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EDITED TRANSCRIPT

CCXI.OQ - ChemoCentryx Inc and Vifor Fresenius Medical Care Renal Pharma Corporate Update Call to Discuss Results from Topline Data from the ACCOLADE Clinical Study

EVENT DATE/TIME: DECEMBER 21, 2020 / 9:30PM GMT

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CORPORATE PARTICIPANTS

Thomas J. Schall *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

CONFERENCE CALL PARTICIPANTS

Anupam Rama *JPMorgan Chase & Co, Research Division - VP and Analyst*

Edward Andrew Tenthoff *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

Edward Patrick White *H.C. Wainwright & Co, LLC, Research Division - MD of Equity Research & Senior Healthcare Analyst*

Joseph Patrick Schwartz *SVB Leerink LLC, Research Division - MD of Rare Diseases & Senior Research Analyst*

Michelle Lim Gilson *Canaccord Genuity Corp., Research Division - Analyst*

Steven James Seedhouse *Raymond James & Associates, Inc., Research Division - Research Analyst*

Yanan Zhu *Wells Fargo Securities, LLC, Research Division - Associate Analyst*

Lee Roth

PRESENTATION

Operator

Good afternoon and welcome to the ChemoCentryx ACCOLADE Phase II trial top line data conference call. (Operator Instructions) As a reminder, this conference call will be recorded.

I would now like to turn the call over to Lee Roth of Burns McClellan. Mr. Roth, please go ahead.

Lee Roth

Thank you, Sarah. Good afternoon, and once again, welcome to the ChemoCentryx's ACCOLADE trial top line data conference call. Earlier this afternoon, the company issued a press release providing an overview of the top line data. This release, along with a slide deck that you will find helpful as you listen to the call is available on the Investor Relations section of the company's website at chemocentryx.com.

Joining me today on the call is Dr. Thomas Schall, President and Chief Executive Officer of ChemoCentryx; and Susan Kanaya, Executive Vice President, Chief Financial and Administrative Officer of ChemoCentryx. Dr. Schall will provide an overview of the top line results from the avacopan ACCOLADE trial before opening the call to your questions.

During today's call, we will be making certain forward-looking statements, which those of you following the slides can see if you look at Slide 2. These forward-looking statements are based on current information, assumptions and expectations that are subject to change and involve a number of risks and uncertainties that may cause actual results to differ materially from those contained in such forward-looking statements. These risks are described in the company's filings made with the Securities and Exchange Commission, including our annual report on Form 10-K filed on March 10, 2020. You are cautioned not to place undue reliance on these forward-looking statements and ChemoCentryx disclaims any obligation to update such statements.

In addition, this call contains time-sensitive information accurate only as of the date of the live broadcast, December 21, 2020. ChemoCentryx undertakes no obligation to revise or otherwise update any forward-looking statements to reflect events or circumstances after the date of this live conference call.

With that said, it's now my pleasure to turn the call over to Dr. Thomas Schall. Tom?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Thank you, Lee, and thank you to everyone joining us today. On this call, I will share an overview of aggregate top line data from what we, at ChemoCentryx, believe to be the largest blinded, placebo-controlled clinical trial in the ultra-rare disease of C3 glomerulopathy or C3G, at least the largest performed to date. The ACCOLADE trial demonstrated the capability of avacopan, our orally administered small molecule, highly selective inhibitor of the complement C5a receptor in this disease of C3G, a devastating disorder for which there are no approved therapies today.

I will present today data that shows that renal function in C3G improves with avacopan therapy and findings that echo the marked renal improvements that we saw before with avacopan in ANCA-associated vasculitis. The data-rich overview today will include results relating to the primary endpoint, which we selected approximately 5 years ago, a point I will come back to as well as data on several key and all prespecified secondary endpoints.

Slide 3 in the deck that has been distributed, and is on the link, summarizes the 6-month data, which signposts our directions forward. Although avacopan achieved the 35% average advantageous difference versus placebo in the biopsy-based C3 histologic index of disease activity, as we'll discuss in a few minutes, patient-to-patient variability, as can happen in a trial in ultra-rare diseases, where the n or patient sample number is necessarily constrained, was too great for statistical significance, but I'll present a few more details on this point in a moment.

But in the central and some would say crucial measure of renal improvement, avacopan did achieve statistical significance relative to placebo in estimated glomerular filtration rate, or eGFR, a prespecified endpoint. This is a notable finding in the view of many. And although avacopan achieved a similar outcome in benefiting kidney function in ANCA-associated vasculitis patients, such an increase has not, to our knowledge, been previously observed in a controlled blinded C3G trial.

There were also favorable results for avacopan in 3 other secondary endpoints as well: reduction in proteinuria, at times significant, a reduction in urinary MCP1, and an improvement in the important C3 histology index of disease chronicity. Avacopan was shown to be safe and well-tolerated during the course of the C3G study, and we plan to present the data to the Food and Drug Administration and to explore the use of avacopan in C3G based on the data from the ACCOLADE trial.

Now our journey to this point in the understanding of C3G has been necessarily long and arduous and painstaking. So I'm going to share the background that led us to what I believe today is the promising outlook. As shown on Slide 4, C3G is potentially a life-threatening affliction characterized by uncontrolled activation of the complement system. When one examines kidney biopsies under the microscope, they can see active inflammation from the deposition of complement products, including C5 and C5a in and around the glomeruli, the kidney's filtration units. Over periods of time, one also observes a progression of fibrosis or scarring in and around the kidney.

