Vertex Pharmaceuticals Incorporated

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Debjit Chattopadhyay Analyst

All right. Good morning, and thank you for joining Guggenheim's Inaugural Healthcare Innovations Conference. I am Debjit, one of the therapeutic analysts, and my privilege to welcome Dr. Reshma Kewalramani, President and CEO of Vertex. Thank you for your time, if I may call you, Reshma.

Reshma Kewalramani Executive

Of course.

Debjit Chattopadhyay Analyst

Well, let's start with the business model. CF is a monopoly business, but the company has, over the last, let's call it, 2, 3 years, moved into specialty settings and more recently into IgAN, which is going to be a competitive market. Let's talk through that evolution and thought process on the business model there.

Reshma Kewalramani Executive

Yes, sure thing. First of all, good morning, all. It's a nice, intimate setting. So hopefully, we can ask each other a lot of questions and get through quite a lot of material. Debjit, thank you for hosting.

You're very correct that there has been the planned evolution of the business model

delivering over the last 2, 3 years or so. We like to think about our business model as one that's based on delivering disproportionate success.

And that comes from two components. One is the R&D part of our strategy. And that has to do with going after diseases of high unmet need, but I think all good companies do that, diseases where we have validated targets, endpoints that line up to biomarkers and efficient development and regulatory pathways but also this other side, which has to do with specialty markets only. And by specialty markets, we don't mean a disease treated by a specialist. We mean a market where we can have low SG&A spend so that we can reinvest in R&D.

CF was the first example of this model working.

The next example is CASGEVY, which is the CRISPR/Cas9-based therapy for sickle cell disease and beta thalassemia. And as Debjit points out, now it's far broader than that. There is an acute pain NDA and PDUFA date that's pending in January, along with another CF PDUFA date also in January. There are four programs in Phase III, three of those just went into Phase III last quarter, and there's a whole pipeline behind that. So yes, this is what we had hoped would occur.

This is what we talked about happening. And it's great to see that it's happening. Maybe the only surprise is it's happening a little bit faster than we had imagined.

Debjit Chattopadhyay Analyst

Appreciate that. You sort of framed Vertex as a modality-agnostic, disease-focused company. Given the litany of diseases that you just laid out, where do you think are some real unmet needs that you would see Vertex innovating in the coming years?

Reshma Kewalramani Executive

Yes. So this concept of being a disease-first company, it sounds simple enough and it makes all the sense in the world to us. It's not the most common model. Most companies in biopharma are either platform-based, a mRNA company, a gene therapy company, a gene editing company, a company that works on a particular kind of small molecule, or a therapeutic area company, oncology, neuroscience, renal, what have you. We are not that.

We are explicitly not that. We are not only not modality-dependent, we are not a therapeutic area-oriented company.

That is to say simply because we have R&D in cystic fibrosis. We don't imagine that means we know anything about COPD, or that we should do something in asthma. We do R&D in diseases that are in our metaphorical sandbox. It's an imaginary box where we put all of the diseases of interest. There's between 12 and 24 such diseases.

And all of those diseases fit that R&D strategy that I outlined, where we have validated targets, where we have biomarkers that translate, where we have efficient regulatory and development pathways, et cetera.

So when you look at our sandbox, Debjit, if there is a disease in there, it means there is a high unmet need. If there isn't high unmet need, it simply doesn't make it into our sandbox. So

whether you look at acute pain or IgAN or something like our type 1 diabetes program, if it's in our sandbox, it's because there is either no therapy, in that category, I would have something like myotonic dystrophy type 1, or the therapies that exist are suboptimal, something like using opioids for acute pain.

Debjit Chattopadhyay Analyst

So I think it was December 2, 2021, when you first put out APOL1-mediated FSGS data. I was on my way to Boston, which is if I remember it, that kind of marked the transition where people started paying attention to the pipeline. You've had some disappointments, especially on the liver side of alpha-1 antitrypsin. Any learnings from that, that will prevent you from going back into that indication, which is still a completely unmet medical need?

Reshma Kewalramani Executive

Yes, so in APOL1-mediated kidney disease, it was one of these, like it was made for Vertex. It's a disease that's genetically identified. The disease itself, I happen to be a nephrologist, so I know a little about this area, the disease itself was identified like in 2010 right here in Boston and has this wonderful story of the alleles and what the protein does. And we were able to make a small molecule that has the opportunity to interdict on that channel. And we did a -- if I do say so myself, we did a smart Phase II study, where we were rapidly able to get proof of concept.

And I do think it was the start of the turning point of us talking about the strategy and delivering proof-of-concept results that marched out exactly what we said would happen.

In AATD, this is a different disease, also a genetic disease, also one in which there's high unmet need. And our approaches there have fallen short. So in AATD, our small molecule approach actually demonstrated for the first time a statistically significant improvement in what's called functional AAT, that's the protein that doesn't work in these patients. But it wasn't at the level that we thought was transformative to advance to Phase III.

