Individualized Dosing in Wet Age-Related Macular Degeneration

A Discussion of the HARBOR Year 2 Results

A panel discussion with John W. Kitchens, MD; Geeta A. Lalwani, MD; and Charles C. Wykoff, MD, PhD
Individualized Dosing in Wet Age-Related Macular Degeneration

A roundtable discussion on the anti-VEGF trial data for wet AMD (HARBOR, CATT, and VIEW).

John Kitchens, MD: What do you think are the most important lessons we learned from looking at the anti-VEGF trial data from HARBOR, CATT, and the VIEW 1 and 2 studies?

Charles C. Wykoff, MD, PhD: This is an amazing time in the treatment of wet age-related macular degeneration (AMD), but I still think there is a lot of work left to do. The trials you mentioned look at what I consider to be relatively short-term treatment of wet AMD. There is great safety and efficacy data for 6, 12, and even 24 months of treatment from many prospective randomized trials, but our patients are living decades. While I believe the studies have shown that there are good short-term treatments for these diseases, we need to do more long-term follow-up of our patients.

Geeta Lalwani, MD: We have learned a lot from these comparative trials. CATT compared monthly dosing to as-needed dosing (PRN) with the use of bevacizumab (Avastin, Genentech) and ranibizumab (Lucentis, Genentech). The CATT showed that both dosing strategies were highly effective, but that monthly dosing produced slightly better gains in visual acuity. This trial also found the efficacy of the 2 drugs to be very similar. The HARBOR trial, which looked at dosing frequency as well as an increased dose with ranibizumab, found similar results with its PRN strategy, although visual acuity gains were not as pronounced. Unfortunately, the larger dose did not demonstrate an increased efficacy as we had hoped. The results of these 2 studies lent support to the PRN approach that most retinal specialists were already using. The VIEW trials were the first ones to compare fixed dosing frequencies with aflibercept (Eylea, Regneron)—0.5 mg monthly, 2.0 mg monthly, and 2.0 mg every two months—with monthly dosing of ranibizumab (Figure 1). All arms of aflibercept in the VIEW 1 and 2 achieved the primary endpoint compared to ranibizumab. The addition of aflibercept to the market has increased our armamentarium to treat AMD.

Dr. Kitchens: Dr. Wykoff mentioned that all the data we have are from short-term trials, but there are some very long-term trials out there, some as long as 7 years. Can either of you comment on those trials?

Dr. Wykoff: The only longer-term trials I am aware of are the HORIZON and SEVEN UP trials. Both of these trials were insightful, and concerning at the same time, because, on average, the patients continued to lose vision over time. There are a lot of questions about why this was observed. There could have been some selection bias, because the study only followed a subset of the patients long-term. The patients who dropped out of the trial may have been doing very well, and maybe that is why they did not come back for treatment beyond a certain point. Still, the long-term data showed that even patients who do very well in the short-term may have setbacks in the long-term, possibly related to progression of their underlying dry AMD.

IMPORTANCE OF TWO-YEAR DATA FOR WET AMD

Dr. Kitchens: What do you think the second year data from these pivotal studies—HARBOR, CATT, and VIEW—tells us about each of these different anti-VEGF medications, collectively and individually?

Dr. Lalwani: Most of the trials that had a PRN arm started with a loading dose phase followed by the PRN phase. The differences between the PRN groups versus the groups treated monthly was even more pronounced...
in the second year than in the first year. In the CATT trial, for instance, PRN ranibizumab and bevacizumab looked similar to monthly treatments after year 1, but the year 2 data showed an increased stratification between the 2 treatment regimens.

Dr. Wykoff: For me the second year CATT data were particularly interesting because of the crossover between monthly and PRN dosing. It was very informative to look at the results for the patients who were dosed monthly in the first year and then randomized into two groups, one continued monthly dosing and one switched to PRN dosing. The results of this reaffirmed that monthly dosing is superior to PRN dosing. An argument can be made that the approximately 2-letter difference seen at the end of the second year of CATT is not clinically meaningful for our patients, but there is clear evidence from many prospective trials that monthly dosing is superior when you consider purely visual outcomes.

From the patients’ perspective, it is unfortunate that a switch from monthly dosing to PRN dosing after 1 year resulted in loss of the benefit of monthly treatment. This was seen with both medications, bevacizumab and ranibizumab.

Dr. Kitchens: What do you think the year 2 data from VIEW 1 and VIEW 2 tells us about potential differences or similarities of the two medicines?

Dr. Wykoff: The problem with the second year VIEW data is that it was not really a PRN year—the trial used a modified quarterly dosing strategy. All participants received a minimum of treatment every 12 weeks, whether they needed it or not. This makes the data tricky to interpret. The number of injections in the aflibercept arms were reduced by approximately one-half an injection in the second year of VIEW 1 and 2 compared to the ranibizumab arm. Clinically, it would be nice to know the effect of aflibercept’s potentially-reduced dosing requirements without the mandatory minimum of quarterly injections.

**INTEGRATING DATA FROM TRIALS INTO A CLINICAL PATIENT MANAGEMENT REGIMEN**

Dr. Kitchens: Do the results from CATT change the way you manage your patients?

Dr. Lalwani: Not significantly. After reading the results of the CATT trial, I began having a different discussion with patients than before. I started to tease out not only which drug I would prescribe, but how often I was going to treat certain patients. I still tailor treatment to individual patients, but the data showed that you may only see a difference of 1 or 2 letters between monthly dosing and PRN, which indicates that monthly dosing is superior.

Dr. Wykoff: What concerns me most about the CATT data is the potential side effect profile. Safety is an inflammatory subject with many retina specialists, both related to compounding pharmacy issues and systemic exposure. I try to think about what the science says and how it applies to my patients in the economic realities of life. It worries me that ranibizumab appeared to be safer than bevacizumab to some extent. It was a wakeup call for how I treat my patients. I always tell patients that we need to treat their eye disease, but the worst thing I could do is give them some problem they do not already have, such as endophthalmitis or some systemic event.
Individualized Dosing in Wet AMD

Dr. Kitchens: I am more comfortable following people on a PRN basis because of CATT, although I typically use a treat and extend protocol. If a patient wants to be treated on a PRN basis, I can now tell them that we have a good study that shows that PRN treatment is effective as long as they are monitored monthly. I think, doctors will often treat patients on a PRN basis but not require monthly visits for monitoring, which is in essence a modified treat-and-extend PRN strategy. If a patient comes in dry, the doctor may ask him or her to return in 6 or 7 weeks instead 1 month later. That could result in a 10 or 11 week treatment interval, which is enough time for a hemorrhage to occur or other problems.