So -- excuse me for a moment. Roughly half the patients with C3G experience ultimately, as the progression of these changes occur in the kidney, the horrors of kidney failure, leading either to dialysis, kidney transplant, which all too often fails by succumbing to the same underlying C3G or even worse. There is no cure, and there is no FDA-approved therapy. This is a disease that can strike the young, adding a sad economic burden to the frequent tragic clinical consequences. We saw a potential role for avacopan to fill a therapeutic niche in C3G, given its mechanism of action by selectively targeting the C5a receptor and so blocking the production of the inflammatory neutrophils that can cause kidney and glomerular damage.

Previous clinical studies in C3G have been generally small, typically open label and typically measuring biomarkers with just a handful of patients. And this is no wonder, given the extreme scarcity of patients in this quite rare disease. It is extremely difficult to determine the number of C3G patients in the U.S. But prevalence is low, estimated at perhaps 1,000 to 3,800 patients per year or so and with the newly diagnosed population estimated at, say, a few hundreds per year.

I will note that both the FDA and the European Medicines Agency, EMA, have granted us, unsurprisingly, orphan drug designation for avacopan in C3G.

Our approach in the ACCOLADE trial was somewhat different than other trials that have gone before or even other trials extant now. We attempted to be as thorough and methodical as possible. In a disease where each patient enrolled as a trial milestone, we were determined to both attempt

to enrich the number of screening subjects that qualified for randomization and attempt to prespecify clinical endpoints that could render a Phase II clinical trial even to be potentially registrational, given the ultra-rare nature of this disorder.

Slide 5 shows the original and still core design of the Phase II randomized, double-blind, placebo-controlled multicenter ACCOLADE trial, which we're aiming for patients with high levels of circulating C5b-9 complexes in their blood. These individuals were selected because C5b-9, or circulating MAC complex, is an easily read and reliable marker of complement activation down the C5 pathway, including ultimately C5a generation.

And the thought of -- at the time was that if people had genuine active C3G in their kidney later to be proven by biopsy if they weren't already diagnosed by biopsy with C3G, then this soluble MAC complex would be an excellent marker and an enricher of the patient population. They would then qualify these individuals for the trial if they were ultimately proven by biopsy to have active inflammatory C3G. That biopsy also established a baseline against which the primary endpoint that we selected at the time, an improvement in the C3 histologic index of disease activity could be assessed by means of another biopsy at week 26.

Again, I'll remind you that we started these efforts over 5 years ago. And at that time, the level of knowledge in this disease made screening by use of the high levels of the C5b-9 complex in the blood, again easily and reliably measured, very sensible and also the use of this new and unvalidated and, frankly, still unvalidated biopsy-based C3G histology index for disease activity, the logical choice for primary endpoint.

Accordingly, we set up a study to randomize patients either to avacopan given by mouth 30 mg twice daily versus placebo. I will note that all of these subjects have protocolized standard concomitant background medications, which are generally well balanced between these groups. After 26 weeks, all patients were then to receive avacopan for a further 26 weeks, after which all the patients will also be followed for 8 weeks without study drug.

We added after the inception of this protocol design with some new science and debate among the key opinion leaders in the C3G community, a second stratum in the trial, shown in Slide 6. Essentially, what we were doing there is adding people with a separate independent group, again with its own control to -- with not high levels of C5b-9, generally lower or normal levels. And that was based on the argument that active C3G might not be exhibited with circulating levels of C5b-9, that the action was really in the kidney. So we added that second stratum in order to get a comprehensive view with one well-controlled trial, and our stats plan contemplated both the primary analysis of the original high C5b-9 stratum as well as the inclusion of the lower stratum as well in a combined analysis.

Interestingly, our trial design alone has already caught us something very valuable about the C3G disease world. As you can see at the bottom of Slide 6, the higher C5b-9 stratum, originally considered to be the primary patient population, in fact, is validated. They tend to convert at biopsy, and I'll remind you, we take the biopsy last in the screening process. They tend to convert at very high levels of rate at biopsy as being bona fide C3G patients whereas the low C5b-9 patients, while not unknown in having biopsy-proven C3G, converted a much lower rate. Interestingly, to presage, some results to come, however. Once we know they have C3G, it doesn't seem to matter for clinical outcome whether they have high or low levels of circulating MAC complex.

So what we decided, once we fully enrolled the original stratum, stratum 1, and noticed the rates of conversion in the low or normal C5b-9 stratum, stratum 2, we realized it would take us many, many more months or even years to enroll stratum 2 to its originally and -- contemplated number. And therefore, we knew this is simply not feasible. So today, we present the data we have from both strata, as I'll outline in the next few slides, and I'm presenting the 26-week primary endpoint data time point.

On Slide 7, I show you the baseline characteristics of stratum 1, the original primary patient population for the primary endpoint. What I don't show is the fact that the average age of the study is about 30 years, which is about what we predicted. You can see from this slide that most people have C3 glomerulopathy versus dense deposit disease or DDD. Also, we were a little surprised at the duration of disease, about 4 years since the time of initial diagnosis. And this is a somewhat more chronic disease population than we have predicted that may have had some effect on some of our readings, by the way.

Finally, it is notable that the avacopan group in this primary population has a somewhat worse kidney profile at baseline. In fact, some would say significantly worse kidney disease at baseline, as exemplified by lower levels of GFR on average, higher levels of proteinuria, higher levels of urinary MCP1 at baseline.

So while I'll show you the data from the primary endpoint as originally envisioned from this primary population, much of the data today will combine all the patients we have, which is shown on Slide 8. And as you can see, the combined strata means that about 75% of the folks that we will analyze are in the high C5b-9 stratum, as you can see and the other characteristics conform generally to the other characteristics that I've just described.

Let's go to Slide 9 and talk about endpoints. At the time we set up this trial, as I mentioned, this was, and still, is an ultra-rare disease -- as I said, an ultra-rare disease, where very little controlled clinical research has been done. We decided, as I said, on a primary endpoint based on biopsy, and that is the C3 histology index of disease activity. This is a different way of measuring disease than the C3 index of chronicity, and I'm going to talk about the chronicity score in a second. But the primary endpoint was disease activity, that's a score ranging from 0 to 21, looking at mostly inflammatory components in and around the glomerulus.

The secondary endpoints were defined as renal function as assessed by change from baseline in estimated glomerular filtration rate, change from baseline in the -- essentially the proteinuria index, change from baseline in urinary MCP1, which is a marker of kidney inflammation that's well characterized and a change from baseline in, again, the biopsy-based C3 histology index of disease chronicity. Now chronicity measures not so much the active acute inflammation in and around the glomerulus, but the progression of indices of fibrosis, scoring 0 to 10 on that scale.

So let's go to Slide 10 and look at the original primary endpoint determination. Your eyes tell you the story. The original primary population, the high C5b-9 group is on the right -- the combined C5b-9 strata high and normal are on the right and the original high C5b-9 stratum, 75% of the population, is on the left. As I said, your eye tells you the story. The primary endpoint measured by biopsy after 26 weeks, on average, separates well with avacopan in an advantageous way. The score tends to worsen on placebo. It tends to stay stable or even decrease, that's an improvement with avacopan. In fact, we had modeled a delta for avacopan of 35 points over placebo in terms of average percent improvement from baseline in this C3 histologic activity score. We actually achieved that. But you can see here the patient variability was too high for statistical significance.

So let's have a comment or 2 here about this primary endpoint. Five years or so after we chose this as our primary, we have some more science around what's going on in the field as well as what's going on with avacopan. And with the benefit of hindsight, I hate to call it 2020 hindsight, we now know that 2 of our secondary endpoints would have been better candidates for the primary than this C3 histologic activity score.

So in Slide 11, let's just consider some of the aspects before I go on to the other data and the secondary endpoint. First, I'll remind us all that there's simply no accepted path for registration endpoints in C3 glomerulopathy. Most sponsors are trying to employ essentially our best-educated guesses. Biomarkers traditionally take too long or too much and to really show separation over the time of a trial that most of us want to take on, 6 months or a year of continuous dosing.

Biopsy-based endpoints presented the possibility, and still do, of real advances, but they have to stick disadvantages as well. For example, we're only sampling a tiny fraction of the glomeruli in a given kidney, maybe a dozen or 20 out of 1 million or so. So nevertheless, we think that this is an interesting and important contribution in the field. We know that during the trial conduct, sometime in 2018, a key paper by Kidney -- in Kidney International by Andy Bomback, Leal Herlitz and colleagues who advised us on the trial, concluded that, in fact, when they looked at the C3 histology index in a natural history fashion, and they separated out the activity score versus the chronicity score, they found that a 1 unit increase in the total chronicity score, a defined secondary endpoint in our study, measured, which measures again the rate of progression of fibrosis, had a 3x greater effect on long-term outcome than a 1 unit increase in the total activity score at baseline.

So before I give you that data from our chronicity endpoint, let me also just mention that the other secondary endpoint that, in retrospect, would have made perfect sense for a primary was eGFR, which measures the renal function of all the glomeruli. But before the avacopan ADVOCATE data, few, if any, experts would have advised that because few, if any, agents have shown the ability to improve eGFR, instead progress with a new experimental agent was generally measured in terms of the ability to slow the rate of eGFR decline. And in fact, that is still a registration standard in some chronic kidney diseases. And given the small number of patients involved in the C3G trial and the relatively short duration of 6 months or even a year, setting eGFR as a primary endpoint seemed at that time a futile endeavor.

Now we know better or as I'll show you in a few moments with results from our secondary endpoint, let's go to Slide 12. Let's stay with histology for a moment. We are still with the C3 index of severity, but now it is the score for chronicity. This is an accurate predictor, most believe, of C3G progression according to the paper I just referenced. This chronicity score tends only to advance, by the way. It is measuring after all histologic evidence of the progression of the scarring process.

The goal overall would be to slow this down and achieve a lower score over a period of time. And avacopan does that in the 6 months that we have measured to date, as you can see on Slide 12, both in terms of percent change from baseline and importantly in a statistically significant sense, the actual unit change from baseline. You can see that we have a much slower significant progression of the -- by chronicity score.

And in fact, on the far right, you can see that we have kept more people either stable. And in fact, a few have reads that are even better than baseline, which is quite interesting. But far fewer are progressing or worsening on the chronicity score. And again, I've said this reference by the paper, a 1 point increase in chronicity over a 1-year time is associated with a 59% increase risk of end-stage renal disease, death or need for transplant. So this is actually a very compelling finding.

An even more impressive outcome was observed in patients on the eGFR scale. So we will turn to Slide 13, where, again, I think your eye begins to tell you the story. The chart on the left side shows the change from baseline in eGFR over the 26 weeks with the combined stratum, again, of all patients that come into the study, irrespective of their eGFR at baseline. As you can see, the condition of the patients on the placebo group, the blue line, tends generally to deteriorate. Conversely, the avacopan group heads in the other direction, improving eGFR with an early separation of the curves, and ultimately, at week 26 with a statistically significant separation, as you can see.

An even more impressive outcome was observed in patients with eGFR levels below 60 ml per min, this is a prespecified endpoint, those with stage 3 or worse chronic kidney disease. And as you can see here, the avacopan group separates out by almost 20% improvement over the course of 6 months. This is about a 5 ml per min increase from baseline in these patients versus about 1.5 ml per min decrease in the placebo group.

I think many observers would consider these eGFR data remarkable. And they are also reminiscent of the effects of avacopan achieved in improving kidney function in the ADVOCATE pivotal trial of ANCA-associated vasculitis, as most of you know. Thus reinforcing, I believe, the important role that avacopan can play in a variety of kidney disorders. So I believe, fundamentally, the avacopan-induced renal function improvements seen here in C3G also will be central to our discussion with regulatory agencies.

