=766) due for completion in 2024..
Reference Product: Ranibizumab		
CKD-701 (Chong Kun Dang Pharmaceutical)	nAMD	Approved in South Korea.
LUBT010 (Lupin)	nAMD	Approved in India, distribution started.
Ximluci/Xlucane (Xbrane Biopharma/Stada Arzneimittel)	nAMD	Launched in Europe. U.S. application resubmitted.

BEVACIZUMAB BIOSIMILAR

HLX04-O (Essex Bio-Technology/Shanghai Henlius Biotech). U.S. patients started enrollment in the Phase III trial in nAMD that had already dosed patients in the European Union and Australia (n=388, NCT04740671), and the first patients were dosed in a Phase III trial in

China (n=388, NCT05003245). Both trials are using ranibizumab, not the reference product bevacizumab, as the comparator. Both trials are set for completion this year. Results from a Phase I/II single-arm study in nAMD (n=20, NCT049933352), completed last year, demonstrated acceptable safety and tolerability in treated patients. The biosimilar is already approved in China for cancer indications.

RANIBIZUMAB BIOSIMILARS

CKD-701 (Chong Kun Dang Pharmaceutical). South Korea last year approved CKD-701. A Phase III trial in nAMD with ranibizumab as the comparator in 2022 found the biosimilar met predefined equivalence criteria (n=312, NCT04857177). The trial was conducted in South Korea. Chong Kun Dang has a host of affiliations with U.S. companies, including Pfizer and Amgen.

LUBT010 (Lupin). A Phase III comparator trial with the reference product in nAMD in India is now listed as "unknown status" (n=600, NCT04690556). However, Lupin did receive approval in India for LUBT010 for all indications the reference product is approved for. Lupin is distributing LUBT010 in the Middle East.

Ximluci/Xlucane (Xbrane Biopharma/ STADA Arzneimittel). Ximluci launched last year in Europe. In 2022 STADA withdrew the BLA it filed with the FDA, but resubmitted it last year and the FDA accepted it. The Biosimilar User Fee Amendment goal date is set for April. A Phase III in nAMD (n=582, NCT03805100), completed in 2022, demonstrated equivalency with the reference product. Bausch + Lomb has an agreement with Xbrane and STADA to commercialize Ximluci in the United States and Canada.

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trial in DME (n=128, NCT05727891) is ongoing. The trial is also evaluating the therapeutic effect of Tonabersat on biomarkers of active kidney disease. Completion is scheduled for yearend.

UBX1325/Fuselotoclax (UNITY Biotechnology)

Here's yet another new name. UBX1325 is a potent small-molecule inhibitor of B-cell lymphoma-extra-large (Bcl-xL) that aims to inhibit the function of proteins that senescent cells rely on for survival. The first patients were dosed in the Phase II ASPIRE study (n=40, NCT06011798) in DME. Study completion is anticipated at yearend. Forty-eight week results from the Phase II BEHOLD trial in DME (n=65, NCT04857996) demonstrated a 6.2-letter BCVA gain from baseline after one injection and led to about 50 percent of patients going without rescue injections.[8]

In nAMD, Part B of the Phase II ENVISION study (n=51, NCT05275205) enrolled patients who had failed on previous anti-VEGF therapy. Patients switched from aflibercept every eight weeks to a combination of aflibercept and UBX1325 at week 24 maintained vision gains achieved with aflibercept alone through week 48. In the UBX1325 monotherapy arm, patients maintained VA for the duration of the study. Forty percent of UBX1325 patients didn't need anti-VEGF rescue through 48 weeks and 64 percent achieved an anti-VEGF treatment-free period of over 24 weeks.

Umedaptanib pegol (formerly RBM-007, Ribomic)

Umedaptanib pegol is an anti-fibroblast growth factor-2 aptamer that's the focus of four clinical trials in nAMD: the Phase I SUSHI trial (n=9, NCT03633084);[9] and three Phase II trials (TOFU, n=94, NCT04200248; RAMEN, n=40, NCT04640272; and TEMPURA, n=5, NCT04895293). TOFU evaluated intravitreal umedaptanib pegol monotherapy and combination therapy with aflibercept alongside aflibercept monotherapy.[10]

RAMEN is an extension study of TOFU subjects who received four monthly umedaptanib pegol injections. While the studies demonstrated safety and what Ribomic describes as "striking" improvements in BCVA and anatomy in some treatment-naive patients, umedaptanib pegol showed no added benefit either alone or in combination with aflibercept. The company says it needs to evaluate umedaptanib pegol in early nAMD and alongside anti-VEGF agents.

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Investigative therapies for inherited retinal disease

NEW: 4D-110 (4D Molecular Therapeutics)

4D-110 is a CHM transgene insert using the proprietary vector 4D-R100, which is designed to provide targeted delivery via intravitreal administration and to transduce all retinal layers. The dose-escalation Phase I CHORUS study (n=13, NCT04483440) in patients with choroideremia is ongoing, with completion estimated in 2027.

4D-125 (4D Molecular Therapeutics)

4D-125 is designed to deliver a functional copy of the retinitis pigmentosa GTPase regulator (*RPGR*) gene to retina photoreceptors. The Phase I/II EXCEL study (n=21, NCT04517149) in x-linked retinitis pigmentosa (XLRP) completed enrollment, but the enrollment target is half of what it was last year. Full study completion is anticipated in 2029.

NEW: ACDN-01 (Ascidian Therapeutics)

Ascidian describes this as the "first-ever" clinical-stage RNA exon editor and the only therapy targeting the genetic cause of Stargardt disease. The U.S. Food and Drug Administration approved an investigational new drug (IND) application and granted it fast track designation. Ascadian says it expects to open enrollment in a Phase I/II trial in Stargardt and other *ABCA4* retinopathies in the first half of the year.

AGTC-501/rAAV2tYF-GRK1-RPGR (Beacon Therapeutics)

This recombinant adeno-associated viral (AAV) vector-based therapy targets mutations in the *RPGR* gene. The Phase I/II SKYLINE trial (n=42, NCT03316560) is continuing to recruit patients, with completion set for 2026. A Phase II/III VISTA trial evaluating the vector is still planned but isn't yet recruiting (n=63, NCTO4850118). Syncona last year acquired Applied Genetic Technologies Corp. and folded it into Beacon Therapeutics.

