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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

GET REAL: A Guide to Evolving Treatment of nAMD and DME Using Real-World Data

Announcer:

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Dr. Khanani:

Hello, and welcome to this CME webinar, Get Real: A Guide to Evolving Treatment of nAMD and DME Using Real-World Data. I'm Mr. Arshad Khanani from Sierra Eye Associates. It's my pleasure to have my good friend and colleague, Dr. Ted Leng, from Stanford University. Welcome, Ted.

Dr. Leng:

Thanks, Arshad, for having me.

Dr. Khanani:

I'm looking forward to our discussions because you have done a lot of work on real-world data, and with the new treatments that we have available, I think it’s really important as a field for us to generate that data. And we really appreciate your expertise and your knowledge. And thank you for being here.

So, let's talk about real-world data on anti-VEGF therapy. But before we get there, let's talk about evolution of treatments for nAMD and DME over the last two decades. Obviously, everyone is aware that, you know, especially for neovascular AMD, we have evolution of anti-VEGF therapy. Before the anti-VEGF therapy was available, we had patients losing vision, even with treatments like PDT. We had first approval for pegaptanib, it's a tongue twister, in 2004, and then evolution of bevacizumab, ranibizumab, aflibercept, brolucizumab, and some biosimilars coming in the space. But the most exciting thing that has happened over the last few years was targeting an additional pathway, dual inhibition of VEGF-A as well as Ang2. You know, so as a field, if we look at retina or other fields, we are moving towards targeting multiple pathways to have better outcomes in terms of whether it’s anatomy, durability, and hopefully vision in the future. And then, of course, the recent approval of aflibercept 8 mg.

Dr. Leng:

No, it's been a revolution, you're right, Arshad. And the paradigm shift in how we're taking care of these patients with both neovascular AMD and DME. And I think our patients are so lucky today that we have so many options for the treatment of these conditions. So, by looking at real-world data, we have a much more robust photo of what's going on with patients out there once these drugs are released.

You know, I think one thing that we've seen is that we are seeing a large treatment burden in both conditions, neovascular AMD and DME. And, you know, one other thing that we've also seen is that, you know, unfortunately, over long periods of time, we are not

treating our patients as often as they probably need to be treated. And, you know, we're seeing a decline in vision over time.

There's been some published studies looking at patients from their registered clinical trials over 7 or more years and showing the volume of injections decreases over time, and visual acuity also decreases over time. Here's a study that was just published this year in 2024 in Ophthalmology Science that I was a part of, looking at IRIS registry data. And you can also see here, the change in vision over the 6-year follow-up. And these are the blue bars. And the first year you get vision gains, and the second year as well, but over the long period of time, we are having loss of vision, year over year, as well as a reduction in injection of intervals. Well, you know, as you mentioned, most of these eyes needed 4- to 8-week interval injections, but over the study here, we can see that patients were receiving between four and five injections per year by the last year of follow-up in year 6. In DME, we also had a very similar result here. Injection frequency decreases over time and is also correlated with vision loss here over time.

Dr. Khanani:

So, I think the question is, so we have this real-world dataset that patients are losing vision, they're not getting enough injections. So, in your opinion, you know, what are the two big unmet needs? Is durability number one? Is getting better vision outcomes second? Is it a combination? Because, you know, we know that if you give more injections, patients do gain vision, but of course there is a ceiling effect on vision. But I think we are, as a field, it seems like the biggest unmet need obviously is durability because we have great treatments that are not being utilized at the maximum, you know, frequency. But at the same time, I think the vision decline, even with maximum treatment, could be an issue. What are your thoughts in terms of what are we looking for as a field for novel therapies?

Dr. Leng:

I absolutely agree with you. I think that there is a ceiling effect. I think the treatments are quite effective. And we have reached our maximal efficacy at this point with the mechanisms we have been using for these eyes. And I think the durability is the real question here. There are many reasons why patients aren't coming in for probably the injections they need to maintain and sustain division gains that they're seeing in the first year. So, it's either lack of access or, you know, scheduling issues with our clinics, where these patients are being lost to follow-up and not coming in on their scheduled appointments.

And so, and there's also fatigue that sets in with patients, right? They can't come in every month or two for forever. And so, I think, you know, having new therapies that maintain the efficacy we're seeing, but allow for extended duration between treatments is, you know, definitely an unmet need.

Dr. Khanani:

No, I think I totally agree with you. I think there's fatigue, there's so many factors, right, especially looking at DME. These patients have other doctors, almost 28 or so visits per year. And it becomes really challenging if they have bilateral disease to inject these patients, you know, on every 4- to 8-week basis, especially if they're driving themselves, they're in there every month, essentially. So, I think I agree with you the novel therapies, can we extend the treatment interval without compromising on the visual acuity gains, as well as anatomy?

So, now let's look at a polling question. Here's one.

Here's another polling question.

