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EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc R&D Day

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PRESENTATION

Stephane Bancel *- Moderna, Inc. - CEO & Director*

Well, good morning, everybody, or good afternoon or good evening for those of you joining online. Welcome back to Moderna R&D Day. Some of you have been with us for 6 years now. The first one was September 2017 in New York City. And welcome to those of you that are coming to this first time to Moderna R&D Day.

The team and I are very excited to share with you a lot of new clinical data, a lot of news on some of our key Phase III programs today in the respiratory space. So, of course, we'll be making forward-looking statements. Investing in Moderna entails risk. You can find all the risk factors on our website or the SEC website.

As you know, since the first day when we started Moderna, the period has really excited us about the potential of using mRNA as a new drug modality was the software like nature of mRNA. mRNA, as you all know by now, is an information molecule. And that's the piece that's really got us very excited about what we could do for patients using this new technology, if we could find a way to make it work. And the vision that we've always had for the company since the beginning was because mRNA is an information molecule, if we invest in science over time, we should create a lot of different applications of this technology where you bring mRNA to different cell type.

And today is an exciting day, of course, because of liver rare disease data we're going to share with you. And the idea was that because mRNA is information, if one drug will work in one application, as long as you keep the chemistry of mRNA, the lipid, the manufacturing process all the same,

you should be able from the first molecule or a proof of concept, be able to scale those applications very quickly. And that was the vision of the company as we started it.

So we're very excited today because you can see on the far right, we are established modalities, with, of course, a respiratory franchise that the team is going to talk about our latent virus franchise also. And today, we are very exciting to see some really encouraging data on the rare liver disease that the team will share with you. As you know, we already showed proof of concept with chikungunya for systemic and secured applications. And we are very excited to be able to get the data later this year in Q4 on personalized cancer vaccine. As you can see on the left, we have a few modalities that are still early stage in exploratory with Triplet and VEGF in the clinic and CF on its way to the clinic.

If I look at the world principle of how we operate and we scale the company, we wait for a proof of concept and then be able to scale very quickly. As you can see on the slide, in 2019, we had 7 vaccine programs in development. And today, at R&D Day 2022, we have 32 vaccine programs in development. That is a remarkable number. It's multiples of number of programs that large vaccine companies have in development.

And if you think about the maturity of the pipeline and the speed at which we are able to execute. In 2019, at the R&D Day, we have done no Phase III program. Today, we have 4 late-stage programs in vaccines that are in Phase III, and 24 programs are today in the clinic of the 32 program I just spoke about. The big exciting news, of course, today is the encouraging interim data that we are going to show you on the PA program. The good news is first because it's a Phase I/II study is that the drug was well tolerated from a safety standpoint. And as you will see, some of the study participants have had many, many doses summed up through the year to prove the study.

As you will see as well, we are very encouraged by the reduction in the number of metabolic decompensation events, which are basically the clinical manifestation of disease. And we're also very pleased of recent discussions that we had with regulators about using the MDA as a primary end point of a pivotal study. The other piece that you're going to see today is a very early glimpse into the GSD1a program that the team will share with you. And based on those very interesting proof of concept that we've seen in man, we're announcing today our 6 rare disease program in the liver with the OTC program using exactly the same lipid at the GSD1a program that you're going to see today. And those 6 programs, of course, do not include the CF program because, of course, it's rare disease, but using a different technology with our partner, Vertex getting into (inaudible).

As you know, these slides I've been using for many, many years the potential of mRNA in terms of being able to make not only intracellular protein, transformative protein, secretive protein and very complex protein or protein systems, is what we really believe is going to have a very transformative impact on patients over the next years and the next decades. We're, of course, very excited that now for a week or 2, the Omicron boosters have been authorized around the world. I already got a lot of text during the weekend of friends very proud sending me photos of Omicron vial where they got their booster this weekend and more countries coming in the next days and next weeks around the world.

The Phase III for flu is fully enrolled. RSV is almost there in terms of enrollment for its Phase III. The rare disease and, of course, looking forward to getting the data on PCV in Q4.

So with this, the day is basically going to be split after a quick remarks by Stephen. We're going start on therapeutics. Talk a bit about immuno-oncology because of a Phase II coming soon. We'll take a coffee break, and then we will spend time with Jacquie and team on vaccines, respiratory and CMV. Before APAC give you some thoughts around commercial launch readiness because with all those Phase III, of course, we are working actively to launch those products. And I'll come back with a couple of slides to close before we come all up to take your questions. So with this, have a great morning.

Stephen Hoge - *Moderna, Inc. - President*

Thank you, Stephane. And thank you again for all of you who made the trip to be with us today. As Stephane said, I'll do a little bit of framing on where we are in R&D across the pipeline, and why we've chosen the programs we have to speak to today. And some of the top line data that we're really excited to share.

So we have a pretty large portfolio, as you all know well. There are over 30 programs in clinical development, the dosing in humans in different stages, different vaccines. And importantly, almost 10 now therapeutics of different types. And we're incredibly excited to see the early data

emerging from that. As the portfolio has gotten large, we've had to select down those things we talk about at days like this. And so while we're fortunate, thanks to your support, to do multiple investor days throughout the year. We cover vaccines deeply, and we cover science and technology. We've chosen for this R&D day to focus on those programs that are either in their pivotal studies, their Phase III studies in the case of vaccines or are in patients right now.

And so we're dosing in the target patient population. And as you can see here, those include, therefore, the 3 respiratory infectious disease vaccines that we'll speak about at the end of the day, our cytomegalovirus vaccine program, 3 rare diseases PA, probronic acidemia, MMA or methomylonic academia and the GSD1a program, all of which, again, are dosing in patients as right now, and we'll share some early data on 2 of those. And then we'll provide a quick update on our personalized cancer vaccine program, which is partnered with Merck, Michelle Brown will come up and share where that is, and we are looking forward to the fourth quarter just around the corner and seeing the primary analysis from that study.

Okay. So just a quick summary of the things we'll be talking about. As I mentioned, we've got interim data from our propionic acidemia program, which is an ongoing Phase I/II study. It is a multiple dose study. And so as you're well aware, we've been dosing in that study for quite a long time, and it is about repeat dosing over time. We'll also share early data from the first patients in our ongoing GSD1a study. That's a little bit different because it's a single-dose study and involves a metabolic challenge. So the purpose of the drug is to provide people the ability to fast overnight, and we're able to do that in a controlled and very safe environment in a clinical study even after a single dose.

And so that's data that we'll be bringing forward today, and Dr. Rezvani will share. And then, of course, I mentioned the personalized cancer vaccine data with data expected. And we'll also provide the update I mentioned on all of the Phase III studies, including how excited we are to see those progress towards potential pivotal readouts and filings.

Okay. So Stephane framed how we look at building that pipeline. It's a large pipeline. But at the end of the day, Moderna is a platform technology company. We believe that we're creating a new way to make medicines across all of these different therapeutic areas. And the best place to exemplify that is actually on the far right-hand side of this slide, our respiratory vaccines. We saw, we believe, with the COVID-19 vaccine, evidence of what our platform could do to suppress respiratory virus infections, morbidity and mortality. We're quite proud of that work and the approval and the work that's still going on with that vaccine and Arpa will speak to some of that.

But that led us to rapidly accelerate what we're doing in respiratory vaccines more broadly because we feel that proof of concept is substantially derisking to the technology. And when we say rapidly accelerate at Moderna, we mean something generally unprecedented, we believe, which is that we have started 2 global pivotal Phase III studies with programs that had not even been in clinic in their target patient population 2 to 3 years ago. And as we'll update you today, we're well on the way. We've completed enrollment in the first one with influenza and the RSV vaccine were well on the way there as well. And so we're incredibly proud of that demonstration and what it means to derisk a modality and then really move quickly, measured in quarters, not decades.

We're on that path with CMV with our latent virus vaccines, although we have not had proof of concept in the first clinical study there. We continue to build the pipeline of programs that will move forward because we take a high degree of confidence from that established respiratory vaccine precedent that we have an incredibly powerful vaccine platform. And so that's why we're moving those forward.

Now as we move to the left on this, you'll start to see more and more emerging, what we call modalities, places where we're starting to see early clinical signs. We've got evidence of pharmacology and hopefully, evidence of safety and tolerability and that causes us to want to expand our pipeline, very similar to what we're doing in latent virus vaccines. Of course, on the far left-hand side, you'll see the purely exploratory examples, and Stephane mentioned it, inhaled pulmonary what we're doing in the VEGF program and intratumoral immune therapy.

And I want to spend a moment talking about a pivot point that we think we're approaching, which is how are we doing in our systemic rare intracellular therapeutics programs. Previously, we've taken the same delivery system, as you all would know, in our chikungunya antibody program and saw that we had repeat dose pharmacology and good tolerability and safety. That was in healthy volunteers that was making a recombinant protein for secretion.

The question that we had, still, and before we were going to dramatically expand that pipeline was could we see the potential for clinical benefit in an intracellular, a liver disease, particularly the rare liver diseases that now populate our pipeline. And what we'll be sharing today is some of that early data that says to us, we are actually on that path. It's early. It's emerging, but it points to the potential of this platform to replace enzymes intracellularly in liver of patients suffering from these debilitating diseases. And that is something that we're incredibly excited to accelerate forward.

Now a little bit of framing. For those who have followed the story, we've said this before, but it's probably something that is important to understand as we talk through this data. We actually have 2 distinct lipid nanoparticles with different chemistry and makeup in the clinical trials that we're going to be talking through today. The first one, which we call LMP1, is being used in our organic acidemias. And so that's the PA program that you'll see data on and the update on MMA. It is the same delivery vehicle that we previously shared the data on chikungunya antibody, the secreted protein that I mentioned before. But we didn't stop advancing our platform. And in fact, we continue to explore differences in pharmacology. And we identified a delivery vehicle called LMP2 here, that we eventually took forward in GSD1a.

We thought it was an intriguing difference in the type of pharmacology it could achieve in terms of potency and perhaps even in terms of duration. And we wanted to explore that in the GSD1a program. And so we did. And in fact, the OTC program as Stephane said a minute ago, is going to go forward in LMP2 as well. That doesn't mean we're done with LMP1. As you'll see today, we're very encouraged by that data.

And we'll continue to explore both of these delivery vehicles in clinical trials because we think both are showing encouraging early signs of activity. And we will definitely be thoughtful about the diseases in which we take forward the different delivery vehicles. Now Stephane said, there's also a third delivery vehicle in rare diseases. It's not on this slide. It's the one that we're taking forward with Vertex, which is an inhaled lipid nanoparticle, it is also different. You could call it LMP3, if you wanted, but that's not what we call it. It's also a different lipid nanoparticle that we used for inhaled delivery into the lung.

It is a core part of who we are, that we continue to invest in the science and technology of our platform that when we make improvements in the pharmacology of what we're trying to do with that technology that we move it into our pipeline in the case of medicines. And I would say that I do not think we are done. We will continue to advance new delivery vehicles and develop both preclinical and clinical data are the power of this technology and then continue to improve our medicines to provide the best potential benefit to patients suffering from these diseases.

Okay. So very briefly, before I call Dr. Korson up here, I want to just give a quick summary of some of the data in those 2 different delivery vehicles that we -- I was just thinking about a minute ago. The first is in the propionic acidemia program, that multi-dose study I mentioned, we now have 6 patient years of experience on the drug that's well over 100 doses as you'll see. It has been generally well tolerated, which is really encouraging. We've seen a trend in reduction in biomarkers, and we've been observing a decrease in the frequency of metabolic decompensation events. And I'll let both Dr. Korson and Dr. Glaser from our team, come share what that means, and why that has us encouraged about this early emerging data.

But clearly, evidence, we believe that, that platform technology, that lipid nanoparticle and combination of other technologies that makes up that modality is trending in a positive direction. The second program is GSD1a, and that is, again, an LMP2. It is the second delivery system that we brought forward. based on performance of pharmacology. And here, we have much earlier data. We're looking at one cohort. But again, this is a single dose study. And it's a single dose study that involves a metabolic challenge in a controlled and safe environment. And so we can read through that very quickly. Whereas in the case of the propionic acidemia program, we're waiting over time to measure events. In the case of the GSD1a program because of the structure of that clinical study, we get that data pretty quickly, right after that dose as we challenge with fasting in that clinical trial.

And both patients have demonstrated that it was well tolerated to date and showed an extension of that fast and normalization of some key biomarkers, including glucose, which we think is really encouraging, and we'll share that data. And it gives us that confidence that, in fact, we don't just have 1 delivery system that's working right now in clinical trials. We have 2 that are looking pretty good. Now it's early days. These are rare diseases. For those of us who've been with us and talked about what we've been doing in infectious disease, when we measure effect sizes in tens of thousands of patients, these are 2s and 1s intent. And that is the reality of clinical development in rare diseases. It looks smaller. And therefore, you want to be careful as you're looking at this early data that we don't over interpret it, and we will be careful.

But we are encouraged. We feel good about the science for both of these delivery systems and in both of these diseases. We have more work to do to find the right dose and bring that forward into potential pivotal studies. But we're very, very excited to be sharing where we are today.

Okay. Now I'd like to invite our outside speaker, Dr. Korson and as he makes his way up here, gradually, stairs here, good. Briefly, I just wanted to introduce Dr. Korson again. Dr. Korson joined us previously to talk about these programs a few years ago and some of you may remember that. He's a leader in rare diseases after graduating from the University of Toronto, completing his pediatric residency in genetic and metabolism fellowship at Boston Children's. He was on faculty at tough Medical Center for over a decade. And cofounded and leads and continues to co-direct at SIMD's North American Metabolic Academy. He has also moved on to a number of other roles recently at VMP Genetics, where he is the Director of Education and Physician Support and has been working to help medical centers improve their care for these patients. So a real privilege to have you here. Dr. Korson again, thank you, again, for getting up here so sprightly. Here is this. And I'll leave you in good hands.

Mark S. Korson

Thank you so much. It's a pleasure to be here this morning, and thank you for the invitation to speak about propionic acidemia and methylmalonic acidemia. As a clinician, what I want to do is kind of give you an idea of why what is being done here at Moderna is so important. But if you were talking about metabolic disease, what I want to do is actually give you a little bit of history because the evolution of the field of metabolic medicine actually is the story of PKU or phenylketonuria, and if we understand what has happened with PKU, those -- there are lessons there that directly apply to PA and MMA. So both PKU and PA and MMA are disorders of protein metabolism. Proteins are basically made up of amino acids or protein building blocks in various combinations according to the different protein. In PKU, it is phenylalanine, the amino acid phenylalanine that is broken down to form tyrosine and uses an enzyme phenylalanine hydroxylase to do that.

PKU is a defect in that enzyme, which results in high phenylalanine and low tyrosine levels. And it was actually Dr. Asbjörn Følling in Norway, who first identified the biochemical problems here when he noted that -- he didn't actually note -- the high phenylalanine -- he noted that phenylalanine was converted to phenyl ketons and the presence of phenyl ketones in the urine gave the name PKU. So the symptoms of PKU include severe profound intellectual disability. In fact, it's believe that about 1% of all institutionalized individuals in the 1960s, who are in mental institutions actually were there because of PKU.

These patients have seizures, psychiatric symptoms, anything from mood disorders right through to psychosis. Their hair and skin are lighter than would be expected given their family history and they have untreatable skin rashes. This picture taken from an early report in the 1930s of a woman who is very disabled who would rock back and forth. And to the author it resembles a tailor at work. And so the German term Schneider Sitzen or sitting like a tailor. Here, you can see that it's either the elevated phenylalanine that causes the symptoms or the low tyrosine beyond the block that is deficient that can cause some of the other symptoms.

But knowing that it's the high phenylalanine gave the idea that if one restricted phenylalanine in these patients, one could achieve a therapeutic benefits. And this was the first that was ever tried in the field of metabolic disease, tried in 1954 by Horst Bickel in Manchester with a 2-year-old who was very disabled with PKU. He put that patient on a low phenylalanine diet, the [fee level] drop, the phenyl ketones cleared and she became brighter and was able to start moving forward developmentally. And when he reversed it, put her back on a regular diet, the fee level rose and it was clear that this intervention has made a difference. So the dietary approach for metabolic diseases is to obviously restrict the amount of protein.

However, if you restrict protein too much in order to get those levels down, you end up not providing enough protein overall for protein metabolism. So what the nature of treatment for these disorders, whether it's PKU, PA or MMA, is to give a formula that has all the other amino acids that the patient can tolerate and none of the offending amino acid, but you need a little bit of that offending amino acid for ordinary just basic protein metabolism. So this is the diet of formula and some natural protein, and that's the diet. But because these diets are so synthetic, one needs to add vitamins or minerals to prevent deficiencies. So this is what the diet looks like for patients whether it's PKU, PA or MMA. Foods are forbid -- these foods that are forbidden include meat, milk, dairy products, fish, eggs, beans, legumes, nuts.

It's a huge intrusion into a person's diet. What is permitted? Fruit, vegetables and foods that are naturally lower in their protein content, so grains or starches, but even these are only provided in measured amounts. So for PKU, and this is as late as the 1980s, this is what the diet looked like. Vegetables, fruits, some formulas off to the left and some lower protein foods in the back. That's a really meager diet. These children were hungry.

And this put parents in a terrible position because consider it, if your child is complaining of hunger, are you going to be the parent who ignores your child's cries for hunger because you don't want his levels of phenylalanine to go up and therefore compromises brain. Or are you going to give in because what parents can ignore their child's cry for hunger.

So fortunately, a new industry was born and these are the low protein industry. Where these products were developed in which the higher protein wheat flower was removed and replaced with wheat starch. And so this provided adequate calories and without raising phenylalanine levels. And these patients don't no longer have a problem with hunger.

So with a diet in place, newborn screening was developed, again, because of PKU and the availability of a diet to prevent long-term complications in PKU. So PKU screening began here in Massachusetts in 1962. And with the success of newborn screening, it has evolved into a much larger newborn screening program. This being the recommended uniform screening panel published by the Department of Health and Human Services, PKU is at the top left, but you'll notice in the middle under organic acid disorders, propionic and methylmalonic acidemia are there.

So you have a treatment, you have an early screening program that is terrific. The problem is PKU taught us something. And that is if you treat patients, it was believed in the 1960s and 70s, if you treat patients, you probably only have to treat them for 5 or 6 years because brain development is complete by 5 or 6 years, "nuh-uh" those patients who went off diet at the age of 5 or 6, those girls who then grew up and who started having children, they expose their fetuses to very high phenylalanine levels, which would have been very deleterious to their own brains. In the pregnancy, the high phenylalanine levels actually intoxicated the fetus creating all sorts of problems now referred to as maternal PKU. And of course, these problems are inherent in fetal development, so they're not reversible.

So diet for life became the big call in PKU therapy that really these patients cannot go off diet ever if they want to optimize their brain function and overall well-being. The problem is that's a hard diet. That's a really hard diet. And so patients as they got older, sort of, kind of started giving up, and so their phenylalanine levels rise. Well, inadequate PKU management results in a number of problems like executive function problems where they have difficulty paying attention. They become very rigid in their thinking or they become very hyperimpulsive. They develop psychiatric symptoms, anything like anxiety or depression or agoraphobia, fear of open places, and they have problems staying in relationships contributing and participating in meaningful relationships.

So this became a huge problem where if you have neuro cognitive or neuro psych problems on the lower left, Well, that's going to interfere with your ability to adhere to medical recommendations, which will result in increased phenylalanine levels, which then cause further symptoms and you get into this vicious cycle, which you can't get out of. This is the problem in long-term diet therapy for PKU.

So, we have proof that this is, in fact, not a viable long-term option of therapy. In this very large study of -- well, large study for rare diseases. In the survey of over 3,700 patients found out that almost 3/4 of patients over the age of 30 were running with elevated phenylalanine levels beyond the preferred therapeutic level. And because patients felt they weren't doing well, they stopped monitoring themselves. And so over 1/3 of patients in that same age group ended up not testing anymore because they don't want to know their levels for many reasons. One, it disappoints them; two, they're afraid of disappointing their clinicians. And what became very clear at the bottom is that the vast majority of adults with PKU are simply unable to adhere to such a rigorous diet.

And this results in patients basically being lost to follow-up. So that in the age group of 25 to 45, if you look at the far right, 77% of patients don't come to clinic anymore, what's the point, I can't do it, you have nothing else for me, and they fall away. So when the National PKU Alliance polled this audience, so what is your biggest priority they said, to be able to increase my protein intake without increasing my PKU symptoms, meaning I want a normal life. I want a normal diet. And if I have to participate in a therapy that intrudes into my life at least 3 times a day and sometimes more, and of course, eating is very social. I can't do it, and I won't do it.

So when the patient community spoke up and when the clinician community spoke up, there was an explosion of therapeutic exploration into what would make a more definitive therapy for PKU. And so you see here a number of different products in development, anything from gene therapy to messenger RNA therapy, small molecule therapy, microbiome manipulation in others incredible interest in this area because PKU therapy, the once heralded success story is simply not working.

So why am I talking to you about PKU. This is about PA and MMA today. Well, the lessons we learned from PKU apply here. So let's go back a little bit to the biochemistry for PA and MMA you see on the top, there are 4 amino acids, isoleucine, valine, methionine, threonine, and they all get degraded through this pathway and also things come from other pathways as well. And they all end up in this pathway, which ends up in the Krebs cycle. Krebs cycle, and if you remember, biochemistry is a big energy producing cycle in the body.

So if you have a defect in this enzyme, that's propionic acidemia. If you have a defect in that enzyme, it's methylmalonic acidemia. They are sisters in terms of disorders. And if either of those are defective, then the accumulating organic acids are directly intoxicating the brain and other organs. They cause the blood to become acidic, which compromises brain and heart function. The organic acid suppress normal bone marrow function. So then in large quantities, your white blood cells don't multiply, making it harder to -- make you susceptible to infection and compromise the growth of platelets. And so you're at risk for bleeding.

And finally, these organic acids interfere with the clearance of ammonia, which is the byproduct of protein metabolism and this is a profound neurotoxin. So what you have with PA and MMA is multiple problems that are all connected through organic -- accumulation of organic acids, but in various different parts of the body. And everything on the left that I mentioned, these are all intoxicating aspects of the disease. But if you have defects in that pathway, so that you cannot contribute to the Krebs cycle from here, you're left with a low energy state. So these patients, even on treatment are floppy, they're fatigued, they're slow.

So, these patients are at risk for having metabolic crises or metabolic decompensation events, MDE. This results in problems with feeding, leading to dehydration, problems with as the brain becomes more and more intoxicated, they can fall into coma. They look as if they're septic as if they have a profound infection. If untreated, these patients go on to -- their breathing can stop, they become apneac. Their heart rate slows, they develop seizures, their temperature drops, they can have a stroke or die suddenly.

So, this is a video of an untreated infant with propionic acidemia. And you look at that baby and you think that baby is having a seizure. In fact, that's not the case at all. That is a profound tremor that occurs because an area of the brain that is particularly susceptible to the organic acids is -- controls movements, controls movements, and that is not occurring here, and that's why these children are at risk for these movement disorders.

So what Chuck Venditti who is a leader in organic academic research, especially for MMA, actually documented all the different ways these patients present. In the neonatal period, they could be present in coma or they can present with overwhelming infection or diabetes or infantile spasms, which are severe seizures. As they -- if they have MDEs in childhood, they can have, again, movement disorders, pancreatitis. They can go into multi-organ failure, secondary to infection. Again, diabetes or stroke. These patients during adolescent can just present with mental status changes or cardiac muscle disease or full-blown cardiac arrest. And as adults during MDEs, their movement sort of becomes pronounced they can evolve into a cardiomyopathy, kidney failure and even blindness.

So that's a lot of disease. So how RPA and MMA patients managed. Well, let's go back here. If you put these patients on a protein-restricted diet, like PKU, there's going to be less going down -- less substrate going down this pathway. Well, it's -- and it's the same approach that for PKU, we give them a formula in the lower left. But instead of restricting phenylalanine, we restrict these 4 amino acids, but provide all the other amino acids in normal quantities for these patients to use. But they need a little bit of these 4 amino acids and that comes from natural protein. So they are on the similar diet to patients with PKU. But it's not just -- that's not just the PKU -- a similar PKU -- similar diet to PKU that they have to endure.

They also have to take medications to control their blood acid level. If they get infected or a risk, they have to take antibiotics. They might need assistance or infusions if their platelets drop very low. They did medications to control the ammonia level. And because bacteria in the gut contribute propionate, which adds to this problem, they have to take regular antibiotics to reduce that bacteria colonization.

So the problem is or the success is that we actually have treatments for PA and MMA. The problem is it's not sustainable because you're looking at PKU therapy is -- it can't be sustained in the long term for that population. In PA and MMA, it's that plus all these medications plus MDE, it's simply not a good long-term plan. And the reason is these therapies address only the symptoms, the ammonia, the acidosis, that kind of thing. It's -- they don't address the underlying problem, which causes all of that. And so for a clinician, it's like playing medical whac-a-mole, which is basically this problem occurs and you try to address this. Meanwhile, this rises up and you have to address that it's an awful situation.

Furthermore, these patients and parents have to run intensive care units at home. They have to monitor their diet. They have to measure things that go into the formula. They have to look at ketones in the urine, they have to watch for symptoms, it's a very challenging and inappropriate, I would say, responsibility. So I talked to you a lot about PKU. For MMA and PA, the current therapy is PKU therapy on steroids. So we need a therapy. We, the patient community, we clinicians need a therapy that can provide ultimately working enzyme that will address all these.

And so I thank you, and I thank the folks at Moderna for putting so much time and effort into this.

Ruchira Glaser

Thank you, Dr. Korson.

Hello. I'm Ruchira Glaser, and I'm the Therapy Area Head for our therapeutics portfolio. Now that we've heard from Dr. Korson, the devastating effects that these rare metabolic diseases have not only on patients but on their families. I'm really pleased to be sharing with you today our exciting progress in our propionic acidemia program.

Now, what's remarkable to me is that this is the first time that anyone has delivered an intravenous messenger RNA therapy chronically over repeat doses to multiple patients with a liver-mediated chronic disease. I'm going to share the top line data with you in just a few moments, but what we see so far is encouraging, as you heard from Stephen. We see a good safety and tolerability profile so far. And when we look at the effects of the drug and see how it behaves, we see that the pharmacodynamics are improved when we give the drug more frequently and at higher doses, which is exactly what we may have expected. And finally, you heard about these metabolic decompensation events from Dr. Korson. So we looked at this as well. And we see so far that the frequency of these events is lower in patients who have been treated. So let me share with you some of these details now.

So as you heard from Dr. Korson, patients take in -- people taking all kinds of food, immunoacids proteins, fatty acids. But patients with propionic acidemia cannot process certain amino acids and fatty actives because they're missing propionyl-CoA carboxylase, an enzyme inside the mitochondria. And so as you can see here on the red metabolites get formed and these are abnormal. Now propionic acidemia is caused by changes in 1 of 2 genes, the PCCA or PCCB gene. These genes provide the instructions for making each of the 2 units, the subunits of propionyl-CoA carboxylase. When either of these genes are disrupted, the [enzyme] cannot function properly and we get the metabolic instability that you heard about.

What's really interesting to me about this therapy is that we actually have 2 mRNAs inside of a single lipid nanoparticle. Each of them encodes for the 2 units. So regardless of which genetic mutation you might have is addressed by this single therapy. And you can see here in this cartoon that once the mRNA enters the liver cell, it's translated into the 2 subunits, which then form together inside the mitochondria where they live to form functional protein and restore metabolic stability.

Now I mentioned this is the first time that we have given an intravenous mRNA repeatedly for a chronic disease. So this is a Phase I/II study, and our first goals were to study the safety of this drug and the pharmacodynamics of the drug were how it behaves.

We also looked at biomarkers, including 3 hydroxypropionate. And of course, we look in an exploratory way at those clinical events, the metabolic decompensation events. On the right side, you can see a schematic of the trial design. And what I wanted to share is that we've actually completed dosing in this rare disease of the first, second and third cohort. That's the data that I'm going to show you next.

So when we think about the demographics, these are small studies. We're early in the trial. So they're -- we're looking at 10 patients' worth of data. You can see that there's a wide range of ages and other characteristics of these patients. But let's take a step back and think about the overall experience so far. So overall, as I just said, we have 10 participants dosed. But actually, 3 participants have had over a year of dosing so far. And that amounts to 6 patient years of experience on the drug. We've also delivered over 120 intravenous doses of this drug.

Now the study is ongoing and our independent safety monitoring committee has approved us moving to the fourth cohort, which is the 0.6 milligram per kilogram dose, and I'll talk about that in just a few minutes. Importantly, I'm encouraged by the fact that all participants who have completed the study have chosen to continue on drug voluntarily in our open-label extension study.

Now this is a safety study, first and foremost. So let's talk now about the safety of the drug. It's generally been well tolerated to date. There have been no drug limiting toxicities. There have been no related serious adverse events, and no one has discontinued the drug due to safety events. In fact, the only drug-related adverse events that we have seen have consisted of mild to moderate infusion-related reactions and that has occurred in less than 10% of the doses that we've given so far. So overall, favorable profile.

But let me share now a little bit more detail about the safety of the drug. This table shows you all the adverse events that we measured in the trial. And you can see not surprisingly that most patients experience some form of an adverse event. But you can also see here that there has been zero dose-limiting toxicities, no AEs leading to study drug discontinuation. And when we look at drug-related adverse events, we had 2 drug-related adverse events in the first cohort. So far, we've not seen any drug-related events when we increase the frequency of the dose in the second cohort or when we increase the dose in the third cohort. And I'll talk about these drug-related adverse events in just a couple of minutes.

Importantly, though, there have been no drug-related serious adverse events. But what about all the serious adverse events? Let's look at those a little bit more carefully. Now as you can see, the majority of patients have had some form of a serious adverse event. And that's not surprising when you think about how thick this patient population is with propionic acidemia. In fact, if you look at the serious adverse events, many of these have been infections or procedures that require hospitalization. We know how vulnerable these patients are to infection, and how serious a simple infection can be in this patient population. We also classified those serious adverse events that were related directly to the pathology of this disease. And you can see those here in the middle of the slide. And those included metabolic disorders, vomiting and depression.

Again, no serious adverse events were classified by investigators in this trial as related to drug. But what were the drug-related adverse events. We can see this here in this table. As I mentioned a couple of moments ago, 2 patients in the first cohort had drug-related adverse events. These were mild to moderate infusion-related reactions. Importantly, both of the patients who have had these infusion-related reactions are still on drug today, and they've been on drug for over a year now. And again, as we increase the dose, and increase the frequency of the drug in our second and third cohorts, we've not seen any further drug-related adverse events or infusion-related reactions. So overall, this paints an encouraging picture so far about the safety and tolerability of this messenger RNA therapy.

So now that we've looked at safety, I wanted to talk about the drug's effect. We like to use biomarkers where we can to understand the pharmacodynamics. Now in propionic acidemia, there have been several biomarkers that have been described. But unfortunately, how they behave in a detailed way inside an individual patient has not been well described, which is not surprising because this is a rare disease. So as a result, we don't have, at this time, a clinically validated biomarker to study propionic acidemia. So when we designed the trial, we set out to study one of these biomarkers, 3 hydroxypropionate. And I've shown you this graphic before and remember the abnormal metabolites that are formed when you don't have propionyl-CoA carboxylase in propionic acidemia are shown here in red. And you can see that 3 hydroxypropionate is one of those metabolites.

I want to tell you a little bit about 3HP. It's important to note that 3HP levels in patients are highly variable. On this graph, on the x-axis along the bottom, you can see each subject that participated in the trial. So each of these box plots represent one of the subjects. The y-axis is their 3HP levels. And it's important to note, these are baseline levels. That means these are the levels before any treatment was administered to these patients. And I think you'll see that the levels vary quite a bit in patients when you compare across patients. And this does not seem to be related to things such as whether they had PCCA or PCCB as a genome type.

So this makes it challenging to study these patients with respect to 3HP. So when we think back to the fact that this is the first time that we've delivered an intravenous mRNA to patients with a liver-mediated disease and the variability of the biomarkers before we even start therapy, we decided to do the study in an adaptive design to help us input as much information as we could in these rare patients and make data-driven decisions about the next cohort.

So let me take you through this for just a moment. We would have 3 participants dosed and observe them first and foremost, for safety. We would take their individual 3HP biomarkers and how they behave before and after therapy and input those into our PK/PD models. That, together with the safety of the drug, would then lead us to make a decision about the next dose level. So far, we've made 4 decisions. We started at the lowest frequency and dose because, again, we want it to be safe, first and foremost. Our first decision was to shorten the interval of dosing. We started it every 3 weeks, and we reduced this to every 2 weeks based on the data that we were seeing. And that's what we did in our second cohort. We then

increased the dose from 0.3 milligrams per kilogram to 0.45 milligrams per kilogram. And finally, we've had our independent safety monitoring committee endure increasing the dose further to 0.6 milligrams per kilogram, and this cohort is about to begin dosing shortly.

But what about the individual levels of these 3HP biomarkers? Here, you can see each of the participants that have participated in the study. And the first row is that first dosing level. The second row is the Cohort 2 and the third row is Cohort 3. The red boxes represent each individual's 3HP levels before any treatment, and the blue boxes are at their levels after treatment. And you can see here, that the degree of change in 3HP varies across patients. But importantly, 7 out of 8 of these patients showed a numerical reduction in 3HP. Now when we combine these data by dose, this is what we see. Here in both of these plots, the red dots are their pretreatment levels. and the blue dots are there post-treatment steady state levels.

And so when you look on the left-hand side, at the lower dose, the 0.3 milligrams per kilogram dose, you can see overall a 19% reduction 3HP with drug. When we increased the dose to the 0.45 milligram per kilogram dose, you now see a 34% reduction in drug. You'll see less dots here because this is our most recent cohort. So we'll continue to collect 3HP levels on these patients and study the effect. But so far, we've seen a trend that's suggestive of a potential dose-related response with a greater numerical decline from baseline in the greater dose of 0.4 milligrams per kilogram.

So I want to switch gears to the clinical events. We talked about how central metabolic decompensations are to patients with this disease. They marked the disease and its consequences. So we wanted to study this in our first in human experience. And we define rigorously in our protocol what constituted a metabolic decompensation event. Not only did you have to have symptoms, but you needed to have emergency medical care, whether that be through the emergency room or admission to the hospital. And you also had to have abnormal labs. You have to have either a metabolic acidosis or severely elevated ammonia levels that require treatment.

When you think about the meaningful impact that metabolic decompensations have in this disease, and the objective measures that we can use. It's been encouraging for regulators who have been supportive even in our early discussions with them for using metabolic decompensation events as the primary endpoint for pivotal studies.

So let's look at how these metabolic decompensation events happen so far in our trial. And before I show you the data, I want to explain that the protocol asks that we collect in each patient that entered the study what happened to them the year before they entered the study in terms of their metabolic decompensation event. And when you look at this graph, there's a red line through the center. And everything on the left side of that red line is going to be the metabolic decompensation event that happened in that pretreatment retrospective period.

Now these are the data for the first cohort. So remember, this was the one that had the lowest dose and lowest frequency. Each row represents 1 of the participants. So you have subjects 1, 2 and 3. Each red dot is a metabolic decompensation event. And you can see that 2 out of 3 of these patients not surprisingly had several metabolic decompensation events in the year before they started the study. Now on the right side of the graph are the post-treatment metabolic decompensation events. And just to orient you, the triangles are where these patients are in follow-up, and you'll see that all of the patients in the first cohort have finished over a year of follow-up on the study and the open-label extension trial. And one of them is actually up to 480 days. And you can see that overall, the frequency of metabolic decompensation events is reduced.

You'll also see that some of those red dots are actually pink, and that's because the pink dots represent metabolic decompensation events, which occurred after 2 weeks of getting last dose of drug, and we shaded it this way because, as I mentioned before, we made a decision to change the frequency of the drug based on what we learned with 3 weeks to 2 weeks. Now I also wanted to share with you that we offer these patients, the choice of going to every 2 weeks frequency since we know that, that's the dose frequency that we have chosen. And 2 out of 3 of those patients have decided to switch to every 2 weeks in frequency, and they're going to be starting that shortly.

But what happens when we do look at the patients who had every 2 weeks frequency, so this is the second cohort where we didn't change the dose, but we increased the frequency to every 2 weeks. And this is their metabolic decompensation events before starting treatment. And you can see again that 2 out of 3 of these patients had MDEs before entering the study. Now after we gave the drug, again, you see the triangles, and that shows you where these patients are in follow-up. The first patient in this cohort actually almost at a year of treatment on drug. And the latest patient in this cohort is at about 100 days.

And you can see here that so far, we have not seen any metabolic decompensation events in these patients. Now when we increase the dose, this is our most recent cohort, so they will have the least follow-up. But when we look at their pretreatment MDEs, again, we see frequent metabolic compensation events in these patients before treatment. And after treatment, so far, we see no metabolic decompensation events. So overall, when you look at this graphic, you see on the right side, the post-treatment metabolic decompensation events, which appear reduced in frequency compared to the left side, the year before they started the trial. We analyzed these data and took all the participants who had at least 1 retrospective metabolic decompensation. And we -- that gave us an exposure duration of 3.8 years. We saw a 48% relative risk reduction in MDE frequency. Now this was not statistically significant. This is a small sample size, and we still have more follow-up to do.

None of the MDEs that have occurred so far have happened in patients who have received drug every 2 weeks. So overall, I am encouraged by what we see with metabolic decompensation events especially knowing how clinically impactful each of these events are to our patients. So we're not finished yet, we're still in the middle of the study, as I showed you, but we're expanding our clinical experience. And we have 6 patient years of experience already on drug. All patients who are eligible, as I mentioned, have elected to continue this drug in the open-label extension study, which is encouraging. And overall, the safety shows us that it's generally been well tolerated to date, with no drug-related serious adverse events, no discontinuations due to safety and only mild to moderate infusion-related reactions, which have occurred in less than 10% of doses.

We're still examining 3HP, but we see encouraging early trends, which suggests potentially dose-dependent pharmacology, which is what we'd like to see. And then, of course, as I just showed you, we have encouraging data that shows a numerical decrease in the number of metabolic decompensation events. And we'll continue to follow these patients as they stay on drug over time to see what happens to these MDEs. We're also going to continue to enroll additional cohorts and escalate the dose, as I said, we're at the 0.6 milligram dose next. And once we identify the optimal dose, we're going to expand the number of patients. While we are doing this, we're continuing to engage with regulators. So we can identify together the optimal path to register this drug.

Our teams are working hard, and they're working hard because we're encouraged by what we see. I hope that you see why I personally am cautiously optimistic about the potential for this mRNA therapy to help patients with propionic acidemia, a devastating disease for which there is no cure.

I wanted to just spend 2 minutes shifting gears to methylmalonic acidemia. You heard from Dr. Korson that, that's a very closely related organic acidemia. And we are actually studying methylmalonic acidemia too. And it's an ongoing Phase I/II study. Now I'm not going to share data about this trial today, and that's because this trial started after our PA trial. And so we've just finished enrolling that second cohort. And it's a multiple dose study. So we need to see the effects of multiple doses before we can do our first analysis. And when we have our analysis of safety and pharmacodynamics, we will share that with you, and we expect that in 2023.

So, I wanted to introduce Dr. Jeff Rezvani and our team to talk to you about another metabolic disease, glycogen storage disease type 1a. Jeff?

Geoffrey Rezvani

Thank you very much, Ruchira. So I'm Geoff Rezvani. I'm the Executive Director and Program Leader for Cardiovascular and Emerging Therapeutics and GSD1a. I'm a pediatric endocrinologist and I've had the opportunity to care for patients with inborn errors of metabolism, including PA, PKU, MMA and glycogen storage diseases. So I couldn't be more excited to be here at Moderna, to be able to share this information with you and be part of this.

So what is glycogen storage disease or GSD1a. It's a little bit different than the disease you've heard about earlier today, which are diseases of protein metabolism. This is a disease of carbohydrate metabolism. It's caused by mutations in the enzyme glucose 6-phosphatase, which is key in energy metabolism. That leads to life-threatening hypoglycemia. So your blood sugar can drop, that can cause seizures, brain damage and death in the short term, and then it can also lead to other problems, including liver cancer over time.

So glycogen is one of the storage forms of glucose. So it's used for quickly getting glucose and energy out to the body. So normally, your body stores glycogen, we'll talk about the liver, it's in other places too, but primarily in the liver in this case, for quick release. So glucose 6-phosphatase is what allows that glycogen to be broken down and then released from the liver, so it can be used by the rest of the body for energy.

Now when you don't have that, what's going to happen is you're not going to be able to release that glucose into the body, your glucose is going to drop, your blood sugar is going to drop. And instead, you're going to have those metabolites shunted to these other molecules that you see up there, like uric acid, lactate and triglycerides.

And without going into a lot of the details of the metabolism here, the things that I want you to take away from this are that the glucose, like I said, is going to drop over time. And that lactate or lactic acid is going to start to go up. Lactic acid -- if you remember, if you were a kid and if your gym teacher made you run around and you start to get a stitch around your liver here, that burning sensation. That's from the buildup of lactic acid from your body not being able to quite deliver the amount of energy that in the ways that it wants to.

When I bring those things up because again, this is a little bit different than PA and MMA and that these are things that change minute to minute in the body, that glucose and lactate level and we can measure them almost a minute to minute to see what's happening in these patients and with our medication.

So at the moment, there's no approved therapies for GSD1a. In general, the hypoglycemia can be controlled by eating frequently, sometimes even with continuous feedings through a gastric tube. Now that controls the hypoglycemia, but you still need to eat frequently, sometimes with uncooked corn starch, and this doesn't happen after days or something like this.

This happens after a matter of hours. So if you can imagine having to wake up in the middle of the night and eat or else risk brain damage or death or if you were the parent of one of these children that has this, you can imagine how challenging that would be to take care of how much of a burden it would create. So you can see this has a huge burden of illness and very high stakes for these patients.

So our approach to treating this is the same as all of our rare disease platforms. We encode using mRNA for the missing enzyme, deliver this in an LNP by an IV infusion, goes to the liver and does its job. So we're excited to say that we have an ongoing Phase I study of our mRNA in patients with GSD1a. We've received orphan drug designation from the U.S. FDA. The purpose of this study is to evaluate safety, of course, but also pharmacology of our mRNA in patients, in adult patients with GSD1a.

Importantly, this is a single ascending dose study. So right now, what we're doing is we're checking these patients, we're challenging them with a fast to see how long they can go without eating. What happens to those glucose and lactate levels. We then give them a single dose of our medication. We don't just want it to work that night or anything. We want to see how long it will last as well. So 3 days after that dose, we're going to do another fasting challenge to see if it's changed. And then again, after 8 days, we're going to do the same thing.

We're going to follow a few things there. We're going to see: number one, if they can last longer in that fasting challenge before they start to have problems. Ideally, it's going to be long enough that they could say, sleep through the night and not have to worry about those things. And then we're going to follow the biomarkers as well. And like I said, we can follow these things very easily almost minute to minute with blood sugar and lactate levels. And what we want to see is that blood sugar level staying stable and that lactate level staying stable and not starting to go up. We managed to enroll our first patient in this trial in June of this year, and we got our second patient in recently as well.

So how did we do. Well, as you can see, our 2 patients, both young women, both diagnosed at a young age. Well, the genome -- except the genotype of these patients is a little bit different, and that's important because patient 2 had somewhat more mild disease than patient 1. She seemed to have some residual activity of this enzyme. And we want to know if this medication works, not just in the most severe patients, but in all patients with GSD1.

So as you can see, this intravenous infusion was very well tolerated, only mild adverse events. We saw no vital sign changes up to 12 hours post infusion, no serious adverse events. No meaningful changes in safety labs, including hematology and liver function, and we have follow-up ongoing in these patients.

But how did it work? So I'm going to show you a few things here. And what I want you to keep in mind is what we want to see is on the top there, that fasting duration from baseline to after we give the dose 3 days and 8 days after we give that single dose, we want to see that going up so the

patients can tolerate fasting longer. And then we want to see that glucose staying stable as well, not dropping into a dangerous range during that fast. And we want to see that lactate level also staying low and not spiking there.

So patient number 1. This is before the dose. This is their baseline. She managed to go 4 hours and 48 minutes before becoming dangerously hypoglycemic. So what you can see there, the blood glucose start out around 100, which is in a pretty normal good range there. At about 3 hours, you start to see it drop a little bit. And then by 4 hours, it was really starting to come down and the 4 hours and 48 minutes, she was symptomatic. We had to stop the fasting study because her blood glucose was dangerously low.

Similarly, just like you would expect, that lactate, which started out at a good level, started to spike right around that same time that, that blood glucose started to come down. So exactly what you would expect there.

Now what happened 3 days after we gave her the single dose. 3 days later, she was able to go 8 hours of fasting without having her blood glucose drop dangerously low. And in fact, she probably could have gone longer, but this is when we terminated the fasting study for logistical reasons and because of the protocol. Her glucose during that time, similarly stayed in a nice range there, stayed above 80, which is right where we want it to be all the way out to 8 hours when we terminated the fasting study. And the lactate similarly didn't have that spike happen there. So this is what we were hoping to see with this.

Patient 2 look remarkably similar. Now at baseline, they were slightly different. Like I said, they seem to have some residual activity of this enzyme. So at baseline, they managed to go 7 hours and 10 minutes of fasting. So slightly longer there. But similar to the first patient, what we saw after the single dose is this patient went all the way, in this case, to 10 hours and 15 minutes when we terminated the fasting challenge for logistical reasons.

Similarly, you saw that blood glucose come down at baseline to a dangerous level and that lactate start to go up. And in this case, it stayed much more stable and the lactate level you can see didn't have that spike.

What about at day 8? Well, based on the half-life of the glucose 6-phosphatase enzyme, we would expect that maybe there is some less activity at day 8 at the dose that we were using. But as you can still see, we still saw a great increase in the fasting -- in the length of these patients were able to fast during the fasting challenge. And similarly, the glucose and lactate did exactly what we would expect there. So encouraging results there also. So what's next on this?

We're incredibly, incredibly excited about this data and the opportunity here to help these patients. This is only 2 patients at this point, but they look remarkably consistent. From here, we're going to continue to enroll these cohorts, and we hope to see the same results in the rest of the patients in these cohorts. We'll use this to continue to evaluate the safety of our mRNA as well as LNP2.

We're going to continue to assess fasting tolerance and go up on the doses with these next patients. We're also eventually then going to find the right dose and do multiple doses for these patients. And what we're hoping to do is extend that fasting tolerance out beyond even 8 days. So again, I'm incredibly excited to share this with you, and we hope to share more great information on this in the near future.

Thank you very much. I'll hand it over to Stephen.

Stephen Hoge - *Moderna, Inc. - President*

So I hope you get a sense why now on assessing (inaudible) reduction something all. I'd call Dr. Michelle Brown to read that program, to give you a bit of a preview of things that we expect to come. As I'll remind you, we do expect the primary analysis of this study to read out in the fourth quarter of this year. Michelle?

Michelle Brown

Thank you. Good morning, everyone. So my name is Michelle Brown, and I'm the program leader for oncology. Most of my adult career has been spent in research in cancer, treating oncology patients and developing novel therapeutics. So I'm very excited to represent the personalized cancer vaccine team and provide you with an overview of this program.

So like a fingerprint, each patient's cancer is unique. The personalized cancer vaccine is an individualized immunotherapy that targets specifically a patient distinct tumor mutational profile. To manufacture PCV, we start by collecting patient samples and simultaneously sequencing their DNA and their tumor tissue then using an advanced computational method and our proprietary algorithms, we're able to identify hundreds of mutations. And these are then assessed to understand and predict which ones would be most likely recognized by the patient's immune system and mount antitumor responses.

Then up to about 34 of these neoantigens are selected for incorporation into the vaccine, and this really results in a single PCV for a single patient. Now importantly, this process from the first needle sampling to the first needle administration of PCV can be achieved with high efficiency and completed over several weeks. Now like other Moderna mRNA vaccines, the instructions for these PCV neoantigens are encoded onto a single mRNA molecule and then encapsulated in our lipid nanoparticles.

Once they're administered intramuscularly, this packaged mRNA enters into the cell and then using its own translational machinery, the mRNA is transferred into protein chains. Now the [non-sense] protein is then cleaved by the proteasome back into these neoantigens, which then make their way up into the cell surface and are expressed by the MHC complex. And this is recognized by the T cell receptor.

So the entire process here of PCV neoantigen presentation really should train a patient's immune system to recognize cancer cell [dysporin] and result in CD8-mediated destruction. Now the ability of PCV to induce these immune cell responses in addition to safety and preliminary efficacy is being assessed in our ongoing Phase I trial.

Representatives of the clinical data from this trial. This graph really depicts the neoantigen-specific T cell responses from a non-small cell lung cancer patients whose samples were collected at baseline in and after 4 cycles of PCV monotherapy as detected in red. And what you can see across the graph, is that we had T cell responses detected across all the neoantigen pools that were present in the vaccine.

And importantly, as you see from the change between the gray bars to the red bars, is that these T cells were activated in threefold increases for over 50% of the neoantigens that were present. In addition, these antigens were the ones that were sort of predicted to have the highest binding affinity. So data like this from the Phase I trial really provides us with confidence that our algorithm is: one, able to predict biologically relevant targets; and two, that when PCV is administered into patients, we're actually able to activate the immune system.

Now studies have shown that immune activation can result in antitumor activity. And this has really been seen with the checkpoint inhibitors. And so it was thought that by combining PCV to enhance that neoantigen presentation and a PD-1 to further increase the immune activation, we could really generate significant clinical benefit. And as depicted by the study schematic, the direct effects of PCV PD-1 combination versus PD-1 alone, are being directly assessed with our strategic collaboration partner, Merck, in our ongoing Phase II open label randomized trial in adjuvant melanoma patients.

So in this study, patients with resected melanoma who are at high risk of recurrence, were randomized to receive study treatment. About 100 patients were dosed with the combination and about 50 received standard-of-care pembrolizumab. Now per protocol and per sort of consistency with standard of care, all patients, once they were enrolled in the trial started with pembrolizumab, and were able to continue that up for 1 year. What this meant for the combination arm is that these patients received their first 2 doses of pembrolizumab alone, then 9 doses of the PCV combination and then continued on with their PD-1.

And these -- all these patients are planned to be followed for up to 3 years to assess their long-term clinical benefit. But consistent with adjuvant studies, our primary endpoint is recurrence-free survival. And the primary analysis was prespecified to occur after patients were followed for 12 months and after at least 40 recurrence events were observed on the trial.

As noted on the slide, you can see that the trial enrolled completely in September of 2021. And as you've heard repeatedly from Stephen, what that means is that we anticipate our primary analysis coming through and reading out later this year in 4Q of 2022.

Importantly, this trial started back in 2019. And we know that oncology has had quite a dynamic treatment landscape and that treatment for melanoma patients has really evolved over the past couple of years. But importantly, this trial design and our primary output of recurrence-free survival is still relevant to today's standard of care and the landmark CheckMate 238 and KEYNOTE-054 studies.

So as seen by the Kaplan-Meier curves on this slide, what we see with CheckMate-238 is that approximately 900 patients with Stage IIIb, c and 4 melanoma were randomized to receive either the anti-PD-1 nivolumab or the anti-CTLA-4 ipilimumab, and after about 18 months of minimum follow-up, the landmark 12-month RFS rate was 70.5%, and the hazard ratio was statistically significant at 0.65.

Consistently with the KEYNOTE-054 study, which randomized about 100 patients that had Stage IIIa, b and c melanoma and a minimum of 15 months of follow-up, the Landmark RFS rate for 12 months was at 75.4% and the trial was significant with a hazard ratio of 0.57.

So these 2 studies really established the anti-PD-1s as standard of care. Now we have Moderna believe that the development of novel synergistic approaches using mRNA could further transform the treatment landscape for these patients without adding significant toxicity.

So as I started with, this is a very brief overview of our program. The P201 trial is currently ongoing. It is our randomized open-label Phase II trial to really assess the PCV pembrolizumab combination. Our primary endpoint is RFS and that analysis is expected at the end of this year in 4Q of 2022. Now previous landmark studies have really shown that about 70% to 75% of patients that are treated with standard of care are able to remain disease free for up to 12 months.

But what this really means is that approximately 1 in 4 patients will have their cancer return in less than a year. And what we know is that can cause significant morbidity and result in death. So there is still a high unmet medical need. And it's really our hope that combinations like PCV, pembrolizumab are able to delay and prevent these relapse events and really address that unmet medical need. Therefore, it's not surprising that if our primary endpoint is positive that this will really provide a proof of concept for us for PCV, but also increase our confidence that our mRNA technology can provide benefit for oncology patients.

So we're really excited for the outcomes than what we are going to see in 4Q of 2022 this year. And I think with that, it was a brief overview of our oncology portfolio, but I'm the last piece standing between us and a break.

So I will hand this back over to Stephen.

Stephen Hoge - *Moderna, Inc. - President*

Thank you so much, Michelle. All right. Thank you all. So we'll go to a quick 10-minute coffee break. We'll move from talking about patient numbers in tens and hundreds to tens of thousands. And Jacqueline Miller and the infectious disease team will walk us through that Phase III portfolio. So 10 minutes and then back in this room. Thank you.

(Break)

Jacqueline Miller - *Moderna, Inc. - SVP of Infectious Disease Development*

(technical difficulty)

Even though previously, there has been some indication that people that are seropositive have more local reactogenicity. We haven't observed that to be the case with the 214 bivalent. And then these are the general solicited symptoms. And again, we're seeing the same trend, perhaps a

bit more noteworthy in terms of solicited symptoms being lower than the reactogenicity profile, particularly after the second dose. So we're able to administer this bivalent vaccine. It improved immunogenicity to the BA.1 sublineage and not take additional reactogenicity in the profile.

So now I want to talk a little bit about the longer-term benefits of immunogenicity with this vaccine. I mentioned to you that we met both of the primary endpoints, including superiority against Omicron. This was 1 month after vaccination.

We have to go back a bit in time to the original bivalent that we studied in the clinic. This was a beta bivalent. You may remember in February of the beta variant was really the first 1 to cause a lot of anxiety coming out of South Africa into the rest of the world. And so we actually have followed those subjects not only for 1 month after vaccination, but for 6 months after vaccination.

So on this slide, in the light blue, you see the mRNA-1273 third dose booster at day 29 and then 6 months later at day 181. And there's a [6.6-fold] decrease in antibody titers over that time. Now in the preclinical study in about 20 subjects, we have studied a monovalent data variant vaccine. And so the question is, could beta variant vaccine actually improve immunogenicity against the beta variant.

Well, sure. Immediately post vaccination, we saw numerically higher titers. But 6 months later, that the titers are almost exactly the same against the beta variant with a decrease of 8.2-fold. When we gave the bivalent vaccine containing 25 micrograms of 1273, 25 of the beta subvariant mRNA, you see that post vaccination, the titers are approximately comparable to the beta monovalent vaccine, but 6 months later, we see titers that are approximately threefold higher and really demonstrates the potential for benefit in terms of durability of that neutralizing antibody.

And this slide perhaps brings the point home even further. So what you see on this slide are GMT ratios between the 211 variant over -- the 211 bivalent vaccine, the 1273 vaccine, and you see in dotted line of GMT ratio of 1. That would mean that the antibody titer or equivalent. And you see for 4 different variants of concern, the ancestral strain, the beta, Omicron and the Delta at both day 29 and then 6 months later at day 181, what that GMT raised like.

And while the bivalent always, for all variants of concern, had a higher GMTs ratio. For 3 out of 4 of the strains tested, the ancestral, the beta and then the Omicron, we see that, that GMT ratio increases even further. So really demonstrating while there is superiority at day 29. We anticipate that, that superiority will (inaudible) and may even improve with the 214 bivalent vaccine.

So I also want to show you that a bivalent vaccine 214 had cross-reactive antibody titers against BA4/5. So that is the Omicron sublineage that is currently dominant. And you see on this graph, again, in light blue, mRNA-1273 dark blue with the mRNA 214 at day pre-booster and then 1 month later, in all participants, and then separated by whether or not they had evidence of prior infection before vaccine and also in younger and older age cohorts.

And consistently, we see against BA.4/5, not only is the vaccine immunogenic, but it induces numerically higher titers against an Omicron sublineage BA.4/5, that is different than the one contained in the vaccine. And these are the data that we have submitted to FDA and then presented and defended at the recent ACIP.

So we will be generating clinical data with 222, which is the BA.4/5 sublineage containing bivalent vaccine. We have a master protocol called Protocol 205, and we have continued to add cohorts to that protocol. We will be evaluating the 222 data against a dose of mRNA-1273 at the 50-microgram dose. We have completed enrollment in that cohort and we anticipate reporting out those data by the end of the year, and they will go into a supplemental BLA submission to the U.S. FDA.

Now how have we been able to move these bivalent vaccines forward. Well, we actually have generated clinical data in over 7,000 individuals against various bivalence over the last year. I mentioned 211, which was the original larger cohort study.

We have also studied bivalent vaccines containing delta and then as mentioned, the original vaccine and the Omicron BA.1 sublineage. We also had a few monovalent versions that we've studied, the Delta monovalent and the Omicron monovalent. So the safety of these is really consistent. Actually, the safety profile seems more determined by which dose and the series you're receiving than whether the vaccine contains variant of concern sequence. And so that really allowed us to form this basis and submit our clinical data subsequently.

The other important piece of our file submission is that the manufacture of this vaccine is really identical other than the DNA template that we use for sequence to the original vaccine.

And then finally, we have preclinical data demonstrating at the 222 bivalent vaccine in mice, prevent infection and replication in the lung. So when we do PCR recovery after challenge in the mice, we see substantial reductions in the bivalent vaccine. And so this was really the package on which the U.S. FDA authorized the vaccine and now we're implementing a vaccination program.

Okay. So to give you a little view of the timeline overall, just to give you a sense of how have we been able to go from 10 months to register or have the EUA for the original vaccine to going from June 28 to Labor Day. So essentially the early summer to the end of summer to authorize the 222. And it really is by taking advantage of the platform technology. So in 2021, as I mentioned, we started studying variants of concern, and we have been gathering and submitting the safety data from those variants of concern over time, also presenting and speaking to regulatory agencies.

So they had an understanding of the vision we had for adapting to this evolving virus. We took our omicron BA.1 containing vaccines into the clinic in the first half of 2022. And as I mentioned, these are really critical to underpinning the 222 submission. We have scaled now our manufacturing in the second half of 2022. And with our original authorizations, we really felt accomplished to have gotten most of the authorizations in the first couple of months after the first authorization.

We've now shrunk that down to authorizations within weeks and days of other authorizations. And the reason we can do that is our regulatory submissions really build upon that platform technology, they require little customization for individual countries also because we've been speaking to agencies over time about the consistency of our data. And so again, that has led in the last or so to our EUA authorization in the FDA and conditional approval with the European Union. So 1273 also forms the basis of the rest of the late stage regulatory pipeline.

And you're going to hear more about that from Drs. Nachbagauer and Shaw, but I want to explain a bit how we view these individual monovalent vaccines and then eventually to form combination vaccines. It's actually rather remarkable to me that we're speaking about 2 additional Phase III programs.

So in 2 years at Moderna, we've now brought forward 3 programs in the respiratory portfolio to Phase III, 1 program in latent virus, just to give you a sense of scale in my previous career, it took 8 years to bring 3 products into Phase III. So being able to build upon that form technology, bring products into the clinic based largely on proof of concepts from some of our other products, we now have our mRNA-1273 license. That's really a proof of concept that we're able to use this to induce neutralizing antibodies, also known to be important in the protection of infection in severe disease for influenza and RSV.

Our seasonal influenza vaccine is a quadrivalent vaccine like the seasonal influenza vaccines on the market containing 2 influenza A and H1N1 and H3N2. and 2 influenza B antigens. So 1 from the Yamagata lineage, 1 from Victoria Lineage, it's a 50-microgram dose, so similar LNP mRNA dose to our mRNA-1273 boosters. And we're studying our Phase III in individuals, 18 years of age and older, and we're investigating in immunogenicity compared to a licensed competitor.

We're able to do that because regulatory agencies have issued guidance or the acceptability of that approach. We are also planning an efficacy study in those who are 50 and above, and why 50 and above, these are the individuals who are at most risk for the severe complications of influenza. And if we can demonstrate vaccine efficacy in this population, we can infer efficacy in younger individuals.

We also have our respiratory syncytial virus vaccine now in Phase III. It's a monovalent vaccine encoding for the pre-fusion or pre-F protein of RSV. It's another 50-microgram dose, and we are investigating in an efficacy trial, those who are 60 years of age. [Bob], again, at the highest risk in adults for complications, of respiratory syncytial viruses.

And then we have an immunogenicity study ongoing in those individuals who are 50 years and above. Why? It's important to us to have demonstrated efficacy, immunogenicity safety in populations over 50 years of age, so we can begin to combine.

So what does our (inaudible) pipeline look like? Well, in older adults, we're investigating those respiratory pathogens that we know create the greatest amount of disease burden and hospitalization.

So our initial foray into the combination space is with a vaccine, including COVID and influenza. We're fully enrolled Phase I/II study and are looking to report out our data by the end of the year. And then we're being ready to launch on the basis of those COVID flu data, a COVID flu and RSV combination vaccine.

And again, we believe we can get started with our combination process while awaiting that final efficacy data because we have really solid Phase I/II data neutralizing antibodies. And we have seen in the past those neutralizing antibodies can translate into protection against disease, not only in relevant animal models, but also in humans.

In pediatrics, there also is an unmet medical need for protection from these infections. So the youngest babies and the oldest amongst us are those at the most increased risk. We have an ongoing program of a combination vaccine against human menoneumovirus, or HMPV, and parainfluenza virus Type 3 or PIV3. And then we also will be initiating combination program with RSV and HMPV starting in 2023.

So we are also, though, preparing for the launches of these monovalent vaccines by investigating co-administration. And again, co-administration is an important interim step to moving to full combination vaccines. So we are investigating our RSV vaccine, both as a combination with RSV and influenza given simultaneously as well as RSV and a COVID booster given simultaneously. And we will continue also to investigate combination vaccines, for example, in pediatrics, where we know it's very important for co-administration to be authorized in order to encourage inclusion in the routine pediatric vaccination schedule.

Okay. So with that introduction, it gives me great pleasure to introduce Dr. Raffael Nachbagauer. He's our program leader for the influenza vaccine portfolio.

Raffael Nachbagauer

Good morning. I'm Raffael Nachbagauer, and I'm leading the influenza program here at Moderna, and I'm super excited to share some updates and details on our Phase III programs for [influenza] today. I usually would skip this slide because I think most of us know flu. But after it almost disappear to 2 years and is now starting to make its comeback, I think it's good to remind ourselves of the burden on public health that influenza has on the human population.

During a normal flu season, we see up to 5 million severe cases every year and up to 650,000 deaths worldwide. And in the U.S. alone, we see 710,000 hospitalizations and up to 52,000 deaths, particularly in the older adults, there is a substantial burden, and that's currently not sufficiently met with these vaccines out there.

I'm going to mainly focus on mRNA 1010 today, which is our most advanced clinical candidate. And it's a quadrivalent vaccine, as mentioned earlier today. It has for mRNAs that encode 4 strains of influenza that are recommended by WHO. It's the hemagglutinin or HA protein dose strains, which is the main target for neutralizing responses against influenza, and we are encoding for the -- we are delivering the mRNAs at an equal mass ratio for those core strains.

We have a 2-month strategy for the licensure for mRNA 1010. And this is based on both an immunogenicity and efficacy trial, as you heard earlier today. The rationale for that is that there is an established licensure path for influenza vaccines based on immunogenicity alone, immunogenicity and safety, I should say.

However, this initial licensure comes with the requirement to demonstrate efficacy post-licensure. And therefore, we are planning to do both. Why are we not just running an efficacy trial? Well, the reason for that is that flu epidemiology is quite variable, as you know by now. And that can mean that those trials can take multiple years and it would delay the time to get to the market.

And even more importantly, to highlight the issues with just running efficacy trials is, there's at least 1 example of a vaccine that has been based on accelerated approval that later on field, it's a confirmatory efficacy trial, but in the meantime, demonstrate effectiveness in real-world data and really showed that it was on par with other licensed vaccines, which means that if we only went for the efficacy trial, they would still not be licensed and would not be able to provide a benefit to the population. So that's really we want to pursue both of those, get initial license based on immunogenicity and then follow that with efficacy immediately.

As mentioned earlier today, the Phase III immunogenicity trial in the Southern Hemisphere targeted enrollment of 6,000 participants. And we're happy to announce that we fully enrolled the study in August, and we also got a favorable feedback from FDA and EMA that this study could support the licensure of mRNA.

We are also planning an efficacy trial that's set to start this fall. We are expecting to enroll approximately 20,000 participants. And this trial, as I mentioned, is intended to fulfill the post-licensure requirement to demonstrate efficacy.

And with that, I'm going to dive a little bit deeper into the details of our studies. First, the immunogenicity study, mentioned 6,000 participants have been enrolled. This study was conducted in -- or is conducted in participants 18 and older. About 30% of the participants are 50 to 64 years old and 20% of participants are 65 years and older. The trial is 1:1 randomized between mRNA 1010 and the licensed influenza vaccine comparator. And we are primarily looking at safety and non-inferior immunogenicity against the licensed comparator. We also have a secondary endpoint that looks at superior immunogenicity against the licensed comparator. And the site locations were in Australia, Argentina, Colombia, Panama and the Philippines for this study.

Now switching the efficacy trial. This efficacy study is conducted in 50 in individuals 50 years and older. This is really because this population has the highest burden for influenza. And we're planning to conduct this trial this fall, enroll 23,000 participants and we're aiming for approximately 50% older than 65 years and 10% older than 75 years.

The primary end are, again, safety and then non-inferior relative vaccine efficacy in preventing the first episode of [RT-PCR] confirmed protocol defines influenza-like illness caused by any strain of influenza. This is a very hard approach to -- for those types of efficacy trials. It has been done multiple times. We also, of course, have study points that look at superior rVE vaccine efficacy and we're also looking at a rVE vaccine efficacy based on [additional] definitions. We have the protocol-defined ILI, but also the CDC-defined ILI, for example.

And last but not least, we're also going to look at the potential to prevent hospitalizations associated with influenza illness. It's not likely that we're going to accrue a lot of events in this study, but we're definitely going to measure it and might actually see a benefit there as well.

We are anticipating for the study to be conducted in a single season. But as I mentioned, those studies might have to spend multiple years to really demonstrate the benefit. And once again, that's why our initial immunogenicity trial is going to be so important to get that initial licensure and demonstrate real-world effectiveness in parallel potentially unless we [keep] from the start and demonstrate efficacy right away.

And to summarize what I presented, our Phase III immunogenicity trial is completely enrolled, and we're expecting our readout in the first half of 2023, and we're expecting this trial to support the initial licensure of mRNA 1010.

We are starting a Phase III efficacy trial this fall in Northern Hemisphere. And this trial is intended to fulfill the regulatory requirements to demonstrate efficacy post licensure. And I only talked about mRNA 1010 today, but as a short reminder, you probably have seen our pipeline, and we have a couple more flu programs ongoing.

And most importantly, mRNA-1020, 1030 are already in the clinic. Those are vaccines that encode for additional antigen beyond the HA, the neuraminidase and we anticipate that those vaccines could provide even better position than just the HA alone because you get additional breadth of your responses as well. And then we also have mRNA-1011/-12, which are vaccines with a higher bivalency of HA antigens. And once again, we want to get broader coverage across multiple streams. We're planning to take this vaccine to the clinic early next year, and I'm really looking forward to those results as well.

And I'm going to hand it over to Dr. Christine Shaw, who's going to talk about the RSV programs.

Christine Shaw

Good morning, Christi Shaw, the Vice President and Portfolio Head of Respiratory themes. Today, I'm going to be talking to you about our respiratory syncytial virus older adult program. RSV is a very common seasonal respiratory virus similar to flu, but less well known in older adults in the United States, it causes over 170,000 hospitalizations and 14,000 deaths every year. Globally, even higher, we have more than 1.5 million episodes of acute respiratory infections and 330,000 hospitalizations every year. Many of these infections can also learn to lead to longer sequelae. But the true burden of RSV in older adults is likely much higher than this. And that is because testing for RSV does not happen very much. So it's just not realized what the true burden is. And all of these infections and hospitalizations due to a high medical cost.

So here is a picture of our RSV vaccine. It's called mRNA-1345. It has a single mRNA sequence in a lipid nanoparticle and that sequence encodes for the fusion or the F protein from RSV. It is membrane-anchored and it's also stabilized with modifications to keep it in the prefusion confirmation. This is key because the pre-fusion confirmation is that the display all of the sites or epitopes known to induce protective neutralizing antibodies, both to the RSV A strain and also to the RSV B strain. And the lipid nanoparticle used in this vaccine is the same as our vaccine portfolio generally and specifically also the same as our COVID-19 vaccine.

So as mentioned, we have a pivotal efficacy study ongoing with this vaccine. It is in older adults 60 years and above, placebo-controlled, case-driven design, I will get into more details about the design the subsequent slides.

We're expecting to roll 34,000 individuals, so it's a large study, and it's able, and I will show you also where we're conducting that study in the coming slides. So this -- in this study, the participants randomized 1:1 to either receive a single injection of the RSV vaccine or placebo. And this study actually started out in November of last year as a Phase II portion. It was a Phase II/III study.

In the Phase II portion, it enrolled 2,000 participants approximately. And then we had an independent data safety monitoring board review of some of the data from those participants, and they agreed, we should open up the larger Phase III portion of the study, which we did in February of this year. And in this study, our primary endpoints are safety and efficacy as a standard efficacy study. But I want to point out that any RSV cases from Phase II and Phase III do contribute to the primary endpoint in this study. And again, it is a case-driven city. So our analysis will be triggered after a certain number of cases are met.

Again, I will get into that in a minute. So the study has been ongoing since February for Phase III portion and has enrolled already more than 24,000 of the 34,000 participants. And here, you can see a little more about that enrollment. And in fact, every month since February, the rate moment has increased. So specifically in August, last month, we enrolled more than 7,000 participