# Chapter 5
# Retina

**Tedi Begaj, Ravi Parikh, and Dean Eliott**

**Abstract** In the last 20 years, the field of retina has experienced tremendous innovation in the available clinical tools. Though there are many excellent trials investigating various treatment modalities in multiple retinal subspecialties, the current chapter discusses 10 pivotal trials that shape practice today. Summarized below is a combination of carefully chosen historically important, clinically relevant, and epidemiologically significant articles that span a wide range of pathology.

T. Begaj · D. Eliott (✉)
Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, MA, USA
e-mail: Tedi_Begaj@hms.harvard.edu; Dean_Eliott@meei.harvard.edu

R. Parikh
Manhattan Retina & Eye Consultants, New York, NY, USA
e-mail: Rap120@mail.harvard.edu



J. C. Dohlman, A. C. Lorch (eds.), *Pivotal Trials in Ophthalmology*,
https://doi.org/10.1007/978-3-030-63978-5_5


## Results of the Endophthalmitis Vitrectomy Study (EVS) –1995 [1]

**Purpose**

Historically, intravitreal antibiotics were widely accepted in the management of bacterial endophthalmitis. However, the role of pars plana vitrectomy (PPV) in the initial management of bacterial endophthalmitis was unclear. The Endophthalmitis Vitrectomy Study (EVS) explored the role of initial PPV and the role of intravenous antibiotics in acute post-operative endophthalmitis.

**Methods**

This was a randomized multi-center trial of 420 patients who developed bacterial endophthalmitis within six weeks of cataract surgery (95%) or secondary lens implantation (5%). Participants were assigned to four treatment groups: initial PPV or vitreous tap (TAP), with or without intravenous antibiotics. Treatment was begun six hours after clinical examination and all patients underwent a diagnostic anterior chamber paracentesis. After the initial PPV or TAP, all patients received an intravitreal injection (INJ) of vancomycin and amikacin, and subconjunctival injection of vancomycin, ceftazadime and dexamethasone. Patients in the systemic antibiotic group received intravenous ceftazidime and amikacin for five to 10 days. The primary endpoint was change in best-corrected visual acuity (BCVA) and ocular media clarity from baseline, and was assessed at three-month and final (nine to 12 month) follow-up. Media clarity was assessed both clinically and by photographic grading.

**Results**

At three-month and final follow-up, there was no statistically significant difference in BCVA based on treatment assignment. However, subgroup analysis showed that patients with

light perception (LP) vision did better after PPV/INJ, with three times (33% vs. 11%) greater chance of achieving BCVA ≥20/40, two times (56% vs. 30%) greater chance of achieving BCVA ≥20/100, and half the risk (20% vs. 47%) of severe visual loss (5/200). In terms of media clarity, PPV/INJ led to superior clarity at three months (86% vs. 75% TAP/INJ) and at final visit (90% vs. 83% TAP/INJ). 69.3% of cultures were confirmed positive with the majority being gram positive (~94%). There was no difference in visual acuity outcome or media clarity between patients who did and did not receive intravenous antibiotics. Ocular and systemic serious adverse events (SAEs) did not vary substantially between treatment groups. One participant experienced expulsive hemorrhage in the TAP/INJ group while in the PPV/INJ group, two participants each experienced a dislocated intraocular lens and another had a macular infarct.

**Follow-up Studies**

The current standard regimen for intravitreal antibiotics in cases of suspected bacterial endophthalmitis includes vancomycin for gram-positive coverage and ceftazadime for gram-negative coverage; amikacin has been replaced due to potential retinal toxicity. A subsequent analysis [2] in the EVS showed that ~94% of cases were gram positive (majority coagulase-negative staphylococci) and the remaining 6% were Gram-negative bacteria. Vancomycin was active against all gram-positive isolates while amikacin and ceftazidime were equivalent against gram-negative isolates. The benefit of intravenous antibiotics remains unclear given that bacterial endophthalmitis is predominantly caused by gram-positive organisms, and treatment with intravenous ceftazidime and amikacin (which cover primarily gram-negative organisms) is not the primary treatment choice.

**Key Points**

- In acute bacterial endophthalmitis after cataract surgery or secondary lens implantation, initial PPV/INJ did not provide benefit over TAP/INJ in the patients with hand motion vision or better.

- However, in patients with LP vision, initial PPV/INJ provided substantial benefit over TAP/INJ.
- Intravenous antibiotics (ceftazadime & amikacin) provide no added visual benefit in acute postoperative bacterial endophthalmitis.

## Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration (CATT) – 2011 [3]

**Purpose**

In 2006, the efficacy and safety of intravitreal ranibizumab (Lucentis®) were established (MARINA [4], ANCHOR [5]) for neovascular age-related macular degeneration (AMD). Ranibizumab is a monoclonal antibody fragment that binds vascular endothelial growth factor (VEGF) A while bevacizumab (Avastin®) is a monoclonal antibody that also binds VEGF A. Intravenous bevacizumab was approved by the Food & Drug Administration (FDA) for colon cancer but not for ophthalmic (intravitreal) use; nonetheless it was widely used off-label due to its similar therapeutic target, lower cost, and promising results of previous non-randomized studies. However, the comparative intraocular safety, efficacy, and duration of therapy were unknown. The CATT trial explored the safety profile and efficacy of bevacizumab as compared to ranibizumab.

