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RETINA SPECIALIST

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Sixth Annual Pipeline Report

2023: THE YEAR OF GEOGRAPHIC ATROPHY

A comprehensive look at 87 investigative programs in retina.

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Also Inside

Online Video

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- EYLEA is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) 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), and Diabetic Retinopathy (DR).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

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

03/2021
EYL.21.02.0019

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor 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).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity
EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure
Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- 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)*]

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 other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal 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 EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or 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 and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug 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, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

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 after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use
The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use
In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION
In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].
Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
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Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

EDITORIAL

By Charles C. Wykoff, MD, PhD

Leave some work for tomorrow

On a winter evening as a young attending, I was descending in the parking garage elevator. A much older physician smiled at me, nodded and said with a perceptive smile, "Did you leave some work for tomorrow?"

I don't remember what was on my mind. I was probably stewing over patients and thinking about my manuscripts and research projects behind schedule. His implications were spot on.

Work, especially work as a retina specialist, can be incredibly fulfilling and rewarding. We are clinicians, surgeons, researchers and innovators focused on restoring and preserving humanity's most valued sense.

With the pending pegcetacoplan Prescription Drug User Fee Act action date of February 26, we're likely on the verge of having the first approved therapy for geographic atrophy. Following that anticipated approval, our field will break into a new era. But, our work will not be done. While I believe clinically meaningful, through two years in the pivotal Phase III OAKS and DERBY trials, monthly pegcetacoplan slowed GA lesion growth by just 19 to 22 percent.

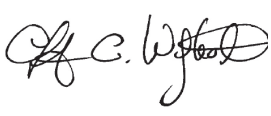
We have much work to do toward educating referring doctors and patients about realistic expectations with this new therapy, defining which patients will benefit most from treatment in the short- and long-term, and accelerating development of next-generation therapies that can be used in combination or as monotherapies with greater durability and efficacy.

Even with work such as this, infused with tremendous meaning, we must balance it with play. Burnout is real. Recent data suggest that more than 30 percent of retina specialists may deserve this label.[1]

One of our challenges is the underappreciated Zeigarnik effect—the ability of incomplete tasks to dominate our attention. In *Cal Newport's Deep Work: Rules for Focused Success in a Distracted World*, one solution he presents is use of a shutdown ritual daily to facilitate transition away from work for the benefit of refreshing our mind and maximizing engaging with our family and friends.

Another simple, free, effective way to decrease stress and the risk of burnout is laughter. As Natalie Dattilo MD, former director of psychology, Brigham and Women's Hospital summarized recently, "As adults, we don't laugh nearly as much as we used to. The idea that we would have fun, play, and make time for those things is often seen as a reward or something you have to earn or something you do when the work is done. But the work is never done."

Work hard? Yes, of course. But make time to intentionally unplug, hug your family, laugh and play along the way. Leave some work for tomorrow. RS



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Why are ophthalmologists a definite maybe about biosimilars? Survey provides answers

Even with the launch of the first two anti-VEGF biosimilars last year, retina specialists seem somewhat ambivalent about using these copy-cat versions of tried and true treatments, a new report based on a survey of ophthalmologists has found.

The report, titled "Special Topix: Ophthalmology Biosimilars Today and Tomorrow," is based on a survey of 80 U.S. ophthalmologists conducted in November 2022. Spherix Global Insights, a consultancy to the life sciences industry, released the report in December 2022.

Chrystal Ferguson, franchise head, ophthalmology, summarizes the key findings: "U.S. ophthalmologists are definitely open to biosimilars, in theory, at this stage, but they have reservations and concerns in practice."

The report gauged movement in ophthalmologists' attitudes toward biosimilars since a December 2021 survey, finding that while familiarity with biosimilars increased in that period, their comfort level with the clinical evidence required for approval actually declined.

Unease with 'extrapolation'

"Being on the biosimilar pathway for approval through the Food and Drug Administration allows a product to go through what's called extrapolation, which means the actual clinical trial piece can be conducted in one particular indication and then those findings are extrapolated to the other indications that the reference product is approved for," Ms. Ferguson says. "So as the ophthalmologists are learning more about this process, they are still feeling a little uneasy with that concept."

The report found that the launches of Byooviz (Biogen) and Cimerli (Coherus Biosciences), both Lucentis (ranibizumab) biosimilars, didn't have much impact on raising awareness about the treatments, according to almost half of the ophthalmologists surveyed. The vast majority of survey respondents—84 percent—were retina specialists, with the rest being general ophthalmologists.

The launch of the two biosimilars has made more ophthalmologists aware of the category, Ms. Ferguson says. "Having Byooviz and Cimerli now on the market has really enabled them to have that conversation and start to dig and to better understand what a biosimilar is and how it can help their patients," she says.

She acknowledges that retina specialists are prone to "wait and see," alluding to the experience with the launch of Beovu (brolucizumab), which Novartis pulled back on in 2020 after reports came out linking the drug to cases of ocular inflammation and vasculitis.

"The Beovu experience of a couple years ago has really sort of hindered a rapid-adoption mindset," Ms. Ferguson says. "So, I think, at this point, the fact that they are available is definitely helping to broaden the education of the community, but isn't necessarily at a point yet where it's tipping attitudes."

The allure of Eylea

An Eylea biosimilar is likely to have broader appeal, the survey found. "I think that what it comes down to is that Eylea gets wider use at this point," she says. "We've spoken to several physicians that have said, 'If there had been a Lucentis biosimilar back in the Lucentis heyday, I would've been all over it, but my Lucentis use has actually decreased over the years.'"

But even at that, ophthalmologists' knowledge about the development of Eylea biosimilars "is pretty minimal," Ms. Ferguson says. "We have surveyed the physicians on the specific aflibercept biosimilars that are in development, and there is very low awareness, very low familiarity with any specific one in development."

Another barrier to retina special-

These two haven't done much to raise awareness about biosimilars among retina specialists, a recently released market study found.

ists embracing biosimilars is that they don't know the companies sponsoring trials. "So, while that's not necessarily a primary barrier, Genentech and Regeneron, Lucentis and Eylea manufacturers, have been household names for years," she says. "So there is a little bit of a latent effect in terms of being able to rely on these unknown manufacturers as partners to the practice and to the patient."

Further along, payers will probably have a key role in driving demand for biosimilars in retina. "There's going to be a really fine line between incentivizing prescribers to use biosimilars and then also putting them off by mandating they prescribe biosimilars," Ms. Ferguson says.

What could 'shake' market

As retina biosimilars evolve, two events could "shake" the market, in her words: the 8-mg high-dose aflibercept, now in clinical trials (the Eylea biosimilars reference the 2-mg formulation); and Outlook Therapeutics' program to develop an ophthalmic formulation of Avastin, typically the first-step therapy in drug formularies. The latter has an FDA action date for possible approval in the summer. Eylea comes off patent later this year.

View the Video

Chrystal Ferguson, head, ophthalmology franchise for Spherix Global Insight, discusses ophthalmologists' attitudes about biosimilars in retina. Available at: https://bit.ly/RetSpecMag-2023-01

As more biosimilars get approved, ophthalmologists' knowledge and comfort level with them may pick up. However, the report specifically noted that most ophthalmologists are unaware that Viatris, a Mylan company, filed for an FDA review of M710/MYL-1701P, its aflibercept biosimilar. The survey found that ophthalmologists aren't likely to embrace an aflibercept biosimilar and even less likely if high-dose aflibercept gets approved.

"Having more affordable treatments is definitely a welcome thing in the ophthalmologist community, but there really just needs to be a lot more personal experience in order to be able to increase that comfort level, and there are several other things in the pipeline that could potentially change that calculus," Ms. Ferguson says.

The Spherix report is available at www.spherixglobalinsights.com.

– Richard Mark Kirkner

IN BRIEF

More than a quarter of U.S. adults age 71 and older had vision impairment in 2021, according to an analysis of the **2021 National Health and Aging Trends Study** published online in ***JAMA Ophthalmology*** (2023;doi:10.1001/jamaophthalmol.2022.5840). A higher prevalence of vision impairment was associated with older age, lower education and income, nonwhite race and Hispanic ethnicity.

The Food and Drug Administration approved the **ML6710i** photodynamic laser for equivalent use with **Visudyne** (verteporfin for injection, **Bausch + Lomb**) photodynamic therapy for treatment of predominantly classic subfoveal choroidal neovascularization due to age-related macular degeneration.

The ZETA-1 Phase II trial of **APX3330** in diabetic retinopathy didn't meet the primary endpoint of a having an unspecified percentage of patients achieve a more than two-step improvement in Diabetic Retinopathy Severity Scale at week 24, according to topline results **Ocuphire Pharma** released. However, the company says additional efficacy endpoints were "directionally favorable." Further results are due in February.

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FEATURES

SIXTH ANNUAL PIPELINE REPORT

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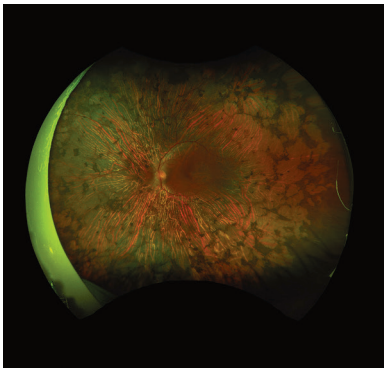

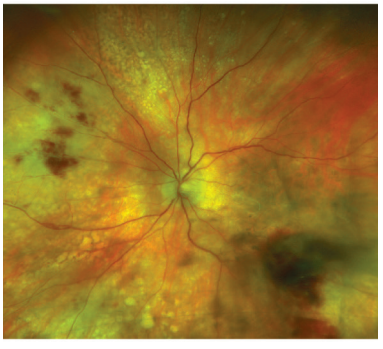

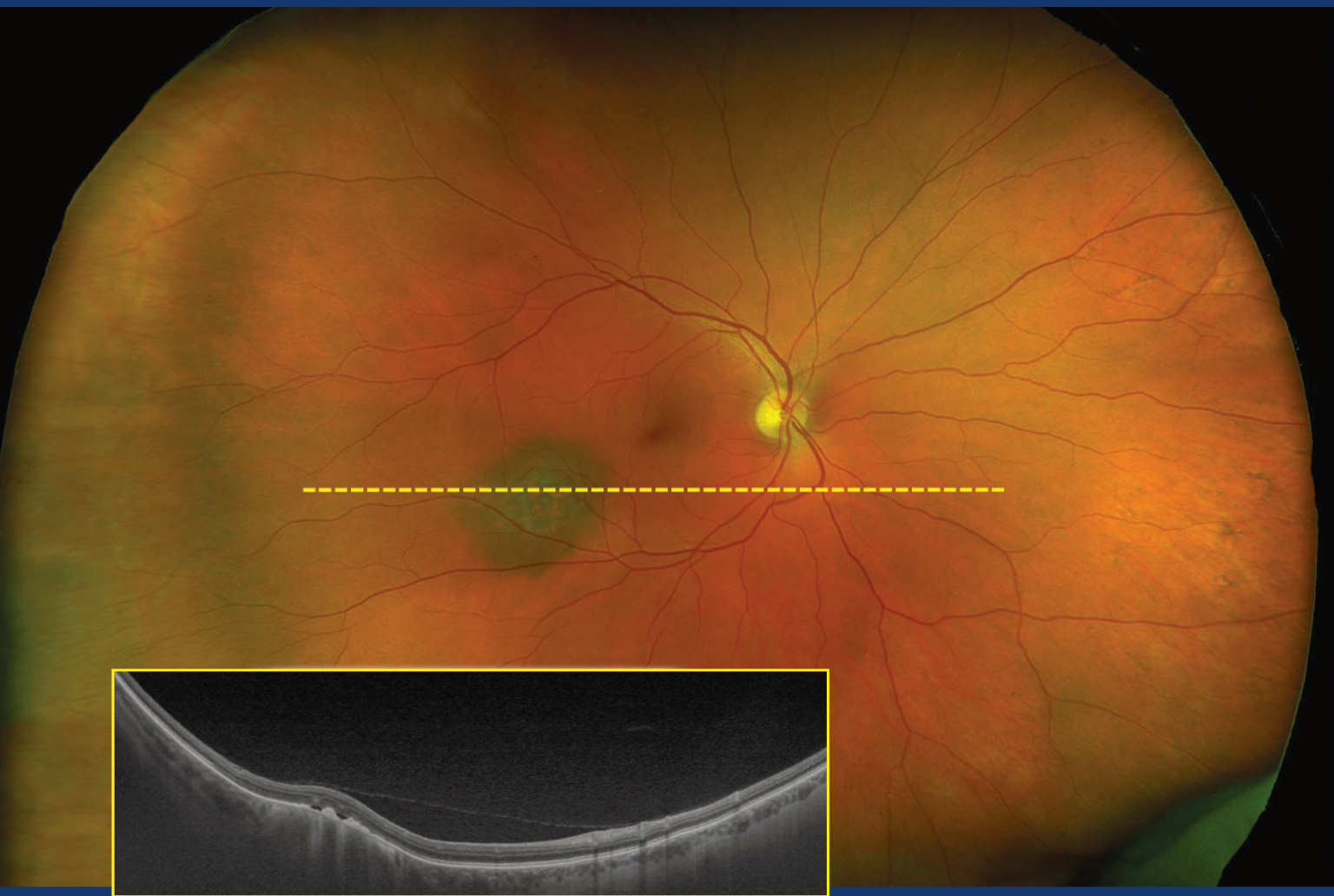

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1. Successful interventions to improve efficiency and reduce patient visit duration in a retina practice; Retina, 2021. 2. Comparison of image-assisted versus traditional fundus examination; Eye and Brain, 2013. 3. The Impact of Ultra-widefield Retinal Imaging on Practice Efficiency; US Ophthalmic Review, 2017.

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The dichotomy of didanosine

Even years after discontinuation, a life-saving drug for HIV patients can have deleterious effects on vision.

By Linnet Rodriguez, MD, and Jason Hsu, MD

Linnet Rodriguez, MD

Jason Hsu, MD

BIO

Dr. Rodriguez is a retina fellow at Wills Eye Hospital, Philadelphia.

Dr. Hsu is codirector of retina research at Wills Eye Hospital, associate professor at Thomas Jefferson University and partner at Mid Atlantic Retinal

DISCLOSURES: Dr. Rodriguez and **Dr. Hsu** have no relevant financial relationships to disclose.

A 62-year-old man presented to our retina clinic with decreased vision in both eyes for the past few years. His medical history was pertinent for human immunodeficiency virus treated with multiple medications.

Work-up and imaging

His visual acuity was 20/40 in both eyes. Intraocular pressures were within normal limits. Anterior segment examination was pertinent for 1+ nuclear sclerosis (NSC) in the right eye and 2+ NSC in the left eye. Fundus examination revealed extensive areas of circumferential and bilateral chorioretinal atrophy localized to the periphery, mostly sparing the macula. The left eye, however, did show a small area of hypopigmentation in the macula (*Figure 1*).

Optical coherence tomography of both eyes showed intact laminations of the retina with intraretinal cysts at the level of the inner nuclear layer. Both eyes showed attenuation of the ellipsoid and interdigitation zone, more pronounced in the left eye (*Figure 2*).

Fundus autofluorescence demonstrated extensive circular patches of hypoautofluorescence extending from the temporal arcades to the periphery in a circumferential pattern. These areas correlated with the chorioretinal atrophy seen on the fundus examination.

Pinpoint areas of hyper- and hypoautofluorescence also appeared along the temporal arcades in both eyes. The macula seemed to be spared in the right eye, but the left eye showed an irregular zone of hyperautofluorescense in the temporal parafoveal area (*Figure 3*).

Fluorescein angiography revealed staining at the edges of the chorioretinal lesions as well as pinpoint areas along the arcades with relative sparing of the macula. The left eye exhibited a small area of staining in the temporal macula (*Figure 4, page 12*).

Additional history and diagnosis

The patient was diagnosed with HIV in 1990. He was initially treated with monotherapy with didanosine (Videx, Bristol Myers Squibb) and later was transitioned to multiple combined regimens with medications, including various nucleoside/nucleotide reverse transcriptase inhibitors, protease inhibitors and integrase strand transfer inhibitors.

Laboratory testing was negative for tuberculosis. Syphilis titers were stable and, based on the infectious disease specialist's recommendation, no repeated treatment was necessary at that point. His CD4 count was 400 with undetectable viral load. Genetic testing was negative for alternative diagnoses, including gyrate atrophy and choroideremia.

Given the patient's medical history, testing and imaging findings, he was diagnosed with didanosine-associated retinal toxicity (DART). Given multiple treatments and macular findings in the left eye, however, a superimposed maculopathy from medications such as ritonavir could not be ruled out.[1]

Follow-up

We treated the patient with topical dorzolamide t.i.d. in both eyes, which resulted

Figure 1. Ultra-widefield pseudocolor fundus images show chorioretinal atrophy and areas of stippled pigmentary clumps in the periphery, mostly sparing the macula.