ATSN-101 (formerly SAR439483, Atsena Therapeutics)

ATSN-101is a subretinally administered AAV-based therapy for Leber congenital amaurosis caused by biallelic mutations in the *GUCY2D* gene. Twelve-month data from the Phase I/II trial (n=15, NCT03920007) found no serious treatment-emergent adverse events.

In high-dose patients, the mean change from baseline in dark-adapted full-field stimulus testing (white stimulus) was greater than in untreated eyes. Some patients exhibited more than 10,000-fold improvements in retinal sensitivity. Study completion is due in 2027. The FDA early this year granted ATSN-101 rare pediatric disease designation.

NEW: ATSN-201 (Atsena Therapeutics)

As Atsena explains it, ATSN-201 "leverages" the novel spreading capsid AAV.SPR, facilitating delivery of *RS1* to photoreceptors in the fovea. Preclinical studies demonstrated that AAV.SPR promotes transgene expression beyond the subretinal injection bleb margins.

The company last year opened recruitment in the Phase I/II LIGHTHOUSE trial (n=18, NCT05878860) in *RS1*-associated XLRP. Completion is set for 2029.

Botaretigene sparoparvovec/AAV-RPGR (MeiraGTx Holdings/Janssen Pharmaceutical Cos.)

Through a one-time administration, the vector otherwise known as bota-vec aims to deliver functional copies of the *RPGR* gene that may counteract the loss of retinal cells in RPGR-associated XLRP. The Phase III LUMEOS trial (n=97, NCT04671433) is still recruiting. Bota-vec has been granted FDA fast track and orphan drug designations. Completion of the LUMEOS trial is anticipated for 2025.

EA-2353 (Endogena Therapeutics)

This is a small molecule agent that selectively activates endogenous retinal stem and progenitor cells that differentiate into photoreceptors. The company completed enrollment last year in the Phase I/IIa trial in retinitis pigmentosa (n=14, NCT05392751). Study completion is set for 2025.

Emixustat (Kubota Vision)

Emixustat is a once-daily oral tablet that aims to inhibit RPE protein 65 (*RPE65*). Two-year results from the Phase III trial in Stargardt disease (n=194, NCT03772665) demonstrated no clinically significant change in total area of macular atrophy measured with fundus autofluorescence between the treated and placebo arms. Kubota still lists the program on its website.

FT-001 (Frontera Therapeutics)

FT-001 is an AAV gene therapy administered by a one-time subretinal injection that aims to deliver a functional copy of the *RPE65* gene. Frontera last year initiated a Phase II trial (n=9, NCT05858983) in patients with biallelic *RPE65* mutation-associated

Investigative device-based therapies

NEW: OcuLenz (Ocutrx Technologies). This augmented-reality headset is set for commercial release in the first half of the year. Designed to be lightweight and user-friendly, according to Ocutrx, the device overlays high-contrast, pixel-manipulated images onto the user's remaining viable field of view. It has 2,500 resolution per eye and a field of view 60 x 40 x 72 degrees horizontally, vertically and diagonally. A Qualcomm Snapdragon XR2 processor powers the device, and it has Wi-Fi and cellular connectivity.

Prima (Pixium Vision). This intraocular implant consists of a photovoltaic subretinal prosthesis for patients with vision loss from atrophic dry age-related macular degeneration. The first in-human study (n=5, NCT03392324) demonstrated the feasibility of implanting the device, with no participants reporting reduction of natural peripheral visual function after 48 months. Pixium says it expects to report full data this year from the PRIMAvera trial (n=38, NCT04676854), its European pivotal study.

SING IMT (Samsara Vision). It stands for smaller-incision, new-generation, implantable miniature telescope, a 10.8-mm telescope implanted in the eye through a small incision similar to cataract surgery. The prospective CONCERTO study (n=125, NCT05438732) of older adults living with stable, bilateral central scotomas due to late-stage AMD and fovea-involving geographic atrophy or disciform scar is set for completion this year. A postmarket European study in late-stage AMD (n=76, NCT04796545) is currently recruiting.

Valeda Light Delivery System (LumiThera). Valeda is a photobiomodulation (PBM) treatment platform. LumiThera has filed a *de novo* request with the U.S. Food and Drug Administration to reclassify Valeda as a Class II device. LumiThera submitted to the FDA data from the LIGHTSITE III trial in dry AMD (n=96, NCT04065490), which showed statistically significant improvement in best-corrected visual acuity at 13 months in the PBM group vs. sham. The data were part of the FDA premarket approval application filed last year.

However, after the FDA reviewed the application, LumiThera determined the best path to market would be the *de novo* route to reclassify the device as a Class II device, which shortens the review time to 150 vs. 180 days. LumiThera last year launched a clinical registry study, EUROLIGHT, to evaluate outcomes on up to 1,000 patients who had previous PBM therapy.

Device (Manufacturer)	Description	Indication	Status
NEW: OcuLenz (Ocutrx Technologies)	Augmented-reality headset.	Retinal disease	Commercial release due by July.
Prima (Pixium Vision)	Implantable phovoltaic vision system	Geographic atrophy	U.S. feasibility study (n=5) found no loss of vision at 48 months. Data due this year from European pivotal trial (n=358).
SING IMG (Samsara Vision)	Implantable miniature telescope	Late-stage age-related macular degeneration.	Prospective trial (n=125) due for completion. Postmarket European study (n=76) recruiting.
Valeda Light Delivery System (LumiThera)	Light-delivery system using photobiomodulation	Dry AMD	Premarket application pulled. Device reclassified as Class II device for regulatory review purposes.

retinal dystrophy. The study is being conducted in China.

NEW: FT-002 (Frontera Therapeutics)

FT-002 is an intraocular injection of recombinant AAV virus carrying the gene that expresses active functional proteins and repairs damaged retinal cells. Frontera last year dosed the first patient in a Phase I XLRP trial (n=18, NCT05874310). Completion is set for 2027.