**Methods**

This was a randomized, single-blinded, multi-center trial of 1185 patients with active choroidal neovascularization (NV), diagnosed by both fluorescein angiography (FA) and optical coherence tomography (OCT). Participants were randomly assigned to four treatment groups: (1) 0.5 mg ranibizumab monthly, (2) 1.25 mg bevacizumab monthly or either medication (3, 4) only when signs of NV were present (as needed). The primary endpoint was noninferiority based on change of BCVA at one year from baseline. Secondary outcomes included percentage of participants with decrease in visual acuity of ≥15 Early Treatment Diabetic Retinopathy Study

(ETDRS) chart letters from baseline, percentage gaining ≥15 letters during the first 36 weeks, number of injections, foveal thickness on OCT, and annual drug costs.

**Results**

At one year, bevacizumab was noninferior to ranibizumab in the mean change in visual acuity letter score from baseline, both when the injections were given monthly or as needed. Similarly, ranibizumab as needed was equivalent to monthly ranibizumab and monthly bevacizumab. However, the comparison of bevacizumab as needed to bevacizumab monthly or ranibizumab monthly was inconclusive.

For secondary outcomes, the proportions of patients either losing ≥15 letters or gaining ≥15 letters did not differ between groups. While all treatments significantly reduced intraretinal or subretinal fluid, monthly or as needed ranibizumab decreased subfoveal thickness more than monthly bevacizumab (196 μm vs. 164um, $p = 0.03$). Monthly ranibizumab also had a higher rate of fluid free patients compared to monthly bevacizumab (43.7% vs. 26%, $p < 0.001$). There were a total of 11.7 (ranibizumab monthly) and 11.9 (bevacizumab monthly) injections, as compared to 6.9 and 7.7 injections in the ranibizumab and bevacizumab as needed groups, respectively. However, the annual costs for study drug per patient differed significantly, as the cost of ranibizumab ($23,000 for monthly treatment and $13,800 as-needed) was >35 times that of bevacizumab ($595 for monthly treatment and $385 as-needed).

In terms of serious systemic adverse events ( SAEs), there was no overall mortality difference between the groups. However, there was a small increased risk for bevacizumab (24.1%) as compared to ranibizumab (19.0%) for any serious SAEs once the dosing-regimen groups were combined ($p = 0.04$). The largest difference was attributed to hospitalizations for infections and gastrointestinal disorders, although a drug-related mechanism was not well understood. Both arterial and venous thrombotic events and ocular adverse events were similar between the groups; however, safety results should be taken with caution, as the study was not powered to detect differences in adverse events based on a specific drug.

**Follow-up Studies**
The follow-up studies (CATT two-year [6] and CATT five-year [7]) showed similar visual outcomes between bevacizumab and ranibizumab at two years, though there was less gain of visual acuity in the as needed treatment groups. Although visual acuity gains at year one and two were lost at five-year follow up, 50% of eyes had BCVA of 20/40 or better.

**Key Points**
- Bevacizumab is equivalent to ranibizumab for neovascular AMD in the first year of follow-up when administered on a similar schedule.
- Bevacizumab is significantly cheaper than ranibizumab, which has important economic implications for the treatment of patients with neovascular AMD in the United States.

## Intravitreal Aflibercept (VEGF Trap-Eye) in Wet Age-related Macular Degeneration (VIEW 1 & 2) – 2012 [8]

**Purpose**
Aflibercept is a soluble decoy receptor fusion protein that has substantially higher binding affinity for vascular endothelial growth factor (VEGF) than either bevacizumab or ranibizumab. Intravitreal aflibercept (Eylea®) showed robust resolution of fluid from the central retina and improvement in visual acuity in a Phase 2 (CLEAR-IT 2 [9]) study in patients with neovascular age-related macular degeneration (AMD). Thus, two similar Phase 3 studies (VIEW 1 and VIEW 2) explored the efficacy and safety of aflibercept as compared to ranibizumab.

**Methods**
This was a randomized, double-masked, multicenter trial of 2419 patients with active subfoveal neovascularization (NV) secondary to choroidal NV. VIEW 1 included patients from the United States of America and Canada while VIEW 2

encompassed Europe, Latin America, Middle East and Asia-Pacific. Participants were randomly assigned to one of four treatment groups: (1) 0.5 mg aflibercept monthly, (2) 2 mg aflibercept monthly or (3) every 2 months, or (4) 0.5 mg ranibizumab monthly. All participants first received three monthly loading doses (at weeks zero, four and eight) and then were subsequently spaced out per treatment group. To establish noninferiority, the prespecified primary endpoint for each study was the proportion of patients who maintained vision at 52 weeks (losing <15 ETDRS letters) with a margin of 10%. The margin was reduced to 7% in the preplanned integrated analysis of both VIEW studies. Secondary outcomes focused on proportion of patients with ≥15 ETDRS letter gain, and anatomic measures (e.g. retinal thickness, persistent fluid).

