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# Updates in Retinal Disease Care: Keeping an Eye on Emerging Anti-VEGF Therapies & Improved Outcomes

**Announcer:**
Welcome to CME on ReachMD. This activity titled Updates in Retinal Disease Care: Keeping an Eye on Emerging Anti-VEGF Therapies & Improved Outcomes is jointly provided by Potomac Center for Medical Education and Rockpointe, and is supported by an educational grant from Genentech, a member of the Roche Group.

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**Dr. Holekamp:**
Hello and welcome to the CME certified ABO MOC eligible activity, Updates in Retinal Disease Care: Keeping an Eye on Emerging Anti-VEGF Therapies & Improved Outcomes jointly provided by PCME and Rockpointe in collaboration with BrightFocus Foundation and supported by an educational grant from Genentech. My name is Nancy Holekamp. I am Director of Retina Services at the Pepose Vision Institute in Chesterfield, Missouri. I'm glad to be joined this evening with my co-presenter Carl Regillo, M.D., Director of Retina Services at the Wills Eye Hospital, and Professor of Ophthalmology at the Thomas Jefferson University in Philadelphia, Pennsylvania. The content we are presenting was developed by myself and Carl. The faculty and non-faculty disclosures are listed here. We will take a few moments to give you the opportunity to review these. These and all pertinent accreditation information can also be found in the syllabus located in the download pod at the bottom left of your screen.

Here is the agenda for this evening's presentation. First, welcome and introduction, then, current state of retinal disease management, followed by clinical updates for new and emerging retinal disease therapies, and finally, a Q&A session and activity roundup. The following educational objectives can also be found on the landing page of this web course. At the conclusion of this activity participants should be able to assess risk benefits of fixed frequent dosing intervals versus individualized dosing intervals for anti-VEGF therapy, select anti-VEGF therapy dosing intervals that provide the best potential outcome for patients with retinal disease, and finally, assess the safety and efficacy of recently approved and emerging retinal disease therapies. And with that, we will begin the presentation. I will begin by talking about the current state of retinal disease management.

First, a word about the prevalence of AMD. It is extremely prevalent in the United States and is only growing as the baby-boomers age. It is estimated that there will be 22 million people affected by AMD by the year 2050 in the United States, that's getting closer and closer all the time. And this health care problem is associated with a huge direct healthcare cost estimated to be approximately 4.6 billion dollars, and that's an estimate from 2016. We're also going to be talking about diabetic eye disease. Again, the global prevalence of diabetes has tripled in the past 20 years, in fact, it's almost 9.3% of the entire global population. And 30% of diabetic individuals will have diabetic retinopathy. In 5 to 10% of patients with diabetic retinopathy will have those sight-threatening complications of PDR and DME and we'll be spending time talking about that.

What we see here is the treatment landscape over approximately 35, 40 years even, and what goes all the way from laser photocoagulation out to anti-VEGF therapies, above the lines we're looking at treatments for neovascular AMD, below the line we're looking at treatments for diabetic macular edema. But the take-home message from this slide is that for the last 15 plus years the treatments for both disease, wet macular degeneration and DME, have focused on intravitreal injections of anti-VEGF monotherapy, and

we see the most commonly used anti-VEGF agents here on this slide. First, we see bevacizumab – it is not FDA approved. Followed by ranibizumab, aflibercept, and brolucizumab, which are all FDA approved. You'll see 3 of them, bevacizumab, ranibizumab, and brolucizumab end with the suffix -mab, that means they are a monoclonal antibody. Now, aflibercept is a slightly different class of anti-VEGF agent. It is a receptor decoy and therefore, we have the suffix of -cept because it's a receptor fusion protein. All of these are anti-VEGF monotherapy. I will have to say that brolucizumab, while FDA approved, is not widely utilized in the United States after the pivotal clinical trials and FDA approval, when it was used in the real world, post marketing surveillance detected a retinal vasculitis – an inclusive retinal vasculitis associated with some injections of brolucizumab in some patients, and this was a type of irreversible permanent vision loss and it's because of this safety concern that brolucizumab currently has limited use, at least in the United States. This is because the other three antibody-based technologies – or other three anti-VEGF agents, 2 of them antibody-based, or aflibercept receptor-based, actually have very, very safe profiles. We see here the data for aflibercept and in the blue box, you see a take-home message – there are no major safety concerns regarding retinal vasculitis or retinal vascular occlusion after intravitreal ranibizumab, bevacizumab, or aflibercept, and it's because we have safer alternatives that these are the 3 agents commonly used.

And how are they used. We have multiple dosing approaches that have been tried in clinical trials. And the clinical trials began with monthly, then they went to bimonthly, then there were clinical trials looking at PRN dosing. We even have a history of early clinical trials looking at quarterly dosing, but later clinical trials looking at quarterly dosing. But I have to tell you, there's been a move toward treat-and-extend dosing, even though none of the pivotal randomized clinical trials that led to FDA approval include, up to this point, treat-and-extend dosing.