The CATT data does reassure me that the 2 drugs are clinically equivalent. I agree that the crossover data is important, because if a patient is doing well with monthly injections over 1 year and then you switch him or her over to PRN dosing, there may be a loss of acuity.

Dr. Lalwani: When we treat patients with ranibizumab in my clinic, we are more comfortable allowing them to go closer to a PRN regimen now, but I have not found that the dosing interval really increases significantly.

Dr. Kitchens: How have the results of the HARBOR study changed the things that you do clinically?

Dr. Lalwani: The dosing intervals in the HARBOR trial extended to almost 10 weeks. Have you increased your interval that much?

Dr. Lalwani: No. I talk to patients about a longer interval, but I still individualize treatment to every extent possible. As I said before, I still want to monitor patients closely for active disease—the study looked at a range of intervals. I would not feel comfortable going right to a an approximately 10-week interval. But, I would not do that with any of the drugs.

Dr. Wykoff: HARBOR was a fascinating trial. I did find it unfortunate that the 2.0 mg dose did not perform better (Figure 2); I was hoping for our patients’ sake that the larger dose would benefit their visual outcomes. It was particularly interesting that the findings regarding the 2.0 mg dose are inconsistent with other trials, such as the SAVE7,8 and LAST9 trials, both of which showed an increase in visual acuity with the higher dose, although importantly both of these studies evaluated recalcitrant wet AMD patients and not treatment naive eyes as enrolled in HARBOR.

I rarely use monthly treatment with my patients. In most circumstances, I use treat and extend. While I agree that more data is needed to support treat and extend, the HARBOR results support less frequent than monthly dosing (Figure 3).

Despite this, the PRN dosing did not meet the primary endpoint in HARBOR, so I do not think it is correct to say that PRN dosing was as effective as monthly dosing. I still find it very interesting that the results of the HARBOR trial led to a change in FDA labeling when the primary endpoint was not officially met. Although patients in the PRN group did very well in the trial, the results showed that PRN dosing was not noninferior to monthly dosing within a predetermined 4-letter margin.
Dr. Kitchens: The HARBOR trial is a data rich trial. There have been more presentations and more data coming from the HARBOR trial than many positive trials that have shown some benefit. HARBOR did not show any difference between the higher dose (2.0 mg) and the standard dose (0.5 mg) of ranibizumab. In addition to the monthly versus PRN dosing regimen, HARBOR was the first trial in which the investigators used spectral domain optical coherence tomography (OCT) and looked specifically at the effect of anti-VEGF therapy on geographic atrophy, results which I hope are forthcoming soon.

I think a point needs to be made that there were some negative outcomes as far as the manufacturer was concerned. Genentech could have tried to bury some of the results that did not show them in a positive light. Instead, they have been very forthcoming in analyzing and releasing the data.

The biggest change I have made based on the HARBOR results, as far as analyzing patients, is that I used to give patients a little bit more volume every time I would treat them. If a patient did not respond or had a pigment epithelial detachment (PED), I would think about giving maybe 0.1 mg versus 0.05 mg. My rationale was that if a normal amount is good, extra would be better. A lot of those patients would have transient problems such as pressure rises within 30 to 60 minutes after their injection—nothing permanent or irreparable. Because of the results of the HARBOR trial, however, I really do not do that anymore. I now use the standard dose routinely.

I tell our fellows to be careful about dosing with patients getting their very first injection. We want patients to have a positive experience, and it can be very frightening for a patient to lose his or her vision right after an injection when the pressure goes up, particularly with their first injection.

Dr. Kitchens: Aside from now having access to and using aflibercept, how have the VIEW studies changed how you take care of patients?

Dr. Wykoff: I think patients are very fortunate to have access to 3 very good anti-VEGF agents. In my experience, some patients respond better to 1 of the 3, and sometimes it is difficult to predict which a patient will respond best to. I do not hesitate to switch between the medications.

I think a point from the VIEW trials that is interesting for clinical practice—and especially from a payor perspective—is how the data was interpreted into the drug’s labeling. As a result of those trials, on-label dosing is to provide a 2.0 mg dose for 3 consecutive months, followed by dosing every 8 weeks. The second bullet point for wet AMD management in the package insert states, “Although aflibercept may be dosed as frequently as 2.0 mg every 4 weeks, additional efficacy was not demonstrated when aflibercept was dosed every 4 weeks compared to every 8 weeks.” This is incredibly confusing to payors because of the disparity in dosing recommendations. Glenn Jaffe, MD, presented a great paper10 at ASRS in 2013 showing that a substantial number of patients do benefit from continued monthly dosing of aflibercept, particularly those patients with recalcitrant wet AMD. An analysis of the subgroup of patients who were wet at each of their first 4 visits in the VIEW trials showed that those patients did substantially better visually with continued monthly dosing versus transitioning to dosing every 8 weeks. When I look at the VIEW data in detail, it makes me hesitant to jump straight to an

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![Figure 3. The proportion of patients gaining 15 lines or more was equal across treatment arms at HARBOR.](image-url)

The last-observation-carried-forward (LOCF) method was used to impute missing data.
8 week dosing pattern in patients who have persistent intraretinal or subretinal fluid after a loading phase. This is supported by other prospective trials.\textsuperscript{11}

**Dr. Lalwani:** As Dr. Wykoff said, we are fortunate to have a number of agents to use, and now I think we are fine-tuning how to treat patients. It is interesting to see focus on the subset of patients who had PEDs; numerous publications have focused on their response to aflibercept, however, previous subanalyses studies with ranibizumab have shown a strong response as well. Rather than using an anatomic focus, I believe that the future of AMD management will mirror in some ways what our colleagues in oncology do, employing complicated, individualized regimens rather than just looking at the frequency and dosing. I think there may be a role for using the different agents to fine-tune how patients are treated.

