Macular Chats

Clinical Trials for AMD
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Transcript of Teleconference with Dr. Manual Amador and Maria Carlson

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Please note: This Chat has been edited for clarity and brevity.

DR. PREETI SUBRAMANIAN: Hello, and welcome. My name is Dr. Preeti Subramanian, Director of Vision Science Programs at BrightFocus Foundation. I'm pleased to be your host for today's Macular Chat, "Clinical Trials for AMD." Macular Chats are a monthly program, supported in part by educational grants from Genentech and Regeneron, designed to provide people living with macular degeneration and the family and friends who support them with information straight from the experts.

BrightFocus Foundation's Macular Degeneration Research Program has supported nearly $53 million in scientific grants exploring the root causes and potential prevention, treatment, and cure of macular degeneration and is currently investing in 49 active projects across the globe.

For today's Chat, we have two guest speakers, Dr. Manuel Amador, who is a Senior Medical Director at Genentech, and Maria Carlson, who is the Clinical Program Director at Genentech. First, we will hear from

Dr. Amador, who, as a clinician epidemiologist, retina specialist, and Medical Director at Genentech's U.S. Medical Affairs Ophthalmology, has dedicated his career to advancing the understanding of retinal diseases and addressing health care inequities. He is Medical Lead for ELEVATUM, the first industry-sponsored retina trial focused on underrepresented populations in the U.S. Dr. Amador, thank you for joining us today.

MANUEL AMADOR: Thank you so much for inviting me. It is a very big pleasure to be joining today, and thanks for having me.

PREETI SUBRAMANIAN: Yes, great. So, can you please start us off today by discussing ophthalmology in general and providing a brief summary of the different types of age-related macular degeneration, including a background on the advanced dry form, which is geographic atrophy?

MANUEL AMADOR: Of course, and thank you for that question. First of all, ophthalmology focuses on the organ of the eye, basically the organ that allows us to see. And one of the layers of that eye is the retina, which is specifically the organ that allows us and patients to see everything in our day-to-day life. A big reminder that this part of the body is very relevant. Although we don't think about it too much or we don't know that much about it, it's basically one of the crucial parts of the body that allows us to be able to see and live our day-to-day life. What it does, the retina, is to translate the reflection of the light that shines on objects back into the eye and translate this information to our brain. That is then interpreted as an image. So, as you can understand, this is a very important part of our body.

The most important part of the retina, which in this organ is the central part, which is called the macula, which is the point of maximum vision. You can imagine that the retina kind of encloses or is in the whole eye or inside the eye, but there's a very specific area of that retina, which is called the macula. Anything that happens to the macula will severely impact the vision. And just like any other organ in the body, the cells in the macula also age and eventually will retire because every single cell in our body will have its own life cycle, lifespan, and they start retiring. When this happens, we call this age-related macular degeneration. So, this is something that's happening in the retina, which, again, is inside the eye.

I recall that in a previous podcast, geographic atrophy was discussed, which, again, is a very severe form of this age-related macular degeneration and is one of the leading causes of blindness. People with geographic atrophy will have very severe problems reading, driving, and especially recognizing faces, because, as I mentioned before, the macula is in charge of the center vision, or the key point of vision, which tends to be the center. There is another type of age-related macular degeneration called wet age-related macular degeneration, and a common question that I get from patients is, "Why is it called wet and the other one is called dry?" It's called wet because the body tries to compensate for those areas of atrophy. Remember that we talked about atrophy, we talked about dryness. These atrophies are those cells that were dying, and now the body tries to compensate with new vessels, but these are not good vessels. These vessels are very immature, and they start leaking and harming the retina. When this happens, and it does not happen to every patient that has dry macular degeneration, but it can happen to some of the people that do have this problem, so we need to be monitoring and we need to be on the lookout for when patients develop wet macular degeneration. The reason is because when it happens, the vision tends to be more threatened and then acutely, it tends to go down very quickly, and it does require treatment.

Now, talking about treatment, what can we do for a patient with these diseases? Fortunately, for both types, there has been a ton of talk for many, many years, especially since the early 2000s, especially approved therapies now exist for both the wet neovascular, the age-related macular degeneration and for geographic atrophy. And now, thanks to these treatments, patients have been able to preserve a little bit more of vision for a little longer or even improve their vision, which is one of our final goals as physicians.

PREETI SUBRAMANIAN: Yeah, thank you very much for that overview and giving a background on the new treatments that are available. In addition to wet AMD and for geographic atrophy, can you tell us a little bit about Genentech's commitment to ophthalmology and the role that the organization is playing in research and new treatments being available?