But why are we moving in that direction in the absence of level-1 evidence? And that's because monthly dosing creates a significant burden for patients, their caregivers, and even doctor's offices. And if you try to reduce that burden with individualized treatment, such as PRN, we know the visual acuity outcomes aren't quite as good, and you still haven't reduced the visit burden.

So, we're going to take kind of a walk-through history of the use of the anti-VEGF agents and the evolution toward treat-and-extend dosing, and this evolution begins with the very first anti-VEGF clinical trial with an antibody fragment, which were the ANCHOR and MARINA trials with ranibizumab. And they were clearly a significant advancement over verteporfin and PDT at that time, but they did create a significant treatment burden because what you see on these grafts are monthly dosing treatment arms.

We then see the VIEW 1 and VIEW 2 clinical trials that compared aflibercept to ranibizumab, and aflibercept was even dosed q8 weeks, but the package insert for aflibercept actually says it's clinically equivalent to ranibizumab, that this clinical trial design said that they were clinically equivalent. And when we moved to the HAWK and HARRIER clinical trials that compared brolucizumab dosed at q8 and q12 weeks to aflibercept dosed at q8 weeks, again, the results were clinically similar. You can see the mean change in BCVA lines are literally on top of each other. What we see here is that ranibizumab was similar to aflibercept and brolucizumab was similar to aflibercept, and when you look across a wide variety of large randomized clinical trials, including the CATT trials using bevacizumab, the take-home message is in the red box – study after study shows that anti-VEGF efficacy is similar across all current treatments. And what really matters is that these were clinical trial patients, and clinical trial patients do well. They have to come back for every single visit.

Here we compare in the left-most column the randomized clinical trial, the pivotal trials that were used for FDA approval. In the middle column we see randomized clinical trials that were very serious, looking at how to use these anti-VEGF agents. We see the visual acuity results marked on the Y-axis are very, very good. But, in that third column when we look at real-world evidence, we see that the visual acuity gains are not nearly what they were in the randomized clinical trial. And if you look at that icon that's a needle, and the number of injections, patients in the real world are getting fewer injections.

Now we're going to pause and have a discussion question, and the question is what percentage of patients with neovascular AMD are undertreated in the first year of therapy. Is it A: 24%, B: 39%, C: 52%, or D: 73%? And what you'll see here is the answer is 73%, and we see that in a real-world observational study called the LUMINOUS trial where 70% of patients with wet AMD got 6 or fewer anti-VEGF monotherapy injections in the first year of treatment, and we know that that is not sufficient to achieve the visual acuity gains we saw in randomized clinical trials.

And how do we know that? Because of the AURA study. Now, this was done largely outside of the United States. And we can see that the visual acuity lines actually go up initially because most people can start on therapy, most people are getting loading doses. It may go up for the first 3 or 4 months, and yet people can't keep up with the treatment paradigm because it creates such a burden. And if you look at that red-dotted line by one year, by about 360 days in Italy patients were at their baseline vision despite the fact that we had anti-VEGF agents available to protect and preserve vision.

From this first section on macular degeneration, I would like one of the take-home messages to be is that regardless of this disease or treatment paradigm, more injections equal better vision with anti-VEGF monotherapy. In these studies, better visual outcomes were associated with frequent monitoring and strict retreatment criteria, which led to frequent injections. That is the end of this section on wet

macular degeneration. But we're going to break for a little discussion question before we start talking about diabetic macular edema, and here's the question.

Which statement is most accurate regarding the efficacy of aflibercept, bevacizumab, and ranibizumab as AMD therapies? Is it A: aflibercept demonstrated greater durability of response than bevacizumab or ranibizumab, B: that ranibizumab has a more favorable safety profile than aflibercept or bevacizumab, C: that aflibercept was significantly more efficacious than ranibizumab, or D: that if you look at the big picture, all have similar efficacy, durability, and safety profiles. And the answer here is D: that anti-VEGF monotherapy treatments that currently exist all work. They all have similar efficacy and durability, and when we talk about bevacizumab, aflibercept, and ranibizumab, they generally have comparable safety profiles.

I'm going to pivot and talk about DME treatment options. And we have intravitreal VEGF blockade, intravitreal corticosteroids, and focal macular laser photocoagulation, and I will tell you that I currently use all 3 in my practice. But, without a doubt, the first-line treatment for center-involved DME is intravitreal VEGF blockade. We have strong level-1 evidence of efficacy from again, the pivotal phase 3 clinical trials of ranibizumab, aflibercept and brolucizumab. We have excellent data from the DRCR network Protocol T that includes bevacizumab. And we can even go further back in time to look at Protocol I from the DRCR network where we learn that anti-VEGF therapy ranibizumab was superior to laser and corticosteroids. We'll kind of take that walk through history and look first at the ranibizumab clinical trial data where monthly injections were so much better than sham. And, when we think back, these studies were done a long time ago, but they were allowed to have sham injections, which is essentially observation, be the control arm in these studies. And we see that anti-VEGF therapy was far superior. Then, we look at the VIVID and VISTA clinical trials. These used aflibercept in phase 3 studies, and here the comparator arm was laser photocoagulation, but you can see laser doesn't really make anyone better, it looks just like a sham-treated arm. And of course, anti-VEGF therapy was better than laser.