Moving now to other measures of renal function. Slide 13 helps us understand -- I'm sorry, the next slide helps us understand significant reductions in other markers, including proteinuria, as you can see, an urinary MCP1, which is on the right-hand side of this chart. Proteinuria is a key marker of kidney disease, as you know, and the rapid reduction of proteinuria is a key predictor of longer-term kidney benefit and improved clinical outcomes. You can see here, just again, like what we saw, at least in a qualitative level in the ADVOCATE trial of ANCA vasculitis, a rapid and pronounced reduction in proteinuria on avacopan. Eventually, at week 16, we have a 35% reduction relative to placebo that's statistically significant. But again, I think you can see that we have a consistent reduction over the placebo group during this randomized-blinded phase. And the same is true for urinary MCP1, a well-characterized marker of renal inflammation.

Finally, as summarized on the next slide, Slide 15, the safety profile of avacopan seems quite good in this disease. It's unremarkable. There's really no imbalance between the 2 groups, very little to report on so far in the study. It seems safe and well-tolerated in C3G.

I would suggest that all these data validate our hypothesis that blocking the C5a receptor and thereby stifling C5a receptor neutrophil-mediated activation is the key to mastering this previously intractable and quite debilitating disease of C3G and probably starts to reflect more broadly, maybe much more broadly on any kidney-related disorder where complement has been implicated in the pathology.

So to conclude, I'll summarize with Slide 15 on our directions. Again, given the fact that we are blazing the trail, I think, in a new territory, where there is no regulatory pathway, no precedent, no approved therapy and yet a clear and unmet need, we will share these results as well as individual case reports with the Food and Drug Administration. The patient population here may be quite small, but their needs are very great. So we plan to explore with the FDA how we might find the use for avacopan in C3G based on the ACCOLADE data. Many of you will know that there is precedents

for granting approval in chronic kidney diseases, including rare ones based on the proven ability to change the estimated glomerular filtration rate. And again, typically, those have been based on merely slowing the rate of decline.

I will state quite clearly, too, that at this moment, we simply did not contemplate additional clinical development in this disorder. This has already been a journey of a half decade or more across the landscape where patients are quite few and far between, although quite ill. So there would be a significant cost given our plans for clinical development in other areas and embarking on further clinical trials in C3G, without some idea about how to use avacopan based on the ACCOLADE data in this disorder.

But more important, the patient need is now. The kidney function regresses in these individuals on a daily basis. So evidence from this trial of ACCOLADE suggests that we cannot just stop that kidney decline, but potentially actually improve it with avacopan in C3G. This could mean a lot for patients and not just maybe delaying the time to potential dialysis or need for transplant, but maybe staving it off indefinitely.

So I'll close today again by summarizing more broadly in brief the next steps for avacopan, which we believe, again, is a unique mechanism of action with diverse applicability and the potential to become a pipeline and a drug on its own. The FDA has accepted for review our regulatory submission in ANCA-associated vasculitis, and I'll remind you that we have a PDUFA target date of July 7. And the EMA in Europe has validated the MAA application as well. We are planning a pivotal Phase III clinical trial of avacopan in patients outside the kidney space in those patients with severe hidradenitis suppurativa, diagnosed with early stage III disease, the most severe disease, and that's based on what we consider to be very strong findings from the Phase II study, AURORA, in hidradenitis suppurativa. And we plan to start a clinical trial of avacopan in lupus nephritis in the first half of this year and other kidney indications are likely to follow as well.

So with that, I'll turn the call back over to the operator for your questions. Operator?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Ed White with H.C. Wainwright.

Edward Patrick White - *H.C. Wainwright & Co, LLC, Research Division - MD of Equity Research & Senior Healthcare Analyst*

So just 2 of them here. I know we're in a holiday week here. I'm just wondering if you have any indication from the FDA when you think you can speak to them about the path forward. And then since there's no -- you don't contemplate any further clinical development, are there any patient advocate groups or KOLs that might advocate use in C3G without approval? And then so perhaps there could be an opportunity for off-label use down the road after it's approved in AAV?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Thank you, Ed. The data are literally brand-new. So we have not had a chance yet to try to schedule that meeting with the FDA. As is our custom at ChemoCentryx, I'd like to say that clinical trial data is a bit like the birth of a child. You can kind of decide when the month is more or less. But when it comes, it comes, and you just have to attend to the delivery. So we have just -- once we knew what the top line data was going to say, we wanted to make sure we got it to the investor community as quickly as possible as well as to others.

So the other questions, I think I'll have to defer until we start to consult with more of those experts. Naturally, 1 or 2 people who have seen in the nephrology world and our expert nephrologists have found this data to be extremely compelling. As I said, they've used the word, in C3G anyway, unprecedented, at least from a blinded controlled study. And most experts when we started just thought we didn't have enough time and not enough patients to see C3G shifting in a significant way. But again, that was based on the old idea that we only hope to get a delay in decline. And

so avacopan once again shows us improvement, and steady improvement over time. So I think there is enthusiasm in that community. If a very comprehensive report could be published, I think it will create some interesting discussion there.

But our first and foremost discussion will not just be with experts, but obviously with regulators so that they know where we are on this, since this is, again, such a high need area for patients. And we'll let the community know when we have anything material in and around those discussions with the FDA.

Operator

Our next question comes from the line of Steve Seedhouse with Raymond James.