**Dr. Kitchens:** I agree that the subset analyses from VIEW 1 and VIEW 2 are very important. Keeping in mind that VIEW 1 and VIEW 2 are the only studies that compared aflibercept and ranibizumab head-to-head, there certainly could be some potential for bias in the data interpretation because company owns that data and can cut it up any way they want. The results, however, show that eyes with a PED do seem to respond better to aflibercept than ranibizumab as far as flattening of the PED, and aflibercept does seem to dry the retina out more rapidly and more efficaciously in the early period. If the patient has a persistent leak, there are some visual acuity advantages to being on monthly aflibercept as compared to every 8 weeks of aflibercept or monthly ranibizumab. Those are the 3 things from VIEW 1 and VIEW 2 that have shaped the way I treat patients. The PED piece of that actually fits with some of the early experience I had with these kinds of patients. James Major, MD, presented about the effect of treatment for refractory PEDs a couple of years ago at ASRS.\textsuperscript{12}

**FACTORS IMPACTING THE DECISION TO TREAT PEDS**

**Dr. Wykoff:** I think that the PED story is fascinating and I think it is still more to understand. I am interested in what Dr. Lalwani thinks, because the investigators in the PrONTO trial\textsuperscript{13} led by Dr. Philip Rosenfeld, MD, out of Bascom Palmer Eye Institute—the first PRN trial and one in which Dr. Lalwani was a major contributor—indicated that PED is not an indication for giving an injection. Should we be treating PEDs? In my practice I usually do not.

**Dr. Lalwani:** That is an interesting question. In year one of the PrONTO trial, we looked at a drop in visual acuity with associated fluid as our criteria for treatment. In the second year, we used any evidence of fluid—aside from a PED—as criteria for treatment. Many subsequent studies used criteria similar to PrONTO to determine the need for treatment, using visual acuity as a criteria only if there was a significant drop. Generally, if a patient has a PED but it has not changed their vision, similar to Dr. Wykoff, I do not treat them. At the same time, some PEDs are different from others. We all know of the very large PEDs, with very real implications if they are left untreated. So, there may be a subset of patients with a PED who will require treatment.

**Dr. Kitchens:** I think PEDs can be categorized as vascular and nonvascular. I do not think anybody is in favor of treating a nonvascular PED, but if you have a PED that responds to 1 therapy or another, do you think that you should treat that?

**Dr. Lalwani:** That is a difficult question. I think the decision is still very individual. Should you put a patient through monthly injections if that is what is required to treat the PED? If the treatment would not change their visual acuity at all, I might wait to see if the PED fluctuates. In those cases of a dynamic PED, I would be more inclined to treat it, but in patients who have a PED that is not really changing and not affecting their vision, I would be hard-pressed to put them through the risk—albeit low—of an intravitreal injection.

**Dr. Kitchens:** Dr. Wykoff, what is your opinion? Take the scenario of a patient whose PED responded to anti-VEGF therapy. During a routine monitoring visit, this patient had no subretinal fluid or intraretinal edema, so you decided not to treat. If at a subsequent visit, you noticed that the PED came back but did not enlarge to the point at which you were concerned about a retinal pigment epithelium (RPE) rip, would you treat them just because you would be able to flatten that PED?

**Dr. Wykoff:** No, I think that a PED in the absence of an associated loss of visual acuity is not an indication for treatment. Part of that is the issue of “do no harm.” Eyes with wet AMD can certainly develop an RPE tear, but any time a retinal physician gives a medication and the patient develops an RPE tear, there will always be concern that the medication may have precipitated that.

**Dr. Kitchens:** Would you treat an asymptomatic patient who had subretinal fluid, but good visual acuity, maybe 20/25?

**Dr. Wykoff:** Asymptomatic patients are fascinating. None of the major clinical trials have studied that patient population. All of the prospective trials that we have
discussed here today require that a patient has associated loss of visual acuity. In that context, the decision to treat has to be completely individualized.

I may consider initial very close clinical observation of an asymptomatic wet AMD patient if the fluid is minimal—these are often patients with small amounts of fluid that might be Vitelliform-related or degenerative-related. In cases such as these, if the other eye has already lost visual acuity due to definitive wet AMD or disciform scarring, I am going to be much more likely to treat the fellow eye. But if it is a first-time conversion and there is a tiny bit of extrafoveal fluid, I may elect to closely observe the patient.

COMPOUNDING AS A FACTOR IN SELECTING AN AGENT

Dr. Kitchens: The real concern I have coming out of the CATT study is something that was not studied, which is compounding. The bevacizumab used in CATT was specifically prepared in a very rigorous and sterile fashion. In the real world, there have been reports of a fungal meningitis outbreak at a compounding pharmacy, and similar events of outbreaks and infections stemming from compounded bevacizumab are well known. That is a definite concern of mine. How do you vet your compounding pharmacies?

Dr. Lalwani: To start with, I review their guidelines to ensure that they meet USP 797 guidelines. We discuss whether they hold the drug, once aliquoted, while they culture it to make sure that nothing is growing before any of those aliquots are sent out.

Dr. Wykoff: We thought a lot about this and our approach has been 2-fold. The first thing we did was to look for the largest distributors in the country, with the thinking that volume may translate into safety, which is certainly not an absolute. Within those, we conducted a vetting process over the phone, requesting documents and information about their processes. Then we investigated the companies that responded most completely. We are still looking for a local source so that we have access to two different sources. Having product from 2 sources is ideal for bilateral injections on the same day so we can reduce the risk of injecting from a contaminated lot.

Dr. Lalwani: Do you ever look at using different lots from the same pharmacy?

Dr. Wykoff: We do. Right now we are using different lots from the same pharmacy, but we would prefer to use different pharmacies.

Dr. Kitchens: I agree. If there is a procedural contamination issue, it could affect 2 different lots. We do not mind if our supply comes from the same lot, as long as it comes from 2 separate pharmacies. If there is a contamination event on a lot basis, then everyone is going to have major issues, but if there is a contamination issue at the pharmacy, the individual pharmacist who is doling out the medicines may contaminate 2 different lots.

Currently, we can keep a supply of bevacizumab in the office to treat patients without a prescription. If a law is enacted that requires each patient to have a prescription before getting bevacizumab treatments, would that alter your treatment patterns?