**Results**

In both studies, at one year, the proportion of patients who maintained vision was similar among all treatment groups–each aflibercept group achieved statistical noninferiority compared to monthly ranibizumab within the prespecified 10% margin. Analysis of the combination of both studies also met the prespecified 7% noninferiority margin. Important secondary outcomes showed similar proportions of patients achieving both ≥15 ETDRS letter gain as well as dry retinas (absence of intraretinal and subretinal fluid) in all treatment groups. Intraocular and systemic SAEs were similar between both medications.

**Follow-up Studies**

The VIEW 1 & 2 trials utilized the same dose but switched to an as-needed regimen with defined retreatment criteria and mandatory dosing at least every 12 weeks in year one to two. The results showed a similar small decrease in BCVA in all four treatment groups [10]. The proportions of patients who maintained ≥15 ETDRS letter gain was also similar between treatment groups. Additionally, the decrease in central retinal thickness was maintained at two years.

In 2019, another study (RIVAL [11]) also compared ranibizumab (0.5 mg) to aflibercept (2.0 mg) in wet AMD using a treat-and-extend regimen after an initial three-month

loading dose. Both the change in BCVA from baseline to month 12 and number of injections were similar between the two groups, suggesting neither is superior to the other in terms of visual gains or treatment burden.

The anti-VEGF trials have led to anti-VEGF agents becoming the standard treatment for AMD variants such as polypoidal choroidal vasculopathy (PCV). Given the success of these agents, the previous treatment–photodynamic therapy using verteporfin (PDT) is being used less. EVEREST II [12] and PLANET [13] were recent large multicenter trials in a continuum of other studies that have evaluated anti-VEGF agents in combination with PDT in the treatment of PCV.

**Key Points**

- Three aflibercept treatment regimens [including monthly (0.5 mg & 2 mg) and every two months (2 mg) after three initial monthly loading doses] were noninferior to monthly ranibizumab in preventing moderate visual acuity loss at one year.
- All three regimens also matched retinal edema and thickness improvement seen with monthly ranibizumab.

## Lutein + Zaexanthin and Omega-3 Fatty Acids for Age-related Macular Degeneration (AREDS2) – 2013 [14]

**Purpose**

Although anti-vascular endothelial growth factor (VEGF) medications are efficacious in treating neovascular age-related macular degeneration (AMD), there are no proven therapies for non-neovascular (dry) AMD. Thus, it is critical to decrease progression from dry AMD to advanced AMD (neovascularization or central geographic atrophy). In 2001, the Age-Related Eye Disease Study (AREDS) [15] showed that daily oral supplementation with high dose antioxidants and zinc reduced the risk of developing advanced AMD at five years by 25% among those with intermediate (category 3) or advanced (category 4) AMD. The AREDS formulation

consisted of vitamin C (500 mg), vitamin E (400 international units), beta-carotene (15 mg), zinc (80 mg as zinc oxide), and copper (2 mg as cupric oxide).

Based on animal and observational studies, other carotenoids (lutein, zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids (DHA & EPA) appeared effective in possibly preventing AMD progression. AREDS2 explored the role of these nutrients in the progression of AMD. A secondary but important goal was to evaluate the elimination of beta-carotene (a carotenoid in the AREDS formulation) given the associated increase in lung cancer rates and mortality in cigarette smokers.

**Methods**

This was a randomized, double-masked, multicenter trial of 4203 patients at high risk of progression to advanced AMD with either bilateral large drusen or large drusen in one eye and advanced AMD in the fellow eye. Participants were randomized to one of four groups: (1) lutein (10 mg) + zeaxanthin (2 mg), (2) DHA (350 mg) + EPA (650 mg), (3) all four nutrients together, or (4) placebo. All participants also continued daily AREDS supplementation. A secondary randomization placed participants into four further groups: (1) original AREDS formulation, (2) no beta-carotene, (3) lower zinc dose or (4) both a lower zinc dose and elimination of beta-carotene. Baseline serum levels and dietary levels of the study nutrients were measured. The primary outcome was the percentage of participants who developed advanced AMD by five years. One important secondary outcome analysis was comparison of advanced AMD development at five years between original AREDS versus no beta-carotene or reduced zinc formulations.

**Results**

At five years, the comparison of each treatment group with placebo revealed no statistically significant reduction in progression to advanced AMD or changes in visual acuity; Kaplan-Meier probabilities of progression to advanced AMD by five years were 31%, 29%, 31%, and 30% for placebo, lutein + zeaxanthin, DHA+EPA, and all four nutrients

together, respectively. A subgroup analysis, although not prespecified, revealed a protective role of lutein + zeaxanthin in participants with the lowest dietary intake of these nutrients (HR 0.74, 95% CI 0.59–0.94; p = 0.01). However, the protective effect was not observed with increased lutein + zeaxanthin intake. The secondary randomization analysis showed that eliminating beta-carotene and lowering zinc did not affect progression to advanced AMD.

AREDS2 participants who received AREDS supplementation with beta-carotene had an increase in lung cancer if they were former smokers or quit smoking more than one year prior to the study; there was no increased risk of lung cancer in the lutein + zeaxanthin group.

