Novartis AG

Shareholder/Analyst Call - Novartis AG

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Event Participants

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Operator Operator

Good morning and good afternoon, and welcome to the Novartis Renal Portfolio Conference Call and Live Webcast. [Operator Instructions] A recording of the conference call, including the Q&A session, will be available on our website shortly after the call ends. With that, I would like to hand over to Ms. Sloan Simpson, Head of Investor Relations. Please go ahead, madam.

Sloan Simpson Executive

Thank you, Melanie, and welcome, everybody, to our Renal Portfolio call. First, the safe harbor statement. The information presented today contains forward-looking statements that involve known and unknown risks, uncertainties and other factors. These may cause actual results to be materially different from any future results, performance or achievements expressed or implied by such statements. For a description of some of these factors, please refer to the company's Form 20-F and its most recent quarterly results on Form 6-K that respectively were filed with and furnished to the U.S.

Securities and Exchange Commission. And with that, I'd like to hand over to Shreeram to start the presentation.

Shreeram Aradhye Executive

Thank you, Sloan. Good morning, good afternoon everyone, and welcome to our investor call focus on our renal portfolio. With me are Mr. Victor Bulto, our President for the U.S. business; and Dave Soergel heads up development for the cardiorenal and metabolic portfolio.

Next slide. Our agenda today covers -- our agenda today will cover our aspirations for a portfolio in renal diseases. We'll discuss our launch capabilities that we're building and then give you an insight into our advancing renal pipeline. And then have time for a Q&A. We expect to speak for about between 35 to 40 minutes, and we'll leave enough time for

adequate questions.

Next slide. As you know, as we transform Novartis into a pure-play medicines company, the core principle behind it has been that focus allows us to build compounding competencies across all other parts of our organization from research, development through commercial. And we believe that these competencies then allow us to exercise better judgment, make good decisions and have a competitive advantage in being able to advance our portfolio in the disease areas of choice.

Our focus today is on renal disease. On this slide, you see our long journey and legacy in the field of transplantation. I should say that this slide actually looks like my own life cycle at Novartis as a transplant nephrologist myself, I came to Novartis because of its commitment to transplantation. We made transplantation possible with the introduction of Sandimmune, cyclosporin in the 1980s, added Simulect as an induction agent, introduced Myfortic, a formulation of mycophenolic acid, and then brought Certican, everolimus to patients with renal transplantation. And while the focus there was the ability to ensure that transplants avoided acute and chronic reaction, our focus now shifts to how we might work preventing the need for transplantation by targeting glomerular diseases, which carry significant risk of progression to end-stage renal disease.

And to that end, we are deploying iptacopan, our internal complement factor inhibitor as internal innovation, and have acquired external opportunities through the recent acquisition of Chinook, giving us atrasentan and Zigakibart.

Next slide. Bringing all of our competencies, we are now focused on building a comprehensive renal pipeline, as you see on Slide 6, with multiple products being in the pipeline, Fabhalta on the inside, and atrasentan and Zigakibart from Chinook. And then on the right side there, a large number of programs at an earlier stage that you'll hear about from Dave during his presentation as well.

Next slide. The primary reason to focus on glomerular diseases is that we are able to build our long understanding of immune-mediated injury to the kidneys, and then evaluate how we might reduce the risk of progression to kidney failure. The multiple glomerular diseases that you see listed here account for over 2 million patients worldwide. And our focus is now on making sure that we can introduce both targeted and foundational interventions to delay the progression of loss of renal function in these patients and reduce the need for renal replacement therapies like dialysis and transplantation.

Let's start now on the next slide with IgA nephropathy. IgA nephropathy is the most common glomerulonephritis. It is -- the prevalence is as shown to you there. It's a disease that has varying manifestations. Kidney biopsy is the gold standard for diagnosis and nearly 50% of patients with this disease and persistent proteinuria progressed to end-stage renal disease over 10 to 20 years.

I have to say that we are at a very exciting time in the care of this heterogeneous and variable disease, where for the longest time when treatment was simply supportive care, we're now at a phase in clinical practice where multiple agents are becoming available.

And if you look at the next slide, this is now reflected in the fact that treatment guidelines are

evolving with the guidance to ensure that patients are given both drugs that are able to control the source of injury, which is the immuno-inflammation that results in the primary loss of nephrons. And then on the right side, we mentions that ensure that the remnant nephrons and the proteinuria that comes from the glomerular injury and the associated inflammation is controlled with blood pressure control, reducing glomerular hyperfiltration and proteinuria as well as managing other risks.

On the next slide, we are very proud of the fact that given these emerging guidance, we have a broad portfolio that allows us to intervene for patients with IgA nephropathy and different parts on the pathogenesis of their disease, as you will hear about from Dave further. On the right, of course, we have now introduced Fabhalta, which targets complement inhibition and reduces inflammation. We brought iptacopan, which reduces glomerular hyperfiltration and can be a part of foundational therapy and Zigakibart, which is the anti-APRIL antibody that has no opportunity to potentially reduce the very source of the pathogenic abnormal IgA production, which is at the basis which serves as the primary driver of the disease. On the next slide, super proud, we just came -- all of us just came back from the American Society of Nephrology. Fabhalta is now approved as the first-in-class, oral Factor B inhibitor for the treatment of IgA nephropathy on the basis of an accelerated approval and proteinuria reduction.

We presented some great additional data at ASM at the New England General publication. I'm personally very proud of the fact that there are very few teams that actually have 2 New England Journal papers and an editorial at the same time as in the American Society of Nephrology meeting. And we just came back from there, and with all the excitement that I heard, this Fabhalta launch in IgA nephropathy is going to serve, as you'll hear from Victor, as a blueprint for all of our future renal launches. And Dave and I are, of course, super excited about the fact that this gives us the opportunity for gathering insights that fully inform all the plans that we are making in this disease area.

With that, Victor, let me hand it over to you.

Victor Bulto Executive

Excellent. Well, thank you very much, Shreeram, and good morning, good afternoon, everyone. Highlighting what Shreeram mentioned at the beginning we designed our current strategy also commercially to focus on 4 key therapeutic areas. And we wanted to build both depth and breadth in these areas where we believe we could establish a leading position and the renal space is certainly one of them. These allows us to create synergies both on the cost side, but also on the top line and also compound commercial capabilities.

And in renal, we're building this breadth and depth with a multiproduct and multi-indication approach. And today, I wanted to walk you all through our thinking from a commercial standpoint.

So if we move to the next slide, you will see that as the most common glomerular disease, actually, IgA nephropathy is the ideal entry point for our renal portfolio. with an incidence in the U.S. of between 7 to 21 per million. It mostly affects younger adults, which means that they will be mostly covered through the commercial coverage. And up to this 50% of these

patients with persistent proteinuria do progress to kidney failure within 10 to 20 years of diagnosis, which highlights on the 1 hand, the urgency to treat these patients, the unmet need, and the fact that the options that were available up until recently were really not addressing all the drivers of IgA nephropathy and are prime for the entrance of new compounds.

Now when we look at the 2024 draft KDIGO clinical practice guidelines for the management of IgA nephropathy, they actually have added a new preferred threshold for proteinuria of 0.3 grams per day while maintaining the recommended threshold of 0.5 grams per day, again, reinforcing the importance of aggressive managing this disease. Moving to the next slide, I wanted to quantify the opportunity, specifically for the U.S. where we see that we have approximately 185,000 prevalent IgA nephropathy patients, 80,000 of them biopsy confirmed for diagnosis. And when we account for severity of disease progression and eGFR values, we end up with a population of about 45,000 that will be potentially eligible patients to be treated with our medicines.

When we look at how these patients are currently treated, we will see that 80% of these patients are actually treated with supportive care already, which is typically a mix of RAS inhibition and potentially SGLT2 as well. It is already a combination market with more than 60% of the patients treated with more than 1 therapy, typically starting with that foundational therapy and adding from there. And we do expect combination therapy to grow. On the one hand, as these new therapies are approved, but also going back to the draft KDIGO guidelines, they do support the use of multiple mechanisms, including combination therapy. It's also important to note that about 40% of these patients are -- use steroids on an annual basis.

And in our conversations with both patients and HCPs that certainly is something that we would like to spare this patient from. And it's also a marker -- indirect marker of the underlying inflammation that these patients have. Also important to note that new IgA nephropathies recently approved, account today for less 15% of these therapies, highlighting, again, the potential that we have with our Novartis medicines to support these patients.

And as I'll describe on the next page, we do see atrasentan ideally suited for 100% of these eligible patients as a foundational ETA therapy and Fabhalta more specifically for patients with both persistent proteinuria and also glomerular inflammation.

Now moving to the next slide -- to this slide, yes, nephrologists, as we speak with them on multiple treatment options for their patients. And we will see that atrasentan as a baseline therapy will be mostly positioned for patients with proteinuria despite RAS inhibition and potentially SGLT2s. We do see it as a foundational ETA therapy added to that supportive care with a seamless addition to supportive care that does not require discontinuation or adjustment of the background therapy.

On the other hand, the orally administered Fabhalta is going to be best used initially in patients with persistent proteinuria and glomerular inflammation. Dave will go through it in more detail, but these are patients that have persistent proteinuria, persistent hematuria, eGFR decline and we're a different approach to managing patients with addressing the complement activation is creating a lot of excitement in the space, and where Fabhalta is the

first and only treatment to target this alternative complement pathway in IgA nephropathy. Now going to the commercialization strategy, we see on the next slide that having a renal portfolio is absolutely critical in a rare or ultra disease because it makes each future launch more effective and efficient. I think it's important to note that 2/3 of nephrologists manage less than 3 IgA nephropathy patients and about 1 C3G patient and that there's about 10,000 nephrologists in the U.S., which makes, of course, reach challenging if we're only launching one indication. As you will see on the right-hand side that about 2/3 of the nephrologists treating C3G do overlap with IgA nephropathy treating HCPs, which allows for substantial synergies as we go to market.

Now also important to note that, of course, there's a 100% overlap between the HCPs that will potentially use atrasentan, iptacopan and Zigakibart in the future for the treatment of IgA nephropathy, creating those portfolio synergies. Now in order to optimally address this market, we have deployed a robust renal footprint early. So we deployed our medical field teams about 2 years prior to launch, our commercial teams about 9 months prior to launch, and we have an integrated customer-facing team of more than 100 FTEs that have been working on this launch and now executing on it. And that, of course, will be also launching the future potential indications and assets. If we go to the next slide, this robust footprint now allows us to cover more than 70% of all IgA nephropathy HCPs with an initial focus of about 800 early adopters in 14 key accounts.

That's important because of the long tail of prescribers that I described. And if we think about the early adopters, for example, these 800 HCPs, they currently treat about 25% of the IgA nephropathy patients, and they have been selected both based on the number of patients they treat, but also based on their attitude towards ETA antagonism and complement inhibition for the treatment of these patients.

I have to say that so far, the launch is progressing well since the approval in August. We have strong engagement with 100% of the top accounts. We have already reached 70% of these HCPs -- these priority HCPs and we see more than 90% of the top accounts with at least 1 REMs certified HCP. So we have about 1,000 HCPs already REM, which is a proxy for interest in using the therapy. So very pleased so far with how the launch is going.

Now if we move to the next slide, I also want to highlight one of the key challenges in rare and ultrarare launches that is understanding where patients are. It's important to note that for these diseases, it's typically ICD-10 codes are not as useful to identify where the patients are, particularly the IgA nephropathy codes were only available up until only October 2023 onwards. So we had to leverage our machine learning models. We have developed in the past for PNH, SMA, CML and others. So we're compounding our capabilities to work in renal diseases and other therapeutic areas to really predict where the IgA nephropathy cases are, link them to specific nephrologists and accounts, and then we've been validating this with our field teams, and we have about an 84% accuracy in predicting those.

Now that's important, as you will see on the right-hand side because that gives us a very granular understanding of where geographically all these patients are, allows us to deploy our HCP resources in the right place. But also, as you will see in the next slide, implement very targeted DTC capabilities to more effectively reach the right IgA nephropathy patient at the

right moment through the right channel, right? So by really reaching relevant audiences that we define by aggregating different data sets, and engage them in the high relevancy moments where they're ready to absorb the information and use it and connecting through multiple channels, we are able to, for example, reduce the audience size by an 88%, which means our resources are way more efficient, but also effectively bring the right information to patients so that they can be empowered to discuss with their HCPs what options might be best for them. Moving to the next slide. I wanted to highlight our market access strategy.

And of course, as you know, payers have been increasingly suppressing coverage to new specialty drugs in the U.S., and the mitigation requires scale and also a flexible distribution model.

In this case, the scale is achieved by having a multi-indication product. We started with the launch of Fabhalta in PNH last year. And I'm very pleased to say that we very rapidly established leading access with 73% of the patients covered to label 6 months post launch and a path to coverage for about 90% of the patients. So that's going really smoothly.

And now we can leverage that coverage to establish coverage in IgA nephropathy as well. I am pleased as well to say that since launch, we have established coverage to label in about 1/3 of the patients. We expect to, in the coming months, achieve another third and very strong access pathways for the rest of the population given that this is a rare disease. So this is another capability that we will be leveraging as well for the future indications with the ability to establish fast coverage once they are approved. Now finally, I also wanted to go in the next slide to our patient support offerings as well.

As part of our commercial model, in Novartis in the U.S., we have established a function, patient support that focuses 100% on patient support programs. We have heavily invested in it for the past years to do this fully in-house, building our own data and technology stack when most of our competitors rely on third-party vendors.

This patient support program has been built based on the expertise that we have in all the other rare diseases that we operate in. It was refined for Fabhalta in PNH, so it's well tested now and will be, of course, deployed for the subsequent indications and assets in the renal space. It offers patient enrollment, REMS validation, vaccine support where needed, access and affordability, support therapy initiation and ongoing support as well. And today, Fabhalta, we are offering a $0 commercial co-pay just relevant because the vast majority of these patients are commercial. A 12-month reach program to make sure that any patient can start right away their therapy if needed, while we establish full coverage.

And on average, it's taking us about 15 days to dispense the patients creating very strong satisfaction among both HCPs and patients. So in conclusion, and as I hand it over to Dave, I just wanted to highlight on the next slide that we're working to compound capabilities and experiences on the commercial front as well to support all future renal launches, and Fabhalta IgA nephropathy, of course, offers an ideal entry point for our future renal portfolio. We are leveraging portfolio synergies, compositioning multiple MOAs to address what is known to be a highly heterogeneous disease. We're also creating go-to-market synergies across a broad renal portfolio, making launches more effective and efficient, and of course, leveraging a long company legacy in rare and ultrarare spaces. And we are adding that to capabilities that apply

across the patient journey and that we are developing for the entire portfolio, like effective D2C, very effective payer strategies and, of course, robust patient support programs.

So with that, let me hand it over to Dave. Dave, over to you.

David Soergel Executive

Thanks a lot, Victor, really appreciate it. So we'll spend the next few minutes first talking about how we build depth in IgA nephrology by adding Zigakibart and atrasentan to our portfolio through the Chinook acquisition. And then second, talk about how we're building breadth in our portfolio by expanding iptacopan into other glomerular diseases and approaching new research targets. Go to the next slide, please. So sure, I've showed you this schematic earlier.

It's a relatively simple schematic showing the progression of IgA nephropathy from the initial insult in mucosa-associated lymphoid tissue to the production of galactose-deficient IgA, production of immune complexes and the deposition of those immune complexes in the glomerulus with subsequent inflammation and kidney damage. What this simple schematic does not show you though is the complexity that underlies this disease process, specifically, each part, each stage in this pathophysiology has its own variability and its own heterogeneity. And this is why the KDIGO guidelines have recognized that multiple therapeutic options need to be available for patients. And as Shreeram mentioned, that one needs to take care of 2 processes in parallel, the production of abnormal IgA and secondarily, the protection of renal function and the remaining nephrons in the kidney. So this provides you a rationale also for the -- for why we have multiple assets in development for IgA nephropathy with diverse mechanisms of action and different points of intervention.

Next slide, please. So we'll talk first about atrasentan. So let's talk about feel endothelin as a target first in IgA nephropathy. Endothelin is an excellent target for IgAN because the endothelin receptors are typically elevated in IgAN patients and are located at various points in the glomerulus. By preventing binding of endothelin, what we know is that you can reduce mesangial cell activation, kidney fibrosis and inflammation and then also reduce glomerular pressure and proteinuria and thereby protect the kidney.

What we also know is that atrasentan is an excellent molecule to target the endothelin receptor. It's highly potent and highly selective. It has a very well-characterized safety profile with over 5,000 patients exposed to this medicine during development, and it can be seamlessly added to the current standard of care and be a foundational therapy to prevent future nephron loss. Next slide, please. So in Phase III, we've seen excellent UPCR reduction as we saw in Phase II with atrasentan.