Glideuretinol (formerly ALK-001, Alkeus Pharmaceuticals)

Glideuretinol is an oral modified form of vitamin A designed to significantly reduce the propensity of vitamin A dimerization, the process by which molecules bind together to form a dimer, and build up byproducts and lipofuscin in the retina. Results from the Phase II TEASE-1 trial in Stargardt disease (n=140, NCT02402660) demonstrated glideuretinal slowed the growth of atrophic lesions 21 to 28 percent.[1] Completion is scheduled for 2025.

Alkeus reported early results from an open-label extension trial known as TEASE-3 (n=140, NCT 04239625) in early stage Stargardt demonstrated the first three teenage patients were asymptomatic and free of disease progression for two to six years.

jCell (jCyte, Santen)

jCell is an intravitreal injection of human retinal progenitor (hRPC) cells that aims to preserve or potentially restore some vision in RP and related conditions. A Phase II trial evaluating the safety of repeat injections in adults with RP (n=30, NCT04604899) posted results last year. This study used the 6 x 10^6 vector genes per eye (vg/eye) dose. Half of patients had some type of treatment-related adverse event, two of which (6.7 percent) were serious.

Lumevoq/GS010 (GenSight Biologics)

Lenadogene nolparvovec is another name for this candidate, a single intravitreal injection of rAAV2/2-*ND4* for patients with Leber congenital optic neuropathy due to a mutated *ND4* mitochondrial gene. A real-world study last year (n=63) confirmed efficacy and safety in patients a year or more after the injection. Mean BCVA in all eyes increased on average by 22.5 Early Treatment Diabetic Retinopathy

Study letters.[2]

The European Medicines Agency last year signed off on a new Phase III control-vs.-sham trial, called RECOVER. GenSight says it will also engage with the FDA regarding RECOVER. The trial hasn't yet been posted on ClnicalTrials.gov. Results from the Phase III RESCUE trial (n=39, NCT02652767), posted in 2022, showed sustained VA improvement in treated patients.

MCO-010 (Nanoscope Therapeutics)

The MCO platform is designed to deliver light-sensitive multicharacteristic opsins into retina cells. Nanoscope is due this year to complete the Phase IIb RESTORE trial in RP (n=27, NCT04945772). One-year data from the STARLIGHT Phase II trial in Stargardt disease (n=6, NCT05417126) reported that two of three patients with the macular phenotype had a 3-line BCVA improvement, and that the treatment was well-tolerated without any serious adverse events.[3]

Two observational, long-term follow-up studies were initiated last year, both enrolling by invitation only: in RP (n=18, NCT06162585); and Stargardt disease (n=6, NCT048185).

OCU400/AAV-NR2E3 (Ocugen)

OCU400 is a modified gene therapy that targets nuclear hormone receptors (NRH) for RP associated with mutations in the *Nr2e3* gene and rhodopsin, and LCA with mutations in the *CEP290* gene. The FDA granted regenerative medicine advanced therapy designation for the RP indication. Ocugen also says it "received alignment" from the FDA on key pieces of the Phase III trial design. A Phase I/II trial for both indications is recruiting (n=124, NCT05203939).

Ocugen obtained FDA approval last year to enroll pediatric patients in the trial. Early trial results demonstrated a favorable safety and tolerability profile so far, the company reports. Enrollment is expected to conclude this year.

NEW: OCU410 (Ocugen)

OCU410 uses an AAV delivery platform for the retinal delivery of the *RORA* (ROR Related Orphan Receptor A) gene. The FDA last year granted orphan drug designation for treatment of ABCA4-associated retinopathies, including Stargardt disease, RP 19 and cone-rod dystrophy 3 (CORD3), but the trial isn't registered yet. OCU410 is also the focus of a clinical trial in dry AMD.

OPGx-001/OPGx-LCA5 (Opus Genetics)

OPGx-001 is a subretinal AAV-8 vector designed to precisely deliver a functional *LCA5* gene to retinal photoreceptors. The first patient was dosed in a Phase I/II trial in patients with LCA resulting from biallelic mutations in the *LCA5* gene (n=9, NCT05616793). The trial is due for completion in 2027.

Sepofarsen/QR-110 (Laboratoires Théa)

This RNA therapy is indicated for LCA10 due to the c.2991+1655A>G mutation in the *CEP290* gene. Théa last year acquired the rights from ProQR, canceled the transaction, then came back and closed the deal in December. Théa says it will continue development.

ProQR reported in 2022 that the Phase II/III ILLUMINATE trial (n=36, NCT03913143) failed to meet its primary endpoint of improved best-corrected visual acuity. The Phase II/III BRIGHTEN trial in children with LCA10 caused by mutations in the *CEP290* gene (n=15, NCT04855045) is still listed as recruiting, but no update has been posted since March 2022.

Tinlarebant/LBS-008 (Belite Bio)

Tinlarebant is an oral therapy that aims to reduce the accumulation of vitamin A-based toxins, known as bisretinoids, that contribute to retinal pathology in Stargardt disease. Two-year results from the Phase Ib/II study in adolescent patients with STGD1 (n=13, NCT05266014) demonstrated sustained lower decreased autofluorescence lesion growth as well as stabilized VA in a majority of patients.[4] Belite Bio last year completed recruitment in the Phase III DRAGON trial (n=104, NCT05244304) in STGD1. Completion is anticipated in 2025.

NEW: SPVN06 (SparingVision)

SparingVision describes SPVN06 as a mutation-agnostic, AAV gene therapy composed of one neurotrophic factor (rod-derived cone viability factor, RdCVF) and one oxidative stress-reducing enzyme (RdCVF long form), designed to act together to slow or stop the degeneration of photoreceptors.

Initial safety data from the first three-patient cohort treated in the Phase I/II PRODYGY trial in RP (n=33, NCT05748873) demonstrated a favorable safety profile, SparingVision reports. The trial is scheduled for completion in 2029. SparingVision is also developing a preclinical candidate for RP, SPVN20. RS

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The long-term impact of anti-VEGF therapy for DME

A review of real-world evidence that examines the extended effectiveness of treatment.

