

Neovascular Age-Related Macular Degeneration (nAMD): A Review of Emerging Treatment Options

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Abstract: Neovascular age-related macular degeneration (nAMD) is a common world-wide cause of visual loss. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents are an effective means to treat nAMD and reduce its impact on vision compared to either sham treatment or photodynamic therapy. Currently, the approved anti-VEGF drugs include ranibizumab, aflibercept and brolucizumab. In addition, bevacizumab, used as an off-label drug, and has been shown to be effective in treating nAMD. While anti-VEGF agents are effective, its limitations include the requirement for frequent, often monthly injections, and the need for long-term treatment of nAMD. These present significant burdens on the healthcare system and on the patients. In addition, reviews of patients with nAMD treated with anti-VEGF have reported deterioration of vision over time with progression of geographic atrophy. These limitations are partly addressed by exploring different treatment regimens that reduce the frequency of treatments. Newer anti-VEGF drugs have been shown in Phase III clinical trials to have injection intervals as long as 12 or even 16 weeks for a proportion of patients. There is research on newer drugs that affect other pathways, such as the angiopoietin pathway, which may impact nAMD by extending the treatment interval and reducing the burden of treatment. Other measures include the use of sustained-release implants that release the drug regularly over a period of time, and can be refilled periodically, as well as hydrogel platforms that serve to release the drug. The use of biosimilars will also serve to reduce the cost of treatment for nAMD. A new frontier of gene therapy, primarily targeting genes involved in the transduction of retinal cells to produce anti-VEGF proteins intraocularly, also opens a new avenue of therapeutic approaches that can be used for treatment. This review paper will discuss both current treatment options and the newer treatments under development.

Keywords: neovascular AMD, anti-VEGF, retina, gene therapy

Introduction

Neovascular age-related macular degeneration (nAMD) is one of the commonest causes of blindness throughout the world, affecting over 200 million people globally.¹ Its prevalence is expected to increase with the ageing population in many countries.

Vascular endothelial growth factor (VEGF) is a potent endothelial-specific mitogen that elicits angiogenesis and vascular hyperpermeability in response to hypoxia.² VEGF has been implicated in the development of retinal neovascularization, as well as choroidal neovascularization (CNV) in animal models.^{3–5} VEGF is involved in the pathogenesis of AMD, with increased expression of VEGF reported in the RPE and vitreous of eyes with both non-neovascular and neovascular AMD.⁶

Anti-vascular endothelial growth factor (anti-VEGF) agents are medications aimed at blocking the effects of VEGF. The introduction of these agents have revolutionized the treatment of nAMD. In clinical trials, patients treated with intravitreal anti-VEGF agents experienced gains in best-corrected visual acuity (BCVA) which were superior to sham treatment or photodynamic therapy.^{7,8} Treatment with anti-VEGF agents, however, presents a significant burden to

patients, in terms of cost and the requirement for monthly clinic visits and injections due to their chronic nature of the disease and transient treatment effect, which are related to the half-life of the drugs. In addition, real-world studies have shown that the visual gains were suboptimal compared to those attained in randomized controlled clinical trials. Further compounding this is the fact that adherence to treatment regimens is not always ideal, and patients treated with fewer injections tended to experience loss of vision over time. These provided the impetus for the continuing search for newer drugs and durable treatment modalities to address these limitations. The major studies for these anti-VEGF agents have been summarized in [Table 1](#).

Currently, the anti-VEGF agents available for clinical use include ranibizumab (Lucentis; Genentech), aflibercept (Eylea; Regeneron), brolucizumab (Beovu; Novartis), bevacizumab (off-label; Avastin; Genentech), pegaptanib sodium (Macugen; Eyetech) with several studies showing visual and anatomical improvement following treatment.

Ranibizumab

Ranibizumab is a humanized antibody fragment that targets all isoforms of VEGF-A, inhibiting the binding of VEGF molecules to their receptors. It was approved by the FDA in 2006 based on two large phase III clinical trials (MARINA and ANCHOR). The Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) trial⁷ was a 2-year, multicenter, double-blind study that randomized 716 patients with neovascular AMD into three treatment arms: ranibizumab 0.3mg, ranibizumab 0.5mg, or sham intravitreal injection.

Treatment with monthly ranibizumab showed an improvement in mean BCVA compared to baseline as compared to patients in the sham group. At month 12, there was an increase in mean visual acuity of 6.5 letters and 7.2 letters in the 0.3mg and 0.5mg groups respectively, compared to a decrease of 10.4 letters in the sham group ($P < 0.001$ for both comparisons). At 12 months, 94.5% and 94.6% of patients in the 0.3mg and 0.5mg group respectively lost fewer than 15 letters, compared to 62.2% of patients in the sham group. 24.8% and 33.8% of patients in the 0.3mg and 0.5mg groups respectively reported an improvement of 15 letters or more in visual acuity compared to 5.0% for the sham group.

The Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) trial⁸ was a multicenter, double-blind, phase III study which compared Ranibizumab with verteporfin photodynamic therapy (PDT). PDT was regarded as standard of care for classic CNV due to its efficacy and good safety profile.⁹ The ANCHOR trial randomized 423 patients with neovascular AMD (predominantly classic CNV) into three treatment arms: ranibizumab 0.3mg plus sham PDT ranibizumab 0.5mg plus sham PDT or sham intravitreal injections plus active PDT.

Similar to MARINA, the ANCHOR trial demonstrated that monthly ranibizumab injections lead to significant improvements in visual acuity. There was an increase in mean visual acuity of 8.5 letters in the 0.3mg group and 11.3 letters in the 0.5mg group, compared to a decrease of 9.5 letters in the verteporfin group. In the first of 2 years, 35.7% and 40.3% of patients in the 0.3mg and 0.5mg group respectively reported a significant improvement of 15 letters or more in BCVA, compared to 5.6% of the verteporfin group.⁸

While these two studies showed that ranibizumab prevented visual loss and disease progression in the short term, these agents do not assure long-term visual stability or disease quiescence. The SEVEN-UP study was a multicenter cohort study that sought to assess long-term patient outcomes after initiation of intensive ranibizumab therapy.¹⁰ It comprised of 65 participants from the ANCHOR, MARINA and HORIZON studies.^{7,8,11} The HORIZON trial was an open-label, multicentre, extension trial that aimed to evaluate the long-term efficacy and safety of ranibizumab injections. Patients who completed the controlled treatment phase of 1 of 3 randomized 2 year clinical trials (MARINA, ANCHOR and FOCUS) were eligible for enrolment.

The SEVEN-UP study demonstrated that patients previously treated with anti-VEGF were still at risk of vision loss. After a mean of 7.3 years after enrolment into the ANCHOR or MARINA study, only one third of patients had good visual outcomes with 37% of eyes attaining a BCVA of 20/70 or better. Similarly, 37% of eyes had poor visual outcomes with a BCVA of 20/200 or worse. Moreover, progression of disease was seen as 34% of eyes had a significant decline in vision of ≥ 15 ETDRS letters from baseline measurements. Overall, there was a mean decline of 19.8 EDTRS letters from therapeutic peak after 24 months of injections ($P < 0.001$). Conversely, only 43% of patients had stable or improved

Table 1 Summary of the Major Anti-VEGF Studies

Study Name (Year Published)	Treatment Arms	Main Outcomes	Safety Profile
MARINA (2006) Number of subjects = 716	- Placebo - Monthly Ranibizumab 0.3mg - Monthly Ranibizumab 0.5mg	<u>At 2 years</u> 1. Both treatment groups were superior to placebo in maintaining vision (loss of < 15 letters) (p<0.001 for both comparisons) <ul style="list-style-type: none"> • 94.5% of Ranibizumab 0.3mg group • 94.6% of Ranibizumab 0.5mg group • 62.2% of placebo group 2. Both treatment groups were superior in improving vision (gain in ≥ 15 letters) (p<0.001 for both comparisons) <ul style="list-style-type: none"> • 24.8% of Ranibizumab 0.3mg group • 33.8% of Ranibizumab 0.5mg group • 5% of controls 3. Average change in VA <ul style="list-style-type: none"> • Treated groups: 7 letters gained • Controls: 10 letters lost 	Endophthalmitis (0 to 1.3%), Uveitis (0 to 1.3%)
ANCHOR (2006) Number of subjects = 423	- Ranibizumab 0.3mg - Ranibizumab 0.5mg - PDT	<u>At 1 year</u> 1. Ranibizumab was superior to PDT in preventing visual loss (MLV ≤ 15 letters) (p<0.001 for each comparison) <ul style="list-style-type: none"> • 94.3% of Ranibizumab 0.3mg group • 96.4% of Ranibizumab 0.5mg group • 64.3% of PDT group 2. Patients in the Ranibizumab treatment arms had significantly higher gain in visual acuity compared to the PDT group (gain > 15 letters) (p<0.001 for each comparison) <ul style="list-style-type: none"> • 35.7% of Ranibizumab 0.3mg group • 40.3% of Ranibizumab 0.5mg group • 5.6% of PDT group 3. Patients in the PDT groups had significantly higher rates of severe visual loss (decrease ≥ 30 letters) (p<0.001 for each comparison) <ul style="list-style-type: none"> • 0% of Ranibizumab groups • 13% of PDT group 	Endophthalmitis (0 to 1.4%), Uveitis (0 to 0.7%)

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Table 1 (Continued).