MANUEL AMADOR: That's also a very good question. Why Genentech? Genentech has been around for quite a while. It's been about 45 years now. It became officially part of the Roche Group back in 2009. And we've been very active in ophthalmology, especially ophthalmology research. That's why it matters. And this has been happening since early 2000. In 2021, we launched something actually pretty exciting—I was personally involved—which is called the Advancing Inclusive Research® Site Alliance, where we came out with a number of clinical research centers and the main goal was to make clinical trials more accessible to more people. So, for folks that are listening here, we want to make clinical trials more accessible, which is one of the final goals. It benefits patients, and it benefits the overall development of these drugs. And this was actually the first partnership of its kind that was focused on improving how we recruit the participants and how we retain patients in clinical trials—something that is always one of the main challenges when you are working in clinical trials.

And then just last year, we took this step further and we expanded this Site Alliance into ophthalmology, in which the idea is to tackle all the disparities that we see in eye diseases—especially, for example, in diabetic macular edema—and make sure that every patient, especially those that are underserved or that belong to certain communities, have much better access to care and clinical research. And we are, of course, very committed to making sure that everyone, no matter their background, has a first shot with this disease to be part of these trials, as well as having the best treatments and care for their sight-wrecking disease.

PREETI SUBRAMANIAN: Great, that's so important. Thank you for that. So, let's dive into clinical trials, which is today's topic. And so, to start, can you tell us what exactly is a clinical trial and why they are important?

MANUEL AMADOR: Yeah, so for the people listening, clinical trials are basically just opportunities for everyday people—people like you, people like me—to volunteer. You can volunteer and help test potential new treatments with the main goal to see whether those treatments actually work and whether they are safe for a wider use. So, what a lot of people don't realize is that clinical trials are actually the fastest and the safest

way for us to be able to discover new treatments. A lot of the treatments that we currently use in our bodies went through a process like a clinical trial. That's something that is mandated by the health agency. When we talk about the treatments available today for eye diseases, for example, we owe a huge, huge thank you to all the patients who stepped up and actually were able to participate in those trials. Because without this, we would not have all the development and all the current therapy that we currently have. And it's also, of course, important that these trials are, again, reflective of the real world. That means that we actually like having a more diverse group of participants because diseases not only affect just one kind of person. We need the people in our trials to be also reflective of the actual population that are living and having these conditions.

PREETI SUBRAMANIAN: Yeah, that's great. So, can you tell us about the different phases that are involved in a clinical trial and what each of these phases consist of and what's the goal to achieve with each of these phases?

MANUEL AMADOR: Of course. Clinical trials, you can think about it as different steps. There's different steps for the development of the medication. Clinical trials are the different steps that you need to go through, so usually they're divided into four phases. From each phase, we do expect to gain more information about the potential treatment and the potential risks and how well it may or may not work, along with other aspects of quality of life that we are also assessing. So, the progression of these phases or these steps is based on the maturity of the treatment that is being studied, as well as the potential risks.

So, Phase 1 is called, or we can consider it, early development. It's usually a very small amount of patients, and the assessment is more focused on safety—small population, more focused on safety. Once there is understanding that the drug is potentially safe, we move forward to a new phase, which will be the Phase 2, where, again, we start recruiting more patients that will be receiving other drugs, and at the same time, there are some assessments to, again, assess safety and assess efficacy. Phase 3 are the bigger, bigger trials, which, again, they seem to be a little bit more large scale, and it will be preparing the molecule or the product towards

the approval for the FDA. So, this is the most rigorous type of trial. Also, they're the biggest, the most expensive, and the most rigorous. Once the molecule is approved, we have a final step, which is a Phase 4, which is for postmarketing type of studies in which the molecule has been already approved, but there is still some potential to learn more about it or to use it in different types of diseases or different types to understand a little bit more of the potential of the molecule or the drug for all different types of people, populations, or diseases.

PREETI SUBRAMANIAN: That's great. So, these phases create a clear process for researchers to assess the safety, effectiveness, and long-term effects of new treatments before they're available to the public. So, tell us about the role of the FDA in this process. At what stage do they get involved in the process?