**Key Points**

- Addition of either lutein + zeaxanthin or DHA+EPA, or all four nutrients together to the AREDS formulation resulted in similar rates of AMD progression but without further risk reduction.
- In participants with lowest dietary intake of lutein + zeaxanthin, a protective role for advanced AMD progression was observed in the lutein + zeaxanthin supplemental group, though there was no trend with increasing lutein + zeaxanthin intake.
- Eliminating beta-carotene and lowering the zinc dose did not change risk of advanced AMD progression.
- Given the increased risk of lung cancer in former smokers, beta-carotene could be substituted with lutein + zeaxanthin.

## Three-Year, Randomized, Sham-Controlled Trial of Dexamethasone Intravitreal Implant in Patients with Diabetic Macular Edema (Ozurdex MEAD) – 2014 [16]

**Purpose**

Diabetic macular edema (DME) is the most common cause of vision loss in diabetic retinopathy (DR). Historically, the stan-

dard care for DME included focal/grid laser photocoagulation and diabetic glycemic control. The subsequent development of anti-vascular endothelial growth factor (VEGF) agents led to improvements in the treatment of DME (discussed in the next trial). However, inflammatory mediators and other permeability factors in addition to VEGF play a role in DME, suggesting the potential therapeutic role of corticosteroids. Indeed, two studies [17, 18] showed that an intravitreal fluocinolone acetonide insert improved vision in patients with DME. Furthermore, the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol I [19] showed similar efficacy of intravitreal triamcinolone or ranibizumab in combination with laser treatment in pseudophakic eyes. The DEX implant (Ozurdex, Allergan) is a sustained-release intravitreal implant of dexamethasone, which is a more potent corticosteroid than triamcinolone. The Ozurdex MEAD study evaluated the safety and efficacy of DEX implant in the treatment of DME.

**Methods**

Two randomized, multicenter, masked, sham-controlled, trials of 1048 patients with either type 1 or type 2 diabetes, center-involving macular edema, and a BCVA range from 20/50 to 20/200 were conducted. Participants were randomly assigned to one of three treatment groups: (1) DEX implant 0.35 mg, (2) DEX implant 0.7 mg, or (3) sham injection; one eye per participant was randomized to study treatment. DEX or sham was injected at the baseline visit; however, retreatment was possible after six months if there was residual DME.

If a patient lost ≥15 letters or received any other escape therapy (treatment for DME other than study agents), they were required to withdraw from the study. The prespecified primary outcome was the percent of patients with >15 letter improvement in BCVA from baseline at three years. Among other safety measures, intraocular pressure (IOP) and cataract formation were monitored.

**Results**

At three years, DEX implant was superior to sham, with 22.2% of participants gaining ≥15 letters in the DEX 0.7 mg group, 18.4% in the DEX 0.35 mg group, and 12% in the

sham group ($p < 0.018$). Visual outcomes were consistent over time in pseudophakic patients. In phakic patients the visual benefit was less due to cataract development, although vision improved after cataract surgery. The median number of treatments was four, five and three in the DEX implant 0.7 mg, 0.35 mg and sham groups, respectively.

In phakic eyes, there were significantly more cataract-related adverse events in the DEX 0.7 mg and 0.35 mg as compared to sham (67.9%, 64.1% and 20.4%, respectively). In terms of IOP, about one-third of patients had a clinically significant increase in IOP and approximately 40% required IOP-lowering medications. No implant was removed to control IOP, and three to five (~1–2%) procedures were required for steroid-induced IOP rise in each DEX group. Finally, there was a high rate of patient discontinuation in all groups, but the rate was much higher in the sham group (56.6% vs. 35.9% in DEX 0.7 mg or 33.7% in DEX 0.35 mg) given the lack of efficacy.

**Key Points**

- Dexamethasone intravitreal implant for the treatment of DME improves visual outcomes when compared to sham over three years.
- Although cataract progression limited visual gains in phakic eyes, cataract removal led to improved and sustained visual acuity.
- The DEX implant provides another tool in addition to anti-VEGF for the treatment of DME.

## Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema (DRCR.net Protocol T) – 2015 [20]

**Purpose**

Vascular endothelial growth factor (VEGF) mediates abnormal vascular permeability in diabetic macular edema (DME). In 2012, ranibizumab became the first approved anti-VEGF

treatment for DME, followed by aflibercept in 2014. Similar to its use in AMD, bevacizumab was repackaged and used off-label in the treatment of DME. The DRCR.net Protocol T evaluated the comparative efficacy and safety of intravitreal aflibercept, bevacizumab, and ranibizumab for center-involving DME that caused visual impairment.

**Methods**

This was a randomized, double-masked, multicenter trial of 660 patients with either type 1 or type 2 diabetes and a BCVA range from ~20/32 to ~20/320. Participants were randomly assigned to one of three treatment groups: (1) aflibercept 2 mg, (2) bevacizumab 1.25 mg, or (3) ranibizumab 0.3 mg. The study drugs were injected at the start (week zero) and then every four weeks unless visual acuity was ≥20/20 and the subfield thickness was below the eligibility threshold. Injections were discontinued if there was no improvement or worsening in response from the past two injections. Focal/grid laser photocoagulation therapy was started at ≥24-week visit for persistent DME. The primary outcome was the mean change in visual acuity one year from baseline.