We fast-forward to Protocol T, which compared aflibercept to ranibizumab and to bevacizumab, and this graph shows the allcomers with the primary endpoints at 52 weeks and week 1 of 4, and we see that across 1 and 2 years, aflibercept had the best result. And was statistically significantly better than bevacizumab at both 52 weeks and weeks 1 of 4, and in other analyses, we learned that bevacizumab wasn't as good a drying agent, even in the patients who had relatively good vision of 20/32 or 20/40. And the one thing that I learned from Protocol T is that bevacizumab isn't really quite as good as the other 2 anti-VEGF agents, and what we find is that a lot of clinicians outside of clinical trials are switching back and forth between anti-VEGF agents to better control our patients who have DME.

This is analysis done by Shi et al, where they looked at the IRIS Registry where we can look at thousands and thousands of patients over time, and we see that patients identified by the very first injection they got, whether it was bevacizumab, ranibizumab, or aflibercept, they were pretty much flat, no one was improving vision. This is LogMAR vision that we see down at the bottom. One-line improvement is negative 0.1 line, and no one really achieves that despite what index anti-VEGF agents they're on. And the key to this slide is looking at the right-hand column where you see the icon of the needle, and it shows that everyone is being undertreated. Does it sound familiar? In the real world, we are not using a sufficient number of these injections in the first year to match the clinical trial results that we saw in randomized clinical trials.

Here's a study that I participated in and published back in 2018. It looks at real-world injection frequency in patients being treated for diabetic macular edema, and you'll see that 70% of patients receive 3 or fewer injections. That means their vision might go up for the first 6 months, but no one has this disease for just 6 months, and you really need to be consistent and maintain treatment over a prolonged period of time. That's the impetus for the evolution of going from monthly to bimonthly, or then individualizing the treatment to PRN or treat-and-extend. But, in diabetic patients, it's even harder than in our wet AMD patients because DME is essentially a biomarker for our sickest patients. They're going to the podiatrist, they're going to the nephrologist, they may be going to the cardiologist. And we see that the median follow-up drop-out time is 3.7 years. And we see the reasons for drop-out, the burden of the periodic follow-up visits, the long distance that many of our patients and our caregivers have to travel. And in DME in particular, we don't get that wow-effect where patients are so much better after the injections, that some of these DME patients are dissatisfied with their treatment benefit.

This slide will describe some of the other factors linked to nonadherence, and I don't want to minimize the fear of injections, or the fear of receiving a poor prognosis.

This ends my section. I just want to show you this last final summary slide, that when it comes to anti-VEGF, A: monotherapy ranibizumab, aflibercept, bevacizumab, and brolucizumab have similar efficacy and durability – durability is roughly 8 to 9 weeks with a range of about 1 to 3 or more months, but all require indefinite frequent treatment evaluations, and the more injections you get the better. And brolucizumab is less frequently used because of safety concerns. Now, when we translate anti-VEGF therapy to the real world, we see that relative undertreatment is still very prevalent and our patients in the real world are getting suboptimal long-term outcomes

beyond year 2 in both neovascular AMD and diabetic macular edema, and at the end of the day, the best outcomes come with a greater number of injections.

I hope I have laid the groundwork that describes why, despite anti-VEGF therapy, we have a major unmet need that could be solved by more durable anti-VEGF therapy. It could decrease the treatment burden, the need for evaluations. It could decrease the risk associated with any treatment, and it could portend the promise of better long-term visual acuity outcomes. And with that, I'm going to turn things over to my colleague, Carl Regillo, who will talk about clinical updates for new and emerging retinal disease therapies.

**Dr. Regillo:**
Thanks, Nancy. For my section, I'll be discussing updates with the new and emerging therapies that we have for these common retinal diseases, and that's mainly wet AMD and DME as been discussed. Most of what's new and emerging is about extending anti-VEGF durability. We have some good anti-VEGF agents that you've heard about, but some better ones, potentially, are on the horizon. And, in fact, a few approaches for therapy are already in our hands.

In extending anti-VEGF durability there's 2 basic approaches. There are traditional anti-VEGF, or anti-VEGF-like agents, that are injected intravitreally in the office, and there are also sustained-release delivery approaches, or sustained-release anti-VEGF types of platforms. So, we'll go into some detail and concentrate mainly on what has just become available, and as you can see, there are 2 now-FDA approved newer therapeutics. There's faricimab and there's the port delivery system.

Starting with faricimab, this is very unique because this is the first of its kind. It's a bispecific monoclonal antibody, so it's not just blocking VEGF-A, it also blocks angiopoietin-2. So, it's a full monoclonal antibody with 2 different fabs, one that binds antiopoietin-2, or ang-2, and one that binds VEGF-A, a target we've been blocking all along. In neovascular AMD, faricimab made it successfully through the phase 3 to 9 LUCERNE studies, and these were prospective randomized controlled studies, Pivotal trials that compared faricimab at 6 mg, which is now the FDA approved dose, to the standard 2 mg aflibercept dose, and that control group, aflibercept, was dosed on-label every 8 weeks in the maintenance phase.