And the lessons learned, the AATD program was the first in our attempts where we were translating from the bench to the bedside. And I think this just tells you when you have the HBE assay as we do in cystic fibrosis, where we've had the opportunity to go through it multiple times and come out the other end with clinical data, we can train the model. Now when we put molecules into the HBE assay, or now when we put molecules into the APOL1 assay, we have a very, very good sense of what we can expect in the clinic. And that is early discovery for you.

Debjit Chattopadhyay Analyst

So let's touch upon the HBE assay, which is almost like the secret sauce behind the cystic fibrosis platform. The mRNA program with Moderna, that's in a multiple ascending dose study. How are you setting benchmarks for what you would call a successful program that deserves to be commercial?

Reshma Kewalramani Executive

Yes. So now switching back to cystic fibrosis, in cystic fibrosis, 90% of people have mutations

such that they make some amount of protein. When that happens, a small molecules can work because they have a hook to hang on to. About 10%, so let's call it, 7,000, 8,000 patients simply don't make any protein. So for them, we have to find a way to introduce a protein for them so that they can have benefit.

Our approach, the lead approach is the mRNA approach with Moderna.

So in that program, we've completed the SAD, we're in the MAD. And if you sort of say, "Give me numbers, I want to know what success looks like," I don't know that I could do that, but let me frame it for you. In the small molecule approaches of which we now have four approved medicines, the ORKAMBI medicine gives you about a 3 percent point ppFEV1 improvement. ppFEV1 is the regulatory-enabling endpoint. But what we're really trying to do is make sure people have less pulmonary exacerbations, less transplant, improved long-term quality of life, they're not being hospitalized, they're not getting into hospital and not dying.

It turns out that something like TRIKAFTA is 14 points on this ppFEV1 scale, so quite different. But if you look at these long-term endpoints that we're trying to mitigate, they are actually more similar than different. So 3 points of ppFEV1 in ORKAMBI gets you about 50%, 60% improvement from exacerbation, for example, 14 points in ppFEV1 in the example of TRIKAFTA gets you like 70% improvement. So it's better, but it's any number in there. ORKAMBI was approved because those patients at that time, F/F patients had nothing.

KALYDECO that came before, it was a 10% improvement in ppFEV1. So I would say that's the spectrum that you're looking at.

Debjit Chattopadhyay Analyst

Got it. Staying with the cystic fibrosis that have a couple of new targets being talked about, I believe, NBD and ICL4, given the secretase assay, has Vertex looked at these compounds and what's come out on the other side doesn't look that great?

Reshma Kewalramani Executive

Yes. So when you think about Vertex and CF, but frankly, when you think about Vertex and any of the disease areas that we are in, those diseases in the sandbox, we look at everything that moves. If it's there in our disease, we look at it, we evaluate it, we think about it deeply. And this comes from a very painful personal experience for the company. I wasn't at the company, but if you talk to Stuart, our Chief Commercial Officer, who was there at the time, he tells you that the hairs on the back of his neck still stand up when people talk about hepatitis C.

Vertex had a medicine called INCIVEK. It was the fastest medicine of its time to go from 0 to $1 billion and it was fastest of any medicine of its time to go from $1 billion to 0. The whole up/down took a little bit less than 2 years. We are very, very paranoid, very, very serious about learning those lessons, we talked about what lessons did we learn. And the lesson that we learned from that experience is it is absolutely essential to not only innovate, that's just not enough.

It's serial innovation and in every disease area, cystic fibrosis, and think about any disease area in our pipeline, T1D, acute pain, IgAN, anything. There's a lead compound and there's a

family of follow-on compounds, every single disease.

And people ask us, "Why do you do this?" We do this because, going back to the question, Debjit, you asked about strategy, we believe in going into these areas of high unmet need. And we believe that cracking open those areas is what brings the most value for patients and shareholders. And if we're going to be the ones who crack open these areas, sure as heck we're going to be the ones who own the waterfront. We're going to be there today, tomorrow and the next day. And so yes, we look at everything.

And we've looked at everything, including the potential approaches that you cite.

Debjit Chattopadhyay Analyst

Awesome. So staying with CF because it is still so much of a CF story, there is still a huge amount of revenue concentration, even assuming successful launches in pain, CASGEVY, maybe even APOL1-mediated kidney disease, IgAN. How are you thinking about, say, one, the run rate of the CF franchise with the launch of vanza and maybe something behind vanza? And if you look at, say, 2035, what does the company look like from the revenue concentration perspective?

Reshma Kewalramani Executive

Yes. I see continued growth in cystic fibrosis for the near, mid- and long term for three reasons, really. One, our cystic fibrosis patients are living longer. And that is not only because of the Vertex medicines, but because health care for CF patients has improved overall. Second, we are continuing to expand into lower and lower age groups.

We're down to 1-month-olds in KALYDECO. We're at the 2-year-olds with TRIKAFTA, but we want to go all the way down. And you, of course, know that KALYDECO works in only a certain set of mutations. So we have a little ways to go to bring all of our medicines down to the lowest age groups. And third, the 7,000, 8,000 patients who won't benefit from the small molecule program, they need the mRNA or equivalent program.

The medicine that we have coming out after TRIKAFTA is a medicine called a vanzacaftor triple. That PDUFA date is January 2. As great as TRIKAFTA is, and it is a wonderful medicine, there are about 6,000 patients or so around the globe who are no longer on TRIKAFTA. So they've tried it and, for whatever reason, they're no longer on it. I expect that those patients might be able to come on to vanzacaftor.

So those are the near-term, medium-term and long-term areas of growth that I see with CF. But I want to make sure that you have a good conceptual view on what we're trying to do with cystic fibrosis. Because you're right, it's an important disease area today, and I expect it to be an important disease area as far as my crystal ball can go.

What we were trying to do in CF is bring medicines that would transform the lives of these patients. And back in 2012, when KALYDECO was approved, there was no medicine that targeted the underlying cause of disease. So goal number one was bring a medicine that could treat all 90% of patients who can't make enough protein. That is checked with TRIKAFTA. Second goal, bring all our patients with cystic fibrosis to what we call carrier levels

of sweat chloride.

So think about the moms and dads of children with CF. The moms and dads have one cystic fibrosis gene, the child has two. These moms and dads have virtually no manifestation of disease, live a normal life. We are trying to bring all our patients to that level of CFTR protein function as read out by sweat chloride. And the third thing that we want to do is bring a medicine for all patients with CF, that's that last 10%.

So if you're thinking about, "Golly, how long are these people going to be in CF," think about those things. As long as we don't meet those goals, we're in CF.

Where do I see us going by 2035? We've talked, Debjit, about the 5 in 5 goal, I think we talked about it starting in January of 2023. So we see 5 approvals by 2025, 5 approvals by 2028, 5 years since 2023. And we're well on track to do that. By 2035, gosh, we should be in far many more areas than that.

I expect us to be in gene editing, obviously, because we're already there with CASGEVY, but I expect that we'll have treated more and more patients, partially because more patients will have simply come on the drug, but partially because I think by then, we will have also solved the gentler conditioning element of beta thalassemia sickle cell treatment, so we can get away for busulfan, which is a tough procedure for patients.

I expect that we'll be in cell therapy with VX-880 and our various follow-ons to VX-880. I expect that many of our late-stage programs, so those 4 programs in Phase III, 2035 is like 10 years away from now, I expect those will have delivered. And I expect many, many more patients will have access to our medicines in CF around the globe. So I do see CF continuing to be important. But you look at some of these other franchises in pain and T1D and IgAN, they are significant, as in multibillion-dollar opportunities.

Debjit Chattopadhyay Analyst

So before we jump to CASGEVY, I just want to think through, where do you see TRIKAFTA being in, say, the U.S. market once vanza launches 3, 4 years out? What's the role of TRIKAFTA? What's the role of vanza? And from an IP perspective, obviously, vanza takes the IP further out.

Why even have TRIKAFTA in the marketplace?

Reshma Kewalramani Executive

Yes, so we've shared the TRIKAFTA patent expiry date is out at least to 2037, and we haven't yet shared vanzacaftor. As many of you might know, we don't force transitions from one of our medicines to another, even though we happily cannibalize ourselves and do head-to-head studies and demonstrate what one medicine can do versus another. So when we developed TRIKAFTA, we did head-to-head studies against SYMDEKO, which at the time was the standard of care for many of these patients.

With vanzacaftor, we did head-to-head studies against TRIKAFTA, so physicians and patients. This community is very educated. They are very knowledgeable. They want to understand what the data is. And for understandable reasons, this is a genetic disease, it runs

in families, kids are born with this.

They want to have access to the best medicine that's going to keep them healthiest for the longest period of time. We don't force substitutions. We don't force transition. So TRIKAFTA is a great drug.

I was a CMO at the company when we did the studies and got the approval. It's one of, what I would call, my original babies. And so if people want to be on TRIKAFTA, that's a wonderful decision. That's fine. If people want to move on to vanzacaftor, that's equally okay.

What people have shown us over time, as we've gone from KALYDECO to ORKAMBI, SYMDEKO to TRIKAFTA, is people have moved to what they consider to be the best medicine, and we've provided the data for that. So I expect we will -- TRIKAFTA will be available. It will be on the market as well vanzacaftor.

Debjit Chattopadhyay Analyst

Yes, the feedback, the initial feedback that we have got from physicians who are both familiar with both drugs seems to be a big willingness to switch to vanza simply because of the pulmonary exacerbation component. And then there is that convenience component in the younger patients, who would prefer once-a-day dosing versus twice-daily. So I'm wondering, what's the internal market research suggests on what the vanza launch is going to look like?

Reshma Kewalramani Executive

Absolutely. So if you ask me what are the advantages of vanza, you've named them. I actually did think that once-daily dosing would be the greatest advantage. It actually turns out to be really important, particularly for kids and teenagers, who may prefer to take a once-daily medicine, it was a little hard to take a medicine twice a day. So it turns out to be not that unimportant.

It has a -- the study design was it's non-inferior to TRIKAFTA, and TRIKAFTA set a very high bar. So that was great to see.

And the secondary endpoint is on sweat chloride, this measure. Sweat chloride is the PD, pharmacodynamic, marker of the protein that doesn't work. The protein that doesn't work in a CF patient is this thing called CFTR. That protein function is read out by sweat chloride, and vanzacaftor has more sweat chloride reductions than even TRIKAFTA. And for the company, there is a royalty burden that's decreased for vanzacaftor versus TRIKAFTA.

When we do market research, as I said, the physicians are very educated in this area, and they follow the area quite closely. There is a high awareness that vanzacaftor is in development and the PDUFA date. There's high awareness of the clinical trial results, and the clinical trial was just presented last month or 2 months ago in September at the North American CF meeting. And there is awareness of the fact that the CFTR protein function is read out by sweat chloride and there's greater improvement in that dimension with vanzacaftor.

Debjit Chattopadhyay Analyst

Got it. So could I pause and see if there are questions from the audience? No? All right. Talk to the cell therapy segment, where Vertex has now invested multiple billions between Semma, CRISPR new facility, et cetera.

Starting with CASGEVY, we just had an unfortunate death in the Beam study. What's the approach that Vertex is taking to move away from busulfan?

Reshma Kewalramani Executive

Yes, really, really important question. So CASGEVY is now approved, and the way in which we use CASGEVY in the clinical trials and the way it's used in the real world today is with busulfan conditioning. Busulfan conditioning works. And that's the reason all folks who need to have a conditioning regimen for their therapeutic to work use busulfan because it actually works. However, it's a tough conditioning regimen.

So what we are working on is a gentler regimen that has to do with -- think about a more targeted approach using an ADC, an antibody drug conjugate, where we target using an antibody, deliver a payload so that we can make niches in the marrow instead of using a very effective but a drug that obliterates the marrow. So instead of obliterating the marrow, what we would do is use this ADC to make niches based on the cells we need to deplete so that the returning edit itself have a place to go. That's what we're working on.

I am really happy with the progress that we're making. And I do believe, certainly in our lifetime, but I think in the next few years. It's not a tomorrow, it's not a next week. But in the next few years, I fully expect that there will be gentler conditioning available. And I say that because we're working on it, our partners at CRISPR are working on it, other biotech and biopharma companies are working on it as is academia.

Many are working on this for oncology indications. That's not what we're looking at, right? We're looking at it for our sickle cell disease and beta thalassemia patients.

But I must say that for the patients who are having these multiple VOCs today, so if you think about the overall population, let's call it, 130,000 people with sickle cell disease and beta thalassemia in Europe and North America, we are targeting about 30,000 patients, 32,000 patients in North America and Europe with busulfan-based conditioning because those patients are so severe that the benefit/risk is positive. There's an additional group of patients in the Middle East, actually not a small number, that we are also working with so that they can benefit from CASGEVY with busulfan-based therapy. But when and if the gentler conditioning comes, that would open it up to the full patient population.

Debjit Chattopadhyay Analyst

So the early traction, clearly there is traction, that surprised many naysayers on this program. There still seems to be a big amount of skepticism of how big CASGEVY could turn out to be. As you go from roughly 45 ATCs to 70-some ATCs, how do you see this evolve just from the visibility that you have, not just from the cell collection side?

Reshma Kewalramani Executive

Yes, absolutely. We said when we started this program, when we started to see the data from

Phase III, when we filed it, that this would be a multibillion-dollar drug, which means it treats many, many patients. I'm more confident than ever before that, that is indeed the case. I feel very positive about the early launch. It is a long journey.

But from everything I can see, I feel very good about where things are and how this will progress.

Debjit Chattopadhyay Analyst

Got it. And how soon do you think those 70-plus ATCs can be activated? And do you think you would need more, especially in the Middle East, for example?

Reshma Kewalramani Executive

Yes. So in the U.S., we are tracking towards the 75, and I think that, that will be adequate. We've done a lot of work on where our patients are. Sickle cell disease and beta thalassemia is not uniformly spread across the U.S. There are areas with more disease and less disease, so I feel pretty good about our numbers there.

I feel pretty good about our numbers in Europe.

We will open more ATCs than we originally said in the Middle East. And that's because the approvals in the Middle East have come fast and the reimbursement has also followed suit. So we are already in Bahrain and we are already in Riyadh in Saudi, and we're going to be making our applications to a few more Middle East countries because there is a high prevalence of disease there.

Debjit Chattopadhyay Analyst

Got it. So on the potentially curative type 1 diabetes drug, the data to date looks pretty spectacular. But unfortunately, you still have that overhang of having to use chronic immunosuppression. Do you think there is a market in that setting, even -- so those patients who have multiple glycemic crises every day sort of define that population and their enthusiasm to go in for chronic immunosuppression.?