**Results**

At one year, the mean improvement in the visual acuity letter score was not significantly different for participants with baseline visual acuities of 20/32–20/40 (aflibercept [+8.0 letters], bevacizumab [+7.5], and ranibizumab [+8.3]). However, in patients with BCVA of 20/50 or worse, the aflibercept group had a larger visual improvement (+18.9 letters) than either bevacizumab (+11.8) or ranibizumab (+14.2). In addition, both aflibercept and ranibizumab decreased central subfield thickness more than bevacizumab, with a final thickness <250 μm in 66%, 36%, and 58% of eyes (aflibercept, bevacizumab, and ranibizumab, respectively).

The median number of injections was nine in the aflibercept group and 10 in the remaining two groups. Focal, grid, or both laser photocoagulation was performed at least once in 37% of aflibercept-treated eyes, 56% of bevacizumab-treated

eyes, and 46% of ranibizumab-treated eyes. However, similar to visual acuity changes, the 20/32–20/40 subgroup had the same number of injections (9) and similar laser photocoagulation rates. Both ocular and systemic SAEs were rare with no significant differences between groups.

**Follow-up Studies**
The two-year [21] Protocol T results showed that all treatment groups had improved vision from baseline. Like the one-year results, patients with good baseline vision (20/32–20/40) had similar outcomes from any of the three agents. Among eyes with worse baseline vision (≤20/50), aflibercept maintained superior outcomes to bevacizumab but not ranibizumab; with no significant difference between ranibizumab and bevacizumab at two years. In addition, there were more adverse vascular events as defined by the Anti-Platelet Trialists' Collaboration in the ranibizumab group that will require further evaluation in future trials.

**Key Points**
- Aflibercept, bevacizumab, and ranibizumab are effective and safe treatments for central-involving diabetic macular edema.
- If DME caused mild visual impairment (20/32–20/40), then there was no significant difference in efficacy between the three study drugs. However, if initial visual acuity was ≥20/50, aflibercept was more effective at improving vision at one year with no statistically significant difference between bevacizumab and ranibizumab.

## Panretinal Photocoagulation Versus Intravitreous Ranibizumab for Proliferative Diabetic Retinopathy, A Randomized Clinical Trial (DRCR.net Protocol S) – 2015 [22]

**Purpose**
The standard of care for patients with proliferative diabetic retinopathy (PDR) has historically been panretinal photoco-

agulation (PRP). PRP decreases vascular endothelial growth factor (VEGF) levels by destroying peripheral retina, which can lead to permanent peripheral visual field loss and at times, can exacerbate diabetic macular edema (DME). Given the success of intravitreal anti-VEGF agents in DME and improvement in severity and progression of diabetic retinopathy [23], these agents were proposed to be efficacious for PDR. Thus, Protocol S evaluated the potential efficacy (noninferiority) of ranibizumab compared to PRP in patients with PDR.

**Methods**

This was a randomized, single-masked, multicenter trial of 305 patients (394 study eyes) with either type 1 or type 2 diabetes and at least one eye with PDR; eyes with DME were allowed. Participants with one study eye were randomly assigned to either: (1) PRP with ranibizumab as needed for DME or (2) ranibizumab 0.5 mg; participants with two study eyes had one eye randomly assigned to PRP and the other eye to ranibizumab. In the PRP group, the procedure (either pattern scan or traditional single shot laser) was started at baseline with additional PRP allowed for increased neovascularization (NV). In the ranibizumab group, injections were given every four weeks through week 12 and then re-treated as necessary based on NV; treatment failure permitted PRP use. DME was treated with ranibizumab at randomization–thereafter, either ranibizumab or focal/grid photocoagulation could be used at investigator discretion. The primary outcome was change in visual acuity from baseline to two years.

**Results**

At two years, the mean improvement in the visual acuity letter score from baseline was +0.2 in the PRP group and +2.8 in the ranibizumab group ($p < 0.001$), meeting the prespecified noninferiority criterion. While 6% of eyes in the ranibizumab group received PRP, 53% of eyes in the PRP group received ranibizumab for DME. As expected, the PRP group had significantly more peripheral visual field loss (531 dB vs. 213 dB in ranibizumab).

In terms of PDR progression, vitreous hemorrhage occurred more in the PRP group and more vitrectomies were performed (15% of eyes vs. 4% of eyes in ranibizumab group). The rates of inactive or regressed NV at the disc or elsewhere, iris NV and neovascular glaucoma were similar between the ranibizumab and PRP groups. There were no significant SAEs between the two groups.

**Follow-up Studies**

A secondary analysis [24] of the two-year Protocol S data showed a higher cumulative probability of worsening PDR in the PRP group (42%) versus ranibizumab (34%). Importantly, eyes in the pattern scan laser group were at higher risk for worsening PDR than eyes in the single-spot group (60% vs. 39%, $p = 0.008$ respectively). However, eyes were not assigned randomly to pattern scan or single-spot PRP, so there could be potential bias and confounding.