Steven James Seedhouse - *Raymond James & Associates, Inc., Research Division - Research Analyst*

A point of clarification, just to start, I want to make sure the potential contributors to variability here were understood. So of, I think, 52 total patients in the whole cohort, 26 per arm, I just wanted to clarify how many or did all of them have biopsies as well as eGFR measurements at week 26, that would be helpful. And then also, maybe just asking that a different way, was your statistics here impacted by dropouts or under-enrollment versus what was originally intended?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. Both really good questions, Steven. Thank you for reminding me. So essentially, we designed the trial originally just around the 44-patient cohort from the original stratum 1 high C5b-9. And again, there, we modeled the 30% delta based on 1 paper at that time with the first iteration of the C3 histological index, and I think there were probably about a dozen people and their sections involved from a study that Andy Bomback and Leal Herlitz did with Gerry Appel and colleagues. Again, that goes back many years. So the variation in their calculations then we took into consideration, and we thought with 44 people even that we could control that variability nicely and see a 30% difference between the 2 groups on average. So again, we hit our average target. We just had a lot more variability. So it wasn't dropouts per se that affected any of the stats. That's for sure.

The 52 that I'm showing you today, again, trying to sort of streamline and for purposes of clarity, they do represent the population at baseline biopsies as well as week-26 determinations. Most, I think we only lost 10% to no -- having no biopsy at week 26. So in both cases, we have at least eGFR determinations, and usually eGFR and biopsy determinations. So again, I don't think we're impacted by attrition there. So the 52 is the base ITT number for efficacy. And that represents, again, they had to have biopsy at baseline in week 26.

If they did not have a biopsy at week 26, their last observation was carried forward and essentially, that would be no improvement. So it's kind of neutral on the stats. So -- and those were a minority of people. So dropouts, it was an interesting trial for the amount of participation and intervention required of the patient, but I don't think we lost much into the stats owing to dropouts or the investment into 2 biopsies.

Steven James Seedhouse - *Raymond James & Associates, Inc., Research Division - Research Analyst*

Got it. So really just higher-than-anticipated variance here, I mean you hit your effect size, intended effect size as well. So maybe the follow-up would be, you mentioned this was selected 5 years ago. What has happened in the field with respect to biopsy and its use in the real-world in clinical development, has it become more prevalent, more important? Or has it sort of faded into the background? In other words, I know that you hit eGFR. And so in retrospect, you hit maybe the higher threshold. But has the field moved on from biopsy? Or is that still important to the KOLs as it was 5 years ago?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. It's -- so I can answer that, I guess, in 2 ways. Make no mistake, with C3G, there's going to be biopsies. There's certainly going to be biopsy at time of diagnosis. It really is a biopsy-intensive disease in terms of confirmation of what the disease actually is. There's also a lot of biopsy. The question is, when we try to think about progression, the question is how often? Because biopsy is obviously invasive. It has some risk. It's not a vast amount of risk, but it's a non-0 risk, obviously. And so people don't want to do it as a matter of a form every few months, typically.

So -- but biopsy is a part of the tracking of this disease. And then, of course, you have the interesting special feature of transplant. A lot of folks do have transplant. Only a few in our study as it turns out. But the way that people try to assess whether that transplant is beginning to succumb when they see renal function declining is obviously looking at biopsies in the transplant, so they can become more frequent as people try to make decisions about how to manage that subject with the transplant that seems to be succumbing.

So there is a lot of biopsy now. Is it more favored, less favored, about the same as 5 years ago? So little progress in this field. I just think that people consider it again to be a valuable tool. Is it a valuable tool for clinical response? This will be the first study that addresses any of that. And I do believe -- fundamentally, I do believe that the chronicity index, which does move in the right direction in terms of thinking about what a therapeutic might do, is going to inform a lot of discussion around that and also how to decrease the variability around the activity index. So I think that the study is going to add a lot of knowledge to that field.

But I have to tell you that you talk to nephrologists in this disorder or any other disorder and what is -- this is a kidney dysfunction. Kidney function is declining. Renal functions going down, almost every measurement in the clinic. And so if you had a way of saying I'm having an effect on renal function, most people would say that's the gold standard, as it is in other chronic kidney diseases. The issue is no and not just ever been able to move eGFR in this disorder, at least across the population. And I think that's why we didn't choose that ourselves 5 years ago as a primary endpoint. So I fundamentally believe it's the GFR thing that will catch a lot of attention. And I do think that the histology stuff is interesting, and will definitely enrich the data set, no question, and also inform the discussion.

Steven James Seedhouse - *Raymond James & Associates, Inc., Research Division - Research Analyst*

Okay. Last question. I appreciate that you don't yet know what FDA feedback will be to this data now that it's in hand. But I think people would be curious if you could characterize what was the level of feedback from the FDA or other regulators that you used in the trial design initially, either directly or indirectly just with -- through guidance or through investigators that work with other sponsors, just how married was FDA upfront to this trial design and this particular endpoint versus looking at some of the secondaries?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. I think other sponsors would tell you this as well. I think you get a consistent result. The FDA has -- with this particular disorder and other quite rare disorders, the kidney, I think they admit that the ideas that we all held dear so many years ago about, well, let's do outcome-based studies. When you have a rare population, you just can't get enough individuals to make those outcome-based studies work numerically. You can't get enough outcome-based and to get separations in any reasonable course of time, even if that reasonable course was used to be considered 2 or 3 years, it's just not going to happen in this kind of disease and certainly in C3G.

So FDA at that time, I think, was very open. I think they've been telling sponsors even to this day, bring us all the data, bring us the latest that you know, let's see what's happening even with markers. That's why so many other sponsors are just solely looking at proteinuria reduction, by the way, solely trying to see how they can try to look at eGFR changes in relatively small patient numbers and again, typically in open-label studies, which is really interesting to me. But that's because FDA has encouraged us all to sort of maybe pool the general knowledge around this disease and see if we can get somewhere, but bring all of the data.