And for the faricimab arm, after the loading phase, it was dosed either every 8, 12, or 16 weeks to the primary endpoint. And then, thereafter, dosed in a variable treat-and-extend-type fashion, which is something that we do in practice fairly routinely now.

What did the study show? Well, it was successful because faricimab dosed in this fashion was noninferior visually, and that was the primary endpoint to aflibercept to the primary endpoint around year 1, and all the way through the end of the trial in 2 years. You can see, essentially, identical or very similar vision gains that were well-maintained over time. And anatomically, faricimab performed well and showed good reductions in OCT central subfield thickness from the very beginning of the trial throughout the entire 2 years, comparable to aflibercept. In terms of efficacy, it performed very well, and where it really shined was in terms of durability. Because the way this study was designed, we could be dosing faricimab every 8, 12, or 16 weeks, and by the end of the first and second years, that's what we're seeing here, we see the distribution of patients being extended out to those treatment intervals. And by the end of 2 years, we're seeing 75, up to 80% of patients being dosed every 12 to 16 weeks, and 60, up to 67% of patients managed to get to 16-week dosing intervals by the end of the trial at year 2. Fairly impressive durability, something we haven't really seen this level of being able to extend treatment intervals with our first-generation agents that we've had in practice for the last 12 to 16 years.

And how did it do with regards to safety, because we have a high safety bar here. Our anti-VEGFs that we've been using in practice are really well tolerated and have very low complication rates. And faricimab actually did very well. There were no differences between faricimab in the clinical trial with any of the adverse events, or serious adverse events compared to aflibercept and specifically, shown here intraocular inflammation rates were comparable, slightly higher, slight imbalance, 3% faricimab versus 2.3% by the end of the study. I believe that's not clinically meaningful in terms of any difference that would matter in practice.

For neovascular MD, faricimab performed very well. It is as effective, both in terms of visual acuity gains and drying of the macula, as assessed by OCT, but it lasts longer, and that's where the added value or advantage comes into play. This was FDA approved for neovascular MD in January 2022, and is now commercially available and starting to be used.

And for DME, at the same time, faricimab is being tested at phase 3-level in the YOSEMITE and RHINE studies looking at how faricimab performed for center-involved DME with some degree of decreased vision. Again, the control group was aflibercept dosed on-label every 8 weeks after the loading phase. And here faricimab was dosed also in a similar 8-week fixed fashion and in a variable, so-called personalized treatment interval, which is like treat-and-extend, which allows for faricimab to be dosed as often as every 4 weeks, but as infrequent as 16 weeks, so it's 4, 8, 12, or 16-week treatment intervals possible in that arm.

This was also a successful study. And before I show you the results, we have this activity survey polling question. Which statement best describes the results of the phase 3 trials of faricimab versus aflibercept in patients with DME? A: Comparable gains in 1 year BCVA were observed for patients treated with faricimab up to 16-week intervals versus the aflibercept dosed every 8 weeks, B: 60 to 65% of

faricimab-treated patients achieved q16-week dosing, at week 96, at the end of the study, it was seen intraocular inflammation events occurred more frequently in patients treated with aflibercept in the study, and then there's the option for D and E combining A and B, or A and C. You'll see this in a moment when I show the data, but the correct answer is D, which means both A and B are correct. C is not correct. Intraocular inflammation was not a more frequent in patients getting the aflibercept.

It was a successful study. It met the primary endpoint, which is the mean change in BCVA from baseline out to the primary endpoint of weeks 48, 56 timeframe, and now out to the end of study beyond weeks 96 to week 100. We see very comparable vision gains in all 3 arms, the 2 faricimab arms versus aflibercept, the control arm, and this was noninferior in both studies. By OCT, we're looking at the reduction in central subfield thickness, which is in effect a measurement of drying up of the macula. And here, there's actually a difference that favors faricimab, meaning there's a greater degree in reduction in OCT central subfield thickness in both studies, and that tells us that faricimab on average dries a little better in this setting of DMEs. Anatomically the outcomes did favor faricimab in these clinical trials. In fact, another way of looking at it is looking at the proportion of patients without intraretinal fluid, which is effectively resolving the DME, the diabetic macular edema here. And you can see at every time point, most of which were statistically significant we see that there's a greater degree of patients in the 2 faricimab arms compared to aflibercept that were without intraretinal fluid all the way to the end of the study. So that again points to greater degrees of reduction, or higher proportions of patients with resolution of DME with faricimab.

And looking at durability, we can look at that so-called PTI arm, the personalized treatment interval, where patients were getting dosed throughout the trial either every 4, 8, 12, or 16 weeks. And we saw results that were actually very similar to the wet MD studies, although a slightly different treatment regimen here, but nonetheless, 78% of patients by the end of this study were being treated at every 12 weeks or less frequent, 12 to 16 weeks. And the proportion of patients being dosed every 16 weeks was about 60 to 65%. There's some very impressive durability and when you look at the mean number of injections in year 2, you can see it's quite a bit less, mean of 3 injections with faricimab versus 8 with aflibercept. You're getting the same vision outcomes with less treatment. Intraocular inflammation is shown here, and I can tell you that all the other adverse events were very comparable and there were no significant differences between faricimab and aflibercept in these trials, and inflammation rates were also comparably low.