So, Ted, talking about real-world evidence, which is the main focus of this program, you have been part of many of these studies, I've been part of many of these studies. And it's exciting to see that, as a field, physicians around the world are trying to generate real-world data, but patients we see in clinic are very different than the very homogenous population in clinical trials based on inclusion/exclusion criteria, based on visual acuity criteria. Many patients with central hemorrhages or advanced disease are excluded. So, I think it's important for efficacy in a real-world population, number one. Number two is obviously safety. We had the experience with brolucizumab, where the trial data didn't reflect what can happen in terms of safety and vasculitis. So, I think it's important, for safety reasons, also to look at multiple logical studies looking at real-world data across a very broad, geographic patient population, as you mentioned. So, these are some of the studies that had been done. You know, obviously, we started the TRUCKEE and TAHOE study, you're very involved with FARWIDE, FARETINA studies. So, we'll cover some of that in this program.

So, here's another polling question.

So, let me discuss a little bit about the TRUCKEE study, Ted. I know you're very aware of it. But for the audience, you know, this is a real-world collaborative, non-pharma supportive study that we initiated with a group of physicians around the country to look at the real-world outcomes for patients with neovascular AMD. As of the latest data that I presented at Angiogenesis, we now have 3,299 eyes of 2,675 patients that were treated with faricimab with 15,000 injections performed. And obviously, we are continuing this study because

not only we want to see the short-term anatomic and visual acuity and safety outcomes, but we are going to also look at long-term durability, especially to your point, Ted, where we have seen in real world, patients lose vision over time in the 3- to 5-year range. Can we decrease that with dual inhibition by giving patients better anatomic outcomes and also lowering the treatment burden, so hopefully, they have better compliance?

And so, TRUCKEE is, again, collaborative, non-pharma supportive. And obviously, the TENAYA and LUCERNE studies led to the approval of faricimab for neovascular AMD, but those studies included naïve patients. So, majority of the patients in TRUCKEE are previously treated, right? Ted, did you use faricimab when it first came out on difficult-to-treat patients to see the benefit over standard of care? That's what I did.

Dr. Leng:

Yeah, I think with any new agent, and you can probably ask around amongst the retina specialists we all know, we tend to use them, you know, and this is unfortunate for new agents, on the most difficult-to-treat cases. Because I think there's, you know, a certain unknown about the risks of a new agent. And also, you want to find a patient that might benefit from a new agent. You know, if someone is stable on any one of the previously existing treatments on a nice interval, you know, there's little – there's less impetus to switch that patient to a new agent. But if you have someone who's poorly controlled with persistent fluid, maybe not the optimal visual acuity gains that you'd expect for an existing therapy, that's an optimal patient to give it a go with a new treatment.

Dr. Khanani:

Yeah, exactly. And that's what we saw in TRUCKEE, majority of the patients were previously treated, majority of them were switched from aflibercept, which was the standard branded agents utilized because of the anatomic control of neovascular AMD. And then the transition to naïve patients come after that, right? So, you go from high-need patients with persistent disease, then you feel comfortable with efficacy and safety, then you go to naïve patients. So, our naïve numbers in TRUCKEE are also increasing. And then what we have seen is that more stable patients that need durability that were on 6 to 8 weeks of aflibercept, now trying to go to out for 16 weeks, are being switched. And I think the previously treated patient population show us the benefit, especially the anatomic benefit, right? Most of us don't expect the visual acuity to get better because these are chronically treated. But our hope is that by controlling anatomy, we are going to have hopefully better outcomes long term.

So, in short term in TRUCKEE study, obviously, we wanted to see the anatomic benefits. So, obviously, the naïve benefit was already established in TENAYA and LUCERNE, but we wanted to see the naïve benefit in real-world patient population, many of them with hemorrhages, subretinal hyperreflective material, you know, some or many with fibrosis, atrophy, things like that, because we didn't exclude anybody in TRUCKEE. And what we saw was a rapid improvement in anatomy in terms of CST, in terms of IRF and SRF resolution, reduction in PED, and then of course, a vision signal that increased over time after the first injection, where we started to see improvement in visual acuity.

But I think the key from TRUCKEE, obviously, the switch patient population, can I control disease in a patient that has persistent fluid with aflibercept given every 4 to 6 weeks? Can we control it with faricimab? And we actually saw that. We saw anatomic improvement in patients who were switched. Now, the anatomic improvements are less now than they were earlier. And the reason for that is that many patients in TRUCKEE now are being switched because of interval, so they're already dry, but we are extending those patients out. That's why the amount of reduction we saw in anatomy, as expected, is getting less but of course, the way to look at is resolution of IRF and SRF in patients who actually had fluid, and you see that there is a significant reduction anywhere from 20 to 25% in terms of resolution of IRF and SRF in patients who were receiving for faricimab just after one injection.

And the other caveat about real-world studies, obviously, is the treatment interval. We wanted to make sure that treatment interval is not favored towards one drug or another. So, what we see in TRUCKEE that the previous interval of treatment and the follow-up were about the same, meaning that this effect is actually from dual inhibition, not from changing of treatment interval.