I can tell you they were really interested in the renal histology index, as we called it at the time. They had consultations with the developers of the index, both outside of our context, but even within our context, and I think they welcomed it as another tool into the -- in the armamentarium of

how we might evaluate the disease and not just as progression but therapeutic effects. So they were highly engaged. That was again some years ago. We'll have to see where they are now.

But I'm not hearing anything from other sponsors or experts that says that anything but the FDA is really quite interested in how we might think about therapeutic effect in reasonably sized trials of reasonable duration. So again, I think overall, based on my FDA discussions as well as what I've heard from others, when we nailed the eGFR endpoint, I thought this is going to be a really interesting discussion. And that's where I think we're going to go. It will be the central point of our discussion with the agency.

Operator

Our next question comes from the line of Michelle Gilson with Canaccord Genuity.

Michelle Lim Gilson - *Canaccord Genuity Corp., Research Division - Analyst*

I guess to start off, are you planning to apply for breakthrough designation with these data?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Michelle, we're kind of -- we're leaving our options open at this point. So with -- not to try to sidestep the question, I'm going to, with your permission, defer it until we have a little bit more ability to think carefully about next steps and where that might take us. But that would certainly be 1 option on the table.

Michelle Lim Gilson - *Canaccord Genuity Corp., Research Division - Analyst*

Okay. And then you presented here week-24 data. And it's -- the trial's open label as patients cross over to month 12. I'm just wondering if you're seeing, I guess, in those data preliminarily, any continued eGFR benefit for patients that have gone beyond 6 months? And then just kind of related to that question, how long would you expect patients to stay on therapy if they are benefiting? And how would it -- how do you think that nephrologists from your early feedback would anticipate avacopan would be used, especially in those patients that are benefiting, which, I guess, it looks like about half of the patients stabilized or improved?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. I think that, in fact, it's maybe a little bit more, but we're trying to get to the numbers a little bit more carefully, and we'll put that out as I know. But let's go back to the -- I don't have any data beyond week 26. So I can't really comment on that. Obviously, as we get those data, we will report them. But yes, it would be very desired to see these effects continuing and certainly at least reaching stabilization.

I'll give you the kind of same answer as I give when people ask me about ANCA vasculitis, how long would a person take this as long as it has a positive effect is my opinion, if I'm answering from a patient's perspective, and I think that in C3G, it's even more germane to the point. I mean these people are young. They're in their 20s and 30 and they've got a lifetime of decline ahead of them otherwise in terms of renal function. If I could take something that reverses or stabilizes that renal function and can do it without effect, I will as a patient want to stay on that.

So again, it's really early. These data are brand-new. As I said, we make sure that as soon as we think we understand materially what the top line result will tell us in any trial, we bring it to the community immediately. So we'll see what the experts say. Already, they're saying this is really interesting. And isn't it interesting that it looks a lot like what we saw in ANCA vasculitis? So I think that helps inform us, at least at these very early steps how people might think about its utility in this disorder.

Michelle Lim Gilson - *Canaccord Genuity Corp., Research Division - Analyst*

And then if I can do one more. Other than elevated C5b-9 and low eGFR, were there any other, I guess, patient groups that did, what, particularly well on avacopan? And then do you have an estimate on the proportion of the C3G population that are -- that have elevated C5b-9? I guess is there a clinical trial experience informed on anything?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. So let me ask that last one first. I mean, again, some of the early experts that don't bother with anyone under this level of C5b-9 because generally, they don't have C3G. And yet that was based on impression, I think, more than actual data. I think the trial itself now actually gives us some evidence that, yes, most people with C3G probably have some evidence of elevated C5b-9. I've put up many caveats there. But at the -- just the broadest brush stroke is to suggest that that's the picture.

And so how would that translate? Again, probably fewer than 1 in 5 in our study who came in with symptomological or presumptive C3G with normal levels of C5b-9, fewer than 1 in 5 actually biopsy confirmed. So it's not like those folks cannot or will not have C3G, they're just going to be fewer. So I guess if I had to guess at this moment, I would say 80% to 90% of C3G will manifest high C5b-9, something on that order.

And we haven't yet looked nor did we necessarily protocolize and, therefore, stratify any other markers. We do know again that proteinuria, high levels of urinary MCP1 were in evidence across the board, in fact higher in the primary population in the avacopan group. So it might speak again to the strength of the effect, frankly, and eGFR. Other than that, no, we didn't really look specifically at other stuff in a prespecified way, although there may be a number of exploratory things that I simply don't have knowledge about yet.

Michelle Lim Gilson - *Canaccord Genuity Corp., Research Division - Analyst*

Congratulations on the data.

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Thank you, Michelle.

Operator

Our next question comes from the line of Joseph Schwartz with SVB Leerink.

Joseph Patrick Schwartz - *SVB Leerink LLC, Research Division - MD of Rare Diseases & Senior Research Analyst*

I was wondering if you could give us the baseline measures on average for the C3 histologic index of disease activity or chronicity and then -- just so we have some perspective on the magnitude of the benefits that you reported. And then are there any patterns to note with this index data that provide any insight into the activity of avacopan in the kidney and maybe some readthrough to other glomerular diseases?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. That's a very thoughtful question, and I meant to cover it in some way in my remarks. So I kind of glossed over it. The C3 index -- histology index of disease activity, which was the first score that we talked about, the primary score, can range from 0 to 21. And again, it's mostly based on things like mesangial expansion, leukocyte infiltration in and around the glomerulus, endocapillary proliferation, crescentic formation, et cetera. And you just tick up the degree of each of these features from 0 to 3, typically, and come up with a score from -- can't be 0 by definition, but up to 21.