By Lucie Y. Guo, MD, PhD, and Theodore Leng, MD, MS

Lucie Y. Guo, MD, PhD

Theodore Leng, MD, MS

Take-home points

- Anti-VEGF medications have been highly effective in clinical trials for improving vision in diabetic macular edema.
- In real-world settings, patients receive injections less frequently than in clinical trials.
- Real-world studies have reported smaller gains in vision than clinical trials.
- Real-world data highlight racial and socioeconomic disparities in the usage and outcome of anti-VEGF therapy.

Diabetic macular edema is the principal cause of vision loss in individuals with diabetic retinopathy, presenting a growing public health challenge in the context of increasing diabetes prevalence. Factors like prolonged diabetes duration, inadequate blood glucose control, and persistently elevated hemoglobin A1c levels raise the risk of DME. Of course, clinical trials have shown the promise of various anti-VEGF therapies in conserving visual acuity for DME patients. Here, we delve into the real-world insights that examine the extended effectiveness of anti-VEGF agents in treating DME.

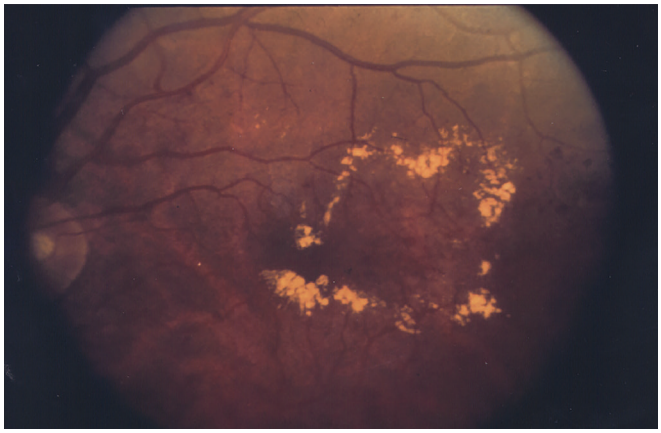

Figure 1. Diabetic macular edema prior to treatment. *(National Eye Institute Media Library)*

Smaller vision gains

Real-world studies have shown that patients with DME (*Figure 1*) exhibit long-term visual acuity gains (*Table, page 34*). However, the magnitude of such vision gains is much smaller compared to randomized clinical trials. The landmark DRCR Retina Network Protocol T trial showed marked visual acuity improvement with all three anti-VEGF agents—+13.3, +9.7 and +11.2 letters at one year with aflibercept, bevacizumab and ranibizumab, respectively.[3] The improvement was greatest with aflibercept (Eylea, Regen-

Bios

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DISCLOSURES: Dr. Guo has no relevant relationships to disclose.

Dr. Leng is a consultant to Genentech/Roche.

eron Pharmaceuticals), with a statistically significant mean difference of 2 to 3 letters at one year.

Nancy Holekamp, MD, and colleagues examined 110 patients (121 study eyes) initiating intravitreal ranibizumab (Lucentis, Genentech/Roche) or bevacizumab (Avastin, Genentech/Roche) for DME and showed a mean corrected visual acuity change of only +4.7 letters at one year.[1]

In a larger retrospective study, Thomas Ciulla, MD, and colleagues examined 28,658 eyes of treatment-naive patients with DME using a database. Baseline visual acuity was 59.2 letters (20/60 Snellen equivalent) and improved by 4.2 letters at one year.[2] They noted the mean one-year VA improvement was greater in patients who had more anti-VEGF injections and in patients with lower baseline VAs, with likely contribution from ceiling effects related to baseline visual acuity.

The VA improvement in this population didn't significantly differ among the different anti-VEGF agents—+4.3, +4.5 and +3.4 letters at one year with aflibercept, bevacizumab and ranibizumab, respectively.

Real-world studies with longer follow-up showed even smaller gains in vision improvement. More recently, our group conducted an unpublished retrospective study among treatment-naive patients with DME, following treatment patterns and VA for up to six years of follow-up. At one year after anti-VEGF initiation, eyes gained a mean of +3.2 letters of vision; by six years, the mean gain was only +0.5 letters.

Fewer injections in the real world

The DRCR Retina Network Protocol T study employed a protocol-specific algorithm with a mean of nine to 10 injections of aflibercept, bevacizumab and ranibizumab, respectively, at one year. After the clinical trial ended, the frequency of office visits and anti-VEGF injections declined.[3]

Multiple studies using real-world data have now shown that frequency of ophthalmology visits and injections are lower than that in clinical trials, highlighting the treatment burden of frequent intravitreal injections in patients with diabetic macular edema. In the study Dr. Ciulla led, the lower treatment intensity of six to seven injections at one year suggested that physicians are using personalized treatment plans, such as as-needed or treat-and-extend regimens, to decrease treatment burden.

This lower injection frequency likely contributes to the smaller VA improvements in the real world than in clinical trials. Our group's study, which stratified VA outcomes by the average number of injections per year, found a +2.8 ETDRS letter improvement in those receiving one to two injections compared to +4.8 letters in those who received more than 11 injections in the first year.

This trend was consistent in subsequent years. In the long-term, patients who received five or more injections didn't experience a best-corrected VA loss from baseline after six years of follow-up, whereas patients who received fewer than four injections a year did.