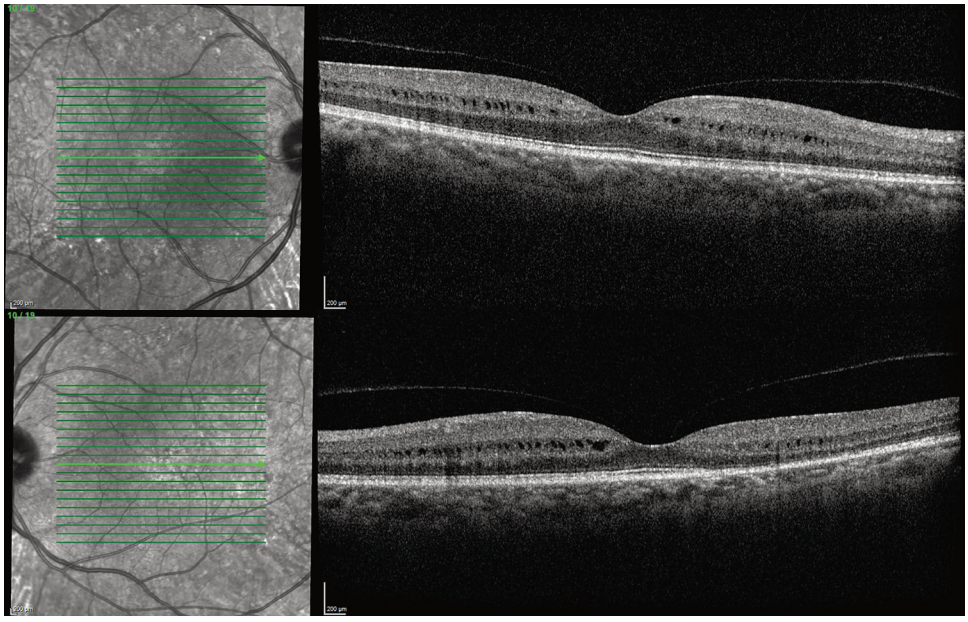

Figure 2. Optical coherence tomography shows intraretinal cysts in the inner nuclear layer and attenuation of the ellipsoid and interdigitation zones, more pronounced in the left eye.

in slight improvement of the bilateral intraretinal cysts. We advised him to continue HIV treatment with elvitegravir-cobicistat-emtricitabine-tenofovir combination therapy (Genvoya, Gilead Sciences) and to avoid didanosine, which he had discontinued years before. Because retinal toxicity due to didanosine can progress despite discontinuation and other antiretroviral medications can exacerbate it, we follow the patient regularly with FAF and fundus photography.

Characteristics of DART

Didanosine is a synthetic purine adenine nucleoside analogue in the nucleoside reverse transcriptase inhibitor (NRTIs) class. The Food and Drug Administration approved it in 1991 for treatment of HIV infection.[2] It was initially used as monotherapy until newer drugs and combination regimens emerged after 1996.[3]

At the molecular level, didanosine has been proven to cause progressive loss of mitochondrial DNA by causing depletion of the DNA polymerase responsible for its synthesis. As a result, there is a shift away from oxidative phosphorylation toward aerobic glycolysis, leading to an increase in lactate secretion and impaired cellular function, which results in atrophy of the choriocapillaries and the outer retina.[4]

Patients can experience a gradual and bilateral decrease in peripheral vision as well as photopsia and nyctalopia.[2] Fundus findings consist of irregular areas of sharply demarcated chorioretinal atrophy that may coalesce. These are usually bilateral and manifest in a circumferential pattern, mostly spanning from the mid-periphery to the ora

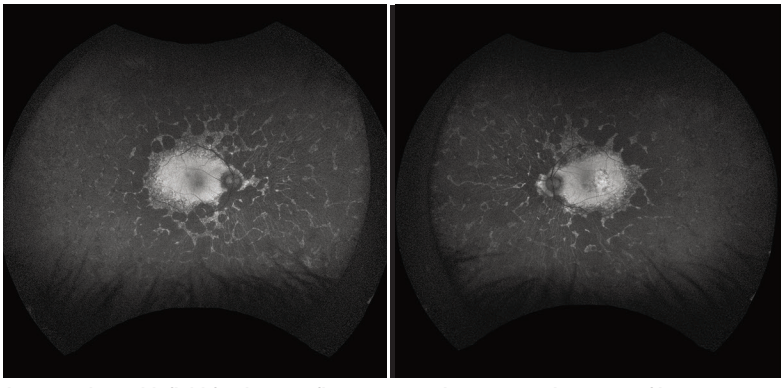

Figure 3. Ultra-widefield fundus autofluorescence shows extensive areas of hypo-autofluorescense from the temporal arcades to the periphery but sparing the macula.

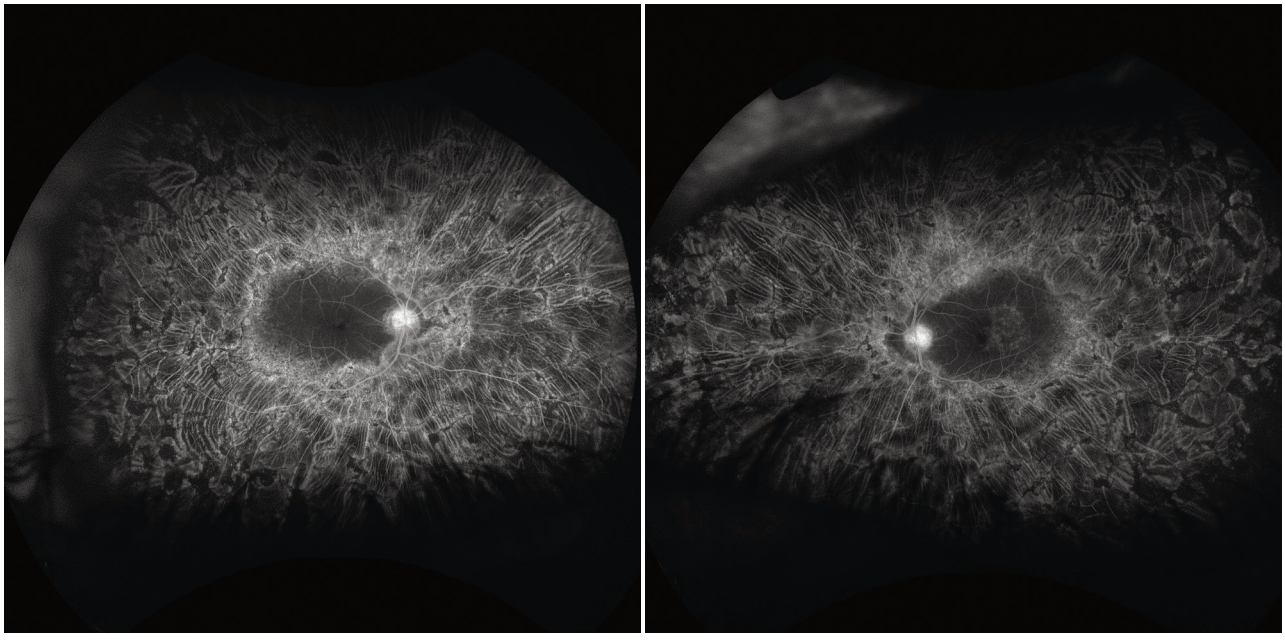

Figure 4. Late-phase ultra-widefield fluorescein angiography shows hyperfluorescence at the edge of the chorioretinal atrophy and along the arcades but sparing the macula.

serrata and sparing the macula. The optic nerve head is uninvolved.[3]

Imaging findings

FAF findings are pertinent for hypoautofluorescence matching the areas of chorioretinal atrophy. FA can show early window defects in the same areas with late staining at the concentric margins.[5] OCT may demonstrate normal laminations of the macula with some intraretinal cysts. These cysts may represent Muller cell dysfunction or structural alterations due to outer retinal changes. OCT of the peripheral retina may show loss of the outer retina, RPE and choriocapillaris.[6,7] Electroretinogram may reveal a bilateral decrease in rod and cone response.[8]

Treatment

There is no proven treatment for DART. Because of advances in highly active antiretroviral therapy, didanosine is rarely prescribed anymore. For patients still on this therapy, they should discontinue it.

Bottom line

Didanosine can cause bilateral circumferential mid peripheral chorioretinal atrophy with macula sparing. Despite medication discontinuation, toxicity may progress. Other antiretroviral drugs may also exacerbate the problem. Patients should be followed regularly with fundus images and FAF. They should also be referred to an infectious disease specialist, when appropriate, for changes in therapy.

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Department Editor ***Akshay S. Thomas, MD, MS***

Masquerade syndromes in uveitis

A review of neoplastic and nonneoplastic masqueraders that can confound and complicate diagnosis.

By Akshay R. Mentreddy, DO, and Jessica G. Shantha, MD

Akshay R. Mentreddy, DO

Jessica G. Shantha, MD

The term "masquerade syndrome" was first used in 1967 to describe a case of conjunctival carcinoma manifesting as a chronic conjunctivitis.[1] In uveitis, masqueraders are diseases that can mimic any form of intraocular inflammation. The list of masqueraders is extensive, but here we simplify them into neoplastic and nonneoplastic disorders that we routinely encounter in a retina practice.

Neoplastic masquerade syndromes

Vitreoretinal lymphoma. VRL is rare but one of the more common intraocular malignancies diagnosed (*Figure 1*). Its prompt recognition is paramount because up to 90 percent of cases have or will develop central nervous system disease.

VRL represents the most common lymphoma of the eye and it's more often a diffuse large B-cell subtype, although T-cell lymphomas can occur. Patients often complain of floaters as a presenting symptom. On examination, patients can present with both anterior and intermediate cell and posterior segment findings, including infiltrates below the retinal pigment epithelium.[2]

Multimodal imaging can be key to making the diagnosis. Characteristic optical coherence tomography findings are RPE nodularity, outer retinal hyper-reflectivity and infiltrates between the RPE and Bruch's membrane. On fundus autofluorescence, these infiltrates will be hyperautofluorescent. A common pattern on FAF is alternating hypo- and hyperautofluorescence. On fluorescein angiography, these lesions will have a granular appearance with staining and blocking.[3]

The diagnosis is made with intraocular specimens from an anterior chamber paracentesis or, more routinely, a vitreous biopsy. Direct visualization of lymphoma cells on cytopathology is the gold standard for diagnosis, but many tests can support the diagnosis of VRL. They include aqueous and vitreous analysis of interleukin (IL)-10 levels and IL-10 to IL-6 ratios, flow cytometry and myeloid differentiation primary response gene 88 testing.[4]

A retinal biopsy can be considered when the vitreous biopsy is negative but clinical suspicion remains high. It's important that a patient hasn't received systemic or local corticosteroids preoperatively; these will increase the yield of lymphoma cells. Deep sequencing is an emerging technology that may be another technique to add to our armamentarium to aid in the diagnosis of lymphoma.[5]

Treatment includes a multidisciplinary team with oncology and can include both local therapy with intravitreal methotrexate or rituximab and systemic chemotherapy.

Uveal lymphoma. Also of B-cell origin, uveal lymphomas can affect the iris, ciliary body and choroid. Like VRL, they respond to steroid treatment, but their nature is far more indolent. A yellow-pink choroidal infiltration is notable on clinical exam, but thickening of the uveal tract appears later in the disease.[6] The appearance of infiltrative choroidal lesions beneath Bruch's membrane is a key OCT finding in uveal lymphoma that helps differentiate it from VRL.[3]

Leukemia. Up to 90 percent of patients with a diagnosis of leukemia can have ocular involvement.[7] While posterior-segment involvement can result from retinal infiltration of neoplastic cells, it can also result from secondary causes such as anemia or hyperviscosity. The retinal manifestations, such as Roth spots, cotton wool spots, venous dilation and vessel tortuosity, can be extensive. However, from a uveitis standpoint, leukemia can manifest as an angiopathy that can resemble a frosted branch angiitis. It can also mimic a hypopyon uveitis and even an intermediate uveitis.[8]

Retinoblastoma. RB represents the

BIOS

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

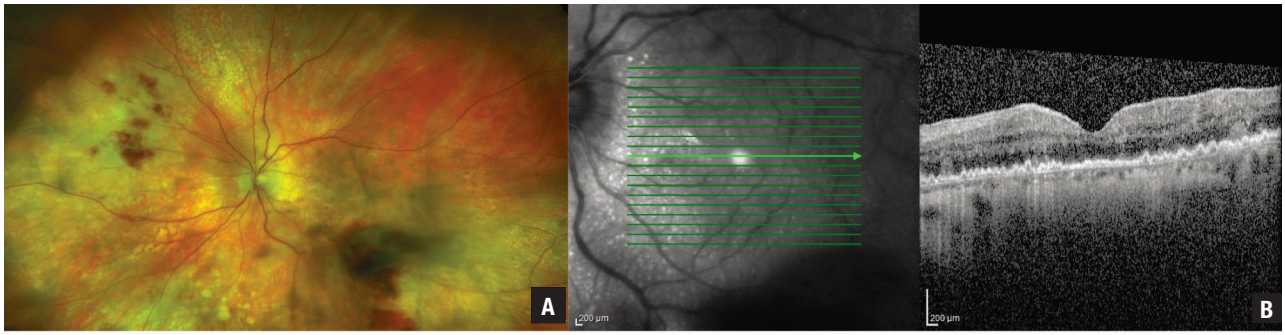

Figure 1. A) Widefield pseudococolor image shows biopsy-proven vitreoretinal lymphoma with vitritis, retinal hemorrhages and multiple areas of varying size circular lesions throughout the periphery. B) Optical coherence tomography highlights the nodular appearance of the retinal pigment epithelium and infiltrates between the RPE and Bruch's membrane. ***(Courtesy Johnathan A. Gonzales, MD)***

most common pediatric intraocular tumor. Particularly, the diffuse subtype presents as a flat, ill-defined mass which can cause a pseudohypopyon masquerading as an anterior uveitis. Additionally, the disease can present with findings of a posterior uveitis, which makes the diagnosis challenging. Indeed, in one study 9 percent of referrals to a clinical service were for uveitis when in fact the true diagnosis was RB.[9]

Metastatic tumors. Given the vascular nature of the choroid, it's no surprise that it represents the most common site for metastasis of systemic solid tumors. The metastasis is typically from the breast or lung. These lesions typically present as creamy white or yellow retinal masses with subretinal fluid and retinal hemorrhage.[10] Metastasis may involve other uveal structures, such as the iris and ciliary body, which can present with an anterior uveitis.[11]

Paraneoplastic retinopathy. This includes diseases such as cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR). Paraneoplastic retinopathy falls under the purview of a paraneoplastic syndrome, which is defined as "signs and symptoms observed from cancer but not directly as a cause of the cancer tissue or its associated sites of metastasis."[12]

Examination findings include anterior and vitreous cell, and vascular attenuation. OCT may demonstrate outer retinal loss, which could mimic a uveitis syndrome.[13] If suspicion for paraneoplastic retinopathy is high, seek out the source malignancy with whole-body imaging and ensure the patient has had age-appropriate cancer screening.

Non-neoplastic masquerade syndromes

Retinitis pigmentosa. The classic triad for RP includes waxy pallor of the optic disc, retinal pigmentary changes and arteriolar attenuation (*Figure 2, page 16*). RP patients can present with cystic macular edema and also have vitreous cell—the result of photoreceptor death[14]—with RPE changes that can often disguise themselves as an intermediate and posterior uveitis.

Rhegmatogenous retinal detachment. Like uveitis, retinal detachments can present with hypotony. Given the presence of cell and pigment, it's important to carefully exclude a far peripheral detachment as a cause for a patient's presumed inflammation. Conversely, Schwartz-Matsuo syndrome can present with cell and elevated intraocular pressure (secondary to blockage of the trabecular meshwork by outer segments of the photoreceptors), which could mimic a hypertensive anterior uveitis.[15]

Intraocular foreign bodies. While IOFBs are easy to recognize and mitigate when entry wounds are present and a patient's history is accurate, the insult can go unrecognized and their onset can be insidious in some cases, particularly with metallic foreign bodies. This can lead to masquerade

signs of conjunctival injection, pigment and anterior-segment cell and flare, all of which could be mistaken for uveitis.[16]

Syphilis. While uveitis clinics commonly test for the great masquerader syphilis as an infectious etiology, its ocular manifestations are vast and merit placement on this list. The Centers for Disease Control and Prevention recommends both treponemal testing—fluorescent treponemal antibody absorption, the *T. pallidum* passive particle agglutination assay, various enzyme immunoassays, chemiluminescence immunoassays and immunoblots—and nontreponemal testing, namely Venereal Disease Research Laboratory or rapid plasma reagin.