The five-year [25] Protocol S showed that although there was substantial loss to follow up, visual acuity was similar between both groups. The ranibizumab group had lower rates of vision-impairing DME (cumulative probabilities of 22% vs. 38% in PRP group). Regarding visual field loss, the differences between the two groups diminished over time. Severe vision loss or serious sequelae of PDR were infrequent in both groups. Altogether, these results supported either treatment for PDR.

Intravitreal aflibercept also appears promising as another treatment for PDR. A Phase 2B non-inferiority trial (CLARITY) [26] in the United Kingdom showed that aflibercept was both non-inferior and superior to PRP in BCVA change at one year from baseline.

**Key Points**

- Ranibizumab was noninferior to PRP in terms of visual acuity change at two years in the treatment of PDR, providing another treatment alternative to PRP.
- Because few eyes in the ranibizumab group received PRP while more than half of eyes in the PRP group received

ranibizumab for DME, the trial essentially evaluated ranibizumab versus PRP plus ranibizumab as needed in the treatment of PDR.
- When choosing treatment for PDR, various patient specific factors should be considered including visit frequency, adherence, and cost.

## Five-Year Safety and Performance Results from the Argus II Retinal Prosthesis System Clinical Trial (Argus II) – 2016 [27]

**Purpose**

Prior to this study, there was no existing proven therapy for the treatment of end-stage Retinitis Pigmentosa (RP) in which the outer retina had substantially degenerated. Retinal prosthesis is one tool that was designed to replace the function of photoreceptors and stimulate secondary retinal neurons, ultimately forming a visual image. In 2002, the first generation retinal prosthesis (Argus® I) was implanted epiretinally in six subjects, showing an increase in spatial vision [28]. The next generation device, Argus® II, evaluated the long-term safety and efficacy of the Argus II System in RP patients with bare light perception (LP) or no light perception (NLP).

**Methods**

This was a prospective, single-armed, multi-center nonrandomized clinical trial of 29 patients with RP and one patient with choroideremia with bare LP or NLP vision. The Argus II System was implanted in the worse-seeing eye. The primary endpoint for efficacy was visual function as tested by three custom-designed assessments. Additionally, two "real-world" secondary visual function assessments were evaluated. All testing was completed with the Argus II System ON and OFF. In terms of safety, all SAEs due to the device or surgical implantation were recorded.

The Argus II System has multiple components; briefly, the intraocular electrode array is placed epiretinally over the

macula and communicates with a receiving antenna outside the eyes fixed by a scleral band. A small camera mounted on a pair of glasses transmits visual information to a processing unit worn on a belt or shoulder. The data generated is sent via radio-frequency telemetry link from an external antenna on the glasses to the receiving antenna on the eye. The electrode then stimulates inner retinal neurons to generate action potentials that travel through the established visual pathway.

**Results**

As a group, patients performed better on the three visual function tests with the system ON versus OFF (using their residual visual capacity). They also performed better with the system ON on an individual basis. These results were consistent with the previous three-year data. Finally, patients also performed better with the system ON on "real-world" visual functional assessments.

At five years, 60% of participants had no SAEs; the remaining events were treated with standard ophthalmic care. However, one patient developed a rhegmatogenous retinal detachment in the implanted eye approximately 4.5 years post-implant, causing neovascular glaucoma one year later. Two devices failed ~ four years post-implant, losing the communicating ability between the external and internal antennas. Three devices were explanted, two due to recurrent conjunctival erosion and the third due to chronic hypotony and ptosis.

**Key Points**

- The Argus II Retinal Prosthesis System functions reliably for at least four years and provides basic visual function to patients with severe vision loss from RP.
- The Argus II System has an acceptable safety profile with few devices failures and explants at 5 years.

## Efficacy and Safety of Voretigene Neparvovec (AAV2-hRPE65v2) in Patients with RPE65-Mediated Inherited Retinal Dystrophy: A Randomized, Controlled, Open-Label, Phase 3 Trial – 2017 [29]

**Purpose**

Inherited retinal dystrophies are rare in the population but cause significant visual impairment. Leber congenital amaurosis (LCA), a RP subtype, has an earlier onset characterized by rapidly progressive vision loss during childhood. Mutations in many genes can lead to LCA; biallelic mutations of the *RPE65* gene, which encodes an enzyme crucial for the visual cycle, leads to disruption of the cycle and eventual blindness.

Using a recombinant Adeno-associated virus (AAV), proof-of-principle for gene augmentation therapy was established and a Phase I trial was safe in all participants. In keeping with progress, the Phase 3 trial of voretigene neparvovec (Luxturna) evaluated safety and efficacy of sequential, bilateral, subretinal administration of voretigene neparvovec in participants with biallelic RPE65-mediated inherited retinal dystrophy.