Socioeconomic disparities

Real-world data has highlighted that significant disparities in anti-VEGF use and outcomes

Outcomes of real-world studies of anti-VEGF treatment in diabetic macular edema

Study/n value (eyes)	Mean BCVA change (letters)	Patients gaining ≥10 letters	Patients losing ≥10 letters
Holekamp et al (121)[1]	One-year change: +4.7 (ranibizumab or bevacizumab)	One year: 31.4%	One year: 10.8%
Ciulla et al (28,658)[2]	One-year change: +4.3 (aflibercept) +4.5 (bevacizumab) +3.4 (ranibizumab)	NA	NA
DRCR one-year results (218)[9]	One-year change: +13.3 (aflibercept) +9.7 (bevacizumab) +11.2 (ranibizumab)	One year: 79% (aflibercept) 61% (bevacizumab) 70% (ranibizumab)	One year: 1% (aflibercept) 4% (bevacizumab) 2% (ranibizumab)
Glassman et al; DRCR Retina Network five-year results (317)[3]	Five-year change: +8.0 (aflibercept) +6.6 (bevacizumab) +7.6 (ranibizumab)	Five years: 47% (aflibercept) 48% (bevacizumab) 47% (ranibizumab)	Five years: 11% (aflibercept) 10% (bevacizumab) 9% (ranibizumab)

depend on patient demographics and insurance coverage. A retrospective study using the IRIS Registry of more than 200,000 patients showed that white race, non-Hispanic/Latino ethnicity and private insurance were correlated with both higher use of anti-VEGF injections as well as higher longitudinal VA across 60 months of follow-up.[4]

Multiple possible explanations exist for such disparities in outcomes. One is the potential differences in characteristics and severity of biological disease among heterogeneous populations. In a study using National Health and Nutrition Examination Survey data, the risk of diabetic retinopathy (*Figure 2*) was higher in Hispanic/Latino patients, even after adjusting for independent variables such as severity of diabetes (duration, hemoglobin A1c level, insulin and oral agent use) and systolic blood pressure.[5]

Another contributor may be access to care and adherence to clinic visits. Compared to patients with neovascular macular degeneration, patients with DME have been noted to have higher rates of nonadherence or appointment cancellation,[6,7] possibly related to the presence of additional comorbidities in DME patients. A retrospective study of more than 2,000 DME patients found loss to follow-up—defined as no office visits within 12 months after an intravitreal injection—in 25.3 percent of patients.[8] Factors associated with loss to follow-up included being Hispanic and Pacific Islander, and having lower adjusted gross income.[8]

Bottom line

Real-world treatment patterns can differ significantly from clinical trial results, since the former are influenced by both personalized treatment patterns based on provider clinical decision, as well as patient's adherence to clinic visits and treatment. So far, real-world results have shown that the frequency of injections as well as improvement in visual acuity with anti-VEGF medications is inferior to that shown in clinical trials.

The real-world evidence highlights how the high treatment burden of diabetes significantly impacts patients' lives. Adherence to therapy is influenced by costs, time constraints, accessibility to care and patient perception of care. Furthermore, real world evidence shows the increasingly disparate outcomes for patients in different ethnic/racial demographic groups and those with minimal or no insurance coverage.

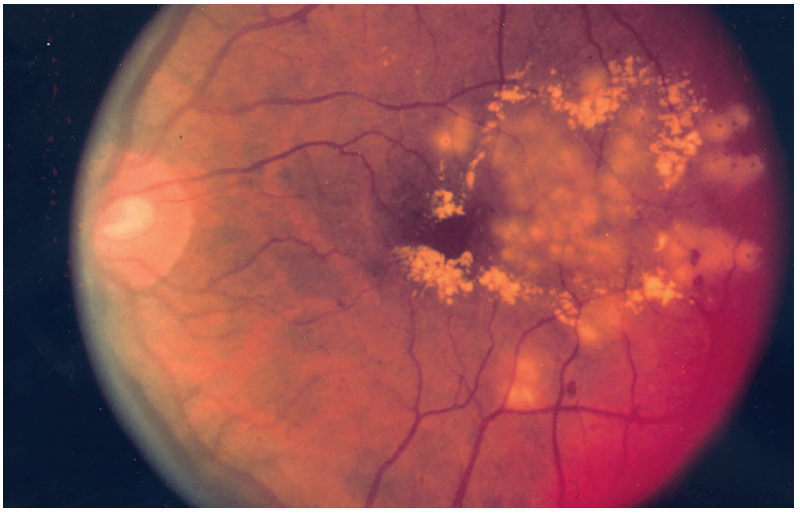

Figure 2. Fundus photo showing the effect of focal laser surgery for diabetic retinopathy. ***(National Eye Institute Media Library)***

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Vitrectomy under oil

The silicone sandwich technique for managing recurrent retinal detachments.

By Miguel Cruz Pimentel, MD, Peter J. Kertes, MD, and Efrem D. Mandelcorn, MD

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Patients with recurrent detachments secondary to proliferative vitreoretinopathy *(Figure 1)* who have already had a vitrectomy with silicone oil tamponade can benefit from vitrectomy under silicone oil.

This technique consists of placing all three trocars to allow the peeling and removal of membranes without removing the silicone oil. Different terminology has been used to describe this technique. We've previously described this as the silicone sandwich technique.

As a modification of the original interface vitrectomy technique, instead of placing two trocars, cannula and fluid-silicone drainage, we prefer to place three trocars and use the infusion connected to air but clamped, as Peter Kertes, MD, and Gholam Peyman, MD, described in 1997[1] and Tarun Sharma, MD, in 2002.[2]

Achieving drainage

You can achieve drainage of the subretinal fluid by increasing the pressure of the infusion connected to air. The efflux of subretinal fluid can be boosted and a combination of passive and active drainage of subretinal fluid can be used.[1,2,]

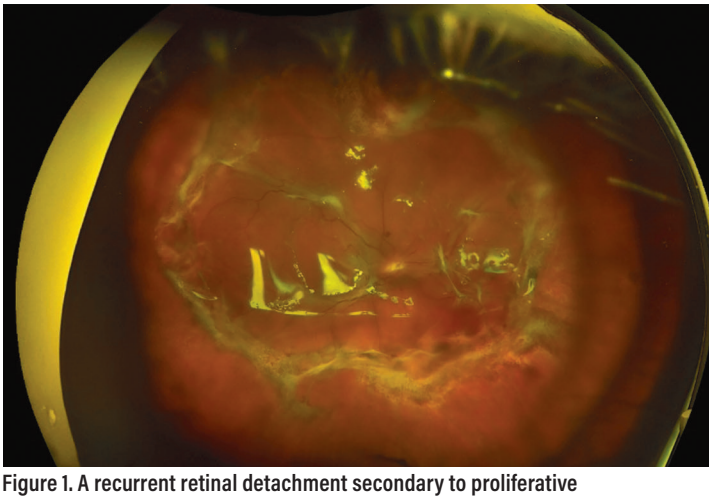
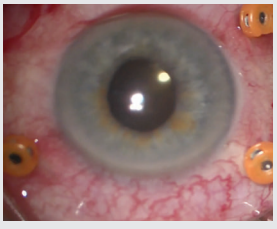


Figure 1. A recurrent retinal detachment secondary to proliferative vitreoretinopathy before surgery.