And then looking at patients who were on aflibercept, how they did. Again, we saw anatomic improvement. And again, because we are now shifting towards more stable population, the good thing to look at is resolution of IRF and SRF. And again, we see that just after one injection, you're getting up to 25% of patients having resolution of fluid. And these are hard-to-treat patients, again, with a similar interval which shows that faricimab is a better drying agent compared to aflibercept 2 mg. And then overall just looking at fluid in switch, in aflibercept switch in naïve patients, we see the consistent signal of rapid improvement in anatomy. And obviously the number is higher for naïve, because they had more fluid to start with compared to switch or all patients.

But I think for me, Ted, and I know you are an AI expert, for me, the exciting thing about TRUCKEE is that we actually use the AI Notal OCT analyzer, the NOA technology, to look at fluid quantification in a subset of TRUCKEE patients for sites that could upload the OCT.

So, here we have patients who actually had fluid and then we use AI to quantify that fluid, and then we use the AI to see how the fluid is resolving and how much improvement we are getting. And if you look at all patients, all eyes, you look at prior aflibercept eyes or treatment-naïve eyes, you see a consistent signal of improvement in fluid. So, these are not patients without fluid, all of these patients had fluid. And you see that 70% of previously treated patients had improvement in fluid, and almost a quarter of them had complete resolution of fluid based on this AI algorithm, which can count or quantify fluid to nanoliters. So, this is really powerful for me, because, as you said, real-world studies are caveats in terms of variable patients, and maybe some were dry, and some didn't have fluid when they came in, or there were other reasons. But here we're using AI to really quantify, and this really confirms the benefit of dual inhibition. Of course, the benefit is more in naïve patients, because these are fresher patients with more fluid.

What are your thoughts on this NOA analysis from TRUCKEE study, Ted?

Dr. Leng:

No, this is really impactful, you know, one, because, you know, using an automated algorithm is, you know, this is kind of proof that these things can actually be applicable for research and real-world, you know, care patients. But I think more importantly, that we are seeing, you know, objective data that this dual inhibition is actually reducing the amount of anatomic activity in these eyes. It's really exciting.

Dr. Khanani:

So, Ted, the other thing is from my clinical practice, and also from TRUCKEE subanalysis is the fact that not all patients are going to improve or resolve after one injection, majority will. But we have that 20 to 30% of patients who actually stay the same, and some may get worse. And I think the learning from here to me is that if you don't see a response after one injection, don't get discouraged. Don't switch the patient back, like I was doing when I first started with using faricimab, or I was extending the patients right away and the fluid will recur. Here, the learning is that continue treatment. And I think what I realized, Ted, is that in previously treated patients, I actually load them with three or four loading doses to kind of maximize the effect. So here, in the TRUCKEE study, we looked at the patients with resolution in IRF and SRF, the number was higher as we injected them four times versus one. So, I think, subset of high-need patients need more treatments.

What are your thoughts on that, Ted?

Dr. Leng:

Yeah, I think this data is really impactful in that it really gives us, you know, confidence to know that your intuitions are correct. You know, I think it does take a certain number of treatments, more than one, in order for that second mechanism to really reach its optimal potential. So, you know, don't be discouraged if you give one injection and there's no change or even a potential worsening, maybe that patient needs three or four treatments before the dual inhibition is really maximized.

Dr. Khanani:

I think that's a really good point, Ted. And let me quickly cover the TAHOE study, it's the sister study for TRUCKEE, but we started it later. It's on DME, so the numbers are much smaller here. But again, majority of the patients are switch patients. I think, you know, obviously, we are trying to see how the switch patients do, but overall, you know, the naïve eyes are doing well as expected and switch patients are also showing anatomic improvements. Of course, the numbers are small, but we are continuing to generate more data and we'll present that in the future.

But I think looking at safety, right Ted, as you mentioned, real world, it's a different patient population and very variable compared to trials. So, we wanted to see the safety. And, you know, in TRUCKEE study, as I said, we had 15,000 plus injections with an IOI rate of 0.07%, endophthalmitis rate of 0.03 with really no cases of retinal vasculitis, retinal artery occlusion. The other interesting thing was that all the patients that had events of IOI and infections, endophthalmitis, they fully recovered their vision, meaning that we didn't have severe cases where patients actually lost vision. And many of them, actually majority of them, were rechallenged with faricimab. That kind of shows me that the anatomic benefit that physicians saw for their patients who got faricimab was so good that they actually switch them back to faricimab, even if they have inflammation. Now, of course, it's a controversial thing to have somebody go back to an agent where they had inflammation, but it seems like the risk-benefit profile here favored to go back to faricimab. And what we saw, that patients actually didn't have recurrent inflammation like we have seen with brolucizumab, where you continue to treat patients with inflammation, they ended up with worse events. So, we still are trying to figure out the cause of that inflammation. It seems like maybe impurities or something. But here, patients, majority of them were switched back and they have done well.

So, here is another polling question.

And there's one more polling question.