In a line, we saw a statistically significant and clinically meaningful reduction in UPCR of 36% at week 36 at an interim analysis. And importantly, when you look at all of the subgroups in a line, we saw benefits across all subgroups baseline demographics or disease characteristics. In addition, in an exploratory SGLT2 inhibitor treated subgroup, we saw a consistency of the result with a proteinuria reduction of 37%. And this has resulted in a New England Journal publication as well at the same -- through the same week as the APPLAUSE data. And the ALIGN study is the basis of our submission to the FDA, which occurred in the first half of this year.

So we go to the next slide, please. Zigakibart -- we'll move to Zigakibart now, which is our anti-APRIL targeting molecule in Phase III. So APRIL is a cytokine that promotes B cell survival and class switching and produces -- that results in the production of abnormal galactose-deficient IgA.

These abnormal galactose-deficient IgA molecules then stimulate immune reaction to them, which prove results in the production of immune complexes, which deposit in the kidney and then attract complement and produce inflammation and fibrosis. What we know is that blocking APRIL decreases the production of this abnormal IgA and prevents the formation of these pathogenic immune complexes. We've seen -- next slide, please, in Phase II, that when you treat Zigakibart that you can see a profound reduction in UPCR of up to 54% and stabilization of eGFR. We have data now that we showed at ASN up to 1.5 years of exposure to Zigakibart. This just shows that these effects are sustained over 1.5-year time frame, and the drug continues to be well tolerated without adverse events leading to study drug discontinuation or deaths in the trial.

So next slide. So on the basis of these very strong Phase II data, we started the Phase III BEYOND trial, which is enrolling patients with biopsy-confirmed IgA nephropathy with proteinuria greater than 1 gram per day and on stable optimized RAS inhibitors with SGLT2 inhibitors or ERAs and MRAs allowed in the trial. 272 patients will be randomized, and we expect UPCR interim analysis in 2026, with the study continuing to confirm the effect on eGFR out to 2 years. Next slide, please. So now we'll touch on the expansion to other renal indications.

And first, we'll talk about iptacopan in C3 glomeruli and then lupus nephritis and how we're building a portfolio there and then future research efforts. Go to the next slide, please. So we'll start with C3G. C3G is an ultra-rare severe form of primary glomerulonephritis that's often diagnosed in adolescents and young adults. It affects about 10,000 individuals in the U.S.

and it typically manifests with a variety of symptoms that are typical of kidney disease like fatigue, edema, hypertension, proteinuria, hematuria and reduced GFR. The diagnosis requires a kidney biopsy and immune fluorescence microscopy. And importantly, there are no approved treatments targeting the disease pathogenesis, which we'll touch on in a second. About 50% of patients who are diagnosed develop kidney failure requiring dialysis or transplant within 10 years of diagnosis. So if you look on the right part of the slide, it describes the disease pathophysiology.

C3G is a disease of the alternative complement pathway. It's characterized by abnormal production of pro-inflammatory C3 fragments that deposit in the kidney and cause inflammation and fibrosis, resulting in proteinuria and progressive kidney damage.

And so the really exciting thing about iptacopan in this disease if we go to the next slide, is that it's a targeted therapy that specifically inhibits Factor B of the alternative pathway. As you can see on this slide, in Phase III, iptacopan reduced UPCR and stabilized GFR at 6 months. We showed those data at ERA several months ago. Now at the ASN, we've shown the 12-month data, showing the crossover of patients who had been on placebo, if you look on the left-hand part of the slide, to iptacopan, confirming that this effect on UPCR in those

individuals exposed to iptacopan for 6 months. In addition, we show persistence and stabilization of effect on proteinuria through 12 months on UPCR and then on the right-hand slide on GFR as well.

So an important feature of the APPEAR-C3G study was we collected historical GFR data from patients who are randomized into APPEAR. And so what you see on the right-hand slide is the historical slope on the left-hand aspect of the graph pre-iptacopan treatment. And you see a decline in GFR of 7.6 CCs per kilo per year, which if you think about it after 10 years would be about 70 CCs per minute decline in GFR, which would lead most patients to require dialysis after about 10 years. And so what you see very importantly is this sort of progressive and relentless decline in GFR when patients are treated with iptacopan is aggregated. And you see a stabilization of GFR that lasts up to a year.

So this is an incredibly exciting result that suggests that iptacopan may be an effective agent for these individuals who really have no targeted therapies now. If you go to the next slide, importantly, when you look at even the highest risk patient population, individuals who have nephrotic range proteinuria of greater than 3 grams per gram on the left-hand part of the slide, where you see a tremendous decline in GFR over time of 12 CCs per minute per meter squared in the pre-iptacopan period, again, you see stabilization of GFR when iptacopan started in these individuals. So this is an incredibly compelling result. I think that shows that iptacopan can be an effective agent even in the severest -- most severely affected patients. Next slide, please.

So now we'll move to lupus nephritis briefly. Lupus nephritis is the most severe organ manifestation of systemic lupus erythematosus. It affects about 110,000 individuals in the U.S. and its clinical manifestations are variable as the manifestations of SLE are also variable, but are typically sort of characterized by progressing nephrotic syndrome, nephritic symptoms like hematuria, proteinuria, and abnormal kidney functions and typically it's confirmed by kidney biopsy. The current management is limited to corticosteroids, which are really the foundation of care, and broad-spectrum immunosuppressants.