MANUEL AMADOR: Also a very good question, because before any treatment can make it to the market, and this is also for our audience, it has to go through a very, very rigorous process. And that includes being reviewed and approved by the FDA, which is the [U.S.] Food and Drug Administration. So, the FDA does play a very big role and very important role in making sure that the data that is coming from our clinical trials is completely solid, that it is reliable, that it is accurate and really reflects how the treatment works. So, clinical trials aren't just one and done; they happen, again, in phases. You have the Phase 1, the Phase 2, the Phase 3, and each one will build on that learned from the previous steps, and the FDA will be monitoring the steps. Only after the treatment has been successfully passed through all those phases is when the FDA considers the approval, and the drug can then be available to the public. So, when you hear that a drug is FDA approved, it means that it has been through all those years of testing and the review to get there.

PREETI SUBRAMANIAN: Great, and you mentioned earlier about the Phase 4, which would be a study that would happen after the FDA approves and the drug is available in the market, is that correct?

MANUEL AMADOR: That is correct. And those are also very exciting trials because when you think about it, the drug has already been approved by the FDA, so it's basically a trial that is focused on a drug that is already

approved, it's already proved to be safe, it's already approved to be efficacious. So, that's even a more interesting type of trial that has some additional information that benefits really well are the patients.

PREETI SUBRAMANIAN: Great, so the FDA provides critical oversight in ensuring the safety, efficacy of the clinical trials. You know, while FDA approves these new treatments, the clinical trials also rely on people willing to take part in the trial, and you talked a little bit about that early on. So, how important are clinical trial volunteers, and how do individuals even get involved in clinical trials if they're interested?

MANUEL AMADOR: This is a very important question, because at Genentech we do focus a lot on enrolling patients in clinical trials because the data required for the review of the approval by the FDA is part of one of my main works. So, if any individual is interested in participating in a clinical trial, there's several ways to access information about the available studies. Genentech especially has a specific site of our clinical trials. It's Genentech-ClinicalTrials.com. This site is a very good resource with all the information that is very clear. It's in very clear language about clinical trials where Roche/Genentech is doing or supporting research. And these resources can be used for patients or their relatives or caregivers, which is also a big, big responsibility for us, something that we also think about or the doctors that are treating the patients or involved in the clinical trials. And patients can also find additional information on the clinical trials at www.ClinicalTrials.gov, where they can read more about where the phases or the trial is going in and get a little extra information about what type of data is being collected.

PREETI SUBRAMANIAN: That's fantastic. So, how much information do clinical trial participants get as they participate in these trials? For example, do they know what dose of treatment they're on? Do they receive the results at the end of the trial? How much information is passed on to the participants?

MANUEL AMADOR: It's a very important question because it's one of the expectations of patients. And we always try to be as communicative as we can with the patients with decisions. There's, of course, research teams that will provide the clinical trial participants with all the information.

Number one, the goals of the trial, if there are active and placebo treatment groups, and the possible risks and side effects. So, the patients always want to be informed of everything. They're also very informed about the tests or all the checkups that they will have, including how often they will be receiving them, where and how long will they have to participate in follow-up appointments, which, by the way, is very crucial for patients to understand because entering a clinical trial is also a commitment, and you want to know if the patient or the person that is receiving the treatment is going to be able to follow through the whole trial. And this is very meaningful for both the patients and for the researchers of the clinical trial. And sometimes researchers would like also to consider keeping some blood or tissues or other samples that will benefit, of course, in future research. But in that case, the participants are always notified and, most of the time, these are optional.

PREETI SUBRAMANIAN: Great. Thank you, Dr. Amador, for that helpful information about clinical trials and the background. So, now I would like to introduce our second guest speaker. With a career spanning over two decades in clinical operations, Maria Carlson currently serves as Clinical Program Director at Genentech Research and Early Development. Maria has specialized in ophthalmology, contributing to the development and execution of multiple clinical trials in late and early stage. Currently, she is focusing on an off-region stem cell therapy program overseeing the Phase 2a GAlette study. Maria, thank you for joining us today.

MARIA CARLSON: Thank you. I'm really happy to be here and taking part in today's discussion.

PREETI SUBRAMANIAN: Great, thank you. So now that we've heard from Dr. Amador about how critical clinical trials are in the research process, can you tell us about ongoing clinical trials at Genentech?