So, just to summarize the learnings from the TRUCKEE and TAHOE studies, we have seen rapid improvement in anatomy in both nAMD and DME patients right out the gate. Majority of them improving or resolving fluid after one injection. We have seen improvements in all anatomic parameters, CST, looking at IRF, SRF, PEDs in patients with nAMD. And not all patients are going to improve after one injection, especially I think the DME patients because there's multiple different cytokines that are involved, and Ang2 does help with inflammation, vascular stabilization. So, in patients that are switching treatment in DME to faricimab, in my experience, it takes even longer to load those patients. And I think my learning is to use faricimab right off the start, I think now I use it in all naïve patients with nAMD and DME, because I know that I'm going to get the best anatomic outcome. And if they were previously on some other agent, I switch them to faricimab quickly because I feel that the sooner you switch, the better outcomes you're going to get. And so, I think we continue to learn and we'll present more data in the future in both studies.

So, Ted, now let's turn to you, so you can talk about FARETINA AMD and FARETINA DME studies.

Dr. Leng:

Well, Arshad, that was a really great review of the studies that you've been leading. And, you know, I think it's been a really great program that you've had here, especially with all the different sites. And I think that's one of the real benefits of real-world data is to get data from lots of geographies and patient populations.

I'm going to be talking about the FARETINA AMD and DME studies which were based on the American Academy of Ophthalmology's IRIS registry. So, for those who are not familiar, this is the largest specialty-specific dataset out there with over 75 million deidentified unique patients, I think over 700 million patient encounters, and represents currently about 70% of all eye care encounters in the United States.

So, you can see the inclusion and exclusion criteria here. But basically, we looked at patients who received faricimab between February 2022 and June 2023. And these data are actually ongoing, so these datasets will continue to refresh and update over time. And you can see here, the number of eyes, you know, look at the very bottom here, it's a very busy slide, but the nAMD is on the left and DME is on the right. We've got over 8,000 patients and 9,000 eyes, 9,500 eyes that were previously treated in the nAMD cohorts, and about 500 eyes that were treatment naïve in AMD. And for DME, we had about 1,300 patients with 1,700 eyes that were previously treated, and treatment naïve about 200 patients and eyes as well.

And this I think reflects the treatment pattern that we've seen as well that you mentioned with the TRUCKEE and TAHOE studies. Most patients who got faricimab initially were previously treated based on the discussion we had of why we would want to treat those patients first. So, 65% of those patients were previously treated. And just as you saw in your study, a majority of them were receiving aflibercept before the switch.

So, you know, one thing that we did see here was the mean number of injections after 12 months of faricimab. So, in the previously treated eyes, we had about, you know, mean number of injections was 7.5. Treatment naïve was 6.5 in wet AMD. And for DME, the mean number of injections in previously treated eyes after a year was 6.6. And in the treatment naïve, it was 5.2. So, what this tells us is that our colleagues out there were beginning to extend treatment durations in these patients, both in the previously treated cohort as well as the treatment-naïve eyes.

And on top of that, what we also did see was an improvement in visual acuity from baseline. So, both in the previously treated and treatment-naïve eyes we are seeing that the visual acuity is improving even though the duration is increasing and the treatment intervals are also increasing. So, on the left side of this chart here, you can see the purple bars, which are the treatment-naïve eyes, and the gray bars which were the previously treated eyes. We do have stability and visual acuity. And that goes along with the increased duration of treatment.

We did have a subset of eyes, about 5,000 eyes, where we had access to OCT in this real-world data analysis, which was really exciting. And we could then use anatomy to back up the findings that we saw with the visual acuity and the treatment data that we just went over. So, what we did see here, again, the previously treated eyes, as you can see on the left, is that the fluid reduced and then the CST improved by about 21 microns over the first seven injections.

Treatment-naïve eyes had improvement over that because there was more fluid at baseline. So, they had about a 55-micron reduction in CST over those first seven injections. And this is very much in line with what you're seeing in your TRUCKEE and TAHOE data.

Here's the DME data, which also shows reduction in fluid in both previously treated eyes by 35 microns, and 75 microns in treatment-naïve eyes.

So, the lessons we learned from both the FARETINA AMD and DME study was that vision improved in the treatment-naïve eyes, and was stable in the previously treated eyes. The CST analysis which I just showed you, showed improvement in both subsets, both previously treated patients had improved anatomy and treatment-naïve eyes also had improved anatomy.

As far as durability is concerned, the last injection interval was 8 weeks or more for previously treated and treatment-naïve eyes. And we did see, again, as you saw in your study, a really great safety signal that the overall incidence of endophthalmitis and intraocular inflammation were very low, much in line with the TENAYA and LUCERNE, YOSEMITE and RHINE studies.

So, next I'll talk about a similar study called FARWIDE, which looked at data from a real-world dataset from United Kingdom. And this was again a real-world dataset. It's a little bit smaller than the FARETINA studies in the U.S., but this had about 3,500 eyes from about 3,000 patients in the AMD study. And the DME study had about 2,600 eyes from 2,000 patients. And I think one of the key differences that we saw in this study in the UK is that there were more treatment-naïve eyes than in the FARETINA study. So, for some reason, in the United Kingdom, in the National Health System from where this data came, they were much more comfortable giving the new faricimab agent to treatment-naïve eyes, so they had a much larger proportion of naïve eyes in their study. And –

Dr. Khanani:

Ted, do you think it's because that, you know, we had that U.S. experience that TRUCKEE and other studies kind of showing that faricimab was safe. So, I think maybe xUS, they felt comfortable using it off the gate in naïve because the safety was already established in the U.S., do you think that's one of the reasons?