Study Name (Year Published)	Treatment Arms	Main Outcomes	Safety Profile
CATT (2011) Number of subjects = 1208	<ul style="list-style-type: none"> - Ranibizumab 0.5mg monthly - Ranibizumab 0.5mg PRN - Bevacizumab 1.25mg monthly - Bevacizumab 1.25mg PRN 	<p><u>At 1 year</u></p> <p>1. Bevacizumab was non-inferior (limit of ± 5 letters) to Ranibizumab on BCVA improvement when matched for regime</p> <ul style="list-style-type: none"> • + 8.5 letters in Ranibizumab 0.5mg monthly group • + 8.0 letters in Bevacizumab 1.25mg group • + 6.8 letters in the Ranibizumab 0.5mg PRN group • + 5.9 letters in the Bevacizumab 1.25mg PRN group <p>2. Bevacizumab was non-inferior to Ranibizumab in the prevention of MVL (≥ 15 letters) ($p=0.29$)</p> <ul style="list-style-type: none"> • 94.4% in Ranibizumab 0.5mg monthly group • 94.0% in Bevacizumab 1.25mg monthly group • 95.4% in Ranibizumab 0.5mg PRN group • 91.5% in Bevacizumab 1.25mg PRN group 	Death from any cause (1.3 to 3.7%), Arteriothrombotic event (2.0 to 2.7%), Endophthalmitis (0 to 1.4%)
IVAN (2013) Number of subjects = 525	<ul style="list-style-type: none"> - Ranibizumab 0.5mg monthly - Ranibizumab 0.5mg PRN - Bevacizumab 1.25mg monthly - Bevacizumab 1.25mg PRN 	<p><u>At 2 years</u></p> <p>1. Bevacizumab was non-inferior (limit of ± 3.5 letters) to ranibizumab. Mean difference of -1.37 letters ($p=0.26$)</p> <ul style="list-style-type: none"> • 67.8 letters in combined Ranibizumab group • 66.1 letters in combined Bevacizumab group <p>2. Discontinuous treatment was non-inferior to continuous treatment. Mean difference of -1.63 letters ($p=0.18$)</p> <ul style="list-style-type: none"> • 67.3 letters in discontinuous regimen • 66.6 letters in continuous regimen 	Death from any cause (3 to 7%), Arteriothrombotic event or heart failure (4 to 7%), Venous thrombotic event (1%), Ocular event in study eye (2 to 3%)

<p>VIEW 1 and VIEW 2 (2012) Number of subjects = 2419</p>	<ul style="list-style-type: none"> - Aflibercept 0.5mg monthly - Aflibercept 2mg monthly - Aflibercept 2mg 2-monthly - Ranibizumab 0.5mg monthly 	<p><u>At 52 weeks</u></p> <p>1. All aflibercept groups were non-inferior (limit of $\pm 10\%$) to ranibizumab in maintaining vision at 52 weeks</p> <p>VIEW 1:</p> <ul style="list-style-type: none"> • 95.1% in Aflibercept 2mg monthly group • 95.9% in Aflibercept 0.5mg monthly group • 95.1% in Aflibercept 2mg 2-monthly group • 94.4% in Ranibizumab 0.5mg monthly group <p>VIEW 2:</p> <ul style="list-style-type: none"> • 95.6% in Aflibercept 2mg monthly group • 96.3% in Aflibercept 0.5mg monthly group • 95.6% in Aflibercept 2mg 2-monthly group • 94.4% in Ranibizumab 0.5mg monthly group <p>2. [View 1] Only the Aflibercept 2mg monthly group was statistically superior to the Ranibizumab monthly group ($p=0.005$)</p> <ul style="list-style-type: none"> • + 10.9 letters in Aflibercept 2mg monthly group • + 8.1 letters in Ranibizumab 0.5mg monthly group 	<p>Endophthalmitis (0 to 1%), Arteriothrombotic event (0.7 to 2.6%)</p>
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Table I (Continued).

Study Name (Year Published)	Treatment Arms	Main Outcomes	Safety Profile
HAWK (2020) Number of subjects = 1775	- Brolucizumab 3mg 12-weekly (after 3 monthly injections) - Brolucizumab 6mg 12-weekly (after 3 monthly injections) - Aflibercept 2mg 8-weekly	<u>At 48 weeks</u> Brolucizumab was non-inferior to Aflibercept in mean BCVA change from baseline ($P<0.01$). Least squares mean BCVA change (ETDRS letters): <ul style="list-style-type: none"> • Brolucizumab 3mg: +6.1 • Brolucizumab 6mg: +6.6 • Aflibercept 2mg: +6.8 <u>At 96 weeks</u> Brolucizumab was similarly non-inferior to Aflibercept in mean BCVA change from baseline ($P<0.01$). Least squares mean BCVA change (ETDRS letters): <ul style="list-style-type: none"> • Brolucizumab 3mg: +5.6 • Brolucizumab 6mg: +5.9 • Aflibercept 2mg: +5.3 	Pooled analysis of data from HAWK and HARRIER reported overall comparable incidences of ocular and non-ocular AEs between Brolucizumab and Aflibercept over 96 weeks. However, intraocular inflammation (iritis and uveitis) was seen at a higher rate with Brolucizumab 6mg vs Aflibercept at week 96 in HAWK (4.7% vs 0.6%) and HARRIER (0.8% vs 0.3%). There were also 10 cases of retinal artery occlusion in the Brolucizumab arms across HAWK and HARRIER.
HARRIER (2021) Number of subjects = 1048	- Brolucizumab 6mg 12-weekly (after 3 monthly injections) - Aflibercept 2mg 8-weekly	<u>At 48 weeks</u> Brolucizumab was non-inferior to Aflibercept in mean BCVA change from baseline ($P<0.01$). Least squares mean BCVA change (ETDRS letters): <ul style="list-style-type: none"> • Brolucizumab 6mg: +6.6 • Aflibercept 2mg: +6.8 <u>At 96 weeks</u> Brolucizumab was similarly non-inferior to Aflibercept in mean BCVA change from baseline ($P<0.01$). Least squares mean BCVA change (ETDRS letters): <ul style="list-style-type: none"> • Brolucizumab 6mg: +6.1 • Aflibercept 2mg: +6.6 	
TENAYA (2021) Number of subjects = 671	- Faricimab 6.0mg up to every 16 weeks - Aflibercept 2.0mg every 8 weeks	1. Faricimab group was non-inferior to the aflibercept group in change of BCVA from baseline <ul style="list-style-type: none"> • Faricimab group gained 5.8 letters (95% CI 4.6 to 7.1) compared to 5.1 letters (95% CI 3.9 to 6.4) in the aflibercept group • Treatment difference of 0.7 letters (95% CI -1.1 to 2.5) 	For both TENAYA and LUCERNE: Intraocular inflammation (1.2 to 2.0%). No cases of retinal vasculitis or occlusive retinitis were reported
LUCERNE (2021) Number of subjects = 658	- Faricimab 6.0mg up to every 16 weeks - Aflibercept 2.0mg every 8 weeks	1. Faricimab group was non-inferior to the aflibercept group in change of BCVA from baseline <ul style="list-style-type: none"> • Faricimab group gained 6.6 letters (95% CI 5.3 to 7.8) compared to 6.6 letters (95% CI 3.9 to 6.4) in the aflibercept group • Treatment difference of 0.0 letters (95% CI -1.7 to 1.8) 	For both TENAYA and LUCERNE: Intraocular inflammation were 2.0% and 1.2% for faricimab and aflibercept respectively. No cases of retinal vasculitis or occlusive retinitis were reported

Abbreviations: MARINA, Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab in the treatment of Neovascular AMD; ANCHOR, Anti-VEGF antibody for the treatment of predominantly Classic Choroidal Neovascularisation in AMD; CATT, Comparison of AMD Treatments Trial; IVAN, Inhibit VEGF in Age related CNV; VIEW, VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD; BCVA, Best corrected visual acuity; MLV, Mean loss of vision.

vision (no loss of letters and gain of ≥ 0 letters) compared to baseline, with only 12% having an improvement of ≥ 15 letters.¹⁰ Unfavourable anatomic features were also evident on multimodal imaging, with most patients developing evidence of macular atrophy or scarring. On fluorescein angiography, 48% of eyes had definite or suspected leakage from CNV, with 68% of eyes showing evidence of exudation on SD-OCT. Notably, 98% of eyes were seen to have macular atrophy, with 90% of eyes showing involvement of the fovea. Macular atrophy was shown to correlate significantly with decreased BCVA ($P < 0.0001$), where a 2.3 letter decrease was seen with every 1mm^2 increase in area of atrophy ($P < 0.0001$).¹⁰

Aflibercept

Aflibercept is a recombinant fusion protein that is comprised of domains from human VEGF receptors 1 and 2. It binds to VEGF-A, VEGF-B and placental growth factor with high affinity, and has been shown to be effective and non-inferior to monthly ranibizumab in 2 large multicenter trials.

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1 and VIEW 2) studies were multinational, double-blind, randomized Phase 3 clinical trials that randomized 2149 (1217 from VIEW 1 and 1240 from VIEW 2) patients into 4 treatment arms: 0.5mg monthly, 2mg monthly and 2mg 2-monthly intravitreal injections of aflibercept, and 0.5mg monthly intravitreal injections of ranibizumab.¹²

The primary end point was noninferiority at 52 weeks of aflibercept compared to ranibizumab in maintaining vision. In both studies, Aflibercept was shown to be non-inferior to Ranibizumab in achieving the primary end point.

The proportion of patients achieving a gain of ≥ 15 ETDRS letters was similar in all treatment groups, ranging from 24.9% to 37.5% in the VIEW 1 study and 29.4% to 34.8% in the VIEW 2 study. Moreover, mean change in BCVA was also similar in all treatment groups, ranging from 6.9 to 10.9 letters gained in the VIEW 1 study, and 7.6 to 9.7 letters gained in the VIEW 2 study. Of note, the aflibercept 2mg monthly injection group was statistically superior to the monthly ranibizumab group (10.9 letters vs 8.1 letters). However, this result was only seen in the VIEW 1 study.

With regards to the primary endpoint of maintaining vision, the proportion of patients that lost ≤ 15 letters in the aflibercept group was similar to the ranibizumab group (95.1% in View 1 and 94.5% for aflibercept in View 2, compared to 93.8% and 94.8% of patients in the ranibizumab group).

The proportion of patients with dry retinas on OCT were also analyzed, with a higher proportion of patients in the 2mg monthly aflibercept group compared to the ranibizumab group (integrated analysis of 72.4% and 62.0% of patients respectively). Of interest, the group receiving aflibercept 2 mg 8-weekly demonstrated a saw-tooth pattern on OCT, with the retinal thickness increasing in the month without injection. There was, however, no worsening of BCVA at the corresponding time points.¹²

Bevacizumab

Bevacizumab is a monoclonal antibody similar in structure to ranibizumab. It has been approved as a systemic therapy for colorectal cancer but intravitreal injection of Bevacizumab is increasingly being used as an off-label treatment for neovascular AMD in view of its cheaper cost.^{13,14} Bevacizumab injections have been shown to be noninferior to ranibizumab in 2 large multicenter trials.

The Comparison of Age Related Macular Degeneration Treatments Trials (CATT) was a multicenter, noninferiority, phase 3 clinical trial that randomized 1208 patients into 4 treatment arms: bevacizumab 1.25mg monthly, bevacizumab 1.25mg “as-needed” (pro-re-nata, PRN), ranibizumab 0.5mg monthly and ranibizumab 0.5mg “as-needed”.¹⁵

The CATT trial showed that similar schedules of bevacizumab and ranibizumab injections had equivalent effects on mean visual acuity at 1 year, though it was indeterminant whether bevacizumab given as needed was non-inferior to monthly ranibizumab.¹⁵ Monthly bevacizumab injections led to a mean gain of 8.0 letters compared to monthly ranibizumab injections with 8.5 letters. In the “as-needed” schedule, the bevacizumab arm had a gain of 5.9 letters, and the ranibizumab arm had a gain of 6.8 letters. Similarly, the proportion of patients who did not have significant decrease in vision (loss of ≥ 15 letters) were 94.0% and 91.5% in the bevacizumab monthly and “as-needed” groups respectively, compared to 94.4% and 95.4% in the ranibizumab monthly and “as-needed” groups respectively.

At 2 years, ranibizumab and bevacizumab had similar effects on visual acuity between similar dosing regimens. However, the “as-needed” regime of either drug showed smaller mean gains in visual acuity (2.4 letters, $P=0.046$) compared to the monthly dosing regime.¹⁶

While both drugs led to a reduction in retinal thickness, the mean decrease in central retinal thickness was highest in the monthly ranibizumab group (196 μm) as compared to other groups.

With regard to safety, although the CATT trial reported a higher number of adverse events in patients who had received bevacizumab compared to ranibizumab (24.1% vs 19.0%, $P=0.04$), the rates of serious adverse effects such as arteriothrombotic events (non-fatal strokes, myocardial infarctions, vascular death) venothrombotic events, as well as death were similar between both groups. The study however, was not powered to ascertain whether this difference came from a true difference in risk, or was attributable to chance.

Similarly, the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial randomized 610 patients into similar treatment arms. It found that bevacizumab was non-inferior to ranibizumab in terms of BCVA at 2 years.¹⁷ At 2 years, BCVA was 67.8 letters in the combined ranibizumab group and 66.1 letters in the bevacizumab group, with a mean difference of -1.37 letters ($P=0.26$).¹⁷ The bevacizumab group had a mean gain of 4.1 letters compared to the ranibizumab group of 4.9 letters. The study also found no difference in terms of total lesion thickness, retinal thickness and new geographic atrophy between both drugs. Frequency of arteriothrombotic events or admission for heart failure were similar between the ranibizumab (6%) and bevacizumab groups (4%) ($P=0.16$). However, mortality was lower in the continuous treatment group compared to the discontinuous treatment group (OR 0.47, $P=0.05$), but did not differ between drugs (OR 0.96, $P=0.91$).¹⁷

Variations in Treatment Regimens

The frequency of intravitreal injections poses a practical challenge to the patient. Most of the early studies on anti-VEGF therapy, such as MARINA and ANCHOR, evaluated the efficacy of anti-VEGF injections administered monthly. Monthly visits to the clinic, however, poses logistical challenges to the patients and healthcare provider, and a potentially significant treatment burden. Conversely, studies such as the PrONTO¹⁸ and CATT showed that patients given PRN dosing of ranibizumab had gains in visual outcomes but with fewer injections compared to monthly dosing of ranibizumab. These studies, however, did not address the challenge of monthly monitoring visits.

As such, a widely adopted approach is that of treat and extend (T&E), where upon initial treatment and stabilization of disease, treatment is still continued but with interval for follow-up and subsequent treatment extended. This is contrasted with a PRN regime that still required monthly follow-up and treatment only if disease activity is present. Studies have shown the T&E regimen is non-inferior to monthly injections.

The TREAT and EXTEND (TREND) study¹⁹ was a multicenter study that randomized 650 patients to receive either a T&E regimen or a monthly regimen. In the T&E regimen, patients received 2 initial monthly doses (at day 1 and 1 month). Subsequently, patients were scheduled for evaluation of disease activity based on visual acuity and OCT findings of retinal fluid. If disease activity was assessed to not be present, the next visit was extended by 2 weeks up to a maximum of a 12 week interval.

At the end of 12 months, the T&E regimen was found to be non-inferior to the monthly regimen, with a mean BCVA gain of 6.2 letters vs 8.1 letters respectively ($P<0.001$ for non-inferiority). Change in central subfield thickness assessed on OCT was similar between both groups, with a change of $-169.2\mu\text{m}$ in the T&E group and $-173.3\mu\text{m}$ in the monthly group. Of note, the T&E group received fewer injections (8.7 vs 11.1) and fewer visits (8.9 and 11.2) compared to the monthly regimens.¹⁹

The length of extension between clinic visits has also been studied. The ALTAIR study²⁰ was a prospective, open label study that randomized 247 patients with neovascular AMD into either 2- or 4-week adjustment T&E aflibercept regimens. Both groups received 3 initial monthly doses of aflibercept before the 2 or 4 week adjustment for a maximum interval of 16 weeks.

At 1 year, both T&E regimes showed improved BCVA with a gain of 9.0 letters and 8.4 letters in the 2 and 4 week groups respectively. These visual outcomes were maintained up to 4 years (7.6 letters vs + 6.1 letters). There was also anatomical improvement with mean decrease in retinal thickness of $-134.4\mu\text{m}$ and $-126.1\mu\text{m}$ at 1 year, and $-130.5\mu\text{m}$

and $-125.3 \mu\text{m}$ at 4 years for the 2 and 4 week groups, respectively. At week 96, 56.9% of patients in the 2-weekly group and 60.2% of patients in the 4-weekly group had their last injection interval of at least 12 weeks, while 41.5% and 46.3% of patients had their last injection interval of 16 weeks in the 2-weekly and 4-weekly group respectively. The authors conclude that both 2 and 4 week adjustment leads to similar results functionally and anatomically.²⁰

Brolucizumab

Brolucizumab is a humanised single-chain antibody fragment inhibitor of all isoforms of vascular endothelial growth factor-A (VEGF A), approved by the FDA in 2019 for the treatment of nAMD. It is the first single-chain antibody fragment (scFv), with a molecular weight of 26kDa, designed for intraocular use.²¹ scFVs are highly concentrated agents that do not depend on large molecular structures but continue to confer full binding capacity to the target.²² In addition, its small molecular size potentially translates to more effective retina and choroid penetration relative to other anti-VEGF therapeutics.²³ In preclinical studies, brolucizumab demonstrated significantly higher binding affinity to VEGF-A isoforms when compared to bevacizumab²⁴ and similar affinity when compared to aflibercept and ranibizumab.²⁵

HAWK (NCT02307682) and HARRIER (NCT02434328) were 2-year, double-masked, phase 3 multicenter studies that investigated brolucizumab compared with aflibercept in treatment-naïve nAMD patients. The primary endpoint of both studies was non-inferiority of brolucizumab to aflibercept in mean BCVA change from baseline to week 48, with a lower limit requirement of the 95% CI set at > -4 letters. After a matched phase of 3 loading doses of both therapeutics, patients in the brolucizumab group were treated on a Q12-weekly interval while Aflibercept was dosed in a fixed Q8-weekly regimen. Treatment intervals were subsequently adjusted based on disease activity assessments at each visit. These assessments were conducted at week 16 and at each scheduled treatment visit during the maintenance phase (weeks 20, 32 and 44 in HAWK; with additional assessments at weeks 28 and 40 in HARRIER). Least squares mean change in BCVA from baseline to week 48 for brolucizumab was non-inferior to aflibercept in both studies ($P < 0.001$, both studies). In addition, of the patients treated with brolucizumab 6 mg, 55.6% and 51.0% remained on the q12-weekly dosing interval until week 48 in the HAWK and HARRIER studies, respectively.²⁶

In HAWK, at week 48, mean changes in BCVA for brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg were $+6.1$ (S.D. 0.69), $+6.6$ (S.D. 0.71), and $+6.8$ (S.D. 0.71) ETDRS letters, respectively. For HARRIER, at week 48, mean changes in BCVA for brolucizumab 6 mg and aflibercept 2 mg were $+6.9$ (S.D. 0.61) and $+7.6$ (S.D. 0.61) letters, respectively.²⁶

The primary endpoints of the HAWK and HARRIER trials were confirmed at week 96.²⁶ Following the same treatment and monitoring protocol, HAWK demonstrated that at week 96, least squares mean change in BCVA for brolucizumab 3 mg, brolucizumab 6 mg, and aflibercept 2 mg were $+5.6$ (SD ± 0.79), $+5.9$ (SD ± 0.78) and $+5.3$ (SD ± 0.78) ETDRS letters, respectively. Week 96 findings in HARRIER revealed least square mean changes in BCVA for brolucizumab 6 mg and aflibercept 2 mg of $+6.1$ (SD ± 0.73) and $+6.6$ (SD ± 0.73) letters, respectively ($P < 0.001$).²⁶ Central subfield thickness reductions were greater with brolucizumab 6 mg compared to aflibercept in both HAWK (least square mean, $-174.8 \mu\text{m}$ vs $-148.7 \mu\text{m}$, 95% CI for treatment difference, -46.2 to $-5.9 \mu\text{m}$; $P = 0.0115$) and HARRIER (least square mean, $-197.7 \mu\text{m}$ vs $-155.1 \mu\text{m}$; 95% CI for treatment difference, -62.0 to $-23.3 \mu\text{m}$; $P < 0.0001$). Both studies also demonstrated a smaller proportion of eyes with intraretinal fluid (IRF) and/or subretinal fluid (SRF) at 96 weeks – HAWK reported that residual IRF and/or SRF was present in 31% ($P = 0.0688$) and 24% ($P = 0.0002$) of eyes treated with brolucizumab 3 mg and 6 mg vs 37% of eyes treated with aflibercept. In HARRIER, 24% of eyes treated with brolucizumab 6 mg ($P < 0.0001$) vs 39% of eyes treated with aflibercept had residual IRF and/or SRF.

HAWK and HARRIER reported comparable incidences of ocular and non-ocular AEs between Brolucizumab and Aflibercept over 96 weeks.^{26,27} However, intraocular inflammation (IOI) (iritis and uveitis) was seen at a higher rate with Brolucizumab 6mg vs Aflibercept at week 96 in HAWK (4.7% vs 0.6%) and HARRIER (0.8% vs 0.3%). A post-hoc analysis of the combined results of HAWK and HARRIER found that eyes received a mean of 3.9 (SD ± 2.2) brolucizumab injects before the onset of first IOI-related adverse events.²⁸ Approximately 90% (61 out of 70 eyes) of the IOI cases were considered mild to moderate and resolved after a course of topical corticosteroids. Overall, inflammation resolved completely in 39 eyes (79.6%), resolved with sequelae in 5 eyes (10.2%), and did not resolve in 5 eyes (10.2%) by 96 weeks. There were also 10 reported cases of retinal artery occlusion (RAO) in the Brolucizumab

arms across HAWK and HARRIER (3 eyes had RAO alone, 7 eyes had both RAO and IOI), Brolicuzumab therapy was withdrawn after the RAO event in 4 of these 7 eyes. In comparison, 2 patients treated with Aflibercept developed IOI with RAO at week 96.²⁸

More recently, post-marketing pharmacovigilance reports following FDA approval have emerged, signalling a spectrum of uncommon findings associated with Brolicuzumab injections. In February 2020, the American Society of Retinal Specialists (ASRS) issued an alert to its members concerning 14 reported cases of vasculitis following Brolicuzumab injections.²⁹ As of late 2021, the post-marketing incidence rate for retinal vasculitis or RAO was 7.0 per 10,000 injections.³⁰ In a recent retrospective analysis of 93 eyes (of 90 patients) treated with intravitreal brolicuzumab injections for AMD, the authors reported a much higher incidence of IOI at 16% (14 eyes). The authors also found that patients who developed IOI (compared to those who did not) were significantly older (79.4 ± 8.1 vs 73.8 ± 8.9 years old, $P=0.0425$), of the female gender (43% vs 13%, odds ratio: 4.95, $P=0.0076$), and were more likely to have diabetes mellitus (64% vs 32%, odds ratio: 3.90, $P=0.0196$). These results suggested that old age, female gender and a history of diabetes mellitus could be risk factors for developing IOI with intravitreal brolicuzumab.³¹

These studies illustrate the limitations of current anti-VEGF treatments, especially in terms of the frequency of injections required, as well as the long-term treatment and potential deterioration of vision once treatment frequency decreases. This has prompted the search for new drugs with longer duration of action, as well as new drug delivery systems to avoid the need for frequent injections.

Faricimab

Faricimab (F. Hoffmann-La Roche Ltd, Basel, Switzerland) is the first bispecific antibody designed for intraocular use. A novel humanized bispecific immunoglobulin G monoclonal antibody, faricimab independently binds to and neutralizes VEGF-A and angiopoietin-2 (Ang-2).^{32,33} In addition, the fragment crystallisable domain of the molecule was designed to decrease the systemic half-life of the antibody and reduce its inflammatory potential.^{32–34}

The angiopoietin/tyrosine kinase (Ang/Tie) pathway plays an important role in the maintenance of vascular stability. Ang-1, which is expressed in pericytes, binds and phosphorylates the Tie2 receptor located on endothelial cells, helping maintain vascular stability and homeostasis. In contrast, Ang-2, which is upregulated under pathological conditions, is associated with inflammation and vascular destabilization, which results in leakage and neovascularization.^{35,36} Ang-2 competes with Ang-1 for Tie2 receptor binding, thus inhibiting Ang-1-mediated activation of tyrosine kinase. This results in destabilization of the endothelial cell, making it more responsive to VEGF.

Faricimab has been evaluated in several Phase 2 and phase 3 studies for neovascular AMD.^{34,37} The TENAYA and LUCERNE studies were phase 3 randomized, double-masked, multicenter studies which evaluated the efficacy and safety of faricimab compared to aflibercept in neovascular AMD.³⁸ The key inclusion criteria were patients with best corrected visual acuity of 78–24 letters, inclusive (which corresponded to 20/32 to 20/320 Snellen equivalent), with subfoveal CNV or juxtafoveal/extrafoveal CNV with a subfoveal component which was related to the CNV activity.³⁸

Patients randomized to receive faricimab 6.0 mg received 4 initial loading doses 4-weekly. Based on assessment of disease activity at weeks 20 and 24, patients were assigned to receive faricimab either 12-weekly or 16-weekly for the rest of the study. The control group received aflibercept 2.0 mg, with an initial 3 loading doses 4-weekly, followed by an 8-weekly treatment interval. The change in BCVA at the primary endpoint was based on an average of the BCVA at the week 40, 44 and 48 visits.

In both TENAYA and LUCERNE, BCVA gains from baseline in the faricimab group was non-inferior to the aflibercept group. In TENAYA, the faricimab group gained 5.8 letters compared to 5.1 letters for the aflibercept group, while in LUCERNE, the gains were 6.6 letters in both groups. The proportion of patients who avoided a loss of ≥ 15 BCVA letters was 94% or higher in both treatment arms. In addition, in the faricimab group, 20% gained ≥ 15 BCVA letters in both the TENAYA and LUCERNE groups, while the proportion gaining ≥ 15 BCVA letters in the aflibercept group was 16% and 22% respectively.

The proportion of patients who were maintained on Q16W treatment intervals was 45.7% and 44.9% for TENAYA and LUCERNE, respectively, with an additional 34.0% and 32.9% maintained at Q12W. Taken together, 79.7% and 77.8% of patients were maintained at Q12W or longer in the first year.³⁸

The rates of adverse events was low for both the faricimab and aflibercept groups, with intraocular inflammation rates of 2.0% and 1.2% respectively. Importantly there were no cases of retinal vasculitis or occlusive retinitis reported in either study.³⁸

Abicipar

Abicipar pegol belongs to a new class of custom-built design ankyrin repeat protein (DARPin) therapeutics. DARPins are a category of small, highly stable, engineered binding proteins containing ankyrin repeat domains that aim to achieve an optimized combination of affinity, molar concentration and half-life, resulting in a longer duration of effect.³⁹

Abicipar is a pegylated protein that binds all isoforms of VEGF-A with a higher affinity and specificity compared to Ranibizumab.

There are two global Phase 3 trials, SEQUOIA (NCT02462486) and CEDAR (NCT02462928), with identical protocols, which recruited over 1600 patients with treatment-naïve AMD. A pooled analysis of these studies reported high rates (over 90%) of stable vision in all three arms, demonstrating Abicipar's non-inferiority compared to ranibizumab, with less frequent injections (6 or 8 vs 13).⁴⁰

There are, however, potential concerns associated with the occurrence of intraocular inflammation. The CEDAR and SEQUOIA trials reported a 15.4% inflammation rate, including a 1.7% rate of severe vision loss.⁴⁰ Results from the follow-on open-label 28-week MAPLE study (NCT03539549)^{41,42} evaluating the use of the modified formulation of Abicipar demonstrated overall lower rates of IOI at 8.9% coupled with a 1.6% incidence of severe IOI.

Notwithstanding, DARPins remain promising drugs and offer the benefit of reduced injection burden. Additional research and clinical trials are required to further develop molecules within this drug class in consideration of safety and efficacy profiles when compared to the established anti-VEGF agents: bevacizumab, ranibizumab and aflibercept.

KSI-301

KSI-301 (Kodiak Sciences Inc., Palo Alto, California) is a novel intravitreal anti-vascular endothelial growth factor (VEGF) antibody biopolymer conjugate (ABC) being evaluated for the treatment of age-related macular degeneration (AMD), diabetic macular oedema (DME) and retinal vein occlusion (RVO). KSI-301 comprises of a humanized anti-VEGF monoclonal antibody conjugated to a high molecular weight phosphorylcholine biopolymer. Its design sought to optimise both size and molar dose to increase intraocular durability.^{43,44}

KSI-301 blocks all isoforms of VEGF-A^{44,45} and has also been shown to have high bioavailability in both the retina and choroid/retinal pigment epithelium (RPE).

The DAZZLE study (NCT04049266) is an ongoing phase 2, prospective, randomized controlled clinical trial designed to evaluate the safety and efficacy of KSI-301, in comparison with aflibercept, in patients with treatment-naïve wet AMD.^{46,47} Patients are randomized to receive either 5mg KSI-301 on an individualized dosing regimen ranging from 3 to 5 months, or to receive standard-of-care 2mg aflibercept on its every 8-week dosing regimen, each after three monthly loading doses. The main outcome is the mean change in BCVA as measured on the ETDRS chart at 1 year and patients will be followed up for 2 years. To date, the study has an estimated enrolment of 550 participants with an estimated primary completion date in November 2021.

Sustained Drug Delivery Platforms

There is pressing unmet needs in terms of finding longer acting agents to reduce treatment burden and risks due to frequent injections. While newer agents have achieved treatment intervals as long as 16-weekly injections, this still presents a long-term burden on the patient. Port delivery systems have gone one step further, reporting results of patients requiring office refills every 6 months (or even longer).^{48,49}

Port Delivery System (Susvimo™)

The port delivery system (Susvimo™, Roche, Switzerland) is an intravitreal reservoir implant placed through a scleral incision in the pars plana. The device is loaded and holds a small volume of highly concentrated ranibizumab (Lucentis,

Genentech) that is slowly released over a four to six-month period, which is then refilled in the office with a custom needle.

At the time of writing, Susvimo had just received FDA clearance. The Phase 3 Archway study (n=418) randomized patients to treatment with PDS Q24W, and treatment with monthly ranibizumab. All patients needed to have at least 3 prior anti-VEGF injections within 6 months of screening and have demonstrated both visual and anatomical response to anti-VEGF treatment. As such, recruited patients are likely at or approaching a ceiling effect for visual gains. The PDS Q24W was both noninferior and equivalent to monthly ranibizumab (adjusted mean VA from baseline +0.2 vs +0.5 letters). 98.4% of patients in the PDS group did not receive supplemental ranibizumab treatment before the first refill-exchange procedure. Ocular adverse events in the PDS group included 4 cases of (1.6%) endophthalmitis, 2 (0.8%) retinal detachments, 13 (5.2%) vitreous hemorrhages, 6 (2.4%) conjunctival erosions, and 5 (2.0%) conjunctival retractions.⁴⁹

Hydrogel Delivery Platform

The proprietary hydrogel platform (Ocular Therapeutix, USA) is a preservative-free, biodegradable polyethylene glycol (PEG) network. The meshwork entraps the drug particles and, when administered, it hydrates and dissolves to release the bound drug particles into surrounding tissue. Following the completion of drug delivery, the hydrogel biodegrades and is cleared from the body. It is sized as a small fibre (25–27g needle) and provides sustained release for 6 months or longer.

Two retinal programs for wet AMD are currently in development. OTX-TKI (Axitinib intravitreal implant) is currently undergoing Phase I trial (NCT03630315) to evaluate the safety, tolerability and efficacy of OTX-TKI for intravitreal use in subjects with wet AMD.⁵⁰ Axitinib is a small molecule tyrosine kinase inhibitor with anti-angiogenic properties. The trial is enrolling and evaluating cohorts of patients with dose elevation: cohort 1 (200µg), cohort 2 (400µg), cohort 3a (600µg) and cohort 3b (400µg + anti-VEGF).

Initial results were presented at ARVO (May 2021) and reported no ocular serious adverse events. Additionally, no subject experienced changes in IOP, and none required steroids. CRT remained stable in cohort 1, but many patients in cohorts 2 and 3a experienced a decrease in CSFT and demonstrated a reduction in intraretinal fluid or subretinal fluid by 2 months. At 6 months, over 50% (across cohorts) of subjects did not require rescue medications.⁵¹

GB-102

GB-102 (Graybuy Vision Inc.) is a depot formulation of sunitinib malate intended for intravitreal injection. It consists of microparticles made from poly-lactic-co-glycolic acid (PLGA) and methoxy-polyethylene glycol (mPEG)-PLGA. The mPEG component is a proprietary hydrophilic, biocompatible surface treatment designed to eliminate inflammation typically associated with ocular administration of PLGA. The surface treatment also facilitates microparticle aggregation upon injection to form an implant-like depot in the inferior vitreous.⁵²

After injection, the microparticles gradually release sunitinib malate and biodegrade into lactic and glycolic acid, which are naturally cleared from the body. Sunitinib malate is small molecule receptor tyrosine kinase inhibitor that is a potent inhibitor of VEGFR-1, -2, and -3, receptors known to play an influential role in wet AMD.