Dr. Lalwani: It would make a huge difference. From a practice management standpoint, a law like that would be very difficult for us. It would be hard to maintain our inventory in a patient-specific manner, which would add significant costs to the running of a practice. It would also be difficult from a patient access standpoint. If a new patient came in with new onset AMD, we would not be able to treat him or her without a prescription, which would delay treatment.

Dr. Wykoff: Earlier treatment generally leads to better outcomes, and therefore it worries me that we might have to delay treatment if there were such a law. Although I think we need more regulation of the compounding pharmacy industry, it would be a disservice to the patients to create these limitations.

Dr. Kitchens: It seems as if lawmakers are putting the onus on the practice rather than where it belongs, which is on the compounding pharmacies.

DETERMINATION OF INADEQUATE RESPONSE TO ANTI-VEGF THERAPY FOR WET AMD

Dr. Kitchens: What are your criteria for determining an inadequate or nonresponse to anti-VEGF therapy?

Dr. Lalwani: Nonresponsiveness may be defined as persistent fluid, in the form of cystoid macular edema, or subretinal fluid. Sometimes a slow response can be termed an inadequate response. For example, if I administered 3 injections and I saw an improvement, but not as quickly as I was used to with the particular anti-VEGF agent used, I might call it inadequate or even a failure. I do not include patients with persistent PEDs as nonresponders.

Dr. Wykoff: My impression is if there is more visual acuity to be gained by further retinal detergescence, then I would define that as an incomplete response. Of course, this is only when there is fluid present. I do not hesitate to switch between the anti-VEGF agents when that is the case early on.
**Dr. Kitchens:** It sounds like you base your decision more on OCT than visual acuity—or is it a combination of the 2?

**Dr. Wykoff:** The topic of OCT and visual correlation is a good one. I think that each disease is a little bit different. When working with diabetics, I find that there is not great correlation, unfortunately. In patients with AMD, I think there is a better correlation, but it is not perfect. There is a great secondary analysis of HARBOR showing that the presence of intraretinal, more than subretinal fluid, correlates with visual outcomes. In other words, intraretinal fluid is damaging for visual function. Hence, if I see persistent fluid, I do not hesitate to switch between the anti-VEGF agents to try and get rid of it.

**Dr. Kitchens:** I think about nonresponse as a 2-axis phenomenon: presence or absence of intraretinal and/or subretinal fluid, and the degree at which the fluid is declining over time. I would not define anyone who has had 1 injection and still has persistent fluid a non-responder, but if after 3 injections the retina is not drying out fast enough, I would consider the patient nonresponsive.

**NUMBER OF INJECTIONS GIVEN BEFORE SWITCHING ANTI-VEGF AGENTS**

**Dr. Kitchens:** At what point do you decide to switch to another agent for a patient who is a nonresponder?

**Dr. Wykoff:** It can be after just 1 injection if there is no change, but it is rare to not see a difference after a shot of any of the anti-VEGFs when you have a treatment-naive patient with wet AMD. If there is significant change, I will continue with whatever medication I have started with until I maximize that drug’s ability to dry the retina. Usually I start thinking about switching if I see no difference on the OCT after 2 or 3 doses.

**Dr. Lalwani:** I usually give about 3 injections before I switch, and that is based on my experience with PrONTO study, which demonstrated that the vast majority of patients are dry on OCT after 3 injections. I think a more interesting question is what it means when we say 1 agent can dry the retina better. What exactly does that mean? Are we looking to have zero cystic changes or are we measuring the central retinal thickness?

**Dr. Kitchens:** I wait for a 3-month period before switching. I like to get an OCT 1 month after their first injection for 2 reasons. First, I want to make sure the patient is responding, and that there is not a masquerade syndrome like central serous retinopathy. Second, I want to encourage the patient that they are getting better. Many times a patient will return 1 month after an injection and has not gained any visual acuity. I think it is important for patients and their families to see that they have actually had an anatomic improvement, and that can almost always be shown on an OCT image. One month after their third injection, I determine whether there is at least a 50% reduction in intraretinal fluid and subretinal fluid. If that is the case, then I continue using the same agent, but if there is not more than a 50% reduction, I will consider switching to another agent at that point. I do not care about PED.

When would you start thinking about switching someone later in the treatment process? Let us use the example of a patient who has been on a medication for 1 year. What factors would make you think about switching medications at that point?

**Dr. Wykoff:** There are 2 scenarios that make me consider switching agents. One is if the retina is not as dry as I think it should be for a given duration of treatment and/or the patient has not had the visual acuity gains that I expected. The second is for patients in whom the treatment burden has become problematic. If I reach a point where I can no longer extend the dosing interval beyond a certain number of weeks in a treat and extend pattern, I might switch to a different agent in attempt to lengthen that interval.

**Dr. Lalwani:** I agree with what Dr. Wykoff said. I would consider making a switch when there is a need to increase the interval between injections. I think that is probably the strongest rationale for trying a switch later in the treatment process.

**Dr. Kitchens:** Do you think there is a difference in durability between the different agents?

**Dr. Wykoff:** I do, but I think that it is very patient-specific. Beyond the issue of durability, I have found that some patients simply respond better to aflibercept than ranibizumab, and I think some patients do better with ranibizumab than aflibercept.

**Dr. Kitchens:** It seems that most people who use bevacizumab as a first line agent choose aflibercept over ranibizumab when it is time to switch for a nonresponder. Why do you think that is?

**Dr. Lalwani:** I think there may be a perception that the chemical structure of bevacizumab is similar to that of ranibizumab, while many view aflibercept as different even though it has the same mechanism of action. And so, the thinking may be, “If I am going to switch agents because the agent I am currently using is not working, why switch to a similar chemical structure?” Additionally, prior to the HARBOR study, the aflibercept trials

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**Individualized Dosing in Wet AMD**

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indicated that longer treatment intervals were possible as compared with the other anti-VEGF agents, so perhaps there is a belief that switching to aflibercept allows for extended intervals or being able to treat less often.

Dr. Wykoff: I think the most convincing reason for many physicians is actually the pharmacokinetic publications that were put out before the VIEW 1 and VIEW 2 clinical dataset. Publications from Stewart\textsuperscript{16} and Rosenfeld\textsuperscript{17} indicated that the half-life of aflibercept inside the eye may be significantly and dramatically longer than that of ranibizumab or bevacizumab—hypotheses that have not been borne out entirely in clinical practice. Nevertheless, physicians are switching from one medication to another thinking that aflibercept will have a longer duration of effect.