Dr. Leng:

I think that's definitely a reason, Arshad. I think, you know, we've seen there with, you know, initial launches in the U.S., and then that treatment experience then, you know, gives a lot more comfort to our colleagues in Europe. But also, I think it also has to do with the just the way the healthcare system in the NHS is set up. They have a much, you know, they're less resource intense than we are in the U.S. And so, I think – and they're much more protocolized as well. They also did a lot more loading doses than we did in the U.S. I think a lot of U.S. physicians started to extend immediately after switching to faricimab. I know you were mentioning before that, sometimes we need to do monthly for a few loading doses. But in the UK, they all did loading doses, they didn't do any extension initially. And so, I think just the protocolized nature of the way they practice medicine there, as well, as you know, the previous U.S. experience, I think led to more treatment-naïve eyes being initially switched over to faricimab in the UK.

Dr. Khanani:

Makes sense. Yeah. I think they're more on guidelines and protocols, more standardized dosing, I completely agree with you.

Dr. Leng:

Yeah, but I think, you know, one of the main findings we did see in the UK study here, the FARWIDE study, was that they also were able to achieve extended dosing intervals over 8 weeks after about four injections of faricimab.

Yeah, so before we move on to another study, Arshad, you know, we've had a lot of data now that we've gone over about faricimab use in the real world. But, you know, recently we had access now to high-dose aflibercept 8 mg that's come out. And what do you think is going to – the real-world data is going to show for that, you know, there hasn't been really anything released yet?

Dr. Khanani:

Yeah, I think, Ted, that's a good question, right? So, any new agent coming in, you utilize, as we discussed, on patients who were previously treated with standard of care. So, in my practice, we're still learning. But what I'm doing is patients who are on faricimab and have persistent fluid at 4 to 6 weeks or cannot be extended, I am experiencing with aflibercept 8 mg to see if I can control anatomy better or I can extend those patients. Of course, the caveat is that the label for 8 mg only allows to have three loading doses monthly, then we have to go 8 weeks. So, very early experience. We will see some of that switch data from TRUCKEE also in the future, hopefully. So, I think it's too early to tell if we are seeing better anatomic outcomes for durability with aflibercept 8 mg.

Dr. Leng:

Yeah, I think my experience has been very similar to yours. I am switching a few patients who had persistent fluid on faricimab or aren't able to extend duration on that as well as patients that are on 2-mg aflibercept in the similar situation. So, you know, we'll have to wait and see what the real-world data are showing to see if there's any improvement in both efficacy as well as durability with this higher dose of aflibercept.

You know, one interesting analysis that was done is this network meta-analysis comparing faricimab with aflibercept, both the 2 mg and

the 8 mg. And this was actually analysis done of clinical trial data, so it wasn't real-world data. It was taking existing clinical trials, which you can see here on the two sides, YOSEMITE, RHINE, PHOTON, TENAYA, LUCERNE, PULSAR, and CANDELA. And using a Bayesian analysis, which is a validated statistical method on these seven studies, and it's called a network meta-analysis because the network nodes, if you want to call it that, are the treatments. So, in the center here, you see faricimab 6 mg given every 4 weeks, aflibercept 2 mg given every 4 weeks, and aflibercept 8 mg given every 4 weeks. So, one thing I want to point out here is that we're trying to compare apples to apples, and that all eyes received, you know, monthly treatment of these three agents in these three different treatment strategies. And this is after just the first 12 weeks of treatment. So, it's very early data that we're looking at to see if there's any difference between these three different treatment strategies.

And let me move on to here to show you what the analysis showed. So, the way you read the slide is that you can see here the error bars on all these three things. Now, because they do cross 0, there was no statistical difference between the two treatment strategies, but you can see the dots are shifted leftward. So, it does kind of favor faricimab in the first 12 weeks of the treatment, and this is the visual acuity gains, and that on average is about 1 to 2 letters, favoring faricimab both in DME and nAMD. And in kind of the purple/blue color was a pooled dataset for both nAMD and DME. So, you know, I think this is really interesting data, we just presented this at the Macula Society Meeting in February 2024.

Now, as far as anatomy is concerned, I think this is actually quite surprising and interesting to me was that the faricimab was statistically different and better than the 8-mg aflibercept using the clinical trial data. So, again, if you look at the top, you can see here a pooled data for both AMD and DME. And those error bars do not cross that line. So, there was a clear favor to faricimab over the 2-mg and 8-mg faricimab, and on the order of 13 to 22 microns. And this was consistent both with the random effects and the fixed effects models.