ADAGIO was a Phase I/2A study which recruited subjects with wet AMD who were treated with a single intravitreal injection of 0.25, 0.5, 1 or 2 mg of GB-102. There were no ocular serious adverse events or dose limiting toxicities. All drug related adverse events were mild or moderate, and the most common reported was the presence of medication in the anterior chamber (the formulation has since been optimized to improve particle aggregation and reduce migration into the anterior chamber). It was reported that a single injection of GB-102 was able to maintain central retinal thickness and visual acuity for six months or more. Injection burden was reduced through the six months by over 80% in all dose groups, particularly in the 1mg group.⁵²

A Phase 2B trial (ALTISSIMO) included 3 treatment arms: group 1 (GB-102 1mg), group 2 (GB-102 2mg) and group 3 (Aflibercept 2mg). Final analysis excluded the GB-102 2mg group due to an interim safety analysis which terminated the development of the 2mg dosing. The reported results showed GB-102 1mg was safe and well-tolerated. There were no drug-related serious adverse events or vision-threatening inflammation. Particle migration to the anterior chamber in patients treated with GB-102 1mg was reduced by 79% as compared to GB-102 1mg patients in the ADAGIO trial, and

no surgical interventions were required. Patients in the GB-102 1mg trial arm (n=21) had a median time to first supportive therapy of five months, and 48% of patients did not require supportive therapy for at least six months. Injection burden was reduced by 58%. The study, however, was not powered to show differences in central retinal thickness or visual acuity.⁵²

Biosimilars

The advent of biosimilars to the reference anti-VEGFs heralds a potential solution to alleviating rising treatment costs, with reports suggesting that these molecules may confer up to a 30% reduction in costs.⁵³ Biosimilars are reverse-engineered from the reference anti-VEGF biologic, and are designed to mimic pharmacokinetic endpoints in order to achieve a similar efficacy and safety profile as the reference product.⁵⁴

In September 2021, the FDA and EMA approved its first retinal biosimilar, SB11 (Byooviz), for use in the same labelled indications as its reference product (RP), ranibizumab (Lucentis).⁵⁵ The approval was based on a totality of evidence (TOE) comprising pharmacokinetic (PK) evidence and a Phase III study comparing SB11 against RP ranibizumab in 705 patients with nAMD. Compared to ranibizumab, SB11 demonstrated a comparable safety, PK and immunogenicity profile at all timepoints up to week 52.⁵⁶ The Least Squares (LS) mean change in best corrected visual acuity (BCVA) from baseline at week 52 was 9.79 letters for SB11, compared with 10.41 letters for RP ranibizumab (difference: -0.62, [90% CI: -2.092, 0.857]).⁵⁶ A second ranibizumab biosimilar candidate, FYB201, developed by Formycon and Bioeq, submitted its biologics license application to the FDA in October 2021. Its TOE reports evidence of equivalence to the RP, as demonstrated in a Phase III RCT evaluating its use in 477 patients with nAMD.⁵⁷ Holz et al reported similar mean BCVA improvements in both FYB201 (+5.1 ETDRS letters) and RP ranibizumab (+5.6 ETDRS letters) arms at week 8. The study met its primary endpoint of equivalence and adverse events reported were comparable between groups.⁵⁷

At the time of writing, various biosimilars remain under development for the treatment of nAMD and successful regulatory approvals may signal a shift towards more cost-effective clinical management and patient care. The advent of retinal biosimilars may place a downward pressure on pricing and in corollary, improve patient and physician access to a critical therapeutic category. Notwithstanding, there are risks inherent to biosimilars and a thorough understanding of the individual biosimilar development programmes will inform understanding of its safety and efficacy in practice.

Gene Therapy

There has been considerable work on gene therapy in ophthalmology, especially in inherited retinal diseases, starting with FDA clearance of Voretigene neparvovec (Luxturna™). The eye is an excellent target for gene therapy as it is small and compartmentalized. Gene therapy can be administered in small doses, and the presence of the blood-retinal barrier prevents systemic dissemination of the gene therapy vector, minimizing systemic immunogenic responses. The lack of cell division in the retina also allows for the use of non-integrating vector systems, thereby reducing the risk of insertional mutagenesis and oncogenesis.⁵⁸

Transduction is the process by which foreign DNA is introduced into a host cell by a viral or non-viral vector. The viral vector can be either integrating, in which DNA material carried by the vector integrates into the host genome, or non-integrating, where the DNA material carried remains episomal in the cell cytoplasm. With the introduction of a gene into the host cell which originally carried a defective copy, the host cell is now able to transcribe the new copy of gene into functional proteins, which treats the original disease.

Over the years, many viral vectors have been evaluated for ocular gene therapy. Currently, the most popular of viral vectors in use are adeno-associated viruses (AAVs) due to their ability to transduce multiple retinal cell types, low pathogenicity and low risk of mutagenesis and oncogenesis because given that they do not integrate with the host genome.⁵⁹ However, AAVs can only carry smaller genes up to 4.7kb due to size limitations. Larger genes (eg ABCA4 gene) need to rely on lentivirus or non-viral vectors for delivery.⁶⁰ Current gene therapy strategy for neovascular AMD focuses on the transduction of retinal cells to produce anti-VEGF proteins intraocularly in sustainable amounts. A single gene therapy treatment could theoretically turn the eye into a biofactory to produce the anti-VEGF protein for the lifetime of a patient. This is indeed a promising and attractive option for treatment of AMD.

RGX-314

RGX-314 (Regenxbio Inc, USA) is being investigated as a potential one-time treatment for neovascular AMD, diabetic retinopathy and other chronic exudative retinal disease for which VEGF plays a role in the pathogenesis. It consists of an AAV serotype 8 vector delivering a gene that encodes a monoclonal antibody fragment that binds VEGF-A.^{61,62}

The Phase I/IIa, open-label, multiple-cohort, dose-escalation study was designed to evaluate the safety and tolerability of RGX-314 gene therapy in subjects with previously treated nAMD. Five genomic copy (GC) doses were studied in 5 cohorts of patients: Cohort 1 (3×10^9 GC/eye of RGX-314), Cohort 2 (1×10^{10} GC/eye of RGX-314), Cohort 3 (6×10^{10} GC/eye of RGX-314), Cohort 4 (1.6×10^{11} GC/eye of RGX-314) and Cohort 5 (2.5×10^{11} GC/eye of RGX-314).⁶³ Eligible participants receive a single dose of RGX-314 administered by subretinal delivery. End of study results have been presented. RGX-314 was generally well tolerated in the 42 study participants. There were no reports of clinically determined immune responses, drug-related ocular inflammation or post-operative inflammation beyond what is expected following routine vitrectomy. Over 2 years, patients in cohort 3 saw sustained visual gain (mean 14 letters) and sustained maintenance of anatomy. Patients in cohort 4 saw stable vision (+1 letter at 2 years) and improvement in central retinal thickness (mean $-57 \mu\text{m}$ at 2 years). Cohorts 3–5 saw 58.7–78.5% reduction in anti-VEGF treatment burden at 2 years. Dose-dependent intraocular RGX-314 protein levels was seen across all 5 cohorts.⁶⁴

AAVIATE (NCT04514653) is a Phase II dose escalation trial evaluating the efficacy, safety and tolerability of suprachoroidal delivery of RGX-314. Twenty patients in Cohort 1 were randomized to receive RGX-314 at a dose level of 2.5×10^{11} GC per eye versus monthly 0.5 mg ranibizumab intravitreal injection at a 3:1 ratio. Twenty patients in Cohort 2 were randomized to receive RGX-314 at an increased dose level of 5×10^{11} GC/eye versus monthly 0.5 mg ranibizumab intravitreal injection at a 3:1 ratio. Cohort 3 is designed to evaluate RGX-314 at the same dose level as Cohort 2 in 20 patients who are neutralizing antibody (NAb) positive. Enrollment is complete across these three cohorts. Regenxbio recently presented initial results for cohort 1. Suprachoroidal delivery of RGX-314 was well tolerated in 50 patients in Cohorts 1–3 with no drug-related serious adverse events. The treatment demonstrated stable visual acuity (mean -2.8 letters) and retinal thickness ($-2.5 \mu\text{m}$) in cohort 1. There was meaningful reduction in anti-VEGF treatment burden (75.9% reduction). The Phase II trial was expanded to include third dose level of RGX-314 (1×10^{12} GC/eye).⁶⁵

Regenxbio is also currently enrolling patients in ATMOSPHERE (NCT04704921), the first of two planned pivotal trials for the evaluation of subretinal delivery of RGX-314 in patients with wet AMD at the time of the writing of this manuscript.⁶⁶

ADVM-022

ADVM-022 (Adverum Biotechnologies Inc, USA) utilizes the AAV2.7m8 capsid, which has highly efficient retinal transduction, and is designed to promote strong expression of the aflibercept protein in the treatment of neovascular AMD.^{67,68} It can be administered via an intravitreal injection in an office setting.^{67,68} OPTIC (NCT03748784) is an ongoing open-label, multicenter, dose-ranging study in patients with a confirmed response to anti-VEGF therapy. Patients were administered a single intravitreal injection of ADVM-022. The incidence and severity of adverse events, change in visual acuity (BCVA), anatomical outcomes on OCT, and number of aflibercept rescue injections were evaluated. The interim results were presented in September 2021 at the Retina Society meeting. There were no systemic adverse events related to ADVM-022. All related ocular adverse events were mild (83%) to moderate (17%), with one case of moderate recurrent uveitis responsive to steroid eye drops in cohort 1. No clinically relevant IOP events were observed. The high dose group had 97% and low dose group had 83% reduction in annualized anti-VEGF injection burden with maintenance of BCVA and central retinal thickness measurements. Both doses recorded aflibercept protein expression within the targeted therapeutic range and which remained stable out to 104 weeks.⁶⁹

Challenges of Gene Therapy

Although these therapies have potential and are promising, there remain significant obstacles to gene therapy for AMD becoming mainstream. The cost of gene therapy, if similar to currently FDA approved Luxturna™, would prove prohibitive for the vast majority of population. Although AAV vectors have the advantages as discussed earlier, there

remain challenges to their use. There are still concerns over their ability to effectively transduce cells, especially if given intravitreally. Subretinal injection of vector, while potentially more efficacious, comes with the surgical risks associated with pars plana vitrectomy and retinotomy. The long-term efficacy and safety of gene therapy remains to be evaluated and chronic suppression of VEGF, given the neurotrophic properties of VEGF, may also be a concern. Nevertheless, gene therapy in AMD remains highly anticipated.