Dr. Kitchens: The 2 studies that are most commonly talked about right now are CATT and VIEW 1 and VIEW 2. Based on the CATT results, many have argued that bevacizumab and ranibizumab are similar in efficacy. VIEW 1 and VIEW 2 indicated that patients can do just as well with less frequent dosing of aflibercept, so there may be a belief that it must be better because you can give it less frequently. There is also the subset of data that shows that nonresponders, under responders, or eyes with persistent leaks are drying more effectively when getting monthly aflibercept compared to monthly ranibizumab.\textsuperscript{18} The only reasonable conclusion from all of this, however, is that in the context of CATT, ranibizumab was equal to bevacizumab, and in the VIEW 1 and VIEW 2 trials, aflibercept performed better than ranibizumab.

**THE IMPORTANCE OF DOSING FREQUENCY FOR WET AMD**

Dr. Kitchens: What do you think is the real importance of the dosing interval? What are some of the key issues around dosing intervals for your patients?

Dr. Lalwani: I believe that 4 things affect the desire to increase the interval between injections. The first and most important issue is response to treatment. Whether you define that in terms of a patient’s actual visual acuity, OCT, or dryness of the retina, response is most important. Second, there is the burden on the patients to return for treatment, and this is obviously very individualized. The third issue is cost, in terms of actual treatment, transportation, or loss of work due to appointments, which is also patient-specific. The fourth issue is practice-related. Over time, monthly visits definitely increase the patient load on an office quickly.

Dr. Wykoff: I agree with Dr. Lalwani. I also think this harkens back to the issue of trying to do as little harm as possible. We all want the best outcomes for our patients, but if you look at the incidence of potential adverse events with an injection, it is not insignificant. For example, the rate of endophthalmitis in all of the prospective trials we have described is fairly high. In the HARBOR trial, there were about five patients out of more than 1,000 who developed endophthalmitis.\textsuperscript{1} That is approximately 1 out of 200 people over the course of a 2-year trial, which seems high. If I can decrease the number of injections I give over time, I truly feel like I am doing my patients a service.

Dr. Kitchens: I agree that interval can be a big issue for a practice. We have 1 central office in Lexington, Kentucky, and 8 satellite offices that are up to 2.5 hours away. We only visit some of those offices once a month, and dosing interval is much more important in a situation like that. If you treat people monthly, that 1 day in the office will be a very long one. We try to get patients on a better interval if it is possible, and so, in those satellites offices, our doctors are more inclined to try and spread out the injection interval.

However, it really comes down to making sure that patient stays dry. It is important to determine the pretreatment baseline to measure progress against. We use OCT because it does not lie, it does not have a bad day, it does not peak with its other eye, and so it can basically tell us exactly how a patient is doing. Snellen charts tell us about visual acuity, but the results may be impacted by dry eye, a cataract, or other things that affect patients’ vision. The one objective measure we have every time is OCT.

When I start treating patients, I set their expectation by letting them know that they will be coming to see me for the rest of their life, but that we will make it fast and efficient for them. They are told they will receive 3 monthly injections, and that 1 month after their third injection, if they are totally dry, we have two choices: We can either give them an injection and they will not have to come back for 6 or 7 weeks, or they will be monitored with monthly visits. Patients will usually tell you why they choose 1 or the other option. If a patient says he or

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—John W. Kitchens, MD
she hates the shots and prefers to monitor the condition, we document that they prefer PRN so we will know that in the future. But if the patient expresses concerns about losing vision, or if monthly visits are not an option, then you know the preference is going to be for treat and extend. I find that about 50% of people choose PRN, and 50% choose treat-and-extend.

REAL WORLD EXPERIENCES WITH THE CURRENTLY APPROVED TREATMENTS FOR WET AMD

Dr. Kitchens: What has your experience been with the currently approved treatments for wet AMD in terms of dosing frequency? Do you think that 1 treatment lasts longer than another?

Dr. Lalwani: My patients come from a highly educated, affluent community, and I often have patients request certain medications. Because of this, I think there is a little bit of selection bias in who gets which drug. I have found that my patients are also more willing and able to assess their own vision, so we can allow them to be on their own longer with a treat-and-extend approach versus what we might do with other patients. I think, ultimately, response to medications varies greatly according to the individual.

Dr. Wykoff: I think different drugs work differently for different folks, so the best agent is different for different patients.

Dr. Kitchens: Dr. Wykoff, describe your patient population. Are they coming in with the latest research off the Internet or are they coming in just asking you to do what is best?

Dr. Wykoff: It is a little bit of both. I have a few different clinics and each has a different patient population in terms of demographics. Almost all of my patients want to come in less often. Most of them do not mind the injections, but they do not want to come into the doctor’s office—it is a hassle driving, getting a sibling or a friend to drive, or there is a copay issue. For this reason, I try to do a treat-and-extend protocol whenever possible.

Some patients do come in with data in hand. Sometimes it is good data, and sometimes it is information that is contrary to common knowledge within the retina community. I spend a fair amount of time addressing patients’ concerns based on what they found on the Internet or in their social networks. I routinely get questions about AREDS vitamins and aspirin, as well as general questions about wet AMD that may not be related to drug choice. In fact, I would say that the drug choice is the least common issue that my patients with wet AMD bring up when discussing information they found online.

Dr. Kitchens: My patients typically come to the office and ask me to choose whatever treatment I think is best. I can count on 1 hand the number of times in 8 years that someone has brought in research papers or Internet printouts. The patients who have requested a certain drug almost always requested bevacizumab, with the altruistic intention of saving Medicare and the government money. One would think that most patients would want an FDA-approved drug, but the ones who actually have a request want to have the bevacizumab over aflibercept or ranibizumab.

Dr. Wykoff: I have had 2 patients who requested bevacizumab for the identical reason you described. The vast majority of patients who request a drug want an FDA-approved medication, or because he or she has read about compounding pharmacy issues or “the cancer issue.” Some of the information out there is very misleading.

Dr. Kitchens: When you talk to a patient about their initial treatment, do you mention compounding and discuss the risks, and do you speak to the patient about systemic safety?