So, here's another way of looking at it. This is called a prediction interval. And what that tells us here is a probability of faricimab achieving increased BCVA or CST reduction compare with aflibercept 8 mg at 12 weeks using the more stringent random effects model. On the left-hand side is the BCVA. And what this shows is that it's 77% or higher chance probability of having better vision after 12 weeks on faricimab, and then on the right was a probability, so 93 to 99% probability of having reduced CST compared with the 8-mg aflibercept at 12 weeks. And I think what this ultimately shows us, that in the first 3 months of treatment between these two agents in the clinical trials, that faricimab outperformed the aflibercept 8 mg in both AMD and DME.

So, Arshad, I mean, what do you think about these data that we're seeing here?

Dr. Khanani:

Great job presenting this. You know, you had a very interesting presentation at Macular Society. Obviously, these are indirect compared cross-trial comparison, but I think I'm not surprised by the results, right. So, TENAYA/LUCERNE, YOSEMITE/RHINE, both show better drying effect of faricimab compared to 2 mg.

We look at TRUCKEE, TAHOE, all the other studies we have discussed, all the FARETINA DME and AMD, FARWIDE, we see a consistent benefit of faricimab in terms of anatomy. And then in the PULSAR and PHOTON studies, we didn't see an anatomic benefit of 8 mg or 2 mg; it was the same. And again, I think you highlighted very well that this is in the head-to-head in the loading phase where everybody's getting the same treatment interval. After that 12 weeks, it can get a little difficult to compare. So, I think if you give these three injections in the same interval monthly times three, what we have seen, and I've seen, is better anatomic outcomes rapid drying with faricimab. And I think that's what this confirms. So, I think another indirect evidence, cross-trial comparison, obviously, showing that what we have seen in other studies being confirmed. So great job, and kudos to you and the team for doing this analysis.

Dr. Leng:

Thanks, Arshad. I think what we'll do next is take a look at a few cases that are representative of what we're seeing here in the real-world data studies. So, I'll turn it back over to you to talk about a few cases to begin.

Dr. Khanani:

Thanks, Ted. I think as you said, we have all this evidence, but the real proof is in the pudding. We need to see improvements in anatomy and vision in patients that are being treated with faricimab. And obviously, as I said earlier, treatment experienced patients we don't expect vision, but treatment naïve, obviously, you would expect visual acuity gain.

So, let's start with a naïve neovascular AMD case. As I said, faricimab is a first-line treatment for naïve patients for me, based on my own experience and all the evidence, we get rapid drying. We actually had a substudy looking at hemorrhage clearance and fibrosis, and we presented that at ARVO, and we are continuing to do that work, because Ang2 can also have antifibrotic effect in preclinical models, obviously not seen in clinical trials because patients with central subretinal hemorrhage and fibrosis were excluded.

So, this is a 73-year-old male, retired, has terminal visual acuity in the fellow eye at count fingers. And then he came in in the good eye with visual acuity of 20/100 and not significant past medical history. And the question obviously was what agent to pick? This is a one-eye patient, we need to give the strongest agent available, some agent that can dry the retina the fastest, and obviously for me it's faricimab. So, we started treating this patient's 20/100 vision with 570 microns of CST, you can see, you know, subretinal fluid, hyperreflective material, intraretinal cyst, patient received one faricimab injection, and there was really a wow effect. Patient came back saying, 'I can see much better than what I did. The foggy area is almost cleared up.' And what we see here is that rapid improvement in anatomy, resolution of IRSS, improvement in subretinal fluid and hyperreflective material and CST going down to 240 from 517, as well as visual acuity improving from 20/100 to 20/50. Very happy patient. Of course, I load all my patients that are naive with three or four injections. Patient received another treatment, CST improved even more, subretinal fluid is resolved, and visual acuity is 20/50 +2 now. And then we gave this patient another injection, and we saw that the anatomy is almost normalized, and this patient's vision is 20/40 with CST of 170 microns. And you see that you essentially normalized the retina with minimal, or actually no fibrosis, and they have the hyperreflective material in the center and now the patient can drive.

So, Ted, very happy patient here that was very pleased. And then we started to extend this patient. You know, once the patients are completely dry, I would extend those patients. And what I do is that based on naïve patient data from TENAYA and LUCERNE studies that extensions are 1 month, or 4 weeks compared to 2 weeks. So, you know, of course in real world we are used to doing treat-and-extend by 2 weeks in most cases. Now, of course, in high-need previously treated patients that I switch, I extend them slowly by 1 to 2 weeks. But in naïve patients, if they're completely dry, based on the evidence from TENAYA and LUCERNE, extend them by 1 month. So, I actually now do that. And as you can see, patient was extended from August 2 nd to October 2nd, again, no disease activity, stable vision, stable retina. So, I was very pleased with this outcome.

And this is a consistent outcome that I've seen in patients that are naive. So, patient is, you know, 8- to 9-week currently, you know, of course, it's one-eye patient and when he went to 9 weeks, there was a little bit of disease activity, so we're staying at around 8 weeks and trying to make sure the patient can continue to have good outcomes with good visual acuity.

What are your thoughts on that case, Ted? And what is your experience in naïve patients?