Ordering only one serologic test is insufficient for diagnosis. A treponemal test is necessary to confirm disease while a nontreponemal test can help to monitor disease activity and gauge treatment response.[17]

A 2017 metanalysis found the optic nerve was the most frequently affected ocular structure, presenting as papillitis, neuritis or neuroretinitis, but that syphilis can present as an anterior or intermediate uveitis as well. While posterior placoid choroiditis can be seen, so can vasculitis and retinitis.[18] Directed testing to rule out syphilis is a must whenever a patient presents with uveitis.

Bottom line

Masqueraders can mimic any form of ocular inflammation. Separating them into neoplastic and nonneoplastic etiologies can help us to identify these pathologies promptly and spare our patients from debilitating vision loss.

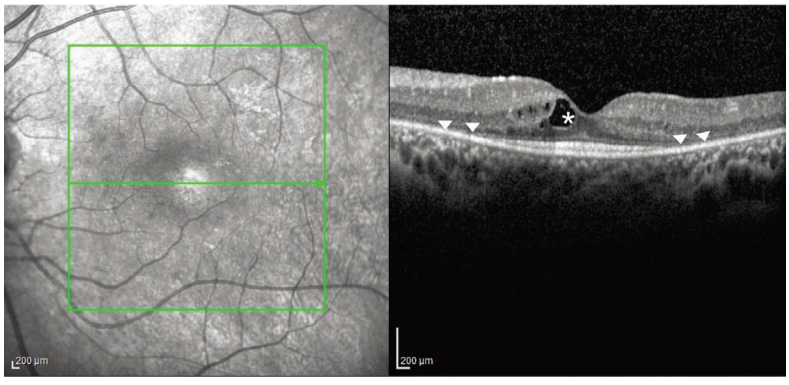

Figure 2. Optical coherence tomography image of retinitis pigmentosa demonstrating cystic macular edema (asterisk) and outer retinal loss (arrow heads).

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The case for Kenalog

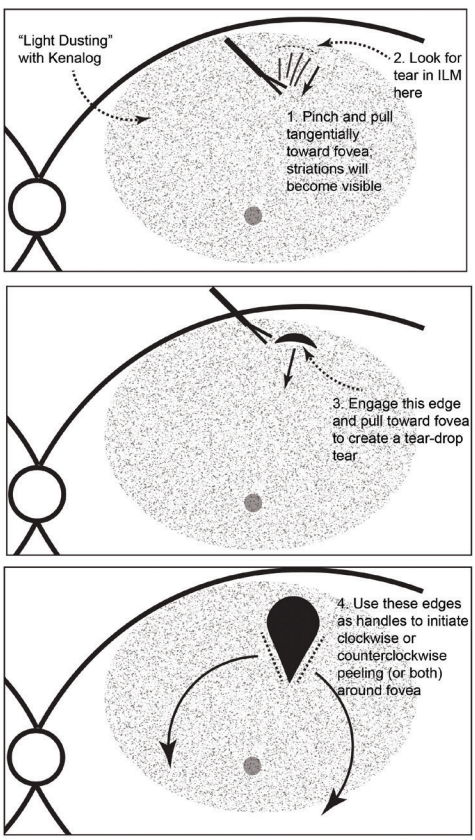
A micro-minority of us use it, with most others preferring ICG or BB. Here's why you should join us.

By Rithwick Rajagopal, MD, PhD

Rithwick Rajagopal, MD, PhD

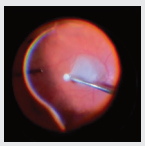
According to the 2022 American Society of Retina Specialists' Preferences and Trends survey, almost half of U.S. retina specialists—48.8 percent—use indocyanine green as their internal limiting membrane peeling adjuvant of choice, compared to 46.9 percent who use Brilliant Blue and a meager 2.8 percent who use triamcinolone.

I'm among that 2.8 percent, as are several of my colleagues in Saint Louis where I practice. Although I've tried ICG and BB many times, I always go back to using Kenalog because I like it better. And I suspect many more than 2.8 percent of you would use it more often if you gave it a fair chance. Here, I explain the advantages of Kenalog and offer some tips on how to use it.



View the Video

Dr. Rajagopal demonstrates how he uses Kenalog to peel internal limiting membrane. Available at: https://bit.ly/VideoPearl_33



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Tips on how to use Kenalog

Concentration is key. Aim for a "light dusting" of the macular surface. Too

(Continued on page 42)

Key steps for peeling internal limiting membrane with Kenalog. Apply a light dusting of Kenalog on the macular surface (1:4 dilution in balanced salt solution). 1. Pinch a distal part of the ILM and pull it toward the fovea tangential to the retinal surface, identifying the tension lines from your instrument. 2. Look for a small rip in the ILM behind the tension line. 3. Release the forceps, grab the newly created torn edge of ILM (this step reduces the risk of pulling at the nerve fiber layer) and pull toward the fovea to create a teardrop-shaped window. 4. Use the lateral edges of the teardrop to serve as handles for extending wide flaps around the entire macular center.

BIOS

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DISCLOSURES: Dr. Rajagopal has no relevant disclosures.

Dr. Hahn is a consultant to Alcon and DORC.

Gaining a new appreciation for endoscopic vitrectomy

It requires a steep learning curve, but it offers multiple advantages over traditional pars plana vitrectomy for even routine cases.

By Sohani Amarasekera, MD, MPH, and Jay Chhablani, MD

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Take-home points

- Endoscopic vitrectomy has unique benefits that traditional pars plana vitrectomy doesn't offer.
- The endoscopic approach can be used in complex retinal cases with media opacities as well as in routine cases.
- Using endoscopic vitrectomy involves a steep learning curve and no formal training requirements for its use exist in surgical retina fellowship in the United States.
- We encourage surgical preceptors to incorporate the endoscopic approach into routine cases so that trainees may gain the facility needed to use this technique and take advantage of upcoming advancements in endoscopic viewing systems.

Endoscopic vitrectomy can be an important addition to the retina surgeon's armamentarium. In ophthalmology, Harvey Thorpe, MD, first described the endoscopic approach in 1934, and then Claude Boscher, MD, and colleagues applied it to vitrectomy in 1981.

Endoscopic vitrectomy involves use of a coaxial instrument that both provides illumination while capturing an image that's viewed through a separate monitor rather than a surgical microscope. Commercially available endoscopic viewing vitrectomy systems include the EndoOptiks Ophthalmic Laser Endoscopy System (Beaver Visitec, *Figure 1*) and the FiberTech Ophthalmic Endoscope (FiberTech). These endoscopes have either rigid or curved probes.[1] Available sizes include larger 19-gauge and 20-gauge probes, as well as 23-, 25- and 27-gauge probes that can be used through traditional microsurgical cannulas.

Unlike traditional pars plana vitrectomy that relies on contact or noncontact "top down" viewing systems, the current endoscopic approach doesn't require clear media or an adequately dilated pupil size.

Advantages of endoscopy

Unique advantages of coaxial illumina-

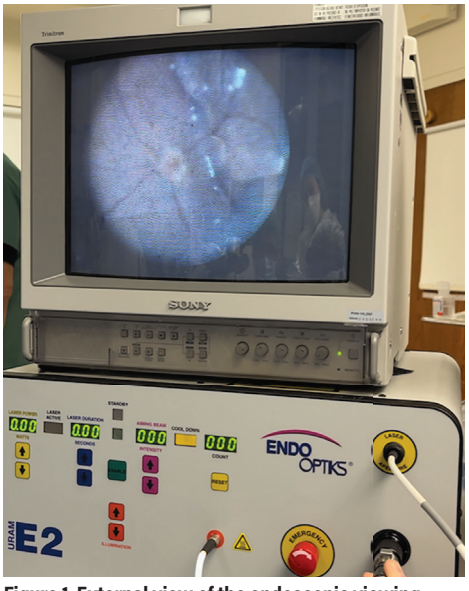

Figure 1. External view of the endoscopic viewing system.

Bios

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Dr. Amarasekera and **Dr. Chhablani** have no relevant disclosures.

tion include improved visualization of otherwise transparent structures, such as the vitreous and subretinal membranes,[2] and the ability to easily magnify an image by moving the endoscope toward it. Further, a hybrid vitrectomy approach uses both traditional PPV in conjunction with an endoscope to allow the greatest range of surgical maneuvers.[3]

These features bestow advantages of endoscopic vitrectomy in the diagnosis and treatment of complex retinal pathology. For example, endoscopy provides unparalleled access to the anterior vitreous cavity. You can reach difficult-to-access retained lens fragments or anterior proliferative vitreoretinopathy that may otherwise contribute to surgical failure, including cyclitic ciliary body membranes (*Figure 2*) and contracted anterior edges of prior retinectomies.[4]

Endoscopy also has benefits when dealing with hazy media. Ocular trauma may result in corneal or lenticular compromise or anterior- or posterior-segment hemorrhage that may delay or limit the use of vitrectomy.

In these cases, traditional PPV may require bringing in an anterior-segment surgeon and donor tissue to use a temporary keratoprosthesis followed by penetrating keratoplasty.[5] In such cases, as Radwin Ajlan, MD, and colleagues noted, endoscopy can ultimately reduce time to surgery as well as the duration of retinal surgery.[6]

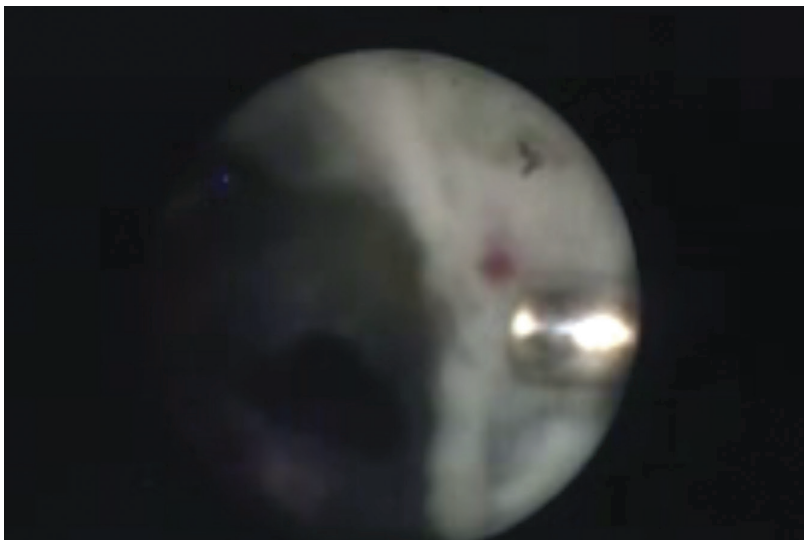

Figure 2. Endoscopic view of the vitrectomy probe at the edge of cyclic membrane.

Dealing with corneal edema

Likewise, in the setting of corneal edema accompanying endophthalmitis, endoscopic vitrectomy may allow for faster intervention with the ability to perform a more comprehensive diagnostic and therapeutic vitrectomy than the traditional approach.[7]

Further, endoscopy provides direct visualization of the posterior segment to help determine the visual potential of an eye with corneal opacification. The endoscopic approach allows for a more reliable prognostication to aid in counseling and surgical planning than other imaging modalities, such as ultrasound alone.[8]

Endoscopy in routine retina cases

However, endoscopy can also be used in routine retinal cases as well (*Figure 3*). For example, groups have documented the benefits of magnified endoscopic views in the identification of retinal breaks[9] and drainage of subretinal fluid in routine retinal detachment repair, as well as in internal limiting membrane peeling for macular holes.[10] These procedures also highlight the benefit of endoscopy in circumventing the need for scleral depression for vitrectomy completion.

What's holding us back?

Despite its obvious benefits, multiple factors have limited the widespread adoption of endoscopic vitrectomy. They include the lack of true stereopsis with existing two-dimensional viewing system and narrow field of view with limited resolution. These anomalies may make it difficult for surgeons to assess distances of intraocular structures and keep the desired focal point in good view.

Additionally, depending on the complexity of the surgical case, some surgeons may prefer, or even require, a bimanual technique. While traditional endoscopic vitrectomy precludes the bimanual technique, use

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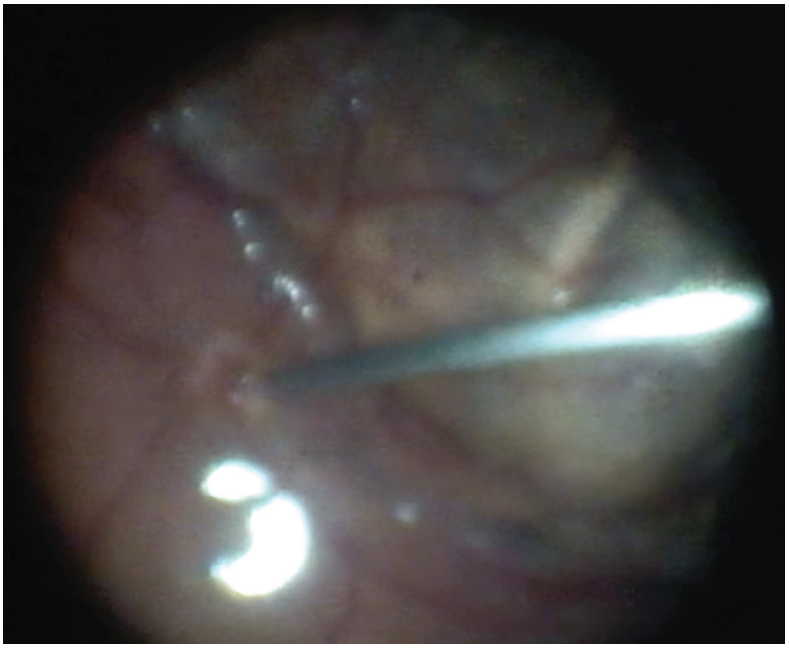

Figure 3. Endoscopic view of the vitrectomy probe being used for fluid-air exchange near the optic disc.

of a chandelier may eliminate this problem.

Perhaps the most commonly cited deterrents of widespread adoption of endoscopic vitrectomy is its steep early learning curve and limited training of vitreoretinal fellows in the endoscopic approach. Therefore, we advocate for a systematic approach to this problem.

Training is lacking

Overall, there's a paucity of data on the training of vitreoretinal surgeons in the endoscopic approach. Currently in the United States, there are no formal requirements for vitreoretinal fellows in the training of endoscopic vitrectomy techniques. It's unknown how many programs train fellows in endoscopy and whether faculty often use this approach. As a result, there may be limited formal opportunities for fellows to learn this important skill during their fellowship.

However, endoscopes are often readily available at ophthalmic surgical facilities, especially in those that also do glaucoma procedures given their use in endoscopic cyclophotocoagulation.

How to learn endoscopy

So, if possible, we encourage trainees to take the initiative to develop endoscopy during their training. A good start is to practice orienting the endoscopic probe in routine cases that don't necessarily require a endoscopic approach.

Focus the probe outside the eye using the surgical drape or speculum as the focal point. Once inside the eye, posterior pole structures, such as the optic nerve and arcades, can serve as landmarks to orient positioning within the vitreous cavity. The endoscope can be withdrawn slightly as needed to increase the field of view and help with reorientation. Take care to avoid lens touch in phakic eyes.

With time, moving the probe within the eye and lighting tissues adequately will become more facile. Looking ahead, developers of multiple viewing platforms are working to integrate three-dimensional viewing with endoscopy.

Bottom line

As endoscopic vitrectomy continues to evolve, we advocate integrating endoscopic techniques into fellowship training to ultimately provide our patients with the most timely and effective surgical care. RS

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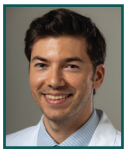
The potential impact of pegcetacoplan

Clinical implications of data from the OAKS and DERBY trials on the future treatment of geographic atrophy.

By Jason T. Szelog, MD, and Caroline R. Baumal, MD



Jason T. Szelog, MD,

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Take-home points

- Geographic Atrophy is a leading cause of blindness in the United States and across the globe, and its prevalence is projected to double over the next two decades as the aging population increases.
- The longstanding dichotomy within advanced age-related macular degeneration—treatable neovascular AMD vs. untreatable geographic atrophy in dry AMD—may disappear as emerging therapies targeting GA become more widely available.
- Pegcetacoplan is the first treatment to demonstrate reduction of GA progression during Phase III trials with results at 24 months.
- Retina specialists should prepare for the upcoming paradigm shift within advanced AMD by familiarizing themselves with the imaging features and therapeutic options for GA lesions.

Geographic atrophy affects approximately 5 million people globally and the bilateral form of the disease is responsible for approximately 20 percent of legal blindness in the United States.[1,2] Progressive and permanent central vision loss is the end result of GA, characterized by irreversible breakdown of the photoreceptor-retinal pigment epithelium-choriocapillaris complex within the macula.[2]

As of this writing, there are no Food and Drug Administration-approved therapies to treat GA, but no less than 12 investigative GA therapies have emerged (*Table, page 25*). One, pegcetacoplan (Apellis Pharmaceuticals) has the potential to be the first commercially available treatment for GA. The FDA has set an action date of February 26 for its New Drug Application (NDA). An NDA for another, avacincaptad pegol (Zimura, Iveric Bio), was filed in December 2022.