View the Video

Dr. Pimentel demonstrates the silicone sandwich technique for managing recurrent retinal detachments. Scan the QR code or go to: https://bit.ly/VideoPearl-38.



After trocars are placed, the silicone oil can act as a third hand for peeling the membranes tangentially. It's important to note that the appearance of the retina and the membranes under silicone oil are different than when viewed under fluid. Take caution to avoid iatrogenic breaks by carefully grasping and remaining tangential to the retina.

Diathermy can be used to mark the breaks, and drainage of the subretinal fluid can best be achieved by using active fluid extrusion with a blunt tip cannula. At this step, it's essential to unclamp the air infusion using a snap, which allows the air to go in and promotes more complete fluid drainage, because this increases intraocular pressure and pushes the retina back into place. The air bubble enhances visualization.[2,3] Alternatively, the drainage can be done without using the air, and with just using the silicone oil as the infusion and topping up as you go to keep the eye inflated.

With retinal reattachment, laser retinopexy can be applied, and the laser can also be used to

BIOS

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DISCLOSURES: The authors and Dr. Felfeli have no relevant disclosures.

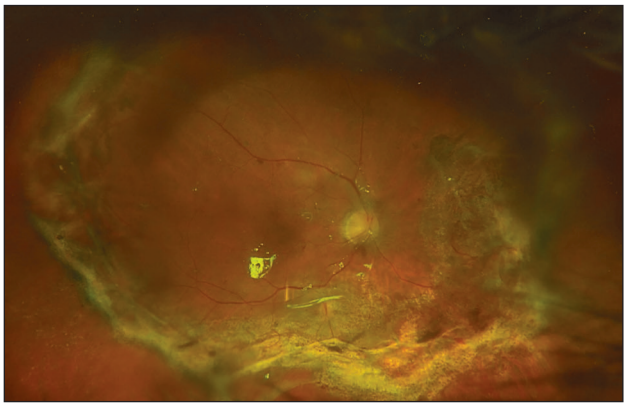

Figure 2. The same recurrent retinal detachment from Fig. 1, secondary to proliferative vitreoretinopathy after surgery.

help ascertain if the subretinal fluid has been drained adequately.

At the end of the surgery, vent the air, reduce the air infusion pressure and supplement the silicone oil fill because some silicone is always lost during the surgery due to inserting and removing the instruments, removing membranes and draining the subretinal fluid (*Figure 2*). We believe that this technique works because infusing air pushes silicon oil onto the retinal surface, creating more tension, which allows for drainage.

Timing of surgery

The timing of this surgery is important and a key to its success. It's best to intervene only when the PVR is significant enough to easily see and peel. This will ensure that the traction that's present can be relieved and the retina reattached. In some cases, despite peeling all that can be seen, the retina remains foreshortened and a relaxing retinotomy is necessary.

Bottom line

This technique has many advantages.[3] It can be done efficiently and minimizes undue manipulation of the retina. It rarely causes progression of the detachment that's present in the same way that removal and replacement of the silicone oil would. As a result, this too will limit liberation of retinal pigment epithelium cells and decrease the risk of recurrent PVR and recurrent detachment.

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AD Drugs and AMD

(Continued from page 7)

confound the results," they concluded.

Ultimately, this study bolsters the body of literature demonstrating the secondary benefits of AChEIs which may play a significant role in treatment decisions for Alzheimer's patients.

"Our research team has a dedicated focus on age-related macular degeneration," Mr. Magagnoli says. [Jayakrishna Ambati, MD] leads the efforts to unravel the molecular basis of macular degeneration with preclinical research examining inflammation. In this manuscript, our exploration of inflammation, coupled with the potential of AChEIs to impact inflammation, guided our hypothesis. The outcomes of our study reveal a potential correlation between AChEIs' anti-inflammatory properties and their ability to reduce AMD incidence. We were excited that our findings supported our hypothesis. Based on our preclinical research regarding inflammatory pathogenesis of AMD, AChEI medications could offer some protection against neuroinflammation.

"Although our study examined class-wide associations of AChEI use, future investigations could explore the effects of individual drugs within this class," Mr. Magagnoli adds. "Understanding how these medications may prevent AMD through mechanisms such as inflammation modulation requires further exploration. A randomized control trial would be needed to evaluate the clinical relevance of this pathway for AMD. There is an ongoing trial of an inflammasome inhibitor in geographic atrophy (NCT06164587)."

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Social Media Spring Cleaning for 2024

Spring cleaning is nearly here, so be prepared to organize all the clutter on those social media profiles.

By Jayanth Sridhar, MD

We're fully into the swing of things in 2024. Spring brings warmer temperatures, melting ice, blooming flowers and, yes, the prospect of spring cleaning. While for many, spring cleaning is confined to the home, for social media-savvy ophthalmologists, it's a great opportunity to focus on sprucing up those digital profiles. Here are your top five action items for "spring cleaning" your social media and online profiles:

• ***Update your LinkedIn professional details:*** Retinal specialists hoping to leverage their social media presence into consulting, speaking and/or clinical opportunities should have a well-maintained LinkedIn account. Blow the cobwebs off your account and make sure it still makes sense. While your educational background may not have changed, your professional photo should be recent, well-illuminated, and reflective of your professional persona (i.e., save the Hawaiian shirt photo for your personal Facebook account). Non-medical employers, such as industry partners, will be interested in your skills, so include any prior speaking or consulting experience in the description that appears at the top of your page. Check your inbox for messages and connection invitations and try to maximize those to enhance your network. Lastly, check out your profile both on a computer and a mobile device to make sure you're happy with the appearance (it'll be slightly different between platforms).