About 10% to 20% of individuals develop kidney failure and require dialysis or a transplant within 10 years of diagnosis. If you look on the right-hand part of the slide, the disease is really characterized by abnormal B-cell function, production of autoantibodies with, again, deposit and -- into the glomerulus, resulting in inflammation, fibrosis, proteinuria and declining renal function. If you go to the next slide, we have a diversity of approaches in lupus nephritis that leverages all of our capabilities as a company. So iptacopan, lanalumab and YTB are all different targeted agents that may be effective in lupus nephritis. They are all different modalities, small molecule, monoclonal antibody or cell therapy and the administration varies as well from oral, subcu to intravenous infusion.

So this -- I think this diversity of approach offers an opportunity to approach this very heterogeneous and diverse disease with such severe consequences for patients. So we really look forward to seeing the results from these studies and hopefully delivering a new therapy to patients to improve their outcomes. And next slide. Last, I'll touch on some of our early research efforts. So as was announced recently, we worked together with investors and former Chinook associates to create a renal-focused, an RNA-focused biotech company.

And the opportunity here is really to leverage our increased understanding of renal disease pathophysiology and using a novel approach to try to target therapies to molecules that haven't been approachable with other interventions previously.

We have an option -- as part of this deal, we have an option to acquire 2 future development-ready compounds on agreed terms. And so we really look forward to seeing Borealis succeed and participating in their success as well. So next slide. So I think what you've heard is that we have compounding competencies across research, development and commercialization where we've continued to build depth in IgA nephrology. And then from that depth and IgAN are expanding our presence in other glomerular diseases and other kidney diseases.

And with this approach, we expect to bring treatment options to patients and their physicians that protect renal function and protect and prevent the need for dialysis or a transplant in the future. Thank you very much. And I think we'll go to Q&A.

Operator Operator

[Operator Instructions] Our first question comes from the line of Peter Welford from Jefferies.

Peter Welford Analyst

I've got 2. So firstly, if we can ask on the C3G data that you've got with iptacopan. Curious, we see other data for drugs in the complement pathway. I'm curious how you would compare particularly focusing on what a lot of clinicians seem to comment on, which is the proportion of patients that managed to achieve at least a 50% reduction in proteinuria, where I believe the proportion with iptacopan was relatively modest. So I guess, how important is that as an end point and how do you sort position this in the complement landscape?

And then just a similar one, if you don't mind, but the Zigakibart, which is just the -- there's an antibody, I believe that just recently read out similar data -- similar mechanism, sorry, there's a few years ahead. I wonder if you could sort of contrast how you would compare your approach to theirs, perhaps both in terms of the patients that you're targeting in BEYOND and the mechanism more if there are differences?

David Soergel Executive

Yes. Great. Thanks, Peter. So for the C3G question, I think it's really difficult to compare across trials. And I think even if you look at the baseline characteristics, in comparing VALIANT to APPEAR, it's very difficult to make a direct comparison.

In addition, proteinuria itself and its response is highly variable within this disease. So I showed you a very simple schematic of how the alternative pathway is the stimulus for this disease, and it is. But how patients manifest in their progression of disease can be highly heterogeneous. And so when you get into these small sample trials, it's very -- and ultra-orphan diseases is very difficult to compare across. What we've seen with iptacopan, I think, is incredibly compelling.

We've seen a clinically meaningful and statistically significant reduction in UPCR. We've achieved the objective, right, which is stabilization of GFR, right, with an orally delivered, easy-to-administer agent. So I think we're very excited about iptacopan in C3G and look forward to

its regulatory approval. With respect to -- did you want to add anything, Victor, to that?

Victor Bulto Executive

No. The only thing I would add, and I think we've gone through the presentation is that we also see the importance of having a presence, establishing access and having synergies from a commercial standpoint that will help us launch the subsequent assets in an environment, as you mentioned, where the heterogeneity of the disease and the sparsity of these patients, right, requires much broader footprint. And we're very confident about our ability to, once and if approved, bring this medicine to market, particularly as well, noting the difference in route of administration, right? So in our discussions with both patients and physicians, the fact that iptacopan is an orally delivered drug, particularly for these patients that will be on this treatment chronically is extremely important as well.

David Soergel Executive

And I think, Peter, your second question was on Zigakibart. So Zigakibart, I mean -- so we're in the midst of running the Phase III trial. I think the anti-APRIL mechanism is a particularly compelling mechanism for this disease for the reasons that we -- that I just talked about. It directly targets the production of this abnormal galactose-deficient IgA and has the opportunity, I think, to stanch the production of these immune complexes that cause renal damage. So we'll see what the data show.

I mean, I think that's the important thing. We're very confident based on the Phase II experience with Zigakibart from Chinook that this will be an important medicine for patients with IgA as well.

Shreeram Aradhye Executive

And Peter, the only thing I'd add is that like Victor said about iptacopan that even though we may be a little bit behind, the reality is that having access to our portfolio and having built all the capabilities, the opportunity to then bring to bear a drug like Zigakibart as the therapeutic landscape evolves on people trying to understand in which setting should the drug be used, the ability to then introduce it and get it to patients is significantly enabled by the broad portfolio and our presence in the field and our relationships in the community as well as payers.

Operator Operator

Our next question comes from the line of Richard Vosser from JPMorgan.

Richard Vosser Analyst

It's just a question on the commercial uptake of Fabhalta in PNH and thinking about the bridge support. So just -- if you could give us an update on that launch, what proportion of patients are now commercial pay, how the bridge program is going and how you expect that proportion on the bridge program to change over, over time over the next 6 to 9 months? But just an update on the launch would be great.

Victor Bulto Executive

Great. Well, thank you very much, Richard, for your question. I mean we will go into more details tomorrow in the part of the earnings call. But what I can tell you is that the launch is progressing very well. As you saw in the market access slide, we very rapidly establish access with about 70% of patients covered to level, which is actually translating into paid fields already.