Dr. Leng:

Yeah, no, I think is a really representative case about the great efficacy and durability of this faricimab agent in naïve patients. I've had similar experience as well, treating naïve patients with faricimab. And, you know, like you mentioned, the wow factor is always a really nice thing to have. I'm sure this patient is, like, super excited, given that that's their one good eye.

You know, I think I'm going to present here a case of a treatment-experienced patient. And, you know, I think if you look here at these stats here, this patient was 20/40 OU in December of 2015, when I first saw him. And he had 58 aflibercept injections given until we switched him. And I think this just speaks to the huge treatment burden of these eyes in these patients. You know, this patient needed q4-week dosing here in the right eye. If I brought him to 6 weeks, he would start leaking again and accumulate subretinal fluid. We were fortunately able to improve him from 20/40 OU to 20/25 OU with this monthly aflibercept treatment. But of course, you know there was this unmet need of treatment burden. And so, in May of 2022, we switched him to faricimab, and he's received nine faricimab injections to date, his visual acuity has remained stable at the 20/25 level. And the real benefit here is that I was able to extend him out to 12 weeks. And that's where he's been since May of 2022 to the present is every 12-week dosing.

What I did with this patient is we did extend him 2 weeks at a time. I know some of our colleagues are doing 1 week at a time extension. But you know, I think it's been within my practice pattern experience that we could still extend these patients by 2 weeks at a time.

So, let's take a look at the OCT. This is the baseline OCT when he first presented in December 2015. He's got a PED with subretinal fluid. At the time of switch, again, his vision had improved to 20/25, the PED is gone, all the fluid is gone. And this is after 58 injections, again, of the 2-mg aflibercept given every 4 weeks. After nine injections of faricimab in January 2024, he's doing great without any evidence of disease activity here on the OCT, and his visual acuity remains at 20/25.

His left eye also had neovascular AMD presented in March of 2015. And you can see here fluid and a PED as well with some exudate. At the time of switch to faricimab in June of 2022, he had received 45 injections of aflibercept 2 mg. He was stable here, you can see complete resolution of the fluid, and doing really well at 20/25. And then he had received 10 injections of faricimab as of January 2024. Now, this eye was not able to extend past the 4-week interval, but he has improved vision to 20/20 in that left eye.

So, I'll turn the slides back to you, Arshad, and you can talk about some cases of diabetic macular edema.

Dr. Khanani:

Thanks, Ted. That was a great case. I think it highlights how you can get extension with dual inhibition and how you may be able to control for it better or have better vision in some patients. And I think it tells me that each eye is different, patients have different needs, and we need to individualize treatment. So, great job in maintaining, you know, vision even with frequent aflibercept in the past and really great job in management. Not all my patients will come in for 45 to 50 every-4-week injections, but I'm glad your patient did.

Now, let's go to a naïve case of DME. This is a 70-year-old male, 5-year history of DME. We have done focal laser in the past, which obviously I don't do much anymore. Also has mild dry AMD in both eyes. Here, we are focused on the right eye with visual acuity of 20/30. Patient obviously has diabetes, hypertension, hyperlipidemia, and is on multiple treatments for medical issues. Now, this patient, when you look at the OCT, you can see there's some drusen, so this is obviously from dry AMD but has intraretinal fluid. We were able to confirm that this is from diabetic macular edema. And here, we can see the baseline visual acuity of 20/30 with central involving intraretinal cyst with CST of 331. Patient received one faricimab injection, again, rapid improvement in anatomy with resolution, almost resolution of the intraretinal cyst, some residual thickening, and visual acuity improving to 20/25. Patient, again, I load my patients that are naïve with three or four injections. Patient came in every 4 to 5 weeks, and you can see continuous improvement in anatomy and vision, hitting 20/20 vision after the third faricimab injection with very good anatomic response. And then patient continued to be extended and we are able to get to q8 weeks in this patient with trace intraretinal cyst with 20/25 vision.

I think the key here is that patient got improvement in anatomy and vision very quickly with faricimab, again, confirming what we have seen in the real-world studies as well as the YOSEMITE and RHINE study. And we are starting to extend this patient. And now this patient is at 14 weeks. You know, in real world, we extend, again, by 2 to 4 weeks depending on the patient. For naïve, as I said, I go almost a month if they can, but sometimes they are traveling or I'm traveling and the clinic schedule is not perfect, but this patient is at 3-month dosing. And what you see here is that continuous improvement in anatomy, vision, and then interval too. So, if I would have just gone to, you know, interval of 3 months or 4 months right out the gate, we may have not achieved these outcomes. So, I think as Ted said earlier, like it takes time for the Ang2 affect to kick in, in terms of stabilizing blood vessel. And here, slowly but surely, we were able to get this patient to 3 months.

Ted, any comments on that naïve DME case? And what is your experience?

Dr. Leng:

Yeah, no, I think that's a great case, Arshad. I'm sure that patient is also really happy with a carrier providing. But I think it does speak to the fact that, you know, we do want to give enough treatment to reach stability before we start extending. And when that's possible, you can have really long extension intervals. I think you had it out to 14 weeks there, which is I think a really good benefit for that patient. So, that really probably was a huge impact on their quality of life.