• ***Be searchable:*** The American Society of Retinal Specialists has a public database available to both patients and doctors ("Find a Retina Specialist") where one can search for retina doctors based on geographic location/zip code. This is a good time to make sure you have a profile and, if you do, verify that your contact details are up-to-date so that referring doctors and patients can find you.

Reviews, reviews, reviews: More and more patients rely on online reviews to decide whether to see a provider. Check out the major publicly available review websites to see what feedback is out there. I would recommend checking your practice/institutional website, healthgrades.com, vitals.com and Google reviews. Any less than stellar reviews should be noted and addressed appropriately (typically by a designated representative at your practice/institution). Note the websites with the highest volume of reviews and aim to direct your 2024 patients to leave reviews there to improve your search engine optimization. Speaking of search engines …

• ***"Google me":*** Or rather, google yourself. Check out the top hits for both websites and images and make sure they jibe with your ideal professional public image. Photos from your college fraternity or sorority parties probably could be removed with an email or two to the right people. The same goes for Instagram photos tagging you on vacation in casual wear. Preventing your personal Facebook and Instagram media from being publicly searchable comes down to our last point, which is that …

• ***Privacy matters:*** Privacy settings for popular social media applications are constantly changing. On Facebook, this is a perfect time to log in to your account and toggle what is available and visible to the public, friends of friends, or just to friends. Most of these apps allow you to see your profile from the standpoint of a random searcher; check it out and make sure you would be happy if a patient or potential professional contact happened to see that same view.

With these five social media "spring cleaning" action items, you're now well-prepared for 2024 and beyond. Now, time to do the hard part: actual spring cleaning. Good luck!

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURE: Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

VABYSMO™
faricimab-svoa injection 6 mg

VABYSMO® (faricimab-svoa) injection, for intravitreal use

This is a brief summary. Before prescribing, please refer to the full Prescribing Information

1 INDICATIONS AND USAGE

VABYSMO is a vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang-2) inhibitor indicated for the treatment of patients with:

1.1 Neovascular (wet) Age-Related Macular Degeneration (nAMD)

1.2 Diabetic Macular Edema (DME)

1.3 Macular Edema Following Retinal Vein Occlusion (RVO)

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

VABYSMO is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

VABYSMO is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

VABYSMO is contraindicated in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering VABYSMO. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management *[see Dosage and Administration (2.6) and Patient Counseling Information (17)]*.

5.2 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been seen within 60 minutes of intravitreal injection, including with VABYSMO *[see Adverse Reactions (6.1)]*. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately *[see Dosage and Administration (2.6)]*.

5.3 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the VABYSMO clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept *[see Clinical Studies (14.1)]*.

The incidence of reported ATEs in the DME studies from baseline to week 100 was 5% (64 out of 1,262) in patients treated with VABYSMO compared with 5% (32 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept *[see Clinical Studies (14.3)]*.

5.4 Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO *[see Adverse Reactions (6.2)]*. Discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity *[see Contraindications (4)]*
- Endophthalmitis and retinal detachments *[see Warnings and Precautions (5.1)]*
- Increase in intraocular pressure *[see Warnings and Precautions (5.2)]*
- Thromboembolic events *[see Warnings and Precautions (5.3)]*
- Retinal Vasculitis and/or Retinal Vascular Occlusion *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to VABYSMO in 2,567 patients, which constituted the safety population in six Phase 3 studies *[see Clinical Studies (14.1, 14.2, 14.3)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO			Active Control (aflibercept)		
	AMD N=664	DME N=1,262	RVO N=641	AMD N=662	DME N=625	RVO N=635
Cataract	3%	15%	< 1%	2%	12%	1%
Conjunctival hemorrhage	7%	8%	3%	8%	7%	4%
Vitreous detachment	3%	5%	2%	3%	4%	2%
Vitreous floaters	3%	4%	2%	2%	3%	2%
Retinal pigment epithelial tear[a]	3%			1%		
Intraocular pressure increased	3%	4%	1%	2%	3%	3%
Eye pain	3%	3%	< 1%	3%	3%	< 1%
Intraocular inflammation[b]	2%	1%	1%	1%	1%	< 1%
Eye irritation	1%	< 1%	< 1%	< 1%	1%	< 1%
Lacrimation increased	1%	1%	0%	1%	< 1%	< 1%
Ocular discomfort	1%	1%	< 1%	< 1%	< 1%	< 1%

[a]AMD only
[b]Including iridocyclitis, iritis, uveitis, vitritis

Less common adverse reactions reported in < 1% of the patients treated with VABYSMO were corneal abrasion, eye pruritus, ocular hyperemia, blurred vision, sensation of foreign body, endophthalmitis, conjunctival hyperaemia, visual acuity reduced, visual acuity reduced transiently, vitreous hemorrhage, retinal tear and rhegmatogenous retinal detachment.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of VABYSMO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of VABYSMO administration in pregnant women.

Administration of VABYSMO to pregnant monkeys throughout the period of organogenesis resulted in an increased incidence of abortions at intravenous (IV) doses 158 times the human exposure (based on C_{max}) of the maximum recommended human dose *[see Animal Data]*. Based on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk to female reproductive capacity, and to embryo-fetal development. VABYSMO should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

An embryo fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received 5 weekly IV injections of VABYSMO starting on day 20 of gestation at 1 or 3 mg/kg. A non-dose dependent increase in pregnancy loss (abortions) was observed at both doses evaluated. Serum exposure (C_{max}) in pregnant monkeys at the low dose of 1 mg/kg was 158 times the human exposure at the maximum recommended intravitreal dose of 6 mg once every 4 weeks. A no observed adverse effect level (NOAEL) was not identified in this study.

8.2 Lactation

Risk Summary

There is no information regarding the presence of faricimab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.

Infertility

No studies on the effects of faricimab on human fertility have been conducted and it is not known whether faricimab can affect reproduction capacity. Based on the mechanism of action, treatment with VABYSMO may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of VABYSMO in pediatric patients have not been established.