Dr. Wykoff: I do. Both of those issues are important and very relevant. This is a very charged issue and it is unfortunate that there is such a huge difference in price between bevacizumab and the other two agents. The economic factors are a reality in practice, but they are different than the scientific issues. The issues with compounding pharmacies are, to me, an issue of science and not economics. The simple fact is that the more times a drug changes hands, the higher the risk of a problem occurring in that process. That does not mean that the drug that is being compounded is a bad drug, or that the compounded drug is less safe because it is less expensive. I try to make that distinction with my patients and I try to explain the important factors of each agent. I think FDA approval is at the core of some of those issues.

Dr. Lalwani: I agree that there is a scientific point that has to be discussed. I do discuss compounding pharmacies when I talk to patients. Many patients have heard about of the fungal meningitis outbreak, and so we discuss those incidents and I go over our rigorous vetting process of pharmacies. I also share with patients how many injections I have given from a certain lot number in recent weeks without issues. At the same time, when I do get consent from patients, it includes that they are receiving a compounded drug. They are aware of exactly what they are getting.

Dr. Kitchens: Do you ask about a prior history of stroke and does that affect your choice?
Dr. Lalwani: I do, and it does affect my choice. I discuss the outcomes of patients who receive anti-VEGF injections within 1 year of a stroke or some sort of thromboembolic event. If I have a patient with a history of stroke, I lean towards treating with an FDA-approved drug.

**FACTORS CONSIDERED IN CHOOSING AN ANTI-VEGF FOR WET AMD**

Dr. Kitchens: I am going to give you 6 different issues that might impact your choice of drug for a patient. Can you rank them as far as what is most important?

- Efficacy
- Safety
- FDA approval status
- Cost to the patient
- Cost to your practice
- Patient preference.

Dr. Lalwani: I would have to say that in this time in which we live, the cost to the patient probably drives decision to go with bevacizumab versus 1 of the 2 FDA-approved drugs. If the patient cannot pay for a drug, they cannot have it, so cost is what is going to decide which agent I choose in that context. Beyond that, I think studies have shown that there is not a huge difference between the efficacy of any of the 3 treatments. They are all fantastic drugs, so I cannot say that efficacy really changes the argument. FDA approval is more important to some extent to the patient. I do not think that there is a large difference between any of these in terms of safety. Least important would be the cost to the practice. In many cases doctors do not have a choice. The choices are typically fairly limited with regard to what is appropriate for a patient, and the practice is going to absorb the cost, whatever it is.

Dr. Wykoff: My order is a little bit different just because I think I interpreted the question a little bit differently. In a theoretical comparison of different drugs, I would put patient preference first. If a patient is asymptomatic and does not want to treat their condition, I will monitor the condition. If he or she has strong opinions about a drug I will defer to their preference—I will, of course, still discuss the risks involved, as I would with any other patient in any clinical setting.

I think that efficacy, safety, and FDA approval are all linked, but for me the second-most important factor is efficacy. I want to get the most improvement in a patient’s vision I can, so that is a huge driver for me. Third is safety, and fourth is FDA approval. FDA approval usually translates to higher cost, and sometimes to improved safety, as we see with ranibizumab versus bevacizumab. Cost to the patient is more important than cost to my practice, which is last.

Dr. Kitchens: I agree. I do not have a strong enough feeling about any of the 3 agents, so if a patient comes in demanding 1 medicine, that is what he or she will get. Obviously, if the cost attached to the preferred medication is problematic to the patient, I will not choose it first as it is very likely he or she will not return after the first injection. The cost to the practice is a significant issue if your practice is losing money on a drug. These drugs are very expensive, so you need to have a really well run practice to be able to offer all options to your patients. If you are losing money on 20 vials of a $2,000 drug, you are not going to stay in business very long.

Obviously safety is a huge thing. You cannot give someone an injection of a medicine that has caused 2 prior episodes of inflammation in their eye and expect...
them to not have inflammation a third time. Finally, we all want to see efficacy, but Dr. Lalwani is right that the agents are so close in that regard, especially when you start a patient on a medicine, that it is last on my list.

GOVERNMENT DATA ON DOSING FREQUENCY AND RELATED COSTS

**Dr. Kitchens:** A recent analysis of CPT claims codes data\(^1\) looked at the mean number of anti-VEGF injections in first and second line patients. What does this data tell us?

**Dr. Lalwani:** For first and second line, there was not a real difference between the injection frequency or costs. Because ranibizumab has been around a while, this data reflects physicians individualizing treatment in an as-needed fashion, as opposed to monthly. However, since aflibercept had only recently been released, it is likely that the data only reflect on-label use of aflibercept with 3 loading doses followed by bimonthly treatment.

**Dr. Wykoff:** My issue with this data is two-fold. First of all, there is no efficacy data. There is no way of telling the impact the injections had on visual outcomes. It might be correct to assume that all the patients are doing the same because everything else in the data is identical, but there really is no way of telling. It is impossible for me to comment on what this means without outcomes associated with it.

Second, this data, in my opinion, is biased against aflibercept. Ranibizumab has been clinically available since 2006, while aflibercept is relatively new. That certainly creates a selection bias. The comparison should be repeated once there is more data on aflibercept.

**Dr. Kitchens:** Do you think someone who primarily uses aflibercept may manage patients differently based on this analysis?

**Dr. Wykoff:** I do not have a great answer for that. I think the problem with mining data like this is there are so many uncontrollable variables. This is the reason we love prospective trials so much and spend so much time on them—they produce cleaner datasets.

**Dr. Lalwani:** I think the numbers are also very low. There were 1300 patients treated with ranibizumab, but only 486 with aflibercept. This is very early on in the use of aflibercept, and that not only creates a patient selection bias, it does not account for how doctors will eventually use the new drug.

**Dr. Kitchens:** There were 3 days between injections in the first line patients, and 5.9 to 6 days in second line patients. Is that a tangible difference?

**Dr. Wykoff:** I believe it is a rounding error. I really do not see any significant differences between the drugs in this dataset.

HARBOR YEAR 2 TRIAL DATA RESULTS

**Dr. Kitchens:** Patients in the 0.5-mg group received a mean 5.6 injections in the second year of HARBOR (Figure 4).\(^2\) Are there any other important findings from HARBOR that we should discuss?