MARIA CARLSON: Yes, I'm happy to dive into this topic. Genentech is currently conducting a Phase 2b study called GAlette using OpRegen®. OpRegen is a cell therapy product that was developed by Lineage Cell Therapeutics for the treatment of GA, secondary to AMD. And it involves the use of retinal pigment epithelial, or RPE, cells that are derived from human embryonic stem cells. The GAlette study wants to look at refining

the OpRegen delivery based on the early but very promising results from the prior first-in-human Phase 1/2a study, which was initiated and administered by our Lineage Cell Therapeutics partners. In that study, the Phase 1/2a study, the RPE cells and OpRegen were generated using a xeno-free feeder system. And that's a system that eliminates the use of animal-derived components, and that reduces the likelihood of immune rejection following subretinal delivery. In that Phase 1/2a study, OpRegen was well tolerated and showed initial signs of improvement in visual function and outer retinal structure. Now, the data from the 12-month primary endpoint provide preliminary evidence suggesting that OpRegen is well tolerated with an acceptable safety profile and mostly mild adverse events. In addition, preliminary evidence of outer retinal structure and visual function improvements with OpRegen was observed in patients with GA and impaired vision. Anatomic improvement with OpRegen correlated with greater gains in best-corrected visual acuity, or BCVA, and was detectable within 3 months of administration.

PREETI SUBRAMANIAN: That's fantastic. Thank you for that overview. So, this study is replacing or providing RPE cells in the area that has lost these cells due to AMD. So, what is the aim that the study is trying to measure here?

MARIA CARLSON: Yeah, good question. So, the study that we are currently conducting, the Phase 2b GAlette study, we're evaluating the optimal surgical delivery methods for a successful subretinal delivery and the safety of OpRegen and also looking at the preliminary activity of OpRegen in patients with GA secondary to AMD. So, subretinal surgical delivery involves surgically placing therapeutic agents into the subretinal space, which is the area between the retina and the RPE. Drilling down a little bit, the RPE is a single layer of cells located in the outermost layer of the retina, between the photoreceptors and the choriocapillaris. It plays a critical role in maintaining the health and function of the retina and the photoreceptor cells. OpRegen has the potential to counteract RPE cell loss by supporting the health and function of remaining retinal cells within areas of GA.

PREETI SUBRAMANIAN: That's great. So, the cells would be placed in the

region where the RPE cells in the eye are lost, so that's fantastic. So, would everyone enrolled in the study receive the active drug, or are there control groups that receive placebos in the study?

MARIA CARLSON: Yeah, that's a good question. So, all patients in this open-label single-arm GAlette study will receive OpRegen. And this is administered as a one-time subretinal injection as part of a surgical procedure.

PREETI SUBRAMANIAN: So, could you also tell us what open label would be? Open-label study.

MARIA CARLSON: Open label, yes, meaning neither the participant or the surgical staff is aware of whether or not drug is being received. So, everyone is aware that they will be receiving OpRegen. It's not masked to either party.

PREETI SUBRAMANIAN: Okay. And who would be eligible for this trial? Can you summarize and read the inclusion and exclusion criteria that would be applied for the study?

MARIA CARLSON: Yeah, definitely. The inclusion criteria include having GA secondary to an AMD diagnosis. Also, the ability to undergo a vitreoretinal surgical procedure. And then again, speaking about best-corrected visual, the score should be greater than or equal to 29 letters or less than or equal to 60 letters in the study eye. And the study eye also has to be pseudophakic. That means a cataract has been removed and an intraocular lens has been implanted. The surgical procedure itself takes about 30 to 60 minutes, during which a patient is sedated or may be given general anesthesia if that's necessary.

PREETI SUBRAMANIAN: And you've mentioned early on, this is a Phase 2 trial, Phase 2b?

MARIA CARLSON: Yeah, this is a Phase 2b study, a 2a study, and it's currently recruiting in the U.S., where we have five sites, and in Israel, where we have two sites. The data from the initial Phase 1/2a study suggests that OpRegen may counteract RPE cell loss by providing support

to the remaining retinal cells within the area of atrophy. And therefore, it has the potential to slow, stop, or reverse GA disease progression. Other assessment is still needed to confirm these preliminary findings and to evaluate the optimal clinical conditions for OpRegen.

PREETI SUBRAMANIAN: Great, definitely the early-phase studies are encouraging. So, how long is this phase to be expected to last, and what are the next steps after this phase of the clinical trial?

MARIA CARLSON: Yes, for this study that we're conducting, the Phase 2a, the first year... there's 1 year that includes screening, enrollment, treatment, and post-transplant follow up. The remaining 4 years of the Phase 2a includes long-term follow up.

PREETI SUBRAMANIAN: Okay, so for those who are interested in learning more about this trial, where can they get the information?

MARIA CARLSON: Yeah, there's lots of information available. ClinicalTrials.gov is one source. It'll give an overview of the trial and more about the inclusion/exclusion criteria and our trial sites. And you could also call the trial information support line. The number is (888) 6626728—and that's in the U.S. only—for more information. Or you can also email global-roche-genentech-trials@gene.com.