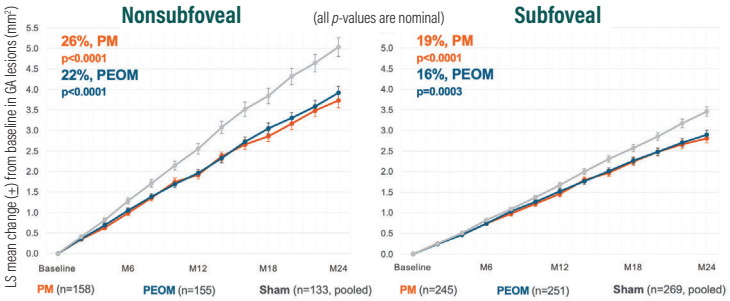

Figure 1. A combined, prespecified analysis from the OAKS and DERBY trials of pegcetacoplan demonstrated 26 and 22 percent reductions in geographic lesion growth with monthly and every-other-month (EOM) dosing, respectively, vs. sham in eyes with nonsubfoveal lesions (p<0.0001 for both); and 19 and 16 percent reductions in lesion growth with the respective dosing intervals vs. sham in eyes with subfoveal lesions (p<0.0001 and p=0.0003). Least square (LS) means were estimated from the mixed-effects model for repeated measures. (Courtesy Apellis Pharmaceuticals)

Bios

EDITOR'S NOTE: This article was invited and submitted before Dr. Baumal was appointed chief medical officer of Apellis Pharmaceuticals.

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DISCLOSURES: Dr. Szelog has no relevant disclosures.

Dr. Baumal, in addition to the aforementioned title as CMO of Apellis, is a consultant to Genentech/Roche, Regeneron Pharmaceuticals, EyePoint Pharmaceuticals, Ora and Alcon.

(*A more comprehensive list of investigative candidates for GA is on page 31*). This article will focus on the OAKS and DERBY trials of pegcetacoplan that enabled the NDA filing.

Targeting complement pathway

GA often grows around the fovea—i.e., extrafoveal—producing scotomas and affecting reading and driving vision. It ultimately progresses into the fovea with reported growth rates ranging from 0.5 to 2.6 mm^2/year, with a median of 1.78 mm^2/year.[3] The prevalence of GA more than quadruples per decade of life after age 50.[4] As a consequence, the overall prevalence of advanced AMD (combined nAMD and GA) has the potential to double over the next 20 years as life expectancy increases.[5]

The etiology of GA involves genetic factors, which continue to be elucidated, along with environment and age. An optimized diet, healthy lifestyle, smoking avoidance and use of AREDS2 vitamins may confer nominal risk reduction.[6] Dysregulation of the complement cascade appears to play a role in GA pathogenesis based on genetic, biochemical and histopathologic evidence. Genetic variants of factors that affect complement component 3 (C3) regulation, such as complement factors B and H, have been associated with advanced AMD.[7,8]

Multiple therapies targeting the complement cascade have been evaluated. Modes of administration include oral and subcutaneous, subretinal and intravitreal injections. Recent Phase III data for pegcetacoplan and avacincaptad pegol support the hypothesis that altering the complement cascade reduces the rate of GA progression.[9,10]

Science behind pegcetacoplan

Pegcetacoplan, also known as APL-2, is a pegylated, highly specific, synthetic peptide that binds C3 and C3b, inhibiting downstream effects of inflammation, opsonization and, ultimately, the formation of membrane attack complex (MAC).[7] C3 is the central convergence point in the complement cascade of all three activation pathways—classic, lectin and alternative.[7]

The Phase III DERBY and OAKS trials evaluated the efficacy of pegcetacoplan to inhibit the rate of GA lesion growth and affect visual function. The potential FDA approval of pegcetacoplan would be pivotal in the management of GA. It may provide a tool to reduce GA progression in patients who, until now, have been otherwise defenseless against the threat of inevitable, irreversible vision loss.

Impact on GA lesion growth

OAKS met the primary endpoint of GA lesion size growth reduction at the 12-month mark, with 22 and 16 percent reduction in growth vs. sham in the monthly and EOM treatment groups, respectively (p=0.0003 and p=0.0052).[11] In DERBY, both treatment groups narrowly missed statistical significance vs. sham, with 12 percent reduction for monthly and 11 percent for EOM (p=0.0528 and p=0.0750) at the 12-month mark.[11]

The design behind DERBY and OAKS

DERBY (NCT03525600) and OAKS (NCT03525613) are parallel Phase III, multicenter, double-masked, randomized sham-controlled trials evaluating the efficacy and safety of monthly and every-other-month (EOM) intravitreal pegcetacoplan for reducing progression of geographic atrophy secondary to AMD.[23,24]

The study excluded patients with GA due to a condition other than AMD, refractive error beyond –6 D of myopia or axial length >26 mm, any history of choroidal neovascularization in the study eye, other active disease-confounding visual functioning, intraocular surgery within three months of randomization or history of macular laser. A history of nAMD in the fellow nonstudy eye was not exclusionary and eyes with subfoveal and nonsubfoveal GA were eligible for inclusion, which differentiates DERBY and OAKS from other GA studies.

DERBY and OAKS respectively enrolled 621 and 637 patients with untreated GA, randomized 2:2:1:1 to monthly (n=403) or EOM pegcetacoplan (n=406), or monthly or EOM sham (n= 402, pooled sham group). The primary endpoint for each trial was change in GA lesion area as measured by fundus autofluorescence from baseline to month 12.

Additional endpoints included 24-month outcomes of secondary visual function tests, such as change from baseline in monocular reading speed, functional reading independence index score, best-corrected visual acuity, low-luminance deficit, monocular critical print size, National Eye Institute Visual Functioning Questionnaire 25-item Version, distance activity subscale scores, change in GA lesion area and systemic APL-2 concentration over time. Evaluation for ocular/systemic treatment-emergent adverse events was performed through 30 months. Microperimetry was an additional secondary endpoint in OAKS only.

Baseline imbalances in factors that affect GA growth were noted between study arms because DERBY and OAKS enrolled a heterogeneous population of GA eyes with foveal and nonsubfoveal lesions. Combining the DERBY and OAKS study data revealed pegcetacoplan had a strong effect on lesion growth in eyes with extrafoveal lesions for both monthly and EOM dosing vs. sham, with 26 and 23 percent reductions, respectively ($p<0.0001$ and $p=0.0002$). This wasn't unexpected; the natural history of GA demonstrates that nonsubfoveal (extrafoveal) lesions grow faster than subfoveal lesions.

At the 18- and 24-month time points in both studies, pegcetacoplan-treated eyes demonstrated meaningful reduction in GA lesion growth vs. sham. The 24-month data showed increased benefit to pegcetacoplan vs. sham for both monthly (DERBY, 36 percent, $p=0.0001$; OAKS, 24 percent, $p=0.0080$) and EOM dosing (DERBY, 29 percent, $p=0.0002$; OAKS, 25 percent, $p=0.0007$).[12]

Diving deeper into findings

The efficacy of pegcetacoplan to reduce GA growth improved over time, most notably between months 18 to 24 (*Figure 1, page 23*). No difference was noted in secondary visual function endpoints between treated and sham groups.

Factors that may have impacted the findings include heterogeneity of the GA population studied, limitations of the current visual function tests (especially in the older, visually compromised study population) and the 24-month duration, which may be too short of an interval to demonstrate a difference.

A post hoc OAKS analysis of microperimetry data evaluating the GA lesion junctional zone suggested a reduced loss of photoreceptor function in treated eyes.[9] Specifically, it found less of a reduction in mean threshold sensitivity within both treatment arms vs. sham at 24 months (0.564 and 0.707 dB higher for monthly and EOM, respectively, $p=0.0650$, $p=0.0202$).

Table. Investigative programs targeting geographic atrophy

Agent name (manufacturer)	Status
ALK-001 (Alkeus Pharmaceuticals)	Phase II/III
ANX007 (Annexion Biosciences)	Phase II
Danicopan (Alexion Pharmaceuticals)	Phase II
Elamipretide (Stealth BioTherapeutics)	Phase II failed to meet endpoints.
IONIS-FB-LRx (Ionis Pharmaceuticals/Roche)	Phase II
NGM621 (NGM Biopharmaceuticals)	Phase II failed to meet endpoints.
OpRegen (Lineage Cell Therapeutics)	Phase I/IIa
Pegcetacoplan (Apellis Pharmaceuticals)	Phase III completed; Prescription Drug User Fee Action date set.
RPESC-RPE-4Q (Luxa Biotechnology)	Phase I/IIa
Tinlarebant/LBS-008 (Belite Bio)	Phase III pending,
Xiflam (InflammX)	Investigative New Drug application amendment filed,
Zimura/avacincaptad pegol (Iveric Bio)	Phase III complete. New Drug Application filed.

Another exploratory post hoc analysis using artificial intelligence to segment optical coherence tomography data showed reduced photoreceptor and RPE loss in pegcetacoplan-treated eyes vs. sham eyes, with a more pronounced and rapid effect on photoreceptor loss.[13]

Clinical impacts of treating GA

With a therapy effective in slowing GA progression on the horizon, retina specialists will soon have to focus on findings that we previously only observed. We know that BCVA alone is a poor marker of GA progression. Thus, thorough evaluation and monitoring for GA lesions will help to identify patients who will benefit from treatment.

Natural history studies have revealed that GA lesion size progresses and grows around the fovea with retinal destruction, increased scotoma, and functional worsening. However, the center of the fovea that corresponds

to BCVA may be preserved until late in the disease. Studies have confirmed that BCVA reflects atrophic changes within the central 1-mm diameter zone of the fovea and correlates poorly with GA lesion size.[14,15]

Critical role of multimodal imaging

Fundus examination and serial monitoring with multimodal imaging, especially OCT and fundus autofluorescence, will play critical roles in risk-stratification by identifying findings known to be associated with GA progression.[16,17]

Findings suggestive of elevated GA progression risk include presence of reticular pseudodrusen, junctional zone abnormalities, multifocal lesion configuration and "banded" or "diffuse" lesion presentation.[3,18,19] GA in the fellow eye, larger lesion size and extrafoveal lesion location are also predictive of progression.[3]

Reticular pseudodrusen are subretinal deposits anterior to the RPE and are most often localized to the superotemporal macula. They're associated with risk of progression from intermediate to advanced AMD, as well as multifocal GA lesion configurations, which tend to progress more quickly than unifocal GA lesions.[3] Additionally, regression of reticular pseudodrusen may predict locations of future GA lesions.[3]

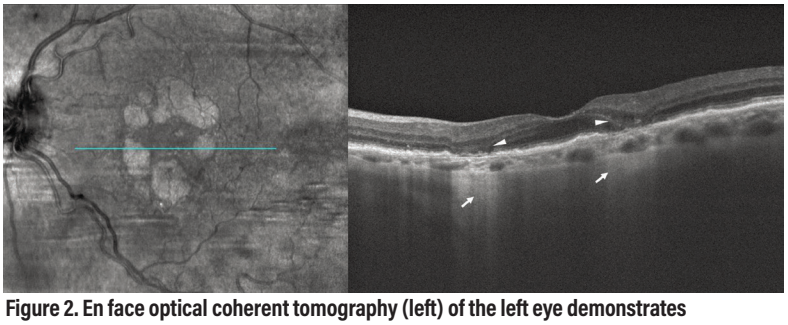

Figure 2. En face optical coherent tomography (left) of the left eye demonstrates multifocal, wreath-like pattern of geographic atrophy wrapping around, but sparing the fovea. Structural spectral domain-OCT (right) reveals hypertransmission of OCT signal through atrophic areas of absent RPE appearing as a bar-code pattern posteriorly (arrows). The diameter of the lesions is greater than 250 µm, meeting the criteria of complete retinal pigment epithelium and outer retinal atrophy (cRORA). Subsidence of inner nuclear and outer plexiform layers and ellipsoid zone disruption overlie areas of RPE atrophy (arrowheads). High-risk features for progression include multifocal GA, foveal-sparing and irregular lesion border.

Lesion abnormalities on OCT, FAF

Abnormalities at GA lesion borders as seen on OCT can be classified into three distinct categories:[18]

- ***Regular***, defined as having a smooth margin with no alterations in the outer retina. It's associated with the slowest progression.
- ***Irregular***, which contain severe alterations in the outer retina and irregular margins and are associated with an increased rate of progression.
- ***Splitting***, defined as separation of the RPE-Bruch's membrane complex into inner and outer portions. It may correlate with a progression rate three times faster than lesions with regular borders.

FAF can also help to evaluate GA lesion borders to predict progression based on levels of hyperautofluorescence abutting the lesion.[20] They are:

- ***None or minimal change***, representing the mildest risk with a median progression of 0.22 to 0.38 mm^2/year. These eyes were thus excluded from DERBY and OAKS.[19,20]
- ***Focal pattern***, the presence of a hyperautofluorescent spot <200µm on the lesion border.
- ***Patchy,*** a spot >200µm.[20]
- ***Banded,*** a circumferential ring of hyperautofluorescence surrounding the lesion.
- ***Diffuse,*** defined as a hyperautofluorescent signal abutting the lesion and extending elsewhere into the adjacent retina.

Median rates of progression with "focal" and "patchy" patterns were 0.56 to 0.81 mm^2/year and 1.02 mm^2/year, respectively.[19,20] "Banded" and "diffuse" patters portend the worst prognosis with progression of around 1.7 to 1.8 mm^2/year.[19,20]

Additional terms to help interpret findings include:

- ***Incomplete RPE and outer retinal atrophy (iRORA)***, defined on OCT

(Continued on page 42)

Sixth Annual Pipeline Report

2023: The year of geographic atrophy

A comprehensive look at 87 clinical programs for investigative treatments in retina.

By Richard Mark Kirkner, Editor

Richard Mark Kirkner

Take-home points

- 2022 was notable for the introduction of the first U.S. retina biosimilars in 2022 along with the approval of faricimab.
- This year's listing includes 21 programs not listed in past years.
- New names have been added for a number of investigative treatments.
- Two programs have been dropped from this year's list: FHTR2163, also known as galegenimab or RG6147, and abicipar pegol.

By the time you read this, the Food and Drug Administration may have already approved pegcetacoplan to be the first treatment for geographic atrophy secondary to age-related macular degeneration. Or not. One of the nuances about magazines is covering an event weeks or days before it happens.

In any event, 2023 is shaping up to be the year of GA, punctuated by the aforementioned pegcetacoplan (Apellis Pharmaceuticals). And in December 2022, Iveric Bio completed filing its New Drug Application for avacincaptad pegol, which may set the stage for FDA action this year.

This year's listing consists of 87 investigative treatments either in or soon to be in clinical trials in six different categories:

- Neovascular age-related macular degeneration, diabetic macular edema, diabetic retinopathy and retinal vein occlusion (*page 29*).
- Geographic atrophy (*page 30*).
- Gene therapies for AMD, DR and DME (*page 34*).
- Biosimilars (*page 36*).
- Inherited retinal disorders (*page 36*).
- Devices (*page 39*).

The categories for GA treatments and devices are new. In all, this year's list includes 87 entries, but not necessarily 87 different candidates; some of them are being investigated in different trials for different indications and are listed twice.

Additions and subtractions

Some drugs are going by new names. Tarcocimab tedromer is the new name Kodiak Sciences has given to KSI-301. Tinlarebant is the name Belite Bio is using for LBS-008. And so on.

This year's list includes 21 new entries, including six previously unlisted biosimilars and four each in treatments for inherited disorders and gene therapy candidates for nAMD, DME and DR.

2022 was known for significant approvals, namely Vabysmo (faricimab, Genentech/Roche) and Cimerli, Coherus Bio-

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 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, Eyecelerator and Ophthalmology Innovation Summit Retina 2022, supplemented with conversations with a multitude of clinical investigators and representatives of trial sponsors. This year's listing includes investigative biological treatments for exudative disease and geographic atrophy, including biosimilars and devices, as well as gene therapies for age-related macular degeneration and diabetic retinal disease and inherited retinal disorders.

sciences' ranibizumab biosimilar. Also notable in the biosimilars space was Biogen's launch of Byooviz, approved in 2021.

Clearside Biomedical and Bausch + Lomb also launched Xipere, the suprachoroidal triamcinolone acetonide suspension, for uveitic macular edema. It remains on the list because the sponsors are pursuing a program in DME.

Some candidates from last year's list aren't on this year's. FHTR2163, also known as galegenimab or RG6147, was dropped because Roche reported last year that it would discontinue the program. Abicipar pegol was removed because Molecular Partners hasn't issued any updates on the agent.

Biosimilar or not?