Dr. Khanani:

Yeah, they're very happy. Lots of happy patients with faricimab. I think we're really seeing anatomic outcomes that are superior and visual acuity changes are also excellent.

So, Ted, now let's go to your case with DME that was previously treated.

Dr. Leng:

Sure. This is a previously treated 70-year-old, Vietnamese man with a history of diabetic macular edema in both eyes from severe NPDR. He presented in November of 2014 to see me, so I've been taking care of him now for almost 10 years. He had 20/40 vision is right and 20/100 in his left eye. And, you know, this patient also had a lot of treatment, he had 96 injections given between November 2014 and July 2022. He also required every month, every-4-week dosing to maintain a dry OCT and maintain visual acuity. And, you know, when we did switch him, we were able to maintain his visual acuity. And, you know, we were able to extend him out to every 12 weeks while his visual acuity was still the same. And we're still in the process of trying to extend him even further. So, he's received about 10 faricimab injections to date.

And we can see here at baseline, the OCT in the right eye here, we have cystic and retinal fluid as well as exudate presented here with these hyperreflective foci and 413 microns. At the time of switch, he did have improved anatomy. This was in July of 2022 last year, or 2 years ago, excuse me, after 96 injections of aflibercept given every 4 weeks. So, to date, he's received 10 faricimab injections and this is as of January 2024. We have now extended him out to a 3-month, or a 12-week interval. And he's very happy, again, with the impact to his quality of life. And his visual acuity is still maintained at that grade level.

You know, to summarize, I think you know real-world data are a very important adjunct to clinical trial data. As we mentioned earlier in this program, the clinical trial data is great. It's really well thought-out, well-collected, and well-aggregated data. But it doesn't always

represent what's happening in the real world. We have, you know, different patient inclusion and exclusion criteria, a lot of patients will be excluded from trials. And so, we would definitely want to see what's happening with patients in the real world once new therapies are brought to market. And, you know, the safety and efficacy of faricimab across these large real-world studies match and also complement the outcomes reported in these clinical trials. You know, we've seen enhanced durability, we've seen improvement of anatomy, both in CST and in the AI analysis of the intraretinal/subretinal fluid in the TRUCKEE study. And the overall incidence of adverse events is also really low in the real-world data, which correlates with the data we've seen in the clinical trials. So, we have very low rates of endophthalmitis, intraocular inflammation in these faricimab-treated patients. So, I think, you know, the whole of the data together, both the trial data and real-world data, really gives us confidence to continue treating our patients with this new agent.

And, Arshad, what do you think?

Dr. Khanani:

No, I think that's a great summary, Ted. I think for me, right, over the last 10 years, we haven't had innovation at this level. You know, obviously we had brolucizumab approved, but safety was not comparable, anatomy was better, and durability was better. I think for any new drug to help our patients, we have excellent drugs, ranibizumab and aflibercept 2 mg. So, I think the bar is very high for any new innovation. And I think it took, you know, aflibercept, I still remember, I'm sure you do, when we were in early treatment, in our early practice in November of 2011, aflibercept was approved. And now it took almost 11 years to get another drug approved and targeting another pathway. So, it's not easy to come up with treatments that are better than standard of care. But it's very exciting as a retina specialist to see the evolution of faricimab. You and I both have been involved with clinical trials, and then now in real-world data generation and our clinical practice. And I think what we have seen is a very consistent effect that faricimab, for me, is a new standard of care based on anatomic improvements that are superior than aflibercept 2 mg in terms of CST, PED, IRF, SRF resolution, hemorrhage clearance, and everything else. And then the visual acuity maintenance with extended treatment interval. So, I think you and I are both very lucky to be a part of this innovation and really helping our patients. As I said, lots of happy patients in our practice. So, for me, it's standard of care now in terms of naïve patients and previously treated patients with fluid, and even stable patients for extension. Obviously, if it's not a barrier based on the payer.

And of course, the recent approval in the retinal vein occlusion, or RVO space, is also interesting. I am now switching my patients who have persistent disease activity and cannot extend interval from other agents to faricimab, and actually also using it on naïve patients with retinal vein occlusion. So, hopefully, we do another study, Ted, on that, if we have time. And it will be hard to find a name, we have TRUCKEE, TAHOE, we need something with a T in the area. So, I know you come to Tahoe a lot for skiing and other things, so we'll have to be creative about that.

Ted, thank you for your time today and bringing your expertise. It's always a pleasure to speak with you. I also want to thank you, to the audience, for attending this webinar. I hope you learned a lot about the latest real-world data. And of course, the cases we presented, which are not one-off cases but rather pretty consistent outcomes that we see in our patients. And for additional opportunities for free CME, please visit the Paradigm course catalog at the website listed again. Thanks again, Ted. It was a pleasure to speak with you.

Dr. Leng:

Pleasure to be here. Thanks, Arshad.

Announcer:

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