**Dr. Wykoff:** I was reassured that the 2.0 mg dose was as safe as the 0.5 mg dose, especially because a 0.3 mg dose is suggested for use in patients with diabetes.

**Dr. Kitchens:** The data for geographic atrophy coming out of HARBOR have not been released yet. Do any of you have any guesses about what might come out of that? Do you think this data will be reassuring or concerning? Also, do you think a 2.0 mg dose is safe with aflibercept as well as ranibizumab? Further, if it is proven that a 2.0 mg dose is safe as far as atrophy is concerned, do you think it is reasonable to say that aflibercept is safe with regards to atrophy?

**Dr. Lalwani:** I think the data on geographic atrophy is going to be very interesting. A recently paper in *Ophthalmology* discussed the differences that surfaced in the CATT trial regarding geographic atrophy in monthly dosing versus PRN dosing with ranibizumab and bevacizumab.\(^3\) I would guess the pending data from the HARBOR trial is going to mimic that.

I do not know whether there is going to be a dosing association. Until we understand the mechanism of inducing geographic atrophy, I do not think that question can be answered. The same goes for aflibercept. I am not sure that we can make the leap to state that another wet AMD medication will do the same thing.

**Dr. Wykoff:** I will take the aflibercept question first and flip it around.

I will start with the basics. I think it is always important to look at things scientifically and then think about how it might be applied to clinical practice. Aflibercept and ranibizumab are different molecules, so it is plausible that they would have different effects inside of the body. For example, aflibercept blocks other factors besides VEGF-A, such as placental growth factor and VEGF-B. There is no reason to think that that extra activity is not going to cause other effects. Some may be beneficial, some may be harmful—it is just different and we need to know more about that.

The second issue is that aflibercept has a fragment crystallizable (Fc) domain and ranibizumab does not. Again, that is a simple fact, not an arguable point. The clinical relevance of that is certainly a different issue.
Because the 2 agents are distinct, a dataset on 1 drug may not be directly applicable to the other drug. Looking at the HARBOR data in particular, I agree with Dr. Lalwani and Dr. Kitchens about the interest in knowing what those results show. I think that my interpretation of the CATT and IVAN\textsuperscript{22} datasets together is that monthly dosing yielded more geographic atrophy at the end of the trial than PRN dosing. The reason that scares me is that in the SEVEN UP trial, 98% of the patients evaluated at that 7 year time point after MARINA\textsuperscript{23} and ANCHOR\textsuperscript{24} had foveal involvement of atrophy. That is almost everybody. None of them had it at the beginning of the first study. This raises an important question: Does long-term blockade of VEGF-A cause geographical atrophy? Certainly the pigment epithelial cells in the retina have low levels of VEGF-A around them in a normal state, and I believe that it is likely there for a reason. There is a great deal of uncertainty around this issue. Maybe it is fine to block VEGF-A indefinitely, but I tend to believe that most things in our body are there for a reason and that blocking it indefinitely may cause issues down the road.

**FUTURE DEVELOPMENTS IN RETINA**

**Dr. Kitchens:** What is the most exciting thing you are looking forward to in the next 3 to 5 years in retina? Is it anti-PDGF, anti-factor D, stem cells, extended release therapy, or something else?

**Dr. Wykoff:** I believe that addressing dry AMD and long-term follow-up of these patients are big issues. I truly hope that potential study sponsors will want long-term follow-up data on these patients. Currently we do not know how these patients do long-term.

**Dr. Lalwani:** I agree that dry macular degeneration is the next thing that needs to be solved.

**Dr. Kitchens:** Are you talking specifically about geographic atrophy or anti-factor D, or about dry AMD as a whole in terms of finding something that is more efficacious at preventing conversion to the wet?

**Dr. Lalwani:** I am alluding more to geographic atrophy and the loss of vision associated with dry AMD.

**Dr. Lalwani:** I think that we have a good control on wet macular degeneration, although it would be nice to have an extended release. However, there are pretty good options for wet AMD right now. We need something for dry macular degeneration, especially if you look at long-term results. Until we address that, especially considering the data indicating that treatment with anti-VEGF may speed up the process of geographic atrophy.\textsuperscript{24}

**PLASMA VEGF**

**Dr. Kitchens:** Robert Avery, MD, has conducted research that shows that anti-VEGF injections have an impact on serum.\textsuperscript{26} What are the implications of this?

**Dr. Wykoff:** This discussion is fascinating, and it is the IVAN data that initially brought attention to this issue. I wish that CATT had looked at the impact on serum VEGF levels as well. The systemic risk issues are not something to be glossed over. Again, I think that you have to separate the science from the emotional response. Scientifically, it makes sense that 1 molecule might last longer in the systemic circulation, and that is indicated by the data from IVAN.

**Dr. Lalwani:** It is also interesting that there was an increase in thromboembolic events with the PRN dosing as opposed to the monthly dosing in CATT. That may be a result of not just the systemic exposure to an anti-VEGF, but possibly also the increased fluctuation of VEGF levels in response to PRN treatment.

**Dr. Wykoff:** The data show that aflibercept suppresses plasma free VEGF more than bevacizumab, but bevacizumab accumulates in the serum more than aflibercept.

**Dr. Lalwani:** It is interesting that there do not appear to be the same safety issues with aflibercept as there are with bevacizumab.

**Dr. Wykoff:** Another study I share with my patients is the Medicare database mining that showed that the baseline risk of a heart attack or stroke in any given year.\textsuperscript{27} The cumulative risk is about 5%. With a patient population that has a 5% baseline risk of stroke or heart attack, it is difficult to see a difference between drugs when these adverse events occur.

**Dr. Kitchens:** The difference will not be apparent at all. Perhaps the patient never returns after the injection. Many of our patients are elderly, and unfortunately elderly people have strokes or heart attacks and die. The problem is that nobody is looking at how many of those events may be related to treatment.

**Dr. Wykoff:** The annual risk was typically between about 1% to 3% in all of these trials, which is approximately half of what you would expect in the population a whole. This indicates that the study looked at a much healthier population of patients with better health habits, and therefore, it is tough to make that comparison.
Individualized Dosing in Wet AMD

Geeta A. Lalwani, MD, is a retina specialist and owner of Rocky Mountain Retina Associates in Boulder, Colorado. She is a consultant to Genentech. Dr. Lalwani may be reached at glalwani@RMRetina.com.