Of course, we have patients going through the bridge but we're already seeing a good proportion of patients going straight to paid fields. We're very pleased with the percentage of patients -- of physicians already REM certified. So again, a good proxy to interest. We have established leading NBRx share already in the market -- in the 8 months, we've been in the market. And we're getting mostly switchers just for your information, right?

So these patients are -- were treated with another therapy, and they're switching now to iptacopan for 2 main reasons. One is optimal hemoglobin control. And we're seeing patients that are coming with all ranges of hemoglobin, we see good control, extremely high satisfaction from patients and HCPs. But we're also seeing patients switching that were -- had hemoglobin levels of 10 that are compelled by the idea of an oral treatment in the space for the first time. We're also very pleased with both compliance and persistency that we're seeing on these patients, right?

That's actually tracking ahead of our expectations. So in summary, all in all, a very good platform. It's working very well. And it's a great, as I mentioned, platform for the launch of a Fabhalta in IgA nephrology, even though in another therapeutic area, there's a lot of common elements that are enabling and allowing an acceleration of Fabhalta launch as well.

Operator Operator

Our next question comes from the line of Simon Baker from Redburn Atlantic.

Simon Baker Analyst

It's on C3G, but from a slightly different angle. Given that there are 2 genes that are implicated in C3G, and given Novartis' expertise in gene therapy, I was just wondering what your thoughts were on gene therapy options for C3G? And broadening out that question on the basis that there are about 80 renal genetic diseases and given your heritage with Zolgensma, what do you see as the opportunity? And what are you doing in the renal space with respect to gene therapy?

David Soergel Executive

Thanks, Simon, It's Dave. Great question. So what I would say kind of broadly is we're very committed to being in the renal disease area as you saw from this presentation. And we're always looking for internal or external innovation. So as we've shown with the acquisition of Chinook.

So we're always watching and looking for opportunities to intervene that are going to -- that's going to make a significant improvement in patients' lives. What I would say about C3G specifically is that iptacopan is a highly potent and effective agent at reducing activity of the alternative complement pathway through oral administration. So it provides, I think, a great

option for patients with C3G once it gets approved. So we look forward to bringing iptacopan to patients with C3G as of now.

Operator Operator

Our next question comes from the line of Graham Parry from Bank of America.

Graham Parry Analyst

So just actually on the Phase II iptacopan data. So there would be proteinuria reduction what was noticeably less in Phase III than we saw in Phase II. Just if you could sort of talk through any kind of explanation for that why we see, I think it was over 50% although not placebo adjusted in the Phase II study? And then secondly, what reimbursement, co-pay or compliance issues do you think you may run into with an oral therapy in C3 glomerulopathy? And how are you planning on addressing those ahead of launch?

Shreeram Aradhye Executive

Dave, do you want to go first then Victor?

David Soergel Executive

Yes, sure. So thanks for the question, Graham. Going from Phase II to Phase III, I mean, we expect to see different going from Phase II to Phase III, especially in modest-sized trials with highly variable endpoints like UPCR. So the important thing is what we've shown is a clinically meaningful and statistically significant reduction in UPCR in the Phase III trial, which is then buttressed by the fact that we could interrupt that decline in eGFR over time and show stabilization of renal function.

So I think the important outcome is that it looks like if -- when iptacopan is approved for C3G, it will provide an option for individuals right now who don't have an option. And I'll pass it to Victor to answer the...

Victor Bulto Executive

Thank you, Dave, and thank you, Graham, for the question. The majority of these patients in C3G are quite young and are mostly covered through the commercial benefit. And these will enable us to offer our $0 commercial copay. So we don't anticipate challenges from an affordability perspective or from an access to the medicine perspective. Of course, we have not established policies, and we will only do that once we get approval for C3G, but we do expect to leverage our presence with Fabhalta on both PNH and IgA nephropathy to establish strong coverage to label that will result in -- not only low co-pays, but also the ability for physicians to prescribe it, hopefully, right away after launch.

Shreeram Aradhye Executive

Graham, I'm just going to take you back to the fact that each time we talk about proteinuria, the whole purpose of measuring an effect on proteinuria was to get an indication of what's going to happen to eGFR. And I think when we were at the ASN yesterday, I think it was quite interesting to see that on the C3G data, people describe that essentially horizontal line on how the eGFR has basically stabilized to be horizontal with no further decline compared to

historical rates. It sort of felt like the primary purpose of treatment had been accomplished. And I think we see that continuing over time.

And to that end, I think the numerical differences in percentage proteinuria reductions as a predictor, we feel, are no longer that relevant. And given the fact that population differences across trials, as Dave pointed out, make it hard to compare specific numbers. But we are now focused on that stable eGFR and look forward to turning that into a potential benefit for patients.

Operator Operator

Our next question comes from the line of Emmanuel Papadakis from Deutsche Bank.

Emmanuel Papadakis Analyst

Perhaps a few follow-ups. So C3G, you've mentioned a couple of times differences in baseline characteristics. Is there any particular aspect of that you'd mentioned? And then it doesn't seem, on the basis of UPCR, any physician would choose iptacopan for those patients. So how many patients do you think would actually prefer an oral versus twice-weekly subcutaneous?

And then maybe a question on overall guidance. I didn't see any update today. I assume the above $3 billion peak guidance is intact. Could you compliment to what extent that was constituted by C3G versus PNH and IgA nephropathy?

Shreeram Aradhye Executive

Victor?

Victor Bulto Executive

Yes, I can take the commercial questions. On both the preference between an oral treatment and subcu treatment and also the guidance. So let me start with the guidance. We have guided Fabhalta to a $3 billion peak across indications worldwide. We haven't provided further guidance on the split of the different indications.