ONS-5010/Lytenava is listed in the large table for nAMD, DME, DR, RVO treatments rather than with biosimilars, although it's actually a biosimilar of Avastin (bevacizumab, Genentech/Roche). The reason: if approved, it would be the first ophthalmic formulation of bevacizumab, whereas the reference product is prepared by specialty pharmacies from batches of the cancer drug. The Food and Drug Administration set an action date for August.

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

Drug name (manufacturer)	Description/active agent
Aflibercept high-dose (Regeneron Pharmaceuticals)	8-mg dose of anti-VEGF-A and anti-placental growth factor (PLGF) agent
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)	Bioerodable dexamethasone implant
AR-13503 (Aerie Pharmaceuticals)	Bioerodable netarsudil implant
AXT107 (AsclepiX Therapeutics)	Intravitreal self-forming gel depot peptide
CLS-AX (Clearside Biomedical)	Suprachoroidal axitinib injection
Conbercept (Chengdu Kanghong Biotechnology)	Recombinant fusion protein targeting VEGF-A and -B and PLGF
EYP-1901 (EyePoint Pharmaceuticals)	Bioerodable vorolanib implant
GB-102 (Graybug Vision)	Pan-VEGF antagonist sunitnib
NEW: IBE-814 (Ripple Therapeutics)	Bioerodable intravitreal dexamethasone implant
IBI302 (Innovent Biologics)	Bispecific anti-VEGF and anti-complement recombinant fully human fusion protein
ISTH0036 (Isarna Therapeutics)	Antisense therapy targeting transforming growth factor-beta (TGF-β) protein
OCS-01 (Oculis)	Topical formulation of high-concentration, preservative-free dexamethasone
ONS-5010/Lytenava (bevacizumab-vikg, Outlook Therapeutics)	Ophthalmic formulation of intravitreal bevacizumab-vikg
NEW: OPL-0401 (Valo Health)	Oral small molecule rho-kinase 1/2 inhibitor.
OPT-302 (Opthea)	Anti-VEGF-C and -D
NEW: OTT166 (OcuTerra Therapeutics)	Small-molecule selective integrin inhibitor eye drop
OTX-TKI (Ocular Therapeutix)	Hydrogel-based sustained-release intravitreal axitinib implant
PAN-90806 (PanOptica)	Topical agent targeting VEGFR-2
RBM-007 (Ribomic)	Oligonucleotide-based aptamer with anti-fibroblast growth factor 2 activity
Risuteganib (Allegro Ophthalmics)	Luminate broad-spectrum anti-integrin peptide
RO7250284 (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
THR-149 (Oxurion)	Plasma kallikrein inhibitor
THR-687 (Oxurion)	Pan-arginylglycylaspartic acid (RGD) integrin antagonist
UBX1325 (Unity Biotechnology)	Small-molecule B-cell lymphoma-extra large (Bcl-xL) inhibitor
Xiflam (InflammX)	Oral small-molecule Connexin43 hemichannel blocker
Xipere (Formerly CLS-TA, Clearside Biomedical)	Triamcinolone acetonide 40 mg/mL suspension for suprachoroidal injection

Investigative agents for nAMD, DME, DR and RVO

Aflibercept high-dose (Regeneron Pharmaceuticals)

Two pivotal trials of this novel 8-mg aflibercept formulation, known as high-dose aflibercept (the 2-mg aflibercept is branded as Eylea), met their primary endpoints. The PHOTON trial in diabetic macular edema and PULSAR trial in neovascular age-related macular degeneration both demonstrated that aflibercept 8 mg 12- and 16-week dosing regimens achieved noninferiority in vision gains compared to aflibercept 2 mg 8-week dosing. Regeneron and Bayer, which holds the aflibercept franchise outside the United States, say they'll submit these data for regulatory review.

AKST4290 (Alkahest)

AKST4290 is an oral inhibitor of the chemokine C-C motif receptor 3 (CCR3) that blocks action eotaxin, an immunomodulatory protein that increases as humans age and contributes to age-related diseases. The Phase IIb PHTHALO-205 trial (n=107, NCT04331730), completed in 2021, randomized patients to either 800 or 1,600 mg of AKST4290 daily or

	Indication	Status
	Neovascular age-related macular degeneration, diabetic macular edema	Primary endpoints met in two pivotal trials. Data to be submitted for regulatory review.
	nAMD	Phase IIb trial (n=107) completed reported comparable outcomes vs. placebo.
	Nonproliferative diabetic retinopathy, proliferative DR	Phase IIb trial enrollment (n=103) completed. Topline data expected this year.
	DME, macular edema associated with retinal vein occlusion	Phase II (n=49) results in RVO reported. Phase III trial in DME planned.
	nAMD, DME	Phase I/IIa (n=18) completed but fell short of enrollment. No update available.
	DME	Enrollment initiated in Phase I/IIa trial (n=18).
	nAMD	Phase I/IIa trial (n=27) showed 90% reduction in anti-VEGF treatment. Six- month extension study results reported.
	nAMD, DME, RVO	Two Phase III trials (n=1,157) completed, results submitted.
	nAMD, NPDR	Enrollment initiated in Phase II nAMD trial (n=150) and Phase II NPDR trial (n=105).
	nAMD, DME, RVO	Program terminated.
	RVO, DME	Phase II trial (n=50) initiated fall 2022.
	nAMD	Phase I (n=36) results in nAMD showed well tolerated. Phase I trial in DME initiated August 2022.
	nAMD, DME	Enrollment initiated in Phase IIa trial.
	DME	Phase III trial (n=482) still recruiting. Completion due in 2024.
	AMD, DME and branch RVO	Phase III (n=228) trail showed noninferiority vs. bevacizumab. Regulatory action date set for August.
	NPDR	Phase I trial (n=120) initiated. Completion due in 2024.
	nAMD, DME	Phase III trials in nAMD with ranibizumab and aflibercept ongoing (n=1,980). Completion expected in 2024.
	NPDR, mild PDR	Phase II trial (n=210) initiated August 2022.
	nAMD; DR	Interim Phase I data (n=20) showed efficacy in nAMD. Phase I DR trial initiated in 2022.
	nAMD, DME, RVO	Phase I/II trial in nAMD(n=51) completed. No update available.
	nAMD	Two Phase II trials (n=108) reported no benefit in previously treated patients. Smaller study (n=5) evaluating outcomes.
	DME, dry AMD	Phase IIa (n=40) results pending.
	nAMD	Phase I enrollment raised from 50 to 251. Completion due 2026.
	nAMD, DME, RVO, NPDR	Phase III trials (n=2,855 combined) in all four indications ongoing. Topline nAMD data failed to show noninferiority vs. aflibercept.
	DME	Phase IIb (n=126) results expected this year.
	DME	Phase II (n=16) failed to meet endpoints. Program terminated.
	nAMD, DME	Positive Phase II data reported in DME (n=65). Phase II nAMD trial (n=46) completed enrollment.
	DME, nAMD	Reportedly in Phase IIb trials for DME and DR; no trials listed at ClinicalTrials.gov.
	DME	DME indication sought outside U.S.

placebo. All participants also received unspecified aflibercept injections. The trial is evaluating visual acuity outcomes after three loading doses of aflibercept in treatment-naive nAMD patients. Placebo patients actually had a more robust improvement in best-corrected visual acuity; 41.7 percent had a >15-letter improvement after 36 weeks vs. 30.6 and 14.3 percent in the low- and high-dose AKST treatment groups. Change in central subfield thickness and time to first aflibercept injection (about 20 weeks) were also comparable across the treatment arms. Alkahest didn't respond to a query for updated information.

APX3330 (Ocuphire Pharma)

Ocuphire reported its Phase II ZETA-1 trial (n=103, NCT04692688) in patients with moderately severe-to-severe nonproliferative diabetic retinopathy or mild proliferative diabetic retinopathy failed to meet its primary endpoint, but met systemic and ocular safety endpoints. The company reports it's preparing for an end-of-Phase II meeting with the FDA.

AR-1105, AR-13503 (Aerie Pharmaceuticals)

AR-1105 is a dexamethasone implant platform for DME and retinal vein occlusion. An open-label six-month study (n=49, NCT03739593) in patients with macular edema due to RVO demonstrated improvements in BCVA. Preparations for Phase III trials in DME are underway.

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

(Continued on page 32)

Investigative programs in geographic atrophy

ALK-001 (Alkeus Pharmaceuticals)

Recruiting ended in 2021 in a Phase II/III trial (n=300, NCT03845582) of this oral modified form of vitamin A, but results still haven't been posted. ALK-001 aims to replace the body's natural vitamin A with a form that makes vitamin A dimers more slowly and prevents toxic vitamin A dimer formation. The geographic atrophy study is due for completion later in the year. Alkeus is also pursuing concurrent trials in Stargardt disease. Alkeus didn't reply to a query for an update.

ANX007 (Annexon Biosciences)

Annexon completed patient enrollment in the Phase II ARCHER trial evaluating this anti-complement factor 1q candidate (n=270, NCT NCT04656561). Annexon says it plans to report topline data on the primary endpoint in the first half of 2023, following 12 months of treatment, with full data expected after conclusion of a six-month off-treatment period. Study completion is set for the end of the year.

NEW: Danicopan (Alexion Pharmaceuticals)

Also known as ALXN2040, Danicopan is an oral factor D inhibitor that's also being investigated as an add-on therapy in paroxysmal nocturnal hemoglobinuria. A Phase II trial (n=332, NCT05019521) is evaluating danicopan as a monotherapy for GA. The trial started late in 2021 and is due for completion in 2025.

Elamipretide (Stealth BioTherapeutics)

The Phase II ReCLAIM-2 study of this cell-permeating peptide (n=176, NCT03891875) failed to meet its primary endpoints—change in low-luminance visual acuity (LLVA) and GA lesion size. But the latest data demonstrated >2-line improvement in LLVA in study participants, results that were promising enough to continue the program, according to Stealth. Elamipretide was generally well tolerated in study participants. The rate of new-onset exudations was 5.3 percent in the elamipretide arm vs. 6.9 percent for placebo.

IONIS-FB-LRx (Ionis Pharmaceuticals/ Roche)

The Phase II GOLDEN study for GA (n=330, NCT03815825) is still recruiting. The primary endpoint is change in GA area at week 49. Secondary outcomes measure key biomarkers: levels of factor B in plasma and serum AH50 activity, as well as LLVA. Study completion has been pushed back to early next year. IONIS-FB-LRx is an antisense inhibitor.

NGM621 (NGM Biopharmaceuticals)

NGM Biopharmaceuticals is sorting through CATALINA Phase II trial results (n=320, NTC04465955) to determine next steps for this monoclonal antibody that aims to inhibit complement component 3 (C3) activity. The trial failed to meet its primary endpoint: A statistically significant reduction in GA lesion area vs. sham over 52 weeks. A post hoc analysis showed a subgroup had a more robust response than the overall study population.[1] This subgroup had a narrower range of GA lesion area than the trial inclusion criteria— 4.17 to 9.64 mm^2 vs. ≥2.5 mm^2 and ≤17.5 mm^2. In this subgroup, NGM621 demonstrated a reduction in the rate of change in GA lesion area (slope) of 21.9 percent (q4 weeks) (n=55) and 16.8 percent (q 8 weeks) (n=52), compared to sham (n=53). Updated CATALINA results are due soon.

OpRegen (Lineage Cell Therapeutics)

This cell-transplant platform consists of allogeneic retinal pigment epithelium cells delivered subretinally. One-year post-transplant results in the ongoing Phase I/IIa trial (NCT02286089) showed that all 24 treated patients reported at least one adverse event (AE) and at least one ocular AE, but around 90 percent of AEs in the first four cohorts were mild in nature. No cases of rejection, acute or delayed intraocular inflammation, or sustained increases in intraocular pressure were reported. A Phase IIa, multicenter, open-label, single-arm clinical study (n=60, NCT05626114) is recruiting. Genentech/Roche has partnered with Lineage to develop OpRegen.

Pegcetacoplan (Apellis Pharmaceuticals)

Anticipation was building last year when the Food and Drug Administration set a Prescription Drug User Fee Act (PDUFA) target action date of November on Apellis' New Drug Application (NDA) for pegcetacoplan. But then Apellis pulled the application back so it could resubmit

it with updated 24-month data from the Phase III Phase III DERBY (n=621, NCT03525600) and OAKS studies (n=637, NCT03525613). With the amended NDA filed, the FDA set a new PDUFA action date of February 26. The 24-month data showed that patients on monthly and bimonthly therapy lost mean threshold sensitivity at a slower rate than sham and had significantly fewer scotomatous points than sham patients.[1,2]

Apellis last year also submitted a Marketing Authorization Application to the European Medicines Agency. Pegcetacoplan targets C3.

NEW: 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 first patient received the cell product transplant in the Phase I/IIa clinical trial last spring (n=18, NCT04627428). The trial is evaluating the safety, tolerability, feasibility and preliminary efficacy of subretinal RPESC-RPE-4W using a dose-escalation, open-label design. Study completion is due in May 2025. Luxa is a joint venture of Seoul-based Y2 Solution Co. and the Neural Stem Cell Institute, Rensselaer, New York.

Tinlarebant/LBS-008 (Belite Bio)

Belite Bio says it has finalized design of its Phase III clinical trial in GA, but the study hasn't been filed with ClinicalTrials.gov yet. Tinlarebant is an oral, small-molecule retinol binding protein 4 (RBP4) specific antagonist. A previous Phase I trial (n=71, NCT03735810) confirmed safety and tolerability of the drug and that oral administration achieved a potentially therapeutic level of the agent. A Phase III trial in Stargardt disease is ongoing.

Xiflam (InflammX)

InflammX said last fall that it planned to initiate by year end separate Phase IIb clinical trials in intermediate dry AMD and GA, but no trials are registered at ClinicalTrials.gov. It submitted an Investigational New Drug amendment last year that it said would allow the DRCR Retina Network to initiate a Phase IIb trial in DME as well as diabetic nephropathy.

Zimura/ avacincaptad pegol (Iveric Bio)

Avacincaptad pegol (ACP), a complement C5 inhibitor, appears to be next GA treatment in the queue for approval and commercialization. Last fall the FDA granted Breakthrough Therapy designation to ACP for GA. In December Iveric Bio filed with the FDA the third and final installment of its NDA. The submission is based on 12-month results from the Phase II/III GATHER1 (n=286, NCT02686658) and Phase III GATHER2 (n=448, NCT04435366) clinical trials. Both trials randomized patients to either ACP 2 mg or sham monthly. Topline data from GATHER2 showed treated patients had a 14.3-percent reduction in the average rate of GA area growth over 12 months (p=0.0064).[3] An update from the Phase III GATHER 2 trial is due in February. An extension study is following patients who completed GATHER2 with monthly ACP 2 mg for up to 18 months (n=400, NCT055326297). ACP is also the subject of a clinical trial in Stargardt disease.

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Product name (manufacturer)	Description	Status
ALK-001 (Alkeus Pharmaceuticals)	Oral formulation of modified vitamin A	Completion of Phase II/III trial (n=300) due later in the year.
ANX007 (Annexon Biosciences)	Intravitreal antigen-binding fragment (Fab) to complement factor q1	Phase II trial (n=270) topline data expected by summer.
NEW: Danicopan (Alexion Pharmaceuticals)	Oral factor D inhibitor	Phase II trial (n=332) under way. Completion due in 2025.
Elamipretide (Stealth BioTherapeutics)	Mitochondria-targeting, cell-permeable peptide for subcutaneous injection	Phase II trial (n=176) failed to meet primary endpoints.
IONIS-FB-LRx (Ionis Pharmaceuticals)	Anti-sense oligonucleotide inhibiting complement factor B	Phase II trial (n=330) recruiting patients. Completion expected 2024.
NGM621 (NGM Biopharmaceuticals)	Humanized IgG1 monoclonal antibody inhibiting complement component 3	Phase II trial (n=320) failed to meet endpoints. Update expected in February 2023.
OpRegen (Lineage Cell Therapeutics)	Subretinally administered allogeneic retinal pigment epithelium cells	Phase I/IIa (n=24) results demonstrated safety. Phase IIa trial (n=60) recruiting.
Pegcetacoplan (APL-1, Apellis)	CC3 inhibitor	Phase III results (n=1,258) reported. Regulatory action date February 26, 2023.
NEW: RPESC-RP-4Q (Luxa Biotechnology)	Allogeneic retinal pigment epithelium stem cell (RPESC)-derived RPE cells isolated from the RPE.	Phase I/IIa trial (n=18) initiated. Completion due in 2025.
Tinlarebant/LBS-008 (Belite Bio)	Oral small-molecule retinol binding protein (RBP4) specific antagonist	Phase III trial pending.
Xiflam (InflammX)	Oral small-molecule connexin43 hemichannel blocker	Reportedly in Phase IIb trials for intermediate dry AMD and GA. No trials listed at ClinicalTrials.gov
Zimura (iVERIC bio)	Avacincaptad pegol CFC5 inhibitor	Phase III trial (n=448) showed efficacy signal. New Drug Application filed with FDA.