Reshma Kewalramani Executive

Yes. So 100%, yes. I was mentioning that I happen to be a transplant nephrologist by training. So I have taken care of a lot of people post renal transplant. And with a kidney transplant, you also have to take immunosuppressives.

This is -- these are off-the-shelf medicines that have been used quite extensively with a very known benefit/risk profile. So 100%, this is an important medicine.

This is VX-880 for type 1 diabetes for those most severe patients, where they're having multiple, what are called, SHEs, symptomatic hypoglycemic episodes. These are people who are losing consciousness. They're having seizures. They're having death. These are people who go to sleep at night who are wearing monitors attached to their iPhone and at least one other friend or family member because they've lost the ability to sense when they're getting hypoglycemic.

So their buzzer goes off, their sound goes off and somebody else so that somebody else can come in and help them if that help is required.

These are extremely serious patients. And I think we've said there's some 60,000, 65,000 people who fit into this category. And remember, the overall population of type 1 diabetes is more than 9 million globally, more than 3 million in North America and Europe alone. So this is an enormous population. And for the -- we are -- if I was channeling my inner David Altshuler, who's our CSO, he happens to be an endocrinologist, he would say that I'm being overly conservative with the estimates.

Because his point is you don't really know how tough it is to be a type 1 diabetic. And the benefit/risk is positive for so many more people than the 60,000 that we're talking about. And that 60,000 that we're talking about are, let's call it, 45,000, who are just very brittle diabetics, these high highs and low lows, and maybe another 15,000 who are type 1 diabetics, who already had a kidney transplant. So they're already on immunosuppressives. So it's not an extra burden for them to take 880.

And the results, if you haven't seen them, we shared them at EASD also in September, they are remarkable. Any of you who know a type 1 diabetic or taking care of a type 1 diabetic, patients with type 1 diabetes don't get off insulin. If you don't take insulin for 5 days or 7 days, you die. That is actually what happens to you. And in this program, we shared data from 12 patients, so still early days, where they got a single full dose of these cells.

And at the time we shared the results, 9 out of the 12 patients were off-insulin. That just doesn't happen.

And we said on the earnings call that we've reached regulatory agreements with the FDA, MHRA, that's the U.K. authority, and the EMA. This Phase I/II program is being converted into a Phase I/II/III program as we speak. It's a total sample size of 50. And the primary endpoint is being off-insulin, proportion of people off-insulin and being without SHEs.

I went a little long, the timer is speaking to us.

Debjit Chattopadhyay Analyst

No, I think we had extra time.

Reshma Kewalramani Executive

Excellent.

Debjit Chattopadhyay Analyst

There's way too much to talk about.

Reshma Kewalramani Executive

All right, well, then let's keep going.

Debjit Chattopadhyay Analyst

20 minutes doesn't do it for Vertex. Sorry, I got distracted. So going back to the diabetes

program again, what can you tell us about the durability? Because that's the one unknown. And when we think about islet cell, cadaveric islet cell transplants, the reason that's not picked up, at least the way I understood it, is every center needs to become a certified center, which becomes a multimillion-dollar expense for every center, and that doesn't happen.

Reshma Kewalramani Executive

Yes. So let's talk about type 1 diabetes a little bit more in depth. The inspiration for doing the VX-880 program and acquiring Semma in the first place comes from the experience of cadaveric whole pancreas transplant. So we've known for many, many years that if you do a whole pancreas transplant for type 1 diabetic, so you take a pancreas from a cadaver and you transplant it, there's very high perioperative mortality. But if you can get past that, because it's a big surgery, if you can get past that, you can see long-lived insulin independence because the new pancreas is doing the work of the beta cells that failed.

So we've known that.

Then we move to islet cells. So islet cell transplants is cadaveric whole pancreas dissected in the lab to get the beta cells out and then simply -- and it is a reasonably simple procedure. You just simply inject it into the portal vein, which is a giant vein that runs to your liver. It turns out that beta cells, these islet cells, don't actually have to reside in the pancreas. They can reside in many different places.

So we have a nice in by going into the portal vein. And they reside and they're happy and they do their job. And that is a far less perioperative mortality because it's just islet cells that you inject either under interventional radiology or just inject it. It's not that hard.

And when we saw those results, so there's a classic study called the CIT007 study, where you have data from cadaveric islet cells, people do very, very well, so durability, 5 years, 10 years, 15 years, longer than that. They're very durable. Not everybody gets long-lived benefit. So then you go, "Okay, why does not everybody get it?" And it comes down to quality and quantity of cells. When you do cadaveric islet cells, what you're basically doing is taking a whole pancreas and trying to dissect out these little islets.

And remember, the other function of your pancreas is it has this endocrine function to do with beta cells and diabetes, it has this other exocrine function that has to do with digestion. So it's basically a bag of digestive enzymes. So as you're trying to get these beta cells out, that's a tricky, tricky job.