And in terms of the C3G preference, I think it all comes down to the hetrogenecity of the disease, as Dave has mentioned. But generally, when patients given the option to use a twice daily oral therapy or to use a subcu pump patch twice a week, I mean that's a clear preference, particularly in this younger population, right? So -- and very encouraged to see as well the high degree of persistency and adherence that we see with Fabhalta in PNH, which can potentially be used as a proxy as well of what we could see, right? So this is one of the elements, of course, that will play into decision-making. Others -- as Shreeram pointed out, will be our ability to support patients, activate patients and HCPs commercially, which we'll allow [indiscernible] to do.

And then from a therapeutic standpoint, Dave, I will pass it over to you to respond to the first question.

David Soergel Executive

Yes. Thanks, Victor. So the -- I think your question related to what baseline characteristics were different in APPEAR between treated and placebo group. And the answer is that the population of the iptacopan treated group was slightly younger, which is consistent with the fact that a lot of them had dense deposit disease at baseline. This is a more severe -- typically a more severe phenotype.

And so when you actually split that eGFR curve, that historically eGFR curve, you actually see a more precipitous decline in the iptacopan treated population. So I think that's consistent with the fact that what we see is some heterogeneity in the study, which is -- can happen in these relatively small Phase III trials.

However, the important thing is that we -- as Shreeram said, we see stabilization of eGFR and the population that's treated with iptacopan which is a critical thing. Because most of these patients are going to end up on dialysis or requiring a kidney transplant. And then of course, after a kidney transplant with C3G, you don't get rid of the disease and the fact a lot of patients have recurrence of C3G after they have a transplant. So having an oral therapy that could impact favorably on protection of renal function is a big benefit to patients.

Emmanuel Papadakis Analyst

Apologies if I was not clear, I was actually referring to differences in the baseline characteristics between VALIANT and APPEAR on a cross-trial basis?

Shreeram Aradhye Executive

Yes. But I think Emmanuel there, as you know, the mix of VALIANT had IC-MPGN patients, some post-transplant patients. Our population incoming baseline GFR was about 8 or 9 mls higher. So our interpretation of the data for us is that we enrolled a population that was a little bit earlier in their disease state. We had a different mix of C3G and subset of C3G like dense deposit.

And I think, therefore, with these high double-digit number of patient populations, comparisons of directly looking at proteinurea reduction comparisons, the cross trial starts getting complicated, which is partly why we [indiscernible] zero in on the fact of what are we achieving in terms of GFR. I hope that makes sense.

Operator Operator

Our next question comes from the line of Kerry Holford from Berenberg.

Kerry Holford Analyst

I'm just thinking about sort of bigger picture here with regard to the approval process in some of these rare kidney disease areas accelerated versus full. Do you expect the reduction in proteinuria to continue to enable accelerated approval for a number of these rare diseases? Or is that route like to become more limited as the competition increases? And then, I guess, associated with that, how confident are you that reduction in proteinuria will remain the primary focus for the regulators? Is there a risk that eGFR stabilization or any benefit [time] becomes increasingly important for getting that initial approval?

Shreeram Aradhye Executive

Thanks, Kerry. It's Shreeram. You are indeed correct that I think that the purpose for approving drugs on the basis of proteinuria reduction was based on the -- not having to wait long when there were no therapies available. We fully expect that as drugs get approved, additional drugs getting approved on the basis of proteinuria reduction alone will need to defend why they are in advance over what is an approved standard of care. So we fully expect that to happen over time.

And when that happens, then I fully expect that regulators will focus in -- on the primary purpose and purposes of renal function assessment and demonstrating a benefit on slowing of decline in -- which is the basis for confirmatory approval now. But I think the answer to your question is, we indeed expect that to happen over time. And Dave, do you want to add something?

David Soergel Executive

Yes. Yes, just to add something really quickly. I mean, I think what we've seen with IgA nephropathy is really an explosion of therapeutic options in that field. That partially has resulted from the fact that proteinuria reduction became a validated surrogate for approval in the U.S. So I think the academic community is certainly interested in pushing for more validated -- more indications where UPCR could be a validated surrogate, and we've seen ongoing work, especially with the [Parasol] group and FSGS to try to extend some of that thinking and try to bring therapies to patients more quickly.

So I think the IGA sets a great framework for accelerated approval and how you actually get that done, but it's going to have to play out in a lot of these other diseases.

Operator Operator

Our next question comes from the line of Christopher Uhde from SEB.

Christopher Uhde Analyst

Chris Uhde from SEB. It's focusing on C3G. So I wondered if you could tell us, you obviously have a skew in your baseline on -- with respect to dense deposit disease. How does the data look in the non-DDD-only patients? And then in terms of the protocol, you've got a requirement that patients beyond maximally tolerated RAS blockade.

What proportion of patients were treated at or above that target dose? And why did you go for maximally tolerated RAS blockade? Was this an FDA or EMA suggestion or requirement, noting that your competitor's trial was only for optimal RAS blockade? And if I could just squeeze in another one on that. So competitor is showing C3G staining post treatment and a big reduction.

You guys haven't shown that data. How does it look in your data set? And I guess the last thing would be sort of with respect to the proteinuria and eGFR. So we have 6-month eGFR follow-up. Did FDA and EMA, at any time, specifically say that would be sufficient?

I mean, I realize that you needed to end up showing 12-month follow-up for at least the FDA.

But why not longer? Why not design the trials with a longer EGFR follow-up before crossover, given that -- I mean, you already have proteinuria as a surrogate endpoint, what's the point this 6 months was supposed to be okay?