Similar to the wet MD studies, maybe slightly higher with faricimab, but there were no problems related to intraocular inflammation such as vascular occlusion, something we watch very closely for in these trials.

In summary with DME, faricimab again performed very well, and in many ways, very similar-like outcomes to the wet MD studies. They worked as well in terms of best corrected visual acuity gains compared to EYLEA, or aflibercept, However, the anatomic outcomes actually did favor faricimab here, greater degrees of drying. And this was all accomplished with less frequent dosing, or less numbers of treatments needed. This is available for use in practice now, because it also was FDA approved for this DME indication back in January 2022. This is among the new options for treating both wet AMD and DME.

Another promising agent that is in clinical trials now is KSI-301. Also, a unique molecule. This is by intravitreal injection. It's an anti-VEGF-A antibody that's covalently bound to a large biopolymer, that's why it's called a biopolymer conjugate. That creates a large molecular entity that increases the half-life and basically, we get greater durability. And in phase 1 testing it did show some promise it worked well as an anti-VEGF agent and did show some extended durability, even out to 4 or 5 months or so. And so, that looked really promising, but unfortunately in the phase 2, 3 wet AMD DAZZLE study, the drug worked relatively well, but in this trial, we pushed the envelop a bit for extending the treatment interval 12, 16, or 20 weeks, and some patients did successfully make it out, but unfortunately for some patients, even as frequently as ever 12 weeks was not enough and those patients contributed to the loss of visual acuity that occurred. The primary endpoint of visual acuity noninferiority was not met in the phase 2, 3 DAZZLE study of wet AMD with KSI. Nonetheless, the program is still active, it's still being tested with wet AMD, albeit at more frequent treatment regimens, and it's also being tested for vein occlusion and diabetic macular edema, and this will all read out. The good news here is that the drug does look effective, it just may not be quite as durable as initially thought. And so, in these trials, it's being dosed allowing for a little bit more frequent dosing of every 2 months, or as least frequently as every 5 or 6 months. So, stay tuned for some additional data on KSI-301 in these phase 3 programs.

Another drug in clinical trials right now, it's in phase 3 testing, is aflibercept high dose. This is quadruple dose aflibercept at 8 mg. It showed some evidence for the potential of extended durability in the phase 2 CANDELA study. And now the phase 3 PULSAR study for wet AMD, and the PHOTON study for DME are underway and we should have some results by the end of 2022 in terms of how this drug performs compared to standard dose, but at less frequent treatment intervals, every 12 or even 16 weeks. This is going to give us some information as to whether or not this quadruple dosing will effectively appreciably extend the half-life of aflibercept and maybe give us some durability that could challenge that of faricimab.

Another drug that we should mention is OPT-302. This is very different. This is a fusion protein that blocks VEGF-C and D, not VEGF-A.

It's not meant to be a standalone therapeutic, it's meant to be injected in combination with an anti-VEGF-A blocker, so it could be ranibizumab, aflibercept, whatever. In phase 2 testing, it did show increased mean visual acuity gains from baseline were greatest in the combination of OPT-302 and Lucentis versus Lucentis, or ranibizumab, alone. With this drug we're not looking at greater durability, we're looking at the potential for better visual gains. And really nothing else is begin tested to try to achieve that goal. For OPT-302, you can see a successful-looking phase 2 study. It's now in phase 3 and data should be forthcoming within another year or so.

Moving on to sustained drug delivery, and when we talk about sustained drug delivery, we're talking about something that's going to give us an effect, and in this case, an anti-VEGF effect for let's say at least 5, 6 months or so. And so, everything listed here has that potential. First up with regards to sustained release implants or devices, and we have the port delivery system. This is now commercially available because it was FDA approved a year ago by the FDA. That was October 2021. We'll talk in great detail about that. Also emerging are these biodegradable microparticles or implants. Most of this is in phase 1, 2 testing, and most of these products are tyrosine kinase inhibitors, which indirectly block VEGF among other potential growth factors.

And then also very exciting and interesting is gene therapy. This has now made it into phase 2 and 3 testing, and that's gene therapy to produce an anti-VEGF protein. So, basically the eye becoming a bio factory to produce the anti-VEGF therapeutic.

For the port delivery system, this was again approved about a year ago in 2021. This is a sustained release delivery device. It's surgically implanted, filled with a high concentration of ranibizumab that is slowly released in to the vitreous cavity. The implant sits in the eye wall and is mostly in the vitreous cavity alluding to the drug as such. And, although it requires a trip to the O.R. to be inserted, it's refilled in the office with this special refill exchange needle. It's a one-time trip to the O.R. to allow for a device to give you sustained delivery of an anti-VEGF drug.