Conclusion

Neovascular AMD continues to be a significant cause of visual loss throughout the world. While the advent of anti-VEGF drugs offered new hope to patients with nAMD, the frequency of injection and requirement for long-term treatment present significant financial and logistical burdens on both patients and healthcare system. Newer drugs with greater durability and longer treatment intervals, improved safety profiles, as well as newer methods of drug delivery, offer potential improvements in treatment of nAMD. Gene therapy may represent the next frontier of treatment for many ocular diseases.

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References

1. World Health Organization. World report on vision; 2019. Available from: <https://www.who.int/publications/i/item/9789241516570>. Accessed February 20, 2022.
2. Miller JW, Le Couter J, Strauss EC, Ferrara N. Vascular endothelial growth factor a in intraocular vascular disease. *Ophthalmology*. 2013;120(1):106–114. doi:10.1016/j.ophtha.2012.07.038
3. Okamoto N, Tobe T, Hackett SF, et al. Transgenic mice with increased expression of vascular endothelial growth factor in the retina: a new model of intraretinal and subretinal neovascularization. *Am J Pathol*. 1997;151(1):281.
4. Tobe T, Okamoto N, Viores MA, et al. Evolution of neovascularization in mice with overexpression of vascular endothelial growth factor in photoreceptors. *Invest Ophthalmol Vis Sci*. 1998;39(1):180–188.
5. Schwesinger C, Yee C, Rohan RM, et al. Intrachoroidal neovascularization in transgenic mice overexpressing vascular endothelial growth factor in the retinal pigment epithelium. *Am J Pathol*. 2001;158(3):1161–1172. doi:10.1016/S0002-9440(10)64063-1
6. Kliffen M, Sharma HS, Mooy CM, Kerkvliet S, De Jong PTVM. Increased expression of angiogenic growth factors in age-related maculopathy. *Br J Ophthalmol*. 1997;81(2):154–162. doi:10.1136/bjo.81.2.154
7. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1419–1431. doi:10.1056/NEJMoa054481
8. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med*. 2006;355(14):1432–1444. doi:10.1056/NEJMoa062655
9. Group T of AMDWPT (TAP) S. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials—TAP report 1. *Arch Ophthalmol*. 1999;117(10):1329–1345. doi:10.1001/archophth.117.10.1329
10. Rofagha S, Bhisitkul RB, Boyer DS, Sada SR, Zhang K. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology*. 2013;120(11):2292–2299. doi:10.1016/j.ophtha.2013.03.046
11. Singer MA, Awh CC, Sada S, et al. HORIZON: an open-label extension trial of ranibizumab for choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology*. 2012;119(6):1175–1183. doi:10.1016/j.ophtha.2011.12.016
12. Heier JS, Brown DM, Chong V, et al. 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
13. Rosenfeld PJ. Intravitreal avastin: the low cost alternative to lucentis? *Am J Ophthalmol*. 2006;142(1):141–143. doi:10.1016/j.ajo.2006.03.036
14. Steinbrook R. The price of sight—ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med*. 2006;355(14):1409–1412. doi:10.1056/NEJMp068185
15. Martin DF, Ying G, Grunwald JE, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897–1908.
16. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. *Ophthalmology*. 2012;119(7):1388–1398. doi:10.1016/j.ophtha.2012.03.053
17. Chakravarthy U, Harding SP, Rogers CA, et al. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382(9900):1258–1267. doi:10.1016/S0140-6736(13)61501-9

18. Lalwani GA, Rosenfeld PJ, Fung AE, et al. A variable-dosing regimen with intravitreal ranibizumab for neovascular age-related macular degeneration: year 2 of the PrONTO Study. *Am J Ophthalmol.* 2009;148(1). doi:10.1016/j.ajo.2009.01.024
19. Silva R, Berta A, Larsen M, Macfadden W, Feller C, Monés J. Treat-and-extend versus monthly regimen in neovascular age-related macular degeneration: results with ranibizumab from the TREND Study. *Ophthalmology.* 2018;125(1):57–65. doi:10.1016/j.ophtha.2017.07.014
20. Ohji M, Takahashi K, Okada AA, et al. Efficacy and safety of intravitreal aflibercept treat-and-extend regimens in exudative age-related macular degeneration: 52- and 96-week findings from ALTAIR: a randomized controlled trial. *Adv Ther.* 2020;37(3):1173–1187. doi:10.1007/s12325-020-01236-x
21. Gaudreault J, Gunde T, Floyd HS, et al. Preclinical pharmacology and safety of ESBA1008, a single-chain antibody fragment, investigated as potential treatment for age related macular degeneration. *Invest Ophthalmol Vis Sci.* 2012;53(14):3025.
22. Evans RN, Reeves BC, Maguire MG, et al. Associations of variation in retinal thickness with visual acuity and anatomic outcomes in eyes with neovascular age-related macular degeneration lesions treated with anti-vascular endothelial growth factor agents. *JAMA Ophthalmol.* 2020;138(10):1043. doi:10.1001/jamaophthalmol.2020.3001
23. Escher D, Schmidt A, Steiner P, Maurer P, Weissgerber G. Single-chain antibody fragments in ophthalmology; 2015. Available from: <https://www.euretinna.org/nice2015/programme/free-papers-details.asp?id=4072&day=0>. Accessed November 28, 2021.
24. Szabó E, Phillips DJ, Droste M, et al. Antitumor activity of DLX1008, an anti-VEGFA antibody fragment with low picomolar affinity, in human glioma models. *J Pharmacol Exp Ther.* 2018;365(2):422–429. doi:10.1124/jpet.117.246249
25. Borrás L, Gunde T, Tietz J, et al. Generic approach for the generation of stable humanized single-chain Fv fragments from rabbit monoclonal antibodies. *J Biol Chem.* 2010;285(12):9054. doi:10.1074/jbc.M109.072876
26. Dugel PU, Singh RP, Koh A, et al. HAWK and HARRIER: ninety-six-week outcomes from the Phase 3 trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology.* 2021;128(1):89–99. doi:10.1016/j.ophtha.2020.06.028
27. Dugel PU, Koh A, Ogura Y, et al. HAWK and HARRIER: phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology.* 2020;127(1):72–84. doi:10.1016/j.ophtha.2019.04.017
28. Singer M, Albin TA, Seres A, et al. Clinical characteristics and outcomes of eyes with intraocular inflammation after brolucizumab: post hoc analysis of HAWK and HARRIER. *Ophthalmol Retin.* 2021;6(2):97–108. doi:10.1016/j.oret.2021.05.003
29. ASRS Clinical Updates. Beovu update for ASRS members; 2021. Available from: <https://www.asrs.org/members/login/960?returnUrl=%2Fclinical%2Fclinical-updates%2F960%2FBeovu-Update-for-ASRS-Member>. Accessed November 28, 2021.
30. Novartis. Brolucizumab Information. Available from: <https://www.brolucizumab.info/>. Accessed February 26, 2022.
31. Mukai R, Matsumoto H, Akiyama H. Risk factors for emerging intraocular inflammation after intravitreal brolucizumab injection for age-related macular degeneration. *PLoS One.* 2021;16(12):e0259879. doi:10.1371/journal.pone.0259879
32. Regula JT, Lundh von leithner P, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med.* 2016;8(11):1265–1288. doi:10.15252/emmm.201505889
33. Regula JT, Leithner PL, Von, Foxton R, et al. Targeting key angiogenic pathways with a bispecific CrossMAb optimized for neovascular eye diseases. *EMBO Mol Med.* 2019;11(5):e10666. doi:10.15252/emmm.201910666
34. Sahni J, Dugel PU, Patel SS, et al. Safety and efficacy of different doses and regimens of faricimab vs ranibizumab in neovascular age-related macular degeneration: the AVENUE Phase 2 randomized clinical trial. *JAMA Ophthalmol.* 2020;138(9):955–963. doi:10.1001/jamaophthalmol.2020.2685
35. Saharinen P, Eklund L, Alitalo K. Therapeutic targeting of the angiotensin–TIE pathway. *Nat Rev Drug Discov.* 2017;16(9):635–661.
36. Campochiaro PA. Molecular pathogenesis of retinal and choroidal vascular diseases. *Prog Retin Eye Res.* 2015;49:67–81. doi:10.1016/j.preteyeres.2015.06.002
37. Khanani AM, Patel SS, Ferrone PJ, et al. Efficacy of every four monthly and quarterly dosing of faricimab vs ranibizumab in neovascular age-related macular degeneration: the STAIRWAY Phase 2 randomized clinical trial. *JAMA Ophthalmol.* 2020;138(9):964–972. doi:10.1001/jamaophthalmol.2020.2699
38. Khanani AM, Heier J, Ruiz CQ, et al. Faricimab in neovascular age-related macular degeneration: 1-year efficacy, safety, and durability in the Phase 3 TENAYA and LUCERNE trials. *Invest Ophthalmol Vis Sci.* 2021;62(8):428.
39. Pflückthun A. Designed ankyrin repeat proteins (DARPs): binding proteins for research, diagnostics, and therapy. *Annu Rev Pharmacol Toxicol.* 2015;55(1):489–511. doi:10.1146/annurev-pharmtox-010611-134654
40. Kunitomo D, Yoon YH, Wykoff CC, et al. Efficacy and safety of abicipar in neovascular age-related macular degeneration: 52-week results of Phase 3 randomized controlled study. *Ophthalmology.* 2020;127(10):1331–1344. doi:10.1016/j.ophtha.2020.03.035
41. Molecular Partners. Allergan and molecular partners announce topline safety results from MAPLE study of abicipar pegol; 2021. Available from: <https://investors.molecularpartners.com/news-releases/news-release-details/allergan-and-molecular-partners-announce-topline-safety-results>. Accessed November 28, 2021.
42. Allergan. A study to evaluate abicipar pegol for safety and treatment effect in participants with neovascular age-related macular degeneration (AMD). Available from: <http://clinicaltrials.gov/ct2/show/NCT03539549>. Accessed November 28, 2021.
43. Al-Khersan H, Hussain RM, Ciulla TA, Dugel PU. Innovative therapies for neovascular age-related macular degeneration. *Expert Opin Pharmacother.* 2019;20(15):1879–1891. doi:10.1080/14656566.2019.1636031
44. Hong L, Huang X, Ngo W, et al. KSI-301: an anti-VEGF antibody biopolymer conjugate with extended half-life for treatment of neovascular retinal diseases. *Invest Ophthalmol Vis Sci.* 2018;59(9):211.
45. Patel SS, Naor J, Qudrat A, et al. Phase 1 first-in-human study of KSI-301: a novel anti-VEGF antibody biopolymer conjugate with extended durability. *Invest Ophthalmol Vis Sci.* 2019;60(9):3670.
46. Kodiak Sciences Inc. A study to evaluate the efficacy and safety of KSI-301, an anti-VEGF antibody biopolymer conjugate, versus aflibercept in patients with neovascular (Wet) age-related macular degeneration. (DAZZLE). Available from: <http://clinicaltrials.gov/ct2/show/NCT04049266>. Accessed November 28, 2021.
47. Kodiak. Third quarter 2020 R&D webinar; 2020. Available from: <https://ir.kodiak.com/static-files/c59bbe11-0e07-4819-b063-fddd4dbc24e4/>. Accessed November 28, 2021.
48. Khanani AM, Callanan D, Dreyer R, et al. End-of-study results for the ladder phase 2 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmol Retin.* 2021;5(8):775–787. doi:10.1016/j.oret.2020.11.004