David Soergel Executive

Thanks, Chris. Apologies, so I don't get every one of the points that you raised, but let me go through those that I captured in order and then you can let me know what I missed. But with respect to the heterogeneity in the baseline characteristics in the population, what we see is we see consistent effects across all subpopulations within a APPEAR. And as we said, the overall results, I think, support a beneficial treatment effect on UPCR and stabilization of GFR in the entire population.

I think the second question you had, had to -- well, a question that you had was about staining. We did show results from C3 deposition score at ASN, showing a statistically significant reduction C3 deposition score in a APPEAR. I don't have an image to show you that looks like the one that you saw from the competitor. But I think that tells you that iptacopan reduces deposit score in the disease. I think importantly, also from other indications, what we see is when you administer iptacopan systemically, you very effectively reduce Factor B alternative pathway activation by biomarker using [indiscernible] and other measures of complement activation.

So we know that the disease has sort of turned off at its core by reducing alternative pathway activation. And then I think the other question had to do with the connection between UPCR and GFR at 6 months. I mean I think the -- whenever we design a trial, you have to take into consideration that patients are going to be able to tolerate placebo control for a certain period of time. And in some situations, when you go longer than a certain time frame, individuals are not willing to be exposed to placebo any longer.

So you have to balance these sort of pragmatic aspects to trial design versus a scientific -- testing your scientific hypothesis. And what we showed is that 6 months is we have the effects that we were looking for. So both in terms of UPCR reduction and GFR stabilization. And continuing the study out we have the power of the crossover where you see in the individuals who have been treated with placebo before and then were treated with iptacopan, you see a confirmation that UPCR reduction of effect that in the placebo-treated group and stabilization across -- of the GFR across the entire population. So I think it actually gives us -- APPEAR gives us very compelling results at the end of the day at the 12-month time point.

Shreeram Aradhye Executive

Yes. And I think if I had to add, I think, Dave, when we were designing -- we were designing APPEAR, APPEAR was the first study of its nature in a randomized controlled setting with a placebo control for a disease that affects young people, and it's known to be pretty aggressive. So I think that it was very clear that the opportunity -- the ability to keep a person on placebo for longer than 6 months was simply considered unrealistic. And frankly, while our trial actually enrolled patients that were at a slightly earlier stage of their disease with incoming GFRs that were higher than what we've seen with our competitor what is noteworthy is that in the competitive trial, over the course of 6 months, there was nearly just

under 8 mls per minute drop in GFR.

So the fact that this population can behave in ways that is pretty aggressive is very clear. And so the ingoing design was based on that patient centric, if you will, principal. But I think the fact that we could then reconfirm the benefits of proteinuria through the placebo to active conversion as well as the sustained benefits of GFR stabilization allow us to make the case for substantial evidence of efficacy. So thanks, Christopher. I think if we can go to the next question, my request is to please limit your question to one question so that we can get done with the few that are still inline.

Operator Operator

Our next question comes from the line of Seamus Fernandez from Guggenheim Securities.

Seamus Fernandez Analyst

So I just had 1 question on the historical data for Zigakibart. I think there were 2 cases in the earlier data set that had some SAEs. Just hoping that you could maybe cover those SAEs and explain to us if it was specific to the patients in those earlier data sets or perhaps it was reflected with -- an issue with the product.

David Soergel Executive

Yes. I mean I'll try to give you some clarity on that, Seamus. So I mean, first of all, there were no AEs in the trial that led to treatment discontinuation. So I think that's the important thing. In any small-sized trial, especially with individuals who have a significant disease, especially when you don't have a placebo control, you might have events that happened in the study.

We had one event that occurred that was a -- listed as a serious adverse event that was not treatment-related. And so I think as of right now, as I said during the presentation, we're -- we're very confident in Zigakibart's safety profile based on the 1.5 years data follow-up we have with this drug. And I think the specificity of the mechanism of action is also an important sort of attribute where targeting April in isolation, I think, gives us an opportunity to be very specific about how we address the disease -- the root cause of the disease.

Seamus Fernandez Analyst

Just to clarify, the Hypogammaglobulinemia cases were deemed not due to study drug?

David Soergel Executive

There was one -- I believe -- I'm not sure -- I can't say specifically what the attribution was, but one did occur after the treatment period, and they were both in individuals who are on corticosteroids. So there are potentially confounding situations going on with those individuals.

Operator Operator

Our next question comes from the line of Stephen Scala from TD Cowen.

Steve Scala Analyst

Just one brief question. Industry-wide, how big do you think the IgAN market could become, for instance, -- do you think it could total more than $10 billion, more than $20 billion? And what portion of that would Novartis capture?

Victor Bulto Executive

Well, Stephen, thank you very much for your question. I mean I'll revert back to the data that we've shared in terms of prevalence, right? So -- and then reflect on the drivers that will give us -- that will lead us there. about 185,000 patients that are prevalent. And today, probably the biggest opportunity for this market to expand is to increase diagnosed prevalent rate.

And that's going to be a key driver of the market. And that today is a little bit challenging because it requires a biopsy. But what we do know is that as we have more entrants in the space, the market will continue to develop, and we will expect an increase there.

So what we have said or what we can guide to is that we do expect both Zigakibart and atrasentan to become blockbusters on their own, right? And that we've guided iptacopan to be a $3 billion plus across indications. So we do expect the market to be a very significant one. And of course, we are deploying a portfolio strategy and a commercial strategy to take a leading place into this portfolio. So thank you very much, Stephen.

Shreeram Aradhye Executive

Okay. So with that, I think I thank you for joining us this morning for our renal-focused call. Look forward to many of you joining our quarterly call tomorrow. Thank you very much.

Operator Operator

This concludes today's conference call. Thank you for participating. You may now disconnect.