We had expected a somewhat higher baseline score to be showing up. So our baseline score, and again, we're validating all these numbers, but I will tell you, it's around 10 or 11. Now that seems pretty reasonable, probably halfway there on that score. But I think we probably would have assumed a somewhat higher number at baseline. And I think what that speaks to, higher, what is that, 12 to 15, 12 to 16, something like that.

And what does that speak to? Again, to me, we were also surprised a little bit by how much chronic disease got enrolled in the trial, 4 years on average. I think we thought we would get more newly diagnosed or much more recent kind of confirmation of disease. So it may well be, and this is somewhat speculative, but some evidence here, it may well be that, that's why the chronicity score was a little bit more informative than the activity score.

And if we had gotten perhaps more newly diagnosed, more active acute people, then we would have seen a statistically greater -- a statistically less variable activity score. Because again, arithmetically, we got the kind of trend that we saw or sought and modeled. It's just that the variability was big.

So in any case, yes, I think it's safe to say our baseline response -- our baseline score was a little bit lower than we thought. We'll get the exact numbers published, I think, fairly soon. And I think that may, may, well, shed light as to why the chronicity index was a little bit more valuable. On chronicity, again, that measures 0 to 10, where you're sort of again tiding up features, 4 or 5 features of scarring in and around the glomerulus. And so you want to delay that progression. And there, we did see a significant change from baseline slowing considerably that progression. So I think that's interesting.

What we have not yet looked at in detail, and I think this was the other part of your question, can we see evidence in the kidney on these biopsies as to what avacopan may or may not be doing? We don't have that analysis yet. We haven't really looked carefully, and we will certainly do so. But again, what we do know, and there's only, again, 10 to 20 glomeruli in these biopsy, fine-needle biopsies, if we'd measured the total output of all million of the glomeruli in these kidneys, we seem to be increasing quite robustly the eGFR.

So how that works remains to be determined, as it does, I think, a little bit in the ADVOCATE ANCA vasculitis study as well. But we do know that the inhibition of short-term inflammation in and around the glomerular capillaries and so on seems to be a big part of it. And we'll have -- but the longer term, is it just healing? Is it the mobilization of precursor cells, et cetera? We will have more to say about that, I think, in the next months.

Operator

Our next question comes from the line of an Yanan Zhu with Wells Fargo Securities.

Yanan Zhu - *Wells Fargo Securities, LLC, Research Division - Associate Analyst*

Congrats on the data. So first question, regarding the activity score, there are different components of the activity score. So I'm wondering, for some of the inflammation-focused components, like leukocyte infiltration or interstitial inflammation, would you derive some information from those scores given that the urinary MCP1 data is -- feels like avacopan is indeed reducing inflammation in the kidney?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Yes. I think almost certainly, we'd expect inflammation being reduced in the kidney. But you're right, with the activity score, we ought to be able to maybe dissect some of that. I will say that the way we did this process to date will explain why I don't have the details, yet. The reading of the activity score, all of the histologic indices, both the activity score, disease activity as well as disease chronicity score was read centrally, 1 blinded reader, that blinded reader entered their data also into a machine algorithm. So there were actually parts that were read by machine like areas and so on that were outlined on these biopsies.

So that person has all the components and the central reader data on master has the components in the score. So we don't yet have those information. And again, my goals today and my duties, I think, to the community was to bring forward the top line results once we knew we had

an answer overall and that were material to the community. So -- but you're absolutely right. The score is based -- or the activity scores based on mesangial hypercellularity, for example; endocapillary proliferation; membranoproliferative morphology; and then things like leukocyte infiltration, which is clearly an inflammatory kind of idea; crescentic formation, which, again, happens as a consequence of inflammatory cell information; and interstitial inflammation.

So we get in to start to dig into some of these components more of the activity score, I do believe we should be able to test the idea that there's an anti-inflammatory component that's leading to some of the phenomenology we see at the level of function, whether it's reduction in proteinuria, reduction in urinary MCP1. And even again, the rapid stabilization in eGFR as it then starts to grow relative to placebo, which starts a pretty steady decline once we start to measure it. So yes, we'll look at those components in more detail. But right now, we only have the overall scores.

Yanan Zhu - *Wells Fargo Securities, LLC, Research Division - Associate Analyst*

Got it. Very helpful. Then would you be able to talk about the plan for the open-label portion, what we might expect data from there? Given that you have seen, you now know the data from the blinded portion with the eGFR data -- positive data readout, would you be inclined to look at the open-label portion for the patients who crossed over from the placebo arm, for example, for the patients you have currently perhaps to observe any trend for eGFR in that subpopulation of patients?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Sure. So again, to speculate, it kind of invites maybe more speculation based on lack of evidence. So I don't have any information right now on the subsequent data. So anything I say will be entirely conjectural. But I will say this in the design, the patients, the sponsor and the practitioner, they're still blinded to what their original treatment was. So again, yes, everyone knows they're getting active avacopan now because they were 6 months into the study or more, but they don't know how they started. So that does allow us to assess certain features, even with the histology. So not everyone -- although they consented originally to a 12-month biopsy, you can imagine that not everyone will go through because that's 3 biopsies in a fairly short order of time. But I think we're going to get a few. I think we're going to get actually an appreciable number of 12-month biopsies. And so that will be interesting because, yes, we might be able to assess different inflections or bends in how people score on the biopsy indices after they crossover to open label.

Now there is some human elements even with a blinded central reader in biopsy. So that could be prejudiced by knowing, a, the initial result; and b, of knowing, of course, that people are on drug now. And so what's nice about the trial design is that biochemical indices can't be biased in that same way.

So I will be quite interested in knowing what happens with things like proteinuria and what happens with eGFR over time. And so yes, that will be, I think, something we'll be looking at. But I don't have any of those data now. And so I won't comment or speculate what will happen. So -- but we'll -- certainly as we look to the future and get those bits of information, they will come again to the community of physicians and the investment community as quickly as we can.