49. Holekamp NM, Campochiaro PA, Chang MA, et al. Archway randomized phase 3 trial of the port delivery system with ranibizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2021;129(3):295–307. doi:10.1016/j.ophtha.2021.09.016
50. Ocular Therapeutix, Inc. CLN-0046: treatment of AMD subjects with OTX-TKI. Available from: <http://clinicaltrials.gov/ct2/show/NCT03630315>. Accessed November 28, 2021.
51. Wong JG, Chang A, Guymer RH, et al. Phase 1 study of an intravitreal axitinib hydrogel-based implant for the treatment of neovascular age-related macular degeneration (nAMD); 2021. Available from: <https://ocutx.gcs-web.com/static-files/3c59d3b0-9995-4e63-a972-e233a7550b1b>. Accessed November 28, 2021.
52. Graybug. Our technologies and Pipeline; 2021. Available from: <https://www.graybug.vision/our-technologies-and-pipeline/#gb102>. Accessed November 28, 2021.
53. Sharma A, Reddy P, Kuppermann BD, Bandello F, Lowenstein A. Biosimilars in ophthalmology: “Is there a big change on the horizon?”. *Clin Ophthalmol*. 2018;12:2137. doi:10.2147/OPHTH.S180393
54. Sharma A, Kumar N, Kuppermann BD, Bandello F, Loewenstein A. Understanding biosimilars and its regulatory aspects across the globe: an ophthalmology perspective. *Br J Ophthalmol*. 2020;104(1):2–7. doi:10.1136/bjophthalmol-2019-314443
55. Samsung Bioepis. FDA approves Samsung Bioepis and Biogen’s BYOOVIZ™ (SB11), LUCENTIS® Biosimilar (ranibizumab-nuna); 2021. Available from: <https://www.samsungbioepis.com/en/newsroom/newsroomView.do?idx=254¤tPage=1>. Accessed November 28, 2021.
56. Bressler NM, Veith M, Hamouz J, et al. Biosimilar SB11 versus reference ranibizumab in neovascular age-related macular degeneration: 1-year phase III randomised clinical trial outcomes. *Br J Ophthalmol*. 2021. 2021–319637. doi:10.1136/bjophthalmol-2021-319637
57. Holz FG, Oleksy P, Ricci F, Kaiser PK, Kiefer J, Schmitz-Valckenberg S. Efficacy and safety of biosimilar FYB201 compared with ranibizumab in neovascular age-related macular degeneration. *Ophthalmology*. 2021;129:54–63.
58. Ali RR. Ocular gene therapy: introduction to the special issue. *Gene Ther*. 2012;19(2):119–120.
59. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. *Nat Rev Drug Discov*. 2019;18(5):358–378.
60. Auricchio A, Trapani I, Allikmets R. Gene therapy of ABCA4-associated diseases. *Cold Spring Harb Perspect Med*. 2015;5(5):a017301–a017301. doi:10.1101/cshperspect.a017301
61. Bordet T, Behar-Cohen F. Ocular gene therapies in clinical practice: viral vectors and nonviral alternatives. *Drug Discov Today*. 2019;24(8):1685–1693. doi:10.1016/j.drudis.2019.05.038
62. Liu Y, Fortmann SD, Shen J, et al. AAV8-antiVEGFfab ocular gene transfer for neovascular age-related macular degeneration. *Mol Ther*. 2018;2(2):542–549. doi:10.1016/j.ymthe.2017.12.002
63. Regenxbio Inc. Safety and tolerability of RGX-314 gene therapy for neovascular AMD trial. Available from: <http://clinicaltrials.gov/ct2/show/NCT03066258>. Accessed November 28, 2021.
64. Ho A. Subretinal delivery of RGX-314 for neovascular AMD: end of Phase I/IIa study results; 2021. Available from: https://regenxbio.com/wp-content/uploads/2021/10/RGX-314_Ph1-2a_data_Allen-Ho_Retina_Society_Oct-2021.pdf. Accessed November 28, 2021.
65. Regenxbio. News releases; 2021. Available from: <https://regenxbio.gcs-web.com/news-releases/news-release-details/regenxbio-presents-positive-initial-data-phase-ii-aaviater-trial>. Accessed November 28, 2021.
66. Regenxbio. Wet AMDL; 2021. Available from: <https://www.regenxbio.com/wet-amd/>. Accessed November 28, 2021.
67. Gelfman CM, Grishanin R, Bender KO, et al. Comprehensive preclinical assessment of ADVM-022, an intravitreal anti-VEGF gene therapy for the treatment of neovascular AMD and diabetic macular edema. *J Ocul Pharmacol Ther*. 2021;37(3):181–190. doi:10.1089/jop.2021.0001
68. Grishanin R, Vuilleminot B, Sharma P, et al. Preclinical evaluation of ADVM-022, a novel gene therapy approach to treating wet age-related macular degeneration. *Mol Ther*. 2019;27(1):118–129. doi:10.1016/j.ymthe.2018.11.003
69. Khanani A. ADVM-022 intravitreal gene therapy for neovascular AMD- phase 1 OPTIC study; 2021. Available from: <https://adverum.com/wp-content/uploads/2021/10/OPTIC-Retina-Society-Meeting-Updated-9-30-2021a.pdf>. Accessed November 28, 2021.

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