The quality is not that good and the amount you can get is not that great. That's this variability. And if a center tries to do this, they have to figure out how to do this, get a cadaver organ, which is not that possible, there are not as many cadavers as we need, then you have to dissect out the particular part and you've got to get the right quality and quantity. So that's the inspiration for the 880 program. But what we do is we make these cells, these beta cells, with high quality and we can make as many as we want.

So you can think infinite amounts in bioreactors in the lab. And therefore, with one infusion, you have an a priori reason to believe, at least I have an a priori reason to believe, that these are going to be durable because they're higher quality, completely consistent and we can

make as many as we want in the lab.

What we also learned from the CIT007 experience is if you need -- and I don't like this term, but that's the term that's used. If you need a top-off, so you've got your first infusion of cadaveric islet cells, but 5 years later or 10 years later, whenever, you needed a second dose, you just give a second dose. It's not a problem. The only problem is back to quality and quantity of cells. In our example, if you needed to get a second dose, we could just give you a second dose because we make them in our labs.

So the durability, our goal here is one-and-done therapy. Our goal is one-and-done potentially curative therapy.

Debjit Chattopadhyay Analyst

Got it. And as you think through the next iterations, the same cells in a device and then the hyperimmune cells in the device, what's unique about the device component? What's gone into the engineering of...

Reshma Kewalramani Executive

Yes. So program one, let's call it, the naked cell program, that's 880, these are allogeneic cells, so you need to protect them from your immune system somehow that's the off-the-shelf immunosuppressives. Program two, back to serial innovation, is called VX-264. That's also in the clinic now. And it uses those same cells that we know work and we put them into a protective proprietary device.

I won't tell you all the details about the device, but I will tell you that the geometry, the specific material and the way in which we've engineered it so that the surface area of cells to blood vessels have all been optimized to prevent the three things that are known to be problematic with devices.

Devices in this area, devices in general, have traditionally been associated with, one, fibrosis; two, a lack of oxygen and nutrients being able to get to your cells and the cells being able to sense glucose; and three, immune invasion. And so we have worked our way through all of these known issues to devise a device that, in small animal studies and large, don't have these issues. Obviously, the proof is in the pudding, and we have to do our clinical trials, and those are underway. The third program in the type 1 diabetes umbrella is the same cells, where we aim to gene-edit the cells to make them what we call hypoimmune or to hide them from the immune system. That third program is still in preclinical research.

The second program is already in the clinic.

Debjit Chattopadhyay Analyst

And should we expect data from the second program in '25?

Reshma Kewalramani Executive

Yes, I think results in '25.

Debjit Chattopadhyay Analyst

Got it. Let's talk a little bit about APOL1-mediated, AMKD. We had data from, I believe, 13 patients. Since then, Vertex did another 66-patient Phase II study, program got expanded. So should we assume the biomarker data at least looked very similar to what we saw from the first 13 patients?

Reshma Kewalramani Executive

Yes, really good question. The true answer is I don't know because it's blinded. So the way this study was designed is, this is the one I was telling you, I thought it was very cleverly designed, we did a IIa study, where we went fairly rapidly to the high dose that we wanted to test. So we -- if you look at The New England Journal paper, you'll see that there's a period of 4 weeks where we used the lower dose and then we went to the higher dose and then we reported out the results at week 12. It was almost a 50% reduction in proteinuria, which is pretty big.

It's 46.7% reduction in proteinuria.

Then we went directly into an adaptive Phase II/III. Everyone talks about adaptive design, nobody actually really does it, but we did. And this particular study had the trifecta, not the TRIKAFTA, but the trifecta of what you tried to do in really innovative designs. So we selected patients based on genotype. We did an adaptive Phase II/III study.

It's already in its Phase III portion. Now Debjit is exactly right, we completed the Phase II part of II/III and now it's in the Phase III part. And the third thing we did is we have agreement with the FDA for a path to accelerated approval. That's really the high fruit of designing clinical trials.

So the way it was designed is in the Phase II/III study, there's a DSMB. The data safety monitoring committee decides whether the study is ready to go to Phase III based on the safety that they see. And they get to see the efficacy and they get to pick what the right dose is. But we don't get to see the results. So they did all that work.

They told us that the dose would be the same as was the dose in the Phase II study, the dose for the last 8 weeks, but I don't actually know any of the results.

Debjit Chattopadhyay Analyst

Got it. And so the big difference in a Phase I study, you had a biopsy-confirmed FSGS?

Reshma Kewalramani Executive

Yes, correct.

Debjit Chattopadhyay Analyst

And now you just are genotyping patients.

Reshma Kewalramani Executive

Correct.

Debjit Chattopadhyay Analyst

What have been some of the challenges with this genotype? Because the study has taken a while to enroll.

Reshma Kewalramani Executive

Yes. We always knew, and I think you and I have talked about the fact that the study is going to take a little time to enroll. This is not going to be like acute pain. Acute pain, the model we use is bunionectomy and abdominoplasty. They're reasonably common procedures.

Those are the procedures that the FDA looks for to get labeling. And the entire study takes 2 days. So it's a rapid program. We always knew AMKD would not look like that.