Now for the poling question. Which statement best describes the results of the phase 3 trial of the port delivery system for patients with neovascular AMD? A: BCVA was stable and similar between the intravitreal ranibizumab arm and PDS arm at week 96 of treatment, B: 20% of PDS patients required supplemental treatment prior to PDS refill, C: device-related vitreous hemorrhage occurred in 14% of patients in the PDS arm, and D: 76% of patients in the PDS arm preferred it over intravitreal injections. And the answer is A: BCVA was stable and similar between intravitreal injections of ranibizumab versus the port delivery system.

In starting with phase 2, it was the first time we had a glimpse to see how well this device could perform. And in phase 2 so-called LADDER study, the primary endpoint was the median time to the first refill of the PDS device in patients with previously treated neovascular AMD and this was compared to ranibizumab, and it performed very well. It performed as well as anti-VEGF injections monthly in terms as corrected visual acuity outcomes from baseline. And when it came to the primary endpoint, the time to refill, there were three different concentrations. It was the high concentration 100 mg/mL device arm, in which the median time to refill was 16 months. In 80% of patients in that arm went 6 or more months without needing a refill. It basically told us we could reliably get good anti-VEGF delivery for at least 6 months in the vast majority of our patients and that led to the study design of the phase 3 trial, so-called ARCHWAY study, which looked at the efficacy and safety of the port delivery system at this high concentration compared to intravitreal injections in standard monthly fashion with ranibizumab and looking at mean change in BCVA from baseline. These are previously treated patients, so what we expect to see is no change in vision. No loss of vision over time. That's exactly what we saw. And PDS was both noninferior and also statistically equivalent at monthly injections in terms of BCVA. You see no change, so that means that the patient's macular status and visual acuity were well-maintained based on BCVA outcomes and OCT outcomes as shown here to the primary endpoint of 40 weeks. And then the study has completed and goes out to now, 3 years, and we can see the device arm port delivery system that is compared to monthly injections for 2 years were essentially identical, both in terms of best corrected visual acuity and OCT. This is telling us that PDS was indeed performing well as a sustained delivery device for ranibizumab.

And in the study, if the device wasn't performing well, there was an option to supplemental intravitreal injection of ranibizumab. And the good news here is the device was highly reliable and most people didn't need any supplemental injections. In fact, at each refill exchange cycle as shown here, 95 to 98% of patients did not require any supplemental treatments. You're really seeing 5% or less of patients at each 6 months refill exchanges did not need anything in addition to the port itself. No additional injections.

So really performed well to control disease, and in fact, patients were very satisfied. Now, this of course is a bias somewhat select group for patients that want the port delivery system that would want to be participating in the clinical trial, but nonetheless, these were patients that had previous injections, actually on average about 5 injections. They could compare their experience with previous injections to the port delivery device experience, which includes the surgery and the refill exchanges over 2 years, and the vast majority, 93% actually preferred having the port delivery versus ongoing intravitreal injections. That's a pretty powerful statement.

And regarding complications and side effects, or adverse events, here's where there are some important differences. As you would imagine, you're dealing with surgery and a device, and so there are going to be some unique or increased complications or adverse events associated with the device compared to intravitreal injections which are really very well tolerated. There were a bit higher rates of

vitreous hemorrhage in the device, and red is showing the port delivery system – 6% versus 3.6% for vitreous hemorrhage. There were some unique complications associated with conjunctival erosion and retraction. You would not expect that with injections, and you don't see any happening there. But, combined about 6.5% for conjunctival issues, which are potentially serious because they can lead to injection because they expose the device, and so most of these will need to be repaired. And then, speaking of infection, that's something that's potentially very serious, we look very closely at. The endophthalmitis rate was a bit higher, 1.6% in patients that had the device versus 0.6% in patients getting intravitreal injections. And that's a 3-fold increase in endophthalmitis rate, and that's associated with having surgery and having a device compared to just a simple injection. For patients that want this device, or are considering this device, they have to realize that there is a different side effect profile and there are some tradeoffs with regards to wanting something that's sustained release, but having to accept some higher rates, albeit acceptable, but nonetheless higher rates of side effects.

As a field, in terms of being comfortable with offering this to patients, we want to know how the device performs over the long run, so we do have some long-term extension study data. The device continues to perform very well in controlling disease, now with some good data and follow-up out to 4 years. And the side effect profile is still looking quite favorable. The port delivery system is FDA approved and now being used in the United States. It's being tested outside the United States in the Velodrome global phase 3 b studies, so I'm sure we'll see that approved in other countries. The device is also being tested in patients with DME and also diabetic retinopathy without DME. So, we're expected to see potentially some other indications, again, for DME and such, and some approvals outside the United States to increase the utilization of this device over time.

Briefly, because there's not a lot of data yet, just a few words about the biodegradable microparticle and implant approach. This is office-based injections either through vitriol, or even a new way, suprachoroidal. Injecting tyrosine kinase inhibitor small molecules that have an anti-VEGF-like effect, but packaged in sustained release either particles or implants. Most of these are in phase 1 or 2 testing, so very preliminary information, albeit some safety is looking pretty good, and biologic activity that's like anti-VEGF is being seen. We're looking here at the durability of 4 out of 6 or more months, so it does classify as it as a sustained release delivery approach. The earliest and first one of these to be tested is GB-102, which is sunitinib, that's the tyrosine kinase inhibitor small molecule packaged in a PLGA microparticle injected intravitreally.