Operator

Our next question comes from the line of Ted Tenthoff with Piper Sandler.

Edward Andrew Tenthoff - *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

Congrats on the data, definitely sort of an exploratory study here. But I think that eGFR really shows that you're on target and just continues to validate avacopan in these kidney disorders. I'm wondering whether or not this is something where you might have post-approval commitments. And again, appreciating that you just have the data, you haven't talked -- spoken to the FDA. But is this something where that would be on the

table where if you were able to get some form of accelerated approval, you would consider doing additional studies while on the market? Or how should we be thinking about that, too?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

I think that's a very fair statement. I think that all options are on the table. We will always do what is the correct thing for the patient, no question. And also balancing what the correct thing is for all of the supporters of this effort. So I think it would be a very fair statement. What I think we and other sponsors would be reluctant to do, and might even be irresponsible in a certain way, again, absent any clear guidance, if you have clear evidence that you can strike to the core of what's going wrong in a rare disease, then I think that it's absolutely the case that you have an obligation to try to bring that to those individuals.

But to the extent -- yes, if it makes sense for the patient, and we have to make commitments post, say, post -- again, it's all hypothetical and all conjectural, but if that were to be the case, sure, we would definitely do the right thing by patients. And -- but we need some clear direction. More to the point, I believe that individuals need to get this therapy for C3G.

Edward Andrew Tenthoff - *Piper Sandler & Co., Research Division - MD & Senior Research Analyst*

Yes. Great. One little quick follow-up and I think someone else may be asked a question along these lines. But just to put it to you again, I know the plans are to start a lupus nephritis study next year and again, we can see continued activity here in the kidney. Is there anything you pick up from this more kidney-focused patient population that can kind of help you craft that trial?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

I do think so. I think what's interesting to me and some others, Ted, lupus nephritis field has been -- they really have been heroic for many, many years now, decades even. And I think they are generally very conservative, though. But may be that there are different camps in lupus. But when you look at the lupus trial, I've noticed they tried to stay away from people with eGFR deficits or fundamentally exclude those. And in fact, when there's an eGFR component to what usually is composite endpoint determination, again, it's -- can we slow the rate of decline? Can we go down to -- instead of minus 3 ml per min, can we slow it to 1 -- minus 1 or minus 1.5 ml per min over a year or whatever?

I just think what our data tells us from ANCA vasculitis now from C3G is why can't we design something into a trial where we actually ask fundamentally, how do we think about eGFR. And in fact, to be absolutely bold as to perhaps be, get nephritis people. But is there something we can build in where we actually ask the question, is there a separation in a positive way that avacopan can generate? So again, for better or worse, we as sponsors always like to answer and ask very big questions. Sometimes we get complicated answers. But to me, we've now got 2 kidney disorders where eGFR declines inexorably, and we've reversed it, we've improved eGFR, why not try that again in other kidney disorders?

Operator

Our last question comes from the line of Anupam Rama with JPMorgan.

Anupam Rama - *JPMorgan Chase & Co, Research Division - VP and Analyst*

Tom, maybe you could talk to us about kind of what gives you confidence in this eGFR benefit that you're seeing here? When I look at the curves, it looks like the real separation here comes after week 20 and you were able to get stat sig there. Maybe you could talk to us about what's a clinically meaningful delta would have the earlier time points been stat sig as well? Because you do see separation. I just don't know if it's significant. You know what I mean?

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Sure. I think I understand the question, but let's just -- let's reiterate. I think when you have a real difference, a real improvement in eGFR, most people think that, that could take a year or more to show up and every other agent that takes that long to see a separation. So for us to show a separation at week 26 and beginning to separate out really distinctly, again by around week 20, I agree with that, I don't think it's unusual at all. And in fact, I find it quite encouraging.

And I would suggest that even with the ANCA vasculitis data, where we see a similar kind of separation, it starts to occur around that time, after week 12 through 16, 20, then you really start seeing separation clearly significant by week 26. So this profile looks very similar.

I mean when you think about, again, how other drugs have gotten approved, I mean let's take -- I don't know, let's take tolvaptan. Tolvaptan, which is now approved for polycystic kidney disease, it was approved based on eGFR, but how? It decreased the rate of decline. It was like minus 2-point-something ml per min over the course of 1 year versus the placebo, which was minus 3.6 ml per min. So it didn't improve anything. It merely decreased the rate of decline. I think if I'm not mistaken, voclosporin, a really nice contribution, which I think should be approved and maybe will be for lupus nephritis. Again, their rate -- they didn't really improve anything in terms of eGFR over the course of their study. They merely reduced the rate of decline.

So what we're seeing here, Anupam, I fundamentally feel is different. I think it's maybe unique. Certainly, it's unprecedented to show in C3G that you get this kind of separation, and that's notable. There are only 1 or 2 other agents that have been shown to increase GFR, and we now know most in the field would accept that those happen through non -- truly nonkidney-related mechanisms, probably through hyperfiltration via interesting knock-on effects on the target. So this is interesting, and it's, I think, really important.

Operator

I'm now showing no further questions. I would like to turn the call back to Thomas Schall for closing remarks.

Thomas J. Schall - *ChemoCentryx, Inc. - Founder, President, CEO & Chairman*

Thank you very much, operator. Again, I so appreciate people being able to get on this call during the holiday season, which I know is very busy for everybody. I appreciate all of the very insightful questions and the great discussion and look forward to sharing more of our progress around this program in C3G and others in the near future. Again, thank you for your time and your attention, and I will sign off and wish you all happy holidays.

Operator

Ladies and gentlemen, this concludes today's conference call. Thank you for your participation. You may now disconnect.