And there's three reasons for it. One, this is a disease that was literally just defined in like 2010 right here at the Beth Israel in Boston by Marty Pollak. So it's not -- when I was a practicing nephrologist, which I was until 2004, I didn't even know about this disease because it didn't actually exist. So there's a big component of simply educating nephrologists. So it's a very recently identified disease.

Two, it's an asymptomatic disease until it's late stages. You wouldn't know you had AMKD. The physician would know because we can see proteinuria or we can see a reduction in GFR. But until the late stages, i.e., like about a couple of years before you're going to go on to dialysis, you may not know. So it's not like pain, where you're like, "Oh, my God, my toe hurts, I need to go see somebody." It's not like that, or cystic fibrosis, where there's universal newborn screening.

So the third big problem is that there isn't universal screening because it's a new disease. We are working hard to genotype patients and we have free genotyping and we are doing that as part of a discrete study. But we're also doing it in other realms. You take all of those into account and you take into account the fact that this is a disease of sub-Saharan Africans, and African American people have not exactly been treated the most fairly, not only in the U.S. but in the Western world.

So there's a little bit of reluctance for our Black patients to come forward.

We've known this, so we've done three things to try to address this. One, we started a genotyping study parallel to the interventional study. So if you're a genotype, you can come in and go to the study. Two, we've opened up lots of sites so that there are sites close to where the patients might be. And three, there is a big educational effort ongoing to ensure that both patients and physicians are more aware of this disease.

Some of you may have been at ASN, and it's probably for the various products being developed for IgAN.

But at ASN, Susie, what is the basketball player's name? Alonzo Mourning. Sorry, I'm still not so good with my sports. Alonzo Mourning has AMKD. He actually had a transplant and came back to win the basketball championship.

What's that called? Whatever the NBA championship is called. He came back after his

transplant and he won that. And he works with us to talk to patients about AMKD because it is a disease only of Black people. So those are the things that we're doing to aid and accelerate recruitment.

But this is going to take a little bit of time. But it's a wonderful drug, and I think it's going to make a big difference.

Debjit Chattopadhyay Analyst

There's one more thing with that, right? You don't need all 466 patients...

Reshma Kewalramani Executive

You do not.

Debjit Chattopadhyay Analyst

To hit your interim. So you do have a leeway there?

Reshma Kewalramani Executive

Yes. I told you that this was the trifecta of study design. And one of the trifectas was accelerated approval pathway already mapped out. I won't tell you the number of patients, but a certain number of patients at the 1-year time point, we can do an interim analysis and we're going to be doing an interim analysis. And if we hit the endpoint, we already have agreement with the agency for accelerated approval.

So 100% correct, we don't need all the patients for the accelerated approval pathway.

Debjit Chattopadhyay Analyst

So just to wrap up on AMKD, you mentioned it's African American disease primarily. We know at least from the hypertension segment, compliance rates in African Americans are about 40%, right? So what pushes compliance rates higher? Do they understand this is a 3- to 4-year from diagnosis to ESRD? And is that a motivating factor?

Reshma Kewalramani Executive

Yes. So compliance rates in CF are the outlier. So compliance rates in CF are exceptionally high. But again, it's because it's a genetic disease, it runs in families, kids are born with it. And it's so symptomatic, it rules your life.

So taking your pills are sort of easy in the course of everything you have to do to monitor your disease, very, very different for AMKD.

But there is a big motivation in that this is also a genetic disease. So people have seen their relatives and loved ones go through dialysis. And as a kidney doctor, that is an unpleasant thing. Even though dialysis is a modality that can keep you alive, it's a horrible way to live. And people have seen this, and they don't want to have anything to do with that.

So yes, I do see that as very motivating for patients to avoid that outcome.

Debjit Chattopadhyay Analyst

And just to wrap up on this, it just came to my mind, you're not enrolling diabetic patients, right? There's -- you're only looking at a subset of nondiabetic AMKD patients with APOL1, whether it's G1, G2, G2/G1, et cetera?

Reshma Kewalramani Executive

Correct. Think of it this way, the current disease, again because of the agreements with the regulators, is a homogeneous proteinuric kidney disease, which they have comfort in for accelerated approvals. So these are all what we would call primary APOL1-mediated kidney disease patients. APOL1, to Debjit's point, is also known to worsen other known kidney diseases.

So for example, you could have APOL1 and diabetes. You could have APOL1 and sickle cell disease. You could have APOL1 and lupus. You could have APOL1 and another kidney disease. We are very interested in that area, more on it later, but we're going to do those studies in a different cohort, not in this primary APOL1 proteinuric cohort.

Debjit Chattopadhyay Analyst

Got it. So staying on with the renal disease franchise, let's talk about IgAN since this is Vertex's biggest acquisition. The whole process, if we understood it correctly, took less than a few weeks to complete?

Reshma Kewalramani Executive

Yes, it depends on if you count weeks in one hand or two.

Debjit Chattopadhyay Analyst

So now that you have a little bit more data, where do you think this program stands versus the competitive landscape?