And in brief, both phase 1 and phase 2 testing did show some biologic activity that looked promising, including some durability for 6 or more months, as was hoped for. However, with this particular product, it was dispersion of the particles and that blurred the vision for some patients and is supposed to remain as a solid depot. If it disperses within the vitreous, our even migrates into the interior chamber, that can cause blurriness that can persist for at least a month or 2, so they just couldn't really solve this problem with dispersion and so this molecule is not going forward in phase 3 testing.

Axitinib, or CLS-AX, is another type of tyrosine kinase inhibitor also a suspension, but here they're getting around the problem of dispersion by introducing it into the suprachoroidal space. So, a special proprietary suprachoroidal injection device as shown here is utilized to inject the suspension in the suprachoroidal space, not the vitreous cavity. Hoping to get the same effect, but without the particles that could potentially blur the vision. And not a lot of data yet, but it's early on in a phase 1, 2 trial with only a couple dose cohorts followed thus far, but it looks so far well-tolerated, and it is starting to show us some benefits, we just don't know the durability of this at this time.

OTX-TKI is also a TKI axitinib, but here it's packaged in a hydrogel fiber that's injected intravitreally. So, we don't have to worry about dispersion here and it slowly releases the TKI over 4, 6, even 8 or 9 months or so. And what you're looking at here is the phase 1 study in which the injection is delivered in mostly patients that had previous treatment. This is called a swimmers lane plot, you see previous treatments with anti-VEGF injections to the left, OTX injected, and then the course of the wet AMD in terms of any rescue injections thereafter, and I'll show several more of these types of graphs with other therapeutics. But what you're seeing is that many patients not needing additional treatments are going out 4 to 6 or more months before they get a rescue therapy, so it's telling us we are getting anti-VEGF effect that seems to last for many of these patients for 6 or more months. Looks promising, especially at the higher doses, and it was well-tolerated. This is being carried forward in another phase 1 study and should be moving along if it shows this level of promise.

And lastly, this EYP-1901. This is a different TKI, but it's also in a somewhat similar implant. It's a bioerodible implant that's injected intravitreally. And this also looked promising at phase 1. The phase 1 DAVIO study shows patients previously treated getting very frequent anti-VEGF injections to the left and you can see the reduction in the frequency of injections, and again, some patients going out even 12 months without needing an injection. We're seeing an anti-VEGF-like effect, variable durability, and this is now moving into phase 2. So, this is looking promising, and again, a good safety profile.

Lastly, for sustained delivery, there's the gene therapy approach. And this is basically 2 programs, but 3 delivery approaches. One product called RGX-314 is an AAV8 viral vector designed to deliver an anti-VEGF antibody fragment.

Effectively, it's ranibizumab. And this is being introduced in the eye either in the subretinal space, which requires a vitrectomy, or via an office-based suprachoroidal injection as I showed you with the TKI program. And that's being tested in both wet AMD and diabetic retinopathy. The ADVM-022 is a modified AAV vector. This vector is designed to deliver or produce an anti-VEGF-A fusion protein much like the aflibercept. With both of these programs, you're introducing a viral vector that will transfect cells in the eye, such as RPE cells, such as pigment epithelial cells elsewhere that then produce the therapeutic protein, the anti-VEGF molecule. And ADVM-022 is being tested in neovascular AMD, the DME program is not moving forward.

For the subretinal RGX approach, this has completed a phase 1, 2 study. Again, a swimmers-lane plot. This is being introduced to patients who had a vitrectomy and subretinal injection of the RGX product in eyes that have been having intravitreal injections for neovascular AMD. So, previously treated, and you can see going up in the dose cohorts 3, 4, and 5, we're seeing a significant reduction in the anti-VEGF treatments that are subsequently needed after the chief therapy is introduced. And in fact, many of these patients are going without any anti-VEGF injections, but not all of them. It's not going to make every eye an injection-free situation for managing neovascular AMD, but it's looking very good in terms of reducing that treatment burden and this is now moving into and is in current enrolling a pivotal phase 3 program, and this is the ATMOSPHERE and ASCENT studies and this is again, subretinal RGX-314. Vitrectomy surgery, one-time administration, and then rescue therapy thereafter as needed. And we'll see how that stacks up to traditional on-label use of ranibizumab and aflibercept. RGX-314, as I mentioned, is also being administered in a suprachoroidal fashion, so there's a gene therapy introduced in the suprachoroidal space hoping to get the same production of the anti-VEGF protein product ranibizumab in the vitreous cavity in a high enough concentration. And so far, so good. This is much earlier phase 2 testing showing great degree of reduction in the anti-VEGF injections needed in patients with previously treated wet AMD, as shown to the right. And these are so far the 2 dose cohorts I the suprachoroidal anti-VEGF AAV8 study, a phase 2 neovascular AMD study. Looking good and tolerated pretty well, too.