8.5 Geriatric Use

In the six clinical studies, approximately 58% (1,496/2,571) of patients randomized to treatment with VABYSMO were ≥ 65 years of age. No significant differences in efficacy or safety of faricimab were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION

Advise patients that in the days following VABYSMO administration, patients are at risk of developing endophthalmitis. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise the patient to seek immediate care from an ophthalmologist *[see Warnings and Precautions (5)]*.

Patients may experience temporary visual disturbances after an intravitreal injection with VABYSMO and the associated eye examinations *[see Adverse Reactions (6)]*. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

VABYSMO® [faricimab-svoa]
Manufactured by:
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***Primary endpoint** of **non-inferiority** vs aflibercept 2 mg in the mean change from baseline in BCVA was measured by the **ETDRS letter** score and **tested** using a margin **of 4 letters. nAMD: VABYSMO met its primary** endpoint of non-inferiority at year 1 **(avg. of weeks** 40, 44, and 48). Differences **in LS means for** VABYSMO were **+0.7 letters (CI:** [95%] **-1.1, +2.5) in TENAYA**; and 0.0 letters (CI: [95%] -1.7, +1.8) **in** LUCERNE. **DME:** VABYSMO met its primary endpoint **of non-inferiority at year 1 (avg.** of **weeks 48, 52, and** 56). Differences **in LS means in YOSEMITE were** +0.7 **letters (CI**: [97.5%] **-1.1**, +2.5) for VABYSMO Q4W–Q16W **and -0.2 letters** (CI: [97.5%] **-2.0, +1.6)** for VABYSMO **Q8W. Differences** in **LS means** in **RHINE** were **+0.5 letters (CI**: [97.5%] **-1.1, +2.1)** for VABYSMO Q4W–Q16W and +1.5 **letters (CI: [97.5%] -0.1, +3.2) for VABYSMO Q8W. A non-inferiority margin** was **not available for** year 2. **RVO:** VABYSMO met its **primary endpoint** of non-inferiority at week 24. Differences **in LS means** for VABYSMO were **-0.6 letters (CI: [95%] -2.2, +1.1)** in **BALATON; and** -0.4 letters **(CI: [95%] -2.5, +1.6) in COMINO.**[1]

†nAMD: 4 **monthly loading** doses **followed by OCT and** visual acuity evaluations 8 and 12 **weeks later to inform** Q16W **(weeks 28 and 44)**, Q12W **(weeks 24, 36, and 48)**, Q8W **(weeks** 20, **28,** 36, and **44)**, or **Q4W** (no **added benefit) dosing. DME:** at least 4 monthly **loading doses followed by extensions ≤4 weeks or reductions ≤8 weeks based on OCT and visual** acuity **evaluations OR 6 monthly loading doses followed by** Q8W. Q4W dosing may be **needed** (no **added benefit). RVO:** every **month (4 weeks) for 6 months.**[1]

INDICATIONS

VABYSMO **(faricimab-svoa) is a** vascular **endothelial growth factor (VEGF) inhibitor** and **angiopoietin-2 (Ang-2) inhibitor indicated for the treatment of patients with** Neovascular **(Wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Macular Edema following** Retinal **Vein Occlusion** (RVO).

IMPORTANT SAFETY INFORMATION

Contraindications
VABYSMO **is contraindicated in patients with ocular or periocular infection, in** patients with active **intraocular inflammation,** and in **patients with known hypersensitivity to faricimab or any of the excipients** in VABYSMO. **Hypersensitivity reactions** may **manifest as rash,** pruritus, **urticaria, erythema,** or **severe intraocular inflammation.**

Warnings and Precautions
Endophthalmitis and Retinal Detachments
Intravitreal injections have been associated with endophthalmitis and retinal **detachments.** Proper aseptic injection techniques **must always be used when administering VABYSMO.** Patients should be **instructed to report any** symptoms **suggestive of endophthalmitis or** retinal **detachment without delay, to permit prompt and appropriate management.**

Increase in Intraocular Pressure
Transient increases in Intraocular **pressure (IOP) have been** seen **within 60 minutes of intravitreal injection, including with VABYSMO. IOP and the perfusion of the optic nerve head should be monitored and managed appropriately.**

Thromboembolic Events
Although there was a low rate of arterial thromboembolic events (ATEs) observed in **the VABYSMO clinical trials,** there is **a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are** defined as **nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).**

The incidence of reported ATEs in the nAMD studies during the first year was 1% (7 out of 664) in patients treated with VABYSMO compared with 1% (6 out of 662) in patients treated with aflibercept.

The **Incidence of reported** ATEs in the DME **studies from baseline** to week 100 **was 5% (64 out of 1,262)** in **patients treated with** VABYSMO **compared with** 5% (32 out of 625) **in patients treated with** aflibercept.

The incidence of reported ATEs in the RVO studies during the first 6 months was 1.1% (7 out of 641) in patients treated with VABYSMO compared with 1.4% (9 out of 635) in patients treated with aflibercept.

Retinal Vasculitis and/or Retinal Vascular Occlusion
Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of VABYSMO. Healthcare providers should discontinue treatment with VABYSMO in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Adverse Reactions
The most common adverse reactions (≥5%) reported in patients receiving VABYSMO were cataract (15%) and conjunctival hemorrhage (8%).

Pregnancy, Lactation, Females and Males of Reproductive Potential
Based **on the mechanism of action of VEGF and Ang-2 inhibitors, there is a potential risk** to **female reproductive capacity, and to embryo-fetal development.** VABYSMO **should not be used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VABYSMO and any potential adverse effects on the breastfed child from VABYSMO. Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment and for at least 3 months following the last dose of VABYSMO.**

You may report side effects to the FDA at (800) FDA-1088 or **www.fda.gov/medwatch.**
You may also report side **effects** to Genentech **at (888) 835-2555.**

Please see additional Important Safety Information in the full VABYSMO Prescribing Information.

References: 1. VABYSMO **[package insert]. South San** Francisco, **CA: Genentech,** Inc; 2023.

BCVA=best corrected visual acuity; CI=confidence interval; ETDRS=Early Treatment Diabetic Retinopathy **Study; LS=least squares; OCT=optical coherence tomography; Q4W**=every 4 **weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.**

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