Reshma Kewalramani Executive

Yes, I am very keen on this acquisition and this program. We did -- speed was our friend here. Not only is the entire area a competitive area, you could imagine that all of the assets in the area are competitive. We have had IgAN nephropathy in our sandbox for some time, just like we used to have type 1 diabetes in our sandbox, except we didn't have, what we thought was, the best tool to get to transformative effects. For type 1 diabetes, we saw that with Semma.

We acquired Semma. For IgAN, we saw that with Alpine and povetacicept, we acquired Alpine.

So what do I like about this? There is a whole group of B cell-mediated diseases. We know these diseases. We know what causes them. They're B cells that have gone wild, let's say.

They are -- these B cells make autoantibodies. Those autoantibodies are the causative element of these diseases. IgAN is just one example of that. Membranous nephropathy is another example, lupus nephritis. It's like a nephrologist's dream come true to think about this in terms of the causative mechanism and then how can you go after it.

So the causative mechanism is B cells, and how can you go after B cells? And to me, the best way to do it is dual inhibition of APRIL and BAFF. APRIL and BAFF are two cytokines that are known to be involved in differentiation, maturation and the production of antibodies from B cells. So hitting the B cell pathway in two places allows you to really tamp down the B cell process that is causing these diseases and then lead to the beneficial effect. When you look at the mechanism of action, dual inhibition, there are medicines, actually there's an approved medicine, with just the BAFF inhibition.

And there are medicines being developed that's just the APRIL inhibition.

But dual inhibition, the good-looking preclinical data, potency, binding, the works, the clinical data at the time we saw this and did the deal, this was like April or so, there were just a few patients in the Phase II RUBY-3 study that were shared. But you could already see that it had 60-plus percent reductions in proteinuria. What I was very excited by was the accompanying reduction in hematuria, which is not as much talked about. But proteinuria and hematuria are clear manifestations of glomerular disease. You, if you don't have kidney disease, don't have proteinuria or hematuria.

So the hematuria data was very important.

And then the third component of this is this is a biologic therapy. It's going to be at-home monthly chronically. You need to have a monthly presentation, small-volume subcu. It's critically important. And this drug already had all of that.

Put it all together, we bought Alpine because we thought it was best-in-class. As we've acquired the company and integrated the company, that just gets truer and truer. And the additional parts that we've been very pleased with is the people. All of our acquisitions we do because we like the asset very much, but it's a lot about the scientists and the people. And we acquired some great people with this acquisition, so very, very excited.

This one is officially in Phase III, screening, enrollment, dosing up and running around the globe. And there's a whole bunch of indications. There were seven total indications when we acquired the company in Phase II between this RUBY-3 and RUBY-4 trial. We'll be looking at these as the cards turn over and saying yes or no, depending on what the results of these studies tell us. I told you a lot about the renal basket, there's a second heme basket as well.

Debjit Chattopadhyay Analyst

So while proteinuria and hematuria still looked great, there was some handwringing about the GFR slope, especially when people looked at comparison to Vera's data. Any thoughts on what -- why you saw that? And maybe any thoughts on the infection side of things as well?

Reshma Kewalramani Executive

Yes, infections, right? Yes. Let's tackle infections first. If you were going to tamp down the B cells, your -- that's the key risk that you're working to mitigate is infections. We studied 80 milligrams and 240 milligrams.

And 240 milligrams looks equally good on efficacy. But there are a tad more nonserious infectious AEs than in 80 milligrams. And therefore, we picked 80 milligrams for IgAN. But you

should see us doing 80 and 240 milligrams in our various Phase II and Phase III studies, picking the right dose for the right indication, depending on how much suppression we need and what the right benefit/risk is.

On Vera or other programs, I won't comment directly on any of them. But what I will say is what you're really looking for as a nephrologist is, at the end of this whole thing, you need to see stabilization of GFR. We've never, even in our wildest dreams, imagined improvement in GFR. That's like not something we could even imagine. But you do want to see stabilization of GFR.

That's important. And it's also important because it's a regulatory-enabling endpoint. So you have to have that.

Beyond that, what would I want to see as a nephrologist if I had a patient in front of me? The deepest protein reduction, so depth of response. I would want to see hematuria resolve and I would want to see this flatlining, if you will, of GFR reduction. Because that's what's going to prevent people from going on to dialysis. When we do these studies in the clinical trial, we're looking at 1 year, 2 years of GFR being flat.

These people are going to live with this disease for the rest of their lives. So I wouldn't be only looking at that, although that's necessary. It is depth of response of proteinuria and hematuria because that's what's predicting whether the glomerulus is back to normal, back to baseline, or as close to that as possible or still inflamed and injured.

Debjit Chattopadhyay Analyst

Well, now we're actually running out the clock, and I don't think we'll get to the pain program. But thank you so much, Reshma, for your time, really appreciate the insights.

Reshma Kewalramani Executive

Thank you very much, Debjit, and thank you all.

Debjit Chattopadhyay Analyst

Thank you.