And then there's also a phase 2 RGX program suprachoroidal delivery for diabetic neuropathy. This is just to improve the level of diabetic neuropathy, not treated DME, but is showing that is a high percentage of patients, 47% of patients were improving 2 or more steps in their level of diabetic retinopathy. That's comparable to what anti-VEGF injections can do and have an improved indication for. This is looking also pretty good with good tolerability.

And then lastly, ADVM-022. This is the viral vector product that we're injecting intravitreally. It went through its phase 1 testing. Phase 1 looked good. There were some problems with implementation, especially at the higher doses, but patients had a tremendous reduction in the need for anti-VEGF therapy after a single intravitreal injection of the ADVM-022 gene therapy product.

We have to balance this looking and working very well with some inflammation that was seen, and so, it's moving into a phase 2 program now at lower doses to try to mitigate the inflammation problem. Any bio vector you're injecting intravitreally will often produce inflammation, so that was not a surprise, but it does require some management. The good news is lower doses should be much less of a problem with inflammation, and if we select the patients that have low levels of neutralizing antibodies, as shown here, we should be able to get a good therapeutic effect with the lower dose almost as good as the higher dose. So, good way to think about going forward in phase 2 to balance efficacy and safety.

In summary, the future is definitely very bright. We've enjoyed close to now 16 years of anti-VEGF therapy for neovascular AMD and also, later on, the introduction or FDA approval of anti-VEGFs for DME. Those are the first-generation agents which work very well but have limited durability. We're now into, safe to say, a second generation, especially with faricimab. FDA approved, looking more durable in working as well. And now the port delivery system, a true sustained delivery approach of anti-VEGF also commercially available and in our hands to use. We're also looking at some other products which may or may not perform as well, high dose aflibercept, KSI-301, maybe some even enhanced efficacy with OPT-302. The jury is still out with all those because they are all still in testing and we don't have definitive pivotal study results yet.

**Dr. Holekamp:**
The BrightFocus Foundation and Advocate for Brain and Eye Health is partnering with us for the program and has provided AMD resources for both clinicians and patients. These resources are also available for download in a download pod on the bottom left of your screen. There are online resources for you regarding AMD diagnosis and treatment that you can access using these URL. Through BrightFocus chats, you can access monthly conversations with scientists and clinical experts, either by phone or online.

AME Community Circle provides a monthly online place where patients can join in conversations and ask questions about AMD, so please share this information with your patients.

Can you discuss any personal experience with the newer therapies PDS and, or faricimab? First, I'll discuss my experience with the port delivery system. I will say that I was in LADDER and ARCHWAY and PAVILION and PAGODA, and when the PDS became FDA approved, it was called Susvimo, and I began offering it to my patients with wet AMD who had responded to at least 2 anti-VEGF

injections. And I've done numerous Susvimo's, and I can tell you that patients love it. I think that we underestimate the amount of fear and anxiety and treatment burden associated with these frequent injections, and patients really love the confidence about coming to the office, even for monitoring, and it's less frequent monitoring, or their refill exchange knowing that they're not going to get an injection.

My Susvimo patients' kind of self-select. As soon as I broach the topic with them of a surgery that may diminish their need for injections and could lead to just seeing me during the post-op period and then every 6 months for a refill, patients will self-select and choose it for themselves. So far, so good. Everything has been going well with Susvimo and my patients love it.

Now, I also have ample experience with faricimab for both web macular degeneration and diabetic macular edema since it's FDA approved for both indications. And I can tell you that I first began switching patients and in diabetic macular edema, I can tell you that my personal results really look like the clinical trial results where I see a significant improvement in the ability to dry the retina and extend out the interval. And for wet AMD patients, I can tell you that I also see an improvement and that I offer it to people who may also already be on somewhat extended intervals, because everybody would like to be at a more extended interval. You may be switching your worst patients who are at a q4 or q6-week dosing interval, but I am not offering it to my patients with a q8, q12, or q10-week interval because everybody would love the chance to be extended, and I can tell you that I am able to extend the majority of patients.

**Dr. Regillo:**
A brief word about home monitoring. This is going to be interesting technology. It may allow us to remotely monitor the level of disease and how well the disease is controlled in patients that have sustained delivery in particular, rather than having to come to the office on a frequent and regular basis. That's also going to be potentially in our future. I can tell you now, I think we're seeing the benefits, the added value with the use of faricimab and the port delivery system in regard to extended durability. Extended durability is not just about decreased treatment burden, meaning having it easier for patients to come to the office, but compliance is likely to improve. And outcomes are highly likely to improve because products that last longer, don't need to be injected as frequently, and in essence, they're more forgiving if patients don't come in on a frequent and regular basis, or necessarily exactly on schedule. We're hoping that the future is not only having patients with reduced treatment burden having to come to the office less frequently, less treatments, and so forth, but also having better vision outcomes. and I think we're going to achieve that. Thank you very much.

**Dr. Holekamp:**
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