AXT107 (AsclepiX Therapeutics)

AsclepiX last year completed a small Phase I/IIa trial in DME (n=6, NCT04697758), but hasn't reported any results. AXT107 aims to inhibit vascular endothelial growth factor A and C and activate the Tie2 pathway as well. Enrollment fell short of the previously stated goal of 18. The company didn't respond to a request for further information by press time.

CLS-AX (Clearside Biomedical)

This injectable suspension of the tyrosine kinase inhibitor (TKI) axitinib is administered suprachoroidally via Clearside's SCS Microinjector platform. Clearside recently reported what it characterized as positive results from the Phase I/IIa OASIS extension study (n=19, NCT05131646) in nAMD.

In the extension study, 67 percent of participants went at least six months without needing additional treatments. They also had a 77 to 85 percent reduction in treatment burden over six months.

The OASIS Phase I/IIa study itself (n=27, NCT04626128) demonstrated that observable signs of the potential biologic effect of suprachoroidal axitinib included stable average BCVA and stable average central subfield thickness, which the extension study confirmed.

Conbercept (Chengdu Kanghong Biotechnology)

Chengdu Kanghong's plans last year to get FDA approval for the anti-VEGF fusion protein conbercept fell through. Available in China since 2013, conbercept targets VEGF-A and -B along with placental growth factor. Results from two Phase III trials in nAMD, PANDA-1 and PANDA-2 (NCT03577899; NCT03630952), each enrolling 1,157 patients, were submitted earlier this year. They're now listed as terminated. Small, independent studies were published last year in RVO.[1,2] Multiple studies in China are evaluating conbercept for polypoidal choroidal vasculopathy, retinoblastoma and other ophthalmic indications.

EYP-1901 (EyePoint Pharmaceuticals)

EYP-1901 is a bioerodable sustained release insert that uses the Durasert platform with the TKI vorolanib. Last year enrollment commenced for the Phase II DAVIO 2 (Durasert and Vorolanib in Ophthalmology 2) trial in nAMD (n=150, NCT05381948). Topline data are expected in the fourth quarter this year and the trial is expected to enroll patients previously treated with anti-VEGF therapy.

Enrollment also started in the Phase II PAVIA trial in NPDR (n=105, NCT05383209). Completion is due in 2025.

GB-102 (Graybug Vision)

Graybug terminated development of this sustained-release, bioerodable platform using the TKI sunitinib. Graybug entered into a merger agreement with CalciMedica with a plan to focus on development of a drug for treating acute pancreatitis.

NEW: IBE-814 (Ripple Therapeutics)

This is a bioerodable, intravitreal implant that, according to Ripple Therapeutics, releases one-tenth the drug load of the corticosteroid dexamethasone. A Phase II trial in RVO and DME launched last fall (n=50, NCT04576689). The company reports that trials so far haven't shown the increase in intraocular inflammation that comes with other corticosteroids in the eye.

IBI302 (Innovent Biologics)

IBI302 (efdamrofusp alfa) is an intravitreal bispecific antibody that targets both VEGF and C3b/C4b pathways. Preliminary results from the Phase I dose-escalation trial in nAMD (n=36, NCT03814291) showed it was well tolerated.[3]

Preclinical studies showed the bispecific fusion protein demonstrated superior efficacy over anti-VEGF monotherapy. The dual-inhibition action was found to further inhibit macrophage infiltration and M2 macrophage polarization.[3]

ISTH0036 (Isarna Therapeutics)

ISTH0036 targets the transforming growth factor-ß (TGF-ß). Isarna initiated enrollment in 2021 in BETTER, a Phase IIa trial evaluating this antisense therapy in nAMD and DME (the trial isn't listed at ClinicalTrials.gov). Results from 18 treated patients enrolled so far demonstrated an acceptable safety profile out to 12 months, with no drug-related adverse events and no signs of ocular inflammation.[4]

The study aims to enroll as many as 30 patients for each indication and is being conducted in Austria and India. The primary endpoint is retinal fluid and central macular thickness reduction, with improvement of BCVA as a secondary endpoint. The trial aims to explore the prevention of fibrosis and epithelial-mesenchymal transition as a key differentiator to anti-VEGF therapies.

OCS-01 (Oculis)

OCS-01 is a topical formulation of high-concentration, preservative-free dexamethasone. The Phase III DIAMOND trial (n=482, NCT05066997) in DME is listed as recruiting, but no updates have been posted since 2021. The trial is due for completion in 2024.

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

ONS-5010 is an ophthalmic formulation of Avastin. Outlook lived up to its word to file a Biologics License Application (BLA) with the FDA for ONS-0510, which the agency accepted last fall. The FDA set a Prescription Drug User Fee Act (PDUFA) date for action by August 29 this year. The application was based on results from the Phase III NORSE TWO trial (n=228, NCT03834753) in nAMD which showed noninferiority vs. ranibizumab.

NEW: OPL-0401 (Valo Health)

Valo Health initiated a Phase II multicenter study to evaluate the safety and efficacy of oral OPL-0401 in patients with mild, moderate and severe NPDR (n=120, NCT05393284). OPL-0401 is a small molecule rho-kinase 1/2 inhibitor. Trial completion is set for 2024.

OPT-302 (Opthea)

Two Phase III trials in nAMD are ongoing: ShORe (n=990, NCT04757610) and COAST (n=990, NCT04757636). They're evaluating intravitreal 2-mg OPT-302 in combination with 0.5 mg ranibizumab or 2 mg aflibercept, respectively. Study completion is set for the end of next year. Opthea says it expects to report topline 52-week results later in the year.

Phase IIb data of OPT-302 in combination with ranibizumab for polypoidal choroidal vasculopathy demonstrated a safety profile that was consistent with standard-of-care anti-VEGF-A monotherapy.[5]

The study also reportedly demonstrated greater improvements in BCVA and less retinal fluid in OPT-302-treated patients than in those on ranibizumab monotherapy at week 24.

NEW: OTT166 (OcuTerra Therapeutics)

Patient enrollment started in the Phase II DR:EAM trial (it stands for Diabetic Retinopathy: Early Active Management) evaluating OTT166 in adults with moderately severe to severe NPDR or mild PDR with minimal vision loss (n=210, NCT05409235). OTT166 is a small-molecule, selective integrin inhibitor eye drop application. OTT166 is designed to be used as an eye drop by the patient at home before DR advances to a vision-threatening stage.

OTX-TKI (Ocular Therapeutix)

Ten-month interim data from the Phase I trial (n=21, NCT04989699) of this intravitreal axitinib implant for nAMD is due in February. Interim seven-month data showed 73 percent of treated patients were rescue-free and had outcomes for change in BCVA and change in central subfield thickness comparable to the aflibercept arm.[6] The company also says it initiated a Phase I trial in DR, but that hasn't been registered with ClinicalTrials.gov.

PAN-90806 (PanOptica)

This topical formulation is a selective inhibitor of VEGF receptor 2. The Phase I/II trial in nAMD has been completed (n=51, NCT03479372), but no updates have been issued. PanOptica didn't respond to an inquiry by press time.

RBM-007 (Ribomic)

Two Phase II studies evaluating RBM-007, an anti-fibroblast growth factor-2 aptamer, for nAMD have shown no benefit of either monotherapy or combination treatment with aflibercept in previously treated patients (TOFU, n=86, NCT04200248; and RAMEN, n=22, NCT04640272).

However, Ribomic says that data from the much smaller TEMPURA IST study (n=5, NCT04895293) demonstrated what it characterized as "a positive trend" for improvement in BCVA and central subfield thickness. Most study participants also reportedly showed improvement in the two endpoints.

Risuteganib (Luminate, Allegro Ophthalmics)

Allegro says it's preparing a Phase IIb/III clinical trial in patients with intermediate dry AMD. Allegro hasn't issued an update on results from the Phase IIa trial of risuteganib in nAMD since 2021 (n=40, NCT03626636). Two studies explored how risuteganib may protect retinal pigment epithelium cells.[7,8] Risuteganib is a small-peptide oxidative stress stabilizer.

RO7250284 (Genentech/Roche)

The Phase I trial in nAMD, now known as BURGUNDY, is still recruiting patients and enrollment has been raised from 50 to 251 (NCT04567303). RO7250284 is a bispecific human Fab form of faricimab delivered via the port-delivery implant used with Susvimo, the port-delivery implant with ranibizumab. Study completion is set for 2027.

Tarcocimab tedromer/KSI-301 (Kodiak Sciences)

This anti-VEGF biopolymer conjugate is the focus of trials in four indications. The BEACON Phase III trial in RVO (n=568, NCT04592419) met its primary endpoint of noninferiority vs. aflibercept for BCVA change at 24 weeks.

Kodiak also reported completing enrollment in the GLOW Phase III

trial of twice-yearly dosing in patients with treatment-naive, moderately severe to severe NPDR without DME (n=253, NCT05066230).

The company also reported what it characterized as disappointing results from the Phase IIb/III DAZZLE flexible-dosing trial in nAMD (n=558, NCT04049266). Topline data showed tarcocimab failed to meet the primary study endpoint of noninferiority vs. aflibercept.

The Phase III DAYLIGHT trial is evaluating monthly tarcocimab in nAMD (n=557, NCT04964089). GLEAM (n=460, NCT04611152) and GLIMMER (n=459, NCT04603937) are evaluating tarcocimab in DME.

THR-149, THR-687 (Oxurion)

An independent data monitoring committee last year advised continuing with the Phase IIb KALAHARI trial in DME (n=126, NCT04527107). The trial is comparing the plasma kallikrein inhibitor THR-149 and aflibercept in anti-VEGF nonresponders. The trial is due for completion by year end, but Oxurion says it expects to report topline data in the second half of the year.

THR-687 is a pan-arginylglycylaspartic acid (RGD) integrin antagonist. Part A dose optimization data from the Phase II INTEGRAL trial in DME (n=16, NCT05063734) failed to meet the key endpoints of improvement in BCVA and CST. Originally slated to enroll 303, Oxurion terminated the trial based on results in 16 patients.

UBX1325 (UNITY Biotechnology)

Unity is pursuing two indications for UBX1325: DME and nAMD. Unity describes UBX1325 as a potent small molecule inhibitor of B-cell lymphoma-extra-large (Bcl-xL) that aims to inhibit the function of proteins that

Gene therapy trials in AMD, DR, DME

4D-150 (4D Molecular Therapeutics)

4D-150 consists of the targeted and evolved intravitreal vector, R100, and a payload that expresses aflibercept and a vascular endothelial growth factor-C RNA interference. The dual transgene payload inhibits VEGF-A, B, C and placental growth factor. A Phase I/II trial in neovascular age-related macular degeneration started in 2021 (n=65, NCT05197270). Interim clinical data from the first cohort (n=5) demonstrated the treatment was safe and well tolerated. A subset of three patients had mediated expression of the aflibercept transgene protein in the aqueous humor 12 weeks after injection. The cohort patients' annualized anti-VEGF injection rates were reduced by 96.7 percent. The study is due for completion in 2026. 4DMT also filed an Investigational New Drug (IND) application for a trial in diabetic macular edema, which the company says it expects to initiate later in 2023.

NEW: EXG102-031 (Exegenesis Bio)

The Food and Drug Administration has cleared the IND application for EXG102-031, a recombinant adeno-associated virus (AAV)-based gene therapy delivered via intraocular injection that aims to express a therapeutic fusion protein that binds or neutralizes all known subtypes of VEGF and angiopoietin-2 (Ang-2).

NEW: FT-003 (Frontera Therapeutics)

Frontera just dosed the first patient in a Phase I trial in nAMD in China (n=18, NCT05611424). Frontera describes FT-003 as a AAV gene-expression system using its proprietary APEX manufacturing platform.

GEM103 (Disc Medicine)

Gemini Therapeutics, acquired last year by Disc Medicine, developed GEM103, a recombinant human complement factor H (CFH) protein, but terminated Phase II studies in both nAMD and (n=50, NCT04684394) and dry AMD (n=62, NCT04643886). Both studies showed the therapy was well tolerated. The dry AMD trial showed GEM103 could reduce complement activation biomarkers while maintaining supraphysiological levels of CFH.

GT005 (Gyroscope Therapeutics/Novartis)

GT005 aims to induce expression of complement factor I. Interim data from the Phase I/II FOCUS trial in geographic atrophy (n=56, NCT03846193) showed the treatment was well tolerated.[2] FOCUS evaluated two delivery methods: transvitreal subretinal injection and with the Orbit subretinal delivery system (SDS). Of the eight patients who had the SDS treatment, six had 20 ocular adverse events, all considered mild and unrelated to treatment. Three other trials of GT005 in nAMD are underway: ORACLE, a long-term follow-up evaluating safety and durability (n=200, NCT05481827), with completion due in 2028; EXPLORE, a Phase II trial of two doses in GA (n=75, NCT04437368), with completion due in 2025; and HORIZON, a Phase II trial of medium- and high-dose therapy in GA (n=255, NCT04566445), with completion due in 2025. Novartis acquired Gyroscope last year.

NEW: IBI324 (Innovent Biologics)

Innovent describes IBI324 as an intravitreal, dual-target specific fully humanized antibody that targets VEGF-A and Ang-2. The first patient was dosed in the Phase I trial in DME (n=21, NCT05489718).

Ixo-vec/ADVM-022 (Adverum Biotechnologies)

Adverum reported two-year results from the Phase I OPTIC trial in nAMD of what it now calls Ixo-vec—for ixoberogene soroparvovec— (n=30, NCT03748784).[1] The trial evaluated two different doses: a 2 x 10^{11} vector genes per eye (vg/eye) and a lower 6 x 10^{11} vg/eye dose. Ixo-vec seemed to be well tolerated and dose-dependent inflammation responded to steroids. All higher-dose patients were inflammation and steroid-treatment free at study conclusion. Annualized anti-VEGF injections declined 81 to 98 percent and aflibercept protein levels were sustained through three years in the extension study.

Fifty-three and 80 percent of the 2E11 and 6E11 dose groups, respectively, were supplemental injection free over two years. All 30 OPTIC participants are enrolled in the OPTIC extension trial (NCT04645212), with completion set for June 2025. The first patient was dosed in the in the Phase II LUNA trial (n=72, NCT05536973), which is evaluating both doses in previously treated nAMD. Completion is set for this year. Adverum also registered a Phase II trial for both doses

in DME (n=36, NCT04418427), which ended in December 2022. Results are pending.

JNJ-1887/HRM59 (Janssen Pharmaceuticals)

JNJ-1887 is an intravitreal treatment that aims to increase expression of a soluble form of CD59 (sCD59) to protect retinal cells. Originally developed by Hemera Biosciences, Janssen, a Johnson & Johnson company, acquired the rights last year to what was known as HRM59 (it's also called JNJ-81201887 and formerly AAVCAGsCD59). A readout of a Phase I dose-escalation study of a single intravitreal injection (n=17, NCT03144999) reported that patients were treated at three escalating doses without steroid prophylaxis, meeting its primary endpoint of safety and tolerability, warranting further investigation.[3] The FDA granted JNJ-1887 Fast Track designation.

NEW: OLX10212 (Olix Pharmaceuticals)

The FDA approved an IND application for this agent that uses an asymmetric small-interfering RNA (siRNA), gene-penetrating technology to target genetic origins of inflammation. The Phase I trial (n=60, NCT05643118) started recruiting patients in December 2022.

RGX-314 (RegenxBio)

This AAV-8 vector contains an anti-VEGF transgene delivered suprachoroidally. Early results of the Phase II AAVIATE trial in nAMD (n=115, NCT04514653) showed 85 patients in the first five cohorts tolerated the suprachoroidal delivery well.[4] Patients in the RGX-314 arms received 2.5×10^{11} or 5×10^{11} genomic copies per eye (gc/eye) dose. They continued to demonstrate stable BCVA and central retinal thickness at six months, as did the ranibizumab control arm. More than 70 percent of patients needed fewer anti-VEGF injections after treatment. Ten of 15, or 67 percent, in the third dose level needed no anti-VEGF injections over six months after administration. RegenxBio says the Phase II/III ATMOSPHERE (n=300, NCT04704921) and ASCENT (n=465, NCT05407636) trials, scheduled for completion in 2023, are expected to support a Biologics License Application (BLA) for nAMD to the FDA next year.

RegenxBio is also conducting the Phase II ALTITUDE trial in center-involved DME using the suprachoroidal delivery platform (n=100, NCT04567550). Interim results from the first three cohorts (n=50) showed that 20 percent had a more than two-step improvement in Diabetic Retinopathy Severity Scale vs. 10 percent of controls and 54 percent had any DRSS improvement vs. 20 percent of controls.[5] Cohort 1 patients got a dose of 1.5×10^{11} gc/eye, which was increased to 5×10^{11} gc/eye in cohorts 2 and 3. None needed prophylactic corticosteroid before or after treatment. The trial is being expanded to include a higher dose of 1×10^{12} gc/eye.

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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 I/II trial (n=65) in nAMD ongoing. Investigational New Drug (IND) application for DME filed.
NEW: EXG102-031 (Exegenesis Bio)	Recombinant adeno-associated virus-based therapy targeting vascular endothelial growth factor and angiopoietin-2 (Ang-2)	nAMD, DME	IND application accepted in January 2023. Phase I trial pending.
NEW: FT-003 (Frontera Therapeutics)	AAV expression system using novel manufacturing platform.	nAMD	Phase I trial (n=18) initiated enrollment.
GEM103 (Disc Medicine)	Recombinant, human complement factor H (CFH)	nAMD, dry AMD	Phase II (n=62) dry AMD and Phase IIa (n=50) nAMD studies terminated.
GT005 (Gyroscope Therapeutics)	AAV-induced expression of complement factor I	GA secondary to dry AMD	Interim Phase I/II (n=56) readout demonstrated safety. Two Phase II trials (n=330).
NEW: 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, DME	Phase I nAMD trial completed (n=30); extension trial ongoing. Phase II trial (n=72) in previously treated nAMD ongoing. Phase II (n=36) in DME completed.
JNJ-1887/HRM59 (Janssen)	Soluble form of CD59 protein	GA secondary to dry AMD, nAMD	Phase I trial (n=17) reported safety of three different doses over 2 years with efficacy signals. Fast Track designation granted.
NEW: OLX10212 (Olix Pharmaceuticals)	Asymmetric small-interfering RNA (siRNA), gene-penetrating platform	nAMD	FDA approved IND application summer 2022. Phase I study started.
RGX-314 (RegenxBio)	AAV8 vector containing anti-VEGF fab transgene	Diabetic retinopathy without center-involved DME, nAMD	Second Phase III trial in nAMD initiated. Phase II readouts in DR without CI-DME (n=40) and nAMD reported. Two-year Phase I/IIa (n=42) data in nAMD reported. Phase II nAMD trial (n=40) due for completion.

senescent cells rely on for survival.

The Phase II BEHOLD proof-of-concept trial in DME (n=65, NCT04857996) met its 24-week safety and efficacy endpoints, including mean change in BCVA. The company says it expects 48-week safety and efficacy data from the trial in the second quarter. It intends to initiate a pivotal study in DME in the second half of 2023.

In nAMD, the ENVISION Phase II trial completed enrollment (n=46, NCT05275205). Patients are randomized to receive either two doses of UBX1325 (10 mcg) at in the first and fourth weeks or aflibercept (2 mg) every eight weeks. The company expects 16-week safety and efficacy results from ENVISION in the second quarter this year.

Xiflam (InflammX)

Xiflam is an oral, small-molecule NLRP3 inflammasome inhibitor that targets the Connexin43 protein and blocks the formation of hemichannels. InflammX last fall submitted an Investigational New Drug amendment that it said at the time would allow the DRCR Retina Network to initiate a Phase IIb trial in DME and DR.

InflammX says the trial will also evaluate the therapeutic effect of Xiflam on biomarkers of active kidney disease. However, no trials have been registered at ClinicalTrials.gov.

Xipere (Clearside Biomedical)

Once known as CLS-TA, Xipere, the suprachoroidal triamcinolone acetonide suspension, already FDA approved for uveitic macular edema, was the subject of the long-completed Phase II TYBEE trial in DME (n=71, NCT03126786). It's no longer listed in Clearside's pipeline on its website, but partner Arctic Vision is pursuing the DME indication for a rebranded iteration known as Arcatus/ARVN001 in Australia, New Zealand and Asia. Both companies list a Phase I DME trial in those countries as active.

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Investigative therapies for inherited retinal disease

4D-125 (Molecular Therapeutics)

The Food and Drug Administration granted Fast Track Designation to 4D-125, which targets inherited retinal dystrophies due to defects in the *RPGR* gene, including X-linked retinitis pigmentosa (XLRP). 4D-125 is designed to deliver a functional copy of the retinitis pigmentosa GTPase regulator (*RPGR*) gene to retina photoreceptors. 4DMT completed enrollment in the open-label Phase I/II clinical trial to evaluate the safety of the maximum tolerated dose (n=43, NCT04517149). Secondary endpoints include assessments of both visual function and anatomical endpoints.

(Continued on page 38)

Anti-VEGF biosimilars in clinical trials

Aflibercept biosimilars

NEW: ABP 938 (Amgen)

Results are pending from a comparator trial with aflibercept in neovascular age-related macular degeneration (n=579, NCT04270747). Primary outcome is change in best-corrected visual acuity at eight weeks. Amgen reported in November 2022 that data were expected by year end, but none have been reported as of press time.

ALT-L9 (Alteogen)

South Korea-based Alteogen reported in January that it completed a Phase I trial in its home country of ALT-L9 in nAMD. ALT-L9 showed similar safety and efficacy to the reference product. The results will aid in the design of a Phase III trial. In 2021, Alteogen completed an earlier Phase I comparator trial (n=28, NCT-04058535) that showed equivalent efficacy in nAMD.

CT-P42 (Celltrion)

Celltrion concluded enrollment in a Phase III trial in diabetic macular edema (n=348, NCT04739306). Completion of the analysis is set for April.

NEW: FYB203 (Formycon/Bioeq)

Enrollment in the Phase III MAGELLAN-AMD trial in nAMD ended last year with results pending (n=434, NCT04522167). Primary outcome is change in BCVA at eight weeks. A sale of U.S. rights to Coherus BioSciences is pending.

LY9004 (Ocumension Therapeutics/ Shandong Boan Biological Technology)

Luye Pharma's biotech subsidiary Boan Biological licensed LY9004, also known as OT-702, to China-based Ocumension. The asset is in Phase III trials for nAMD in China, but not in the United States. Boan holds licensing rights outside China.

NEW: M710/MYL-1701P (Viatris/Momenta)

One-year results of trial in people with central DME (n=355, NCT03610646) demonstrated therapeutic equivalence with the

reference product.[1] In the MYL-1701P vs. Eylea arms, the proportion of eyes that gained ≥15 and ≥10 letters were 32.4 vs. 29.3 percent and 57.4 vs. 58 percent, respectively. The proportions for ≥5- and ≥10-letter losses were 3.4 vs. 4 percent and 1.7 vs. 1.7 percent. Results are pending from an extension study evaluating the safety and efficacy (n=52, NCT04674800).

NEW: SB15 (Samsung Bioepis)

A Phase III comparator trial with aflibercept in nAMD was completed last year (n=449, NCT04450329). It met the primary endpoint: comparable change from baseline in BCVA at week 8. A 32-week interim analysis also demonstrated comparability in other secondary efficacy endpoints, safety, immunogenicity and pharmacokinetics.

SOK583A1 (Sandoz)

Sandoz, a division of Novartis, closed patient enrollment in the Phase III MYLIGHT trial (n=85, NCT04864834) in nAMD comparing SOK583A1 with the reference product. The trial is evaluating change in BCVA after 52 weeks.

Bevacizumab biosimilar

HLX04-O (Shanghai Henlius Biotech)

SHB is enrolling patients in two Phase III studies in nAMD: one in Australia (n=388, NCT04740671) and the other in China (n=388, NCT05003245), with completion dates of June this year and March 2024, respectively. A Phase I safety and efficacy trial in China reported HLX04-O was well tolerated (n=20, NCT04993352).[3] The biosimilar is already approved in China for cancer indications.

Ranibizumab biosimilars

NEW: CKD-701 (Chong Kun Dang Pharmaceutical)

A Phase III clinical trial in nAMD with ranibizumab as the comparator has found the biosimilar met predefined equivalence criteria (n=312, NCT04857177).[4] The trial was conducted in South Korea, where the sponsor company is located. Chong Kun Dang has a host of affiliations with U.S. companies, including Pfizer and Amgen.

NEW: LUBT010 (Lupin)

A Phase III comparator trial with the reference product in nAMD is recruiting patients in India (n=600, NCT04690556). The primary endpoint is change in BCVA at 12 months. Lupin has received Food and Drug Administration approval for a host of generic medications and has two oncology biosimilars—one for Filgrastim, for which it has filed for FDA approval, and the other for Etanercept, which is approved in India, Japan and the European Union.

Ximluci/Xlucane (Xbrane Biopharma/Stada Arzneimittel)

The European Commission granted marketing authorization last fall for what was known as Xlucane and the United Kingdom followed up with approval in January. Launch is set in both markets for early this year. In the United States, Xbrane and Stada withdrew the Biologics License Application it filed with the FDA, postponing that regulatory step to the first quarter of this year. The sponsors last spring completed a Phase III trial (n=582, NCT03805100), which 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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Biosimilar name (manufacturer)	Indication	Status
Reference Product: Aflibercept		
NEW: ABP 938 (Amgen)	nAMD	Comparator trial results pending (n=579).
ALT-L9 (Alteogen)	nAMD	Phase I (n=28) showed equivalence to aflibercept.
CT-P42 (Celltrion Healthcare)	Diabetic macular edema	Phase III trial (n=348) completed. Analysis due in April.
NEW: FYB203 (Formycon/Bioeq)	nAMD	Results pending from Phase II trial (n=434).
LY9004 (Ocumension Therapeutics)	nAMD	Phase III trial in China ongoing.
NEW: M710/MYL-1701P (Viatris/Momenta)	DME	Phase III INSIGHT (n=335) reported comparable efficacy and tolerability with reference agent.
NEW: SB15 (Samsung Bioepis)	nAMD	Phase III trial (n=449) completed.
SOK583A1 (Sandoz)	nAMD	Phase III trial (n=449) demonstrated comparable efficacy with aflibercept.
Reference Product: Bevacizumab		
HLX04-O (Shanghai Henlius Biotech)	nAMD	Phase I trial (n=20) completed. Two Phase III trials (n=388 each) underway.
Reference Product: Ranibizumab		
NEW: CKD-701 (Chong Kun Dang Pharmaceutical)	nAMD	Phase III comparator trial in South Korea (n=312) met predefined equivalence criteria.
NEW: LUBT010 (Lupin)	nAMD	Phase III comparator trial in India recruiting patients (n=600).
Ximluci/Xlucane (Xbrane Biopharma/Stada Arzneimittel)	nAMD	Phase III trial (n=582) demonstrated equivalency with ranibizumab. U.S. Biologics License Application pending.

Molecular Therapeutics anticipates giving additional updates in 2024. The trial is due for completion in 2029.

AGTC-402, rAAV2tYF-PR.7-hCNGB3, AGTC-501 (Applied Genetic Technologies Corp.)

AGTC is pursuing programs in XLRP and achromatopsia. In achromatopsia, a Phase I/II trial is evaluating the vector rAAV2tYF-PR.7-hCNGB3, targeting the *CNGB3* gene (n=32, NTC02599922). A previous program in achromatopsia evaluating AGTC-402 for mutations in the *CNGA3* gene was scrapped based on Phase I/II results (NCT02935517).

In XLRP, positive three-month interim data were reported from the ongoing Phase II SKYLINE trial of AGTC-501 (n=42, NCT03316560), a recombinant adeno-associated viral (AAV) vector-based therapy targeting mutations in the *RPGR* gene. The company says the trial showed robust improvements in visual sensitivity, the trial's primary efficacy endpoint, in multiple patients three months after dosing, with a 62.5 percent response rate in dose group B and a 25 percent response rate in dose group A. SKYLINE is a multi-site expansion of the ongoing Phase I/II study that's randomizing patients to either a high or low dose of AGTC-501. A Phase II/III trial evaluating the vector is planned but isn't yet recruiting (n=63, NCTO4850118). Syncona Ltd. last year acquired AGTC.

ALK-001 (Alkeus Pharmaceuticals)

Recruiting ended in 2021 in a Phase II/III trial (n=300, NCT03845582) of this oral modified form of vitamin A, but trial results still haven't been posted. Alkeus is pursuing two trials in Stargardt disease: the Phase II TEASE trial (n=140, NCT02402660), for which completion is scheduled for 2025; and an open-label extension study of TEASE enrolling by invitation only (n=140, NCT 04239625). The trials are evaluating ALK-001 vs. placebo for up to 24 months. ALK-001 is also the subject of a separate trial in geographic atrophy. Alkeus didn't reply to a query for updated information by press time.

ATSN-101/SAR439483 (Atsena Therapeutics)

ATSN-101, formerly known as SAR439483, is an AAV-based therapy for Leber congenital amaurosis caused by biallelic mutations in the *GUCY2D* gene. Results from a Phase I/II clinical trial (n=15, NCT03920007) demonstrated that patients tolerated subretinal delivery well with the highest dose of 1×10^{11} vector genes per eye (vg/eye) and had meaningful improvements in vision.[1] Trial enrollment ended in July 2022 and study completion is due in 2027.

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

Formerly called AAV-RPGR, this is a recombinant AAV vector designed to deliver functional copies of the *RPGR* gene in patients with XLRP associated with the *RPGR* gene. A readout from the ongoing Phase I/II trial (n=49, NCT03252847) demonstrated what Janssen describes as an acceptable safety profile, along with efficacy assessments that showed improvements in retinal sensitivity, visual function and functional vision.[2]

Three serious adverse events were observed overall. Most were related to the operation to deliver the vector itself and resolved without additional intervention. No dose-limiting events were reported. Janssen reports that a Phase III study is actively dosing patients.

NEW: EA-2353 (Endogena Therapeutics)

Endogena last year initiated a Phase I/IIa trial of EA-2353 in RP (n=14, NCT05392751). Study completion is set for 2025. The company describes the agent as a novel small-molecule candidate that selectively activates endogenous retinal stem and progenitor cells that differentiate into photoreceptors. Endogena also said it would file an Investigative New Drug (IND) application with the Food and Drug Administration for a trial of EA-2351 in GA this year. Endogena didn't respond to a request for an update by press time.

Elamipretide (Stealth BioTherapeutics)

A Phase II study in Leber hereditary optic neuropathy (n=12, NCT02693119) concluded and reported results in 2021. Two of 16 treated eyes had visual impairment and higher rates of mild ocular surface problems than vehicle. Six treated eyes also had mild cataract, as did five eyes first treated with vehicle before switching to elamipretide. Elamipretide is a cell-permeable peptide that targets mitochondrial dysfunction delivered via a 40-mg subcutaneous injection. Stealth didn't post an update on the program in 2022 and didn't respond to an inquiry for an update.

NEW: Emixustat (Kubota Vision)

Emixustat modulates the visual cycle by inhibiting RPE protein 65 (RPE65). Data gathering was completed in the Phase III trial in Stargardt disease in June 2022 (n=194, NCT03772665). A post hoc analysis found that Emixustat treatment resulted in a 40.8 percent reduction in lesion progression compared with placebo at month 24 vs. placebo (p=0.0206, Emixustat n=34, placebo n=21).

Investigative device-based therapies

NEW: Prima (Pixium Vision)

This intraocular implant uses a proprietary "bionic" system, as Pixium Vision calls it, to restore vision in geographic atrophy. Enrollment began in 2022 in the PRIMAvera trial (n=358, NCT04676854), with the first successfully completed implantation of a patient in Italy. The trial is scheduled for completion in 2026. Pixium has a second-generation implant that demonstrated improved vision in rats.[1] A U.S. feasibility study is also recruiting patients (n=5, NCT03392324), with completion scheduled for year end.

Retilux (PhotoOpTx)

This device, worn like an eye patch, delivers laser therapy directly to the affected eye using photobiomodulation (PBM), which uses light in the 630-to-900-nm range. The pilot study (n=135, NCT03866473) compared PBM with sham in eyes with center-involved diabetic macular edema and good vision. PBM patients had two daily treatments for 90 seconds at 670 nm for four months. The primary outcome was change in central subfield thickness at four months. Those in the sham group actually had more robust improvement: 15 (standard deviation 57) vs. 13 (53) µm, according to results posted in September 2022 at ClinicalTrials.gov. The company didn't respond to a request for more information by press time.

Device (Manufacturer)	Description	Indication	Status
NEW: Prima (Pixium Vision)	Implantable "bionic" vision system	Geographic atrophy	U.S. feasibility study (n=5) and European clinical trial (n=358) enrolling.
Retilux (PhotoOpTx)	Worn laser therapy device using photobiomodulation	Center-involved diabetic macular edema	Pilot study (n=135) failed to meet primary endpoint of change in central subfield thickness.
NEW: SING IMG (Samsara Vision)	Implantable miniature telescope	late-stage AMD	Trial enrollment initiated (n=125).
Valeda Light Delivery System (LumiThera)	Light-delivery system using photobiomodulation	dry AMD	Phase III (n-96) trial results demonstrated vision improvement.

NEW: SING IMT (Samsara Vision)

Samsara started enrollment in the prospective CONCERTO study of this implant in patients with late-stage age-related macular degeneration (n=125, NCT05438732). SING IMT stands for smaller-incision, new-generation, implantable miniature telescope. The first U.S. procedures with the SING IMT were performed last summer. The Food and Drug Administration approved a post-market application supplemental study to evaluate improvements in visual acuity and device safety. CONCERTO is recruiting older adults living with stable, bilateral central scotomas due to late-stage AMD and fovea-involving GA or disciform scar.

Valeda Light Delivery System (LumiThera)

LumiThera reported findings from the LIGHT-SITE III trial in dry AMD (n=96, NCT04065490). Patients were randomized 2:1 to PBM or sham. The trial results demonstrated statistically significant improvement in the prespecified primary endpoint in best-corrected visual acuity at 13 months in the PBM group vs. sham (p =0.02). The PBM arm had a sustained, average increase in Early Treatment of Diabetic Retinopathy Study letter score of 5.5 letters from baseline at 13 months (p<0.0001). Fifty-five percent of PBM responders demonstrated a >5-letter improvement on the standard EDTRS eye chart with a mean of 9.7 letters and 26 percent achieved a >10-letter improvement with a mean of 12.8 letters.

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NEW: 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 human *RPE65* gene to the nuclei of the patient's retinal cells. Frontera obtained investigational new drug application approvals last year from regulatory authorities in the United States and China and in January initiated a Phase I trial in LCA-2 in China, which isn't listed at ClinicalTrials.gov. Frontera says it expects a data readout later this year.

jCell (jCyte, Santen)

jCell is an intravitreal injection of human retinal progenitor cells (hRPC) that aims to preserve or potentially restore some vision in RP and related conditions. Results were posted last year from the Phase IIb trial (n=84, NCT03073733) in adults with RP. Patients received either a 3 x 10^6 or 6 x 10^6 dose or sham.

The primary trial outcome was average change in best-corrected visual acuity at 12 months. The sham group had an average letter gain of 3.9 (standard deviation 3.9) vs. 1.3 (14.14, p=0.582) and 2.6 (21.53, p=0.984) in the respective dosing groups. However, a higher percentage of treated patients had a VA improvement of ≥13 letters: 11.5, 16 and 30.4 percent for the sham and low- and high-dose groups (p=0.157). A separate trial is evaluating the safety of repeat injections in adults with RP (n=30, NCT04604899).

Lumevoq/GS010 (GenSight Biologics)

In the latest readout of the RESTORE trial of Lumevoq (lenadogene nolparvovec, n=61, NCT03406104), study participants with LHON due to the *ND4* mutation continued to show improvement in vision after five years of follow-up. Participants received a single intravitreal injection of rAAV2/2-ND4. RESTORE is the long-term follow-up study of the Phase III RES-

Table. Investigative therapies for inherited retinal disease

Product name (manufacturer)	Description
4D-125 (Molecular Therapeutics)	Subretinal delivery of functional copies of RPGR gene
ATSN-101 (formerly SAR439483, Atsena Therapeutics)	Functional copy of *GUCY2D* gene delivered subretinally
AGTC-402 and **rAAV2tYF-PR1.7-hCNGB3** (Applied Genetic Technologies Corporation)	Adeno-associated vector targeting mutations in *CNGA3* and *CNGB3* genes
AGTC-501 (formerly rAAV2tYF-GRK1-RPGR, AGTC)	Recombinant adeno-associated virus vector-based gene therapy
ALK-001 (Alkeus Pharmaceuticals)	Oral modified vitamin A
ATSN-101/SAR439483 (Atsena Therapeutics)	AAV-based therapy targeting *GUCY2D* gene mutations
Botaretigene sparoparvovec/AAV-RPGR (MeiraGTx/Janssen)	Delivers functional copy of *RPGR* gene
NEW: EA-2353 (Endogena Therapeutics)	Selective small-molecule activator of endogenous retinal stem and progenitor cells
Elamipretide (Stealth BioTherapeutics)	Subcutaneous mitochondria-targeting, cell-permeable peptide
NEW: Emixustat (Kubota Vision)	*RPE65* inhibitor
NEW: FT-001 (Frontera Therapeutics)	Delivers functional copy of RPGR gene
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 delivery functional *NR2E3* gene
NEW: OPGx-001 (Opus Genetics)	AAV-8 vector to deliver functional *LCA5* gene.
NEW: Sepofarsen (ProQR Therapeutics)	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
Visomitin (Mitotech)	Topical cardiolipin peroxidation inhibitor

CUE (n=39, NCT02652767) and REVERSE (n=37, NCT02652780) trials, which demonstrated sustained BCVA improvement in treated patients. GenSight says it anticipates approval in the European Union by the end of the year.

MCO-10 (Nanoscope Therapeutics)

Nanoscope completed enrollment in two trials for its ambient-light activated optogenetic monotherapy: STARLIGHT, a Phase II open-label trial (n=6, NCT05417126) in Stargardt disease; and a Phase IIb/III trial in RP (n=27, NCT04945772).

Six-month data from the Stargardt trial are expected by spring. The FDA granted fast-tack designation for the RP indication last fall. Topline data from the RP trial are expected in the spring.

OCU400 (Ocugen)

OCU400 (AAV-NR2E3) is a modified gene therapy that targets nuclear hormone receptors for RP associated with mutations in the *Nr2e3* gene and rhodopsin and LCA with mutations in the *Cep290* gene, for which the FDA granted orphan drug designation.

A Phase I/II trial evaluating OCU400 is currently recruiting patients (n=21, NCT05203939). The trial's drug safety and monitoring board established high-dose OCU400 as the maximum tolerable dose for the dose escalation phase of the study. Enrollment is expected to be completed this year.

NEW: OPGx-001 (Opus Genetics)

The FDA in December 2022 cleared the IND application for a Phase I/II trial in adults with LCA resulting from biallelic mutations in the *LCA5* gene (n=9, NCTo5616793). OPGx-001 is an AAV-8 vector designed to precisely deliver a functional *LCA5* gene to retinal photoreceptors. It's administered via subretinal delivery. Animal and human-induced pluripotent stem cell models demonstrated preservation of retinal structure and visual function when OPGx-001 was administered before peak disease activity. The trial is due for completion in 2027.

NEW: Sepofarsen (ProQR Therapeutics)

Sepofarsen is an RNA therapy for

	Indication	Status
	X-linked retinitis pigmentosa (XLRP)	Enrollment completed in Phase I/II trial (n=43).
	GUCY2D-associated LCA1	Phase I/II trial (n=15) reported high-dose treatment (1E11 vg/eye) yielded vision improvements.
	Achromatopsia	Phase I/II trial evaluating rAAV2tYF-PR1.7-hCNGB3 (n=24) ongoing. AGTC-402 program terminated.
	XLRP	Interim Phase I/II (n=42) data reported. Phase II/III (n=63) planned.
	Stargardt disease	Recruiting in Phase II/III (n=300) trial ended in 2021. Phase II (n=140) and open-label extension study (n=140) ongoing.
	Leber congenital amaurosis	Early Phase I/II trial results (n=15) indicated safety and efficacy signal. Enrollment ended in 2022.
	XLRP associated with the retinitis pigmentosa GTPase regulator (*RPGR*) gene	Phase I/II trial demonstrated acceptable safety profile and efficacy signal; Phase III trial recruiting.
	Retinitis pigmentosa	Phase I/IIa trial (n=14) initiated.
	Leber hereditary optic neuropathy	Phase II trial (n=12) completed in 2021. No update available.
	Stargardt disease	Post hoc analysis of Phase II trial (n=194) reported.
	LCA-2	Phase I trial initiated.
	RP	Phase IIb trial (n=84) failed to meet primary endpoint. Separate trial (n=30) evaluating repeat injections in adults showed sustained visual acuity improvement at 12 months.
	LHON	Long-term results (n=61) showed sustained vision improvement after five years.
	RP, Stargardt disease	Fast-track designation in RP granted in 2022. Data in both indications expected in 2023.
	RP, LCA	Orphan drug designation granted in December 2022. Phase I/II trial (n=21) recruiting patients.
	LCA from biallelic mutations.	Application for Phase I/II trial (n=9) approved in 2022.
	LCA10	Phase II/III trial (n=36) failed to meet primary endpoint.
	Stargardt disease	One-year Phase Ib/II trial (n=13) demonstrated positive results. Phase II trial ongoing in Australia, Taiwan.
	LHON	No update on planned Phase II trial.

LCA10 due to the c.2991+1655A>G mutation in the *CEP290* gene. ProQR was conducting a post hoc analysis of 12-month data from the Phase II/III ILLUMINATE trial (n=36, NCT03913143), but sepofarsen failed to meet its primary endpoint of improved BCVA. An open-label, dose-escalation trial of sepofarsen for the same indication in children ages 8 years and younger is listed as recruiting (n=15, NCT0855045). In August 2022 the company said it would focus exclusively on development of its Axiomer RNA-editing technology and seek a strategic partner for its ophthalmology assets, including sepofarsen.

Tinlareband/LBS-008 (Belite Bio)

Belite Bio last year started enrollment in the U.S. Phase III clinical trial of LBS-008, also known as Tinlarebant, in patients with the STGD1 form of Stargardt disease. Interim one-year results of the Phase Ib/II study in adolescent patients with STGD1 (n=13, NCT05266014) demonstrated stabilization of retinal thickness "in many subjects," Belite Bio reported, along with vision stabilization in nine of 13 patients (69.2 percent).[3] Belite Bio also says it's conducting a two-year Phase II study, which has enrolled 13 subjects at clinical sites in Australia and Taiwan, along with the two-year Phase III trial in adolescent STGD1. Neither is listed at Clinical Trials.gov.

Visomitin/SkQ1 (Mitotech)

Visomitin is a topical cardiolipin peroxidation inhibitor that Mitotech is also developing to treat dry-eye disease and glaucoma. The FDA in 2021 granted orphan drug designation for treatment of LHON, and Mitotech said last year it was planning to start a Phase II trial for the indication but no trial has been posted at ClinicalTrials.gov. The company didn't respond to a query for an update by press time.

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The potential impact of pegcetacoplan

(Continued from page 26)

as vertically aligned signs of photoreceptor degeneration, RPE attenuation or disruption, and increased signal transmission into the choroid <250 µm in diameter in the absence of an RPE tear.[21,22]

- ***Complete RPE and outer retinal atrophy (cRORA)***, when RPE changes and hypertransmission reach 250 µm the lesion is qualified as cRORA (*Figure 2, page 26*).[21,22] iRORA lesions are known to progress to cRORA lesions at variable rates from months to years.[22]

Bottom line

Combined, the DERBY and OAKS data reveal the beneficial effect of intravitreal pegcetacoplan to reduce GA progression vs. sham in eyes with extrafoveal lesions for both monthly and EOM dosing—26 and 23 percent, respectively (p<0.0001and p=0.0002). Given that extrafoveal lesions are one of several findings suggestive of faster growth rate and more aggressive disease, this is further supportive of this medication's potential to impact the quality of our patients' lives. The long-term extension GALE study will provide data on pegcetacoplan use for up to 36 months. RS

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The case for Kenalog

(Continued from page 18)

little, and you may as well do a naked peel. Too much, and you lose all visualization akin to being in a heavy snowstorm. We prefer a 1:4 dilution of Kenalog (directly from the bottle) mixed with sterile balanced salt solution. Avoid having circulator nurses remove the preservative, as that step is an unnecessary potential source of contamination or needle-stick injury. During the course of vitrectomy, the preservative gets washed away and seldom causes any inflammation.

Use Kenalog, not preservative-free Triesence. It's not (all) about cost. Kenalog particles are small and perfectly granular. They allow for the ideal amount of dusting. Triesence tends to settle in clumps and when it does so it becomes a poor visualization aid, although it probably works fine for vitreous staining.

ICG-stainers contend that Kenalog can't identify the ILM. Not true. Just look for the characteristic features: blanching of the peeled macular tissue; petechial hemorrhages; and scrolling of the peeled membrane. While making the initial flap, look for tension lines from the initial forceps grab, and the subsequent tear in the ILM. That will offer the initial handle for the peel (*Figure, page 18*).

Avoid the pitfall of the infusion washing away the Kenalog granules. Redirect the cannula, lower the infusion pressure or fix any leaks in your valved system. The infusion won't cause an issue if the system is truly closed, so suture leaky sclerotomies and replace leaky cannulas.

After peeling, remove the excess Kenalog using passive extrusion, especially for macular holes (*Video*). The granules are easily aspirated in this manner. RS

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)

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 during the first year was 2% (25 out of 1,262) in patients treated with VABYSMO compared with 2% (14 out of 625) in patients treated with aflibercept *[see Clinical Studies (14.2)]*.

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)]*

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 1,926 patients, which constituted the safety population in four Phase 3 studies *[see Clinical Studies (14.1, 14.2)]*.

Table 1: Common Adverse Reactions (≥ 1%)

Adverse Reactions	VABYSMO		Active Control (aflibercept)	
	AMD N=664	DME N=1262	AMD N=622	DME N=625
Conjunctival hemorrhage	7%	7%	8%	6%
Vitreous floaters	3%	3%	2%	2%
Retinal pigment epithelial tear[a]	3%		1%	
Intraocular pressure increased	3%	3%	2%	2%
Eye pain	3%	2%	3%	3%
Intraocular inflammation[b]	2%	1%	1%	1%
Eye irritation	1%	1%	< 1%	1%
Ocular discomfort	1%	1%	< 1%	< 1%
Vitreous hemorrhage	< 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, lacrimation increased, ocular hyperemia, blurred vision, eye irritation, sensation of foreign body, endophthalmitis, visual acuity reduced transiently, retinal tear and rhegmatogenous retinal detachment.

6.2 Immunogenicity

The immunogenicity of VABYSMO was evaluated in plasma samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to VABYSMO in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to VABYSMO with the incidence of antibodies to other products may be misleading.

There is a potential for an immune response in patients treated with VABYSMO. In the nAMD and DME studies, the pre-treatment incidence of anti-faricimab antibodies was approximately 1.8% and 0.8%, respectively. After initiation of dosing, anti-faricimab antibodies were detected in approximately 10.4% and 8.4% of patients with nAMD and DME respectively, treated with VABYSMO across studies and across treatment groups. As with all therapeutic proteins, there is a potential for immunogenicity with VABYSMO.

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 four clinical studies, approximately 60% (1,149/1,929) 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:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990
U.S. License No.: 1048

M-US-00013249(v1.0) 2/22

VABYSMO™
faricimab-svoa injection 6 mg

WHERE 2 WORLDS MEET

The First and Only Dual-Pathway Inhibitor in Retinal Disease[1-5]

VABYSMO Is the First IVT Injection Approved for Q4W-Q16W Dosing Intervals in nAMD and DME[1-4]*

Image not intended to be a patient portrayal.

Visit VABYSMO-HCP.com

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) and Diabetic Macular Edema (DME).

IMPORTANT SAFETY INFORMATION

Contraindications

VABYSMO is contraindicated in patients with ocular or periocular inflammation, in patients with active intraocular inflammation, and in patients with known hypersensitivity to faricimab or any of the excipients in VABYSMO.

Warnings and Precautions

- Endophthalmitis and retinal detachments may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.
- Increases in intraocular pressure have been seen within 60 minutes of an intravitreal injection.
- There is a potential risk of arterial thromboembolic events (ATEs) associated with VEGF inhibition.

Adverse Reactions

The most common adverse reaction (≥5%) reported in patients receiving VABYSMO was conjunctival hemorrhage (7%).

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 Brief Summary of VABYSMO full Prescribing Information on the following page.

*Dosing Information:

In nAMD, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for the first 4 doses, followed by OCT and visual acuity evaluations 8 and 12 weeks later to inform whether to extend to: 1) Q16W (weeks 28 and 44); 2) Q12W (weeks 24, 36, and 48); or 3) Q8W (weeks 20, 28, 36, and 44).

In DME, the recommended dose for VABYSMO is 6 mg (0.05 mL of 120 mg/mL solution) IVT Q4W for ≥4 doses until CST is ≤325 µm (by OCT), followed by treat-and-extend dosing with 4-week interval extensions or 4- to 8-week interval reductions based on CST and visual acuity evaluations through week 52. Alternatively, VABYSMO can be administered IVT Q4W for the first 6 doses, followed by Q8W dosing over the next 28 weeks.

Although VABYSMO may be dosed as frequently as Q4W, additional efficacy was not demonstrated in most patients when VABYSMO was dosed Q4W vs Q8W. Some patients may need Q4W dosing after the first 4 doses. Patients should be assessed regularly and the dosing regimen reevaluated after the first year.

CST=central subfield thickness; IVT=intravitreal; OCT=optical coherence tomography; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; Q16W=every 16 weeks.

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