PREETI SUBRAMANIAN: Great, thank you, Maria, for that information. So, we have time for a listener question, and I want to put this question for Dr. Amador. Dr. Amador, the question is, "What are the pros and cons of participating in clinical trials for AMD?"

MANUEL AMADOR: Thank you, Preeti. The question regarding what are the pros and the cons for participating in clinical trials. You need to think that every single clinical trial has both benefits, but also there's also potential risks. So, it's very important for patients to be very well informed about both of them. Some of the key pros of participating in a clinical trial is, first, you're going to have access to the cutting-edge treatment, which is you may be receiving a new treatment before it's widely available, especially if you are on those previous phases that the trials are on. Also, the fact that you will have very close medical monitoring, something that,

for example, I do when I lead a clinical trial is I am part of the medical monitoring, so I'm always following very closely every single thing that goes on with the patient to make sure that there's standard care and also that if there's any side effects, we make sure that we monitor that and we're able to stop the medication. Of course, the contribution to science and the future for patients will potentially benefit our families in the future or even people that we do not know, but it's very important to participate and contribute for science. And yeah, those are probably some of the main pros.

Some of the cons, there's always unknown risk or potential side effects that are also part of any drug or drug development, so there will potentially or could be unexpected side effects that can occur. So, this is also for patients or people that are interested that we are very aware that this could be a thing, and we, of course, are monitoring very closely to prevent any severe type of event. There's uncertainty. Sometimes patients come with a certain expectation of outcomes. And, of course, there's no guarantee that the treatment will be effective. So, that's another thing, that it's important to moderate some of the expectations that patients have for clinical trials. And one of the big ones is also the time commitment. Patients and the participants in studies need to understand that they might need to be taking some hours off from work or from their daily life or to attend some of the visits or requirements that the trial does require. So, at least some time commitment here that is very crucial. But at the same time, being part of clinical trials and then leading one of these, it's certainly one of the main things that needs to be very well explained to the patient. So, they do need to have some flexibility there. And yeah, I think those are the key ones, I think.

PREETI SUBRAMANIAN: Thank you so much. I think that's really valuable. And as you said, entering into it with an informed decision on, you know, setting the expectations on the outcomes, that's really important since there is no guarantee of the outcome of participating in the trial. So, Dr. Amador and Maria, thank you both for all the information you shared with us today. Dr. Amador and Maria, before we close, I'd love to hear any final thoughts for our audience about clinical trials for macular degeneration treatment. So, we can start with Maria.

MARIA CARLSON: Yes, as Dr. Amador had said earlier, we really truly appreciate the participation of our patients in clinical trials. I really encourage you to seek information, to think it through, speak with your health care providers, and speak with your family. It's a very big commitment, and hopefully you will have all the resources that you need for these important decisions. Dr. Amador?

MANUEL AMADOR: Thank you, Maria. And I want to add to you and echo your idea. It's absolutely true. Education about this topic matters a ton. One of the most important steps for advancing treatment for macular degeneration or any type of condition is to help people understand how clinical trials work. So, the work and this conversation that we have today is very, very relevant. When patients or families know what to expect, they will feel more comfortable about participating, and that can make all the difference. It's not just about funding the treatment, it's also about building the trust and ensuring the access and empowering the people to take part in shaping the future of eye care or any other care for any other disease.

PREETI SUBRAMANIAN: Great, thank you so much for joining us today. And to our audience, thank you for joining us today. Our next Macular Chat will be on Wednesday, May 28, on the topic of Caring for Your Mental Health. And this concludes today's Macular Chat.

Useful Resources and Key Terms

To access the resources below, please contact BrightFocus Foundation: (800) 437-2423 or visit us at www.BrightFocus.org. Available resources include—

- Macular Chats Archive
- Research funded by Macular Degeneration Research
- Macular Degeneration Overview
- Treatments for Macular Degeneration
- Macular Degeneration Resources
- Expert Advice for Macular Degeneration
- Clinical Trials: Your Questions Answered

Helpful low vision tools or resources mentioned during the Chat include—

- ClinicalTrials.gov
- Genentech-ClinicalTrials.com
- Genentech trial information support contact information: global-roche-genentech-trials@gene.com, 8886626728
- Genentech Advancing Inclusive Research® Site Alliance
- OpRegen®, treatment for dry AMD
- GAlette, a Phase 2a clinical trial sponsored by Genentech