John W. Kitchens, MD, is a partner with Retina Associates of Kentucky in Lexington and is a member of the Vit-Buckle Society. He is a consultant to Allergan, Genentech, and Regeneron. Dr. Kitchens may be reached at jkitchens@gmail.com.

Charles C. Wykoff, MD, PhD, is a member of the Retina Consultants of Houston and a clinical assistant professor of ophthalmology with Weill Cornell Medical College, Methodist Hospital, Houston. Dr. Wycoff may be reached at ccwmd@houstonretina.com.

In a pooled analysis of 2-year controlled clinical studies (AMD-1, AMD-2, and a study of LUCENTIS used adjunctively with verteporfin photodynamic therapy), the stroke rate (including both ischemic and hemorrhagic stroke) was 2.7% (13 of 484) in patients treated with 0.5 mg LUCENTIS and 2.9% (1 of 34) in patients in the control arms (adds 2.2% 95% confidence interval 0.8-7.1%)

In Studies RVO-1 and RVO-2, patients received monthly injections of LUCENTIS to be administered by intravitreal injection once a month (approximately 28 days). After three initial monthly doses, less frequent dosing with 4-5 doses on average to be administered by intravitreal injection once a month (approximately 28 days).

LUCENTIS is contraindicated in patients with ocular or periocular infections. LUCENTIS is contraindicated in patients with a history of aseptic meningitis. LUCENTIS is contraindicated in patients with neovascular (wet) age-related macular degeneration (AMD).

Ocular reactions in the DME, AMD, and RVO studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>DME 2-year AMD 2-year RVO 6-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular pressure increased</td>
<td>47% 32% 47% 60% 64% 50% 48% 37%</td>
</tr>
<tr>
<td>Cataract</td>
<td>5% 4% 3% 1% 1% 0% 1% 0%</td>
</tr>
<tr>
<td>Conjunctival hyperemia</td>
<td>1% 1% 0% 2% 0% 0% 0% 0%</td>
</tr>
<tr>
<td>Enzymuria</td>
<td>1% 1% 0% 0% 0% 0% 0% 0%</td>
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<tr>
<td>Macular edema</td>
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In the clinical studies, approximately 79% (2387 of 3005) of patients randomized to treatment with LUCENTIS were ≥ 75 years of age. In the controlled studies, LUCENTIS was not studied (or was less commonly studied) in patients > 75 years of age. Also not known whether ranibizumab can cause fetal harm when administered to a nursing woman.

In the controlled studies, LUCENTIS was administered 7 days (± 2 days) after verteporfin PDT.

In the controlled studies, LUCENTIS was studied (e.g., gender, elderly).

No special dosage modification is required for any of the populations that have been studied (e.g., gender, elderly).

Endophthalmitis and retinal detachments

Intraocular injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyepiece speculum. Adequate anesthesia and a broad-spectrum microbicidal should be given prior to the injection.

Prior to and 30 minutes following the intravitreal injection, patients should be observed for signs of hypotony, where vision will be monitored. Monitoring may also consist of a check for perfusion of the optic nerve head immediately after the injection (see Warnings and Precautions [5.1]). Patients should be monitored for and instructed to report any symptoms suggestive of endophthalmitis without delay following the injection (see Warnings and Precautions [5.1]).

Each vial contains 0.05 mL of LUCENTIS solution (see Dosage and Administration [2.6]). LUCENTIS solution is recommended to be administered by intravitreal injection once a month (approximately 28 days).

Pregnancy Category C. There are no studies of LUCENTIS in pregnant women. An embryo-fetal development toxicity study was performed on pregnant Sprague-Dawley rats. Pregnant animals were injected intravitreally at dose levels of ranibizumab every 14 days starting on Day 20 of gestation, until Day 62 at doses of 0.125, 0.5, and 1 mg/kg. Skeletal abnormalities including incomplete and/or fused vertebrae, cleft palate, and unclosed neural tube were seen in animals treated with 1 mg/kg of ranibizumab. The 1 mg/kg dose resulted in true serum ranibizumab levels up to 12 times higher than C declaring levels (1.0 ng/mL) seen in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/kg, a dose which in truth resulted equivalent as true serum ranibizumab levels in humans. No skeletal abnormalities were seen at the lower dose of 0.125 mg/kg, a dose which in truth resulted equivalent as true serum ranibizumab levels in humans.

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INDICATION

LUCENTIS® (ranibizumab injection) is indicated for the treatment of patients with:

• Neovascular (wet) age-related macular degeneration (wAMD)
• Macular edema following retinal vein occlusion (RVO)
• Diabetic macular edema (DME)

IMPORTANT SAFETY INFORMATION

• LUCENTIS is contraindicated in patients with ocular or periocular infections or hypersensitivity to ranibizumab or any of the excipients in LUCENTIS.

WARNINGS AND PRECAUTIONS

• Intravitreal injections, including those with LUCENTIS, have been associated with endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. Proper aseptic injection technique should always be utilized when administering LUCENTIS. Patients should be monitored during the week following the injection to permit early treatment, should an infection occur.

• Increases in intraocular pressure (IOP) have been noted both pre-injection and post-injection (at 60 minutes) with LUCENTIS. IOP and perfusion of the optic nerve head should be monitored and managed appropriately.

• Although there was a low rate of arterial thromboembolic events (ATEs) observed in the LUCENTIS clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

• Fatal events occurred more frequently in DME patients treated monthly with LUCENTIS compared with control. Although the rate of fatal events was low and included causes of death typical of patients with advanced diabetic complications, a potential relationship between these events and intravitreal use of VEGF inhibitors cannot be excluded.

ADVERSE EVENTS

• Serious adverse events related to the injection procedure that occurred in <0.1% of intravitreal injections included endophthalmitis, rhegmatogenous retinal detachment, and iatrogenic traumatic cataract.

• In the LUCENTIS Phase III clinical trials, the most common ocular side effects included conjunctival hemorrhage, eye pain, vitreous floaters, and increased intraocular pressure. The most common non-ocular side effects included nasopharyngitis, headache, influenza, sinusitis, cough, and nausea.

For additional safety information, please see LUCENTIS Brief Summary on adjacent page.

REFERENCES:


For more information, visit www.LUCENTIS.com.