**Methods**

This was a randomized, open-label, controlled trial involving two centers and five surgeons, with 29 pediatric and adult patients with a genetically confirmed biallelic *RPE65* gene mutation. Amongst other criteria, participants were required to have bilateral best corrected visual acuity (BCVA) of ≤20/60, and able to perform a standardized multi-luminance mobility test (MLMT). Because of the poor baseline vision of the participants, visual acuity was not a meaningful measure of functional vision. Thus the MLTM, which evaluated a participant's ability to navigate a path filled with obstacles, provided a quantifiably measure of visual acuity, visual field and light sensitivity. Separated

by age and baseline MLMT, participants were randomized to a 2:1 assignment of intervention to control. In the treatment group, a subretinal injection of voretigene neparvovec was performed in the first eye followed by the second eye one to two weeks later. The control group became eligible for bilateral treatment one year after baseline evaluation. The primary endpoint was the change in bilateral MLMT performance (change in lux score for the lowest passing light level) at one year relative to baseline. Secondary efficacy endpoints included full-field sensitivity threshold testing (FST), BCVA and visual field testing.

**Results**

At one year, the mean change in bilateral MLMT score was 1.8 and 0.2 lux, in the treatment and control groups, respectively ($p = 0.0013$); monocular MLMT scores were similar to bilateral scores. The mean FST increased >2 log units by 30 days and remained stable over the one year – there was no change in the control group. BCVA, averaged over both eyes, showed a mean improvement of 8.1 letters for intervention participants and 1.6 letters for control participants, but was not significant ($p = 0.17$). Finally, the mean sum total degrees of Goldmann visual field (III4e) nearly doubled in the intervention group and decreased in the control group. No viral vector-related SAEs occurred; while most ocular adverse events were mild and resolved, 10% exhibited a retinal tear and 15% developed a cataract.

**Key Points**

- In this first ever randomized Phase 3 gene therapy trial for a genetic disease, bilateral subretinal AAV resulted in improvement in visual function in patients with LCA (RPE65-mediated inherited retinal dystrophy).
- This landmark study demonstrated proof-of-concept for targeted gene therapy in inherited retinal degeneration.
- No viral vector-related SAEs occurred at the one-year observation period.

## Effect of Bevacizumab Versus Aflibercept on Visual Acuity Among Patients with Macular Edema Due to Central Retinal Vein Occlusion- The SCORE2 Randomized Clinical Trial – 2017 [30]

**Purpose**

Retinal vein occlusion (RVO) is a prevalent retinal vascular disease affecting millions of adults worldwide. Macular edema is the most common cause of vision loss following a RVO. A multitude of studies have investigated the efficacy of anti-vascular endothelial growth factor (VEGF) agents for RVO related macular edema: BRAVO [31] and CRUISE [32] studies demonstrated the efficacy of intravitreal ranibizumab in branch retinal vein occlusion (BRVO) and central retinal vein occlusion (CRVO), respectively, while COPERNICUS [33] & GALILEO [34] showed efficacy of monthly aflibercept for the treatment of macular edema in patients with CRVO.

Similar to its use in AMD, bevacizumab was being used off-label for macular edema from vein occlusions given its previously studied safety profile as well as its efficacy in other retinal diseases. Thus, the SCORE2 trial evaluated the efficacy of bevacizumab as compared to aflibercept for the treatment of center-involving macular edema due to central or hemiretinal vein occlusion (HRVO).

**Methods**

This was a randomized, single-masked, multicenter trial of 362 patients with either CRVO or HRVO, with center-involving macular edema and best corrected visual acuity (BCVA) from ~20/40–20/400. Participants were randomly assigned 1:1 to intravitreal bevacizumab 1.25 mg every four weeks for six months versus intravitreal aflibercept 2.0 mg every four weeks for six months. Participants were further stratified in three baseline groups of good (20/40–20/63),

moderate (20/80–20/100), or poor (20/125–20/400) BCVA. To establish noninferiority, the prespecified primary outcome was a change in ETDRS visual acuity letter score from baseline, with a noninferior margin of five letters at six months.

Eyes that responded well (prespecified protocol-defined) at six months were randomized to continue monthly treatment or treat-and-extend with same assigned drug. If eyes responded poorly, then the bevacizumab group was switched to aflibercept and the aflibercept group to intravitreal dexamethasone implant.

**Results**

Of the 362 participants, 85.5% were diagnosed with a CRVO while 14.4% had a HRVO. At six months, bevacizumab was noninferior to aflibercept in terms of a prespecified gained visual acuity score of five letters ($p = 0.001$). In the bevacizumab group, 61% of eyes had >15 letter gain versus 65% in the aflibercept group. There was no difference in treatment effect between the different baseline visual strata. In addition, both groups showed similar reduction in subfield central thickness from baseline and both received approximately six injections the first six months. However, resolution of macular edema was higher in the aflibercept group (54.4%) than bevacizumab (28.5%). Ocular and systemic SAEs were rare in both groups.

**Follow-up Studies**

Patients who had a protocol-defined "good response" in the first six months of the SCORE2 trial underwent randomization to either continue monthly injections or treat-and-extend (TAE) for an additional six months. The one-year results [35] showed similar visual acuity change from month six to month 12 between monthly aflibercept versus TAE and monthly bevacizumab versus TAE. The TAE schedule led to approximately two fewer injections in each drug group. While promising, caution is warranted due to the large range of the confidence intervals for the visual acuity differences between the monthly and TAE groups, suggesting that the two different dosing regimens may not have similar vision outcomes.

**Key Points**

- In patients with CRVO or HRVO and secondary center-involving macular edema, intravitreal bevacizumab was noninferior to aflibercept after six months of monthly treatment.
- Although more eyes had resolution of macular edema in the aflibercept group, this difference did not change visual acuity outcomes.

## References


1. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. Arch Ophthalmol. 1995;113(12):1479–96.
2. Han DP, Wisniewski SR, Wilson LA, et al. Spectrum and susceptibilities of microbiologic isolates in the Endophthalmitis Vitrectomy Study. Am J Ophthalmol. 1996;122(1):1–17.
3. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med. 2011;364(20):1897–908.
4. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1419–31.
5. Brown DM, Kaiser PK, Michels M, et al. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med. 2006;355(14):1432–44.
6. 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):1388–98.
7. Maguire MG, Martin DF, Ying GS, et al. Five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2016;123(8):1751–61.
8. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. Ophthalmology. 2012;119(12):2537–48.

9. Brown DM, Heier JS, Ciulla T, et al. Primary endpoint results of a phase II study of vascular endothelial growth factor trap-eye in wet age-related macular degeneration. Ophthalmology. 2011;118(6):1089–97.
10. Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. Ophthalmology. 2014;121(1):193–201.
11. Gillies MC, Hunyor AP, Arnold JJ, et al. Effect of ranibizumab and aflibercept on best-corrected visual acuity in treat-and-extend for neovascular age-related macular degeneration: a randomized clinical trial. JAMA Ophthalmol. 2019;137(4):372–9.
12. Koh A, Lai TYY, Takahashi K, et al. Efficacy and safety of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: a randomized clinical trial. JAMA Ophthalmol. 2017;135(11):1206–13.
13. Lee WK, Iida T, Ogura Y, et al. Efficacy and safety of intravitreal aflibercept for polypoidal choroidal vasculopathy in the PLANET study: a randomized clinical trial. JAMA Ophthalmol. 2018;136(7):786–93.
14. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013;309(19):2005–15.
15. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119(10):1417–36.
16. Boyer DS, Yoon YH, Belfort R Jr, et al. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. Ophthalmology. 2014;121(10):1904–14.
17. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology. 2011;118(4):626–35.e2.
18. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology. 2011;118(8):1580–7.
19. Elman MJ, Aiello LP, Beck RW, et al. Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone

plus prompt laser for diabetic macular edema. Ophthalmology. 2010;117(6):1064–77.e35.
20. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. N Engl J Med. 2015;372(13):1193–203.
21. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results from a comparative effectiveness randomized clinical trial. Ophthalmology. 2016;123(6):1351–9.
22. Gross JG, Glassman AR, Jampol LM, et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA. 2015;314(20):2137–46.
23. Ip MS, Domalpally A, Hopkins JJ, et al. Long-term effects of ranibizumab on diabetic retinopathy severity and progression. Arch Ophthalmol. 2012;130(9):1145–52.
24. Bressler SB, Beaulieu WT, Glassman AR, et al. Factors associated with worsening proliferative diabetic retinopathy in eyes treated with panretinal photocoagulation or ranibizumab. Ophthalmology. 2017;124(4):431–9.
25. Gross JG, Glassman AR, Liu D, et al. Five-year outcomes of panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. JAMA Ophthalmol. 2018;136(10):1138–48.
26. Sivaprasad S, Prevost AT, Vasconcelos JC, et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. Lancet. 2017;389(10085):2193–203.
27. da Cruz L, Dorn JD, Humayun MS, et al. Five-year safety and performance results from the Argus II retinal prosthesis system clinical trial. Ophthalmology. 2016;123(10):2248–54.
28. Caspi A, Dorn JD, McClure KH, et al. Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. Arch Ophthalmol. 2009;127(4):398–401.
29. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet. 2017;390(10097):849–60.
30. Scott IU, VanVeldhuisen PC, Ip MS, et al. Effect of bevacizumab vs aflibercept on visual acuity among patients with macular

edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. JAMA. 2017;317(20):2072–87.
31. Campochiaro PA, Heier JS, Feiner L, et al. Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1102–12.e1.
32. Brown DM, Campochiaro PA, Singh RP, et al. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. Ophthalmology. 2010;117(6):1124–33.e1.
33. Heier JS, Clark WL, Boyer DS, et al. Intravitreal aflibercept injection for macular edema due to central retinal vein occlusion: two-year results from the COPERNICUS study. Ophthalmology. 2014;121(7):1414–20.e1.
34. Korobelnik JF, Holz FG, Roider J, et al. Intravitreal aflibercept injection for macular edema resulting from central retinal vein occlusion: one-year results of the phase 3 GALILEO study. Ophthalmology. 2014;121(1):202–8.
35. Scott IU, VanVeldhuisen PC, Ip MS, et al. Comparison of monthly vs treat-and-extend regimens for individuals with macular edema who respond well to anti-vascular endothelial growth factor medications: secondary outcomes from the SCORE2 randomized clinical trial. JAMA Ophthalmol. 2018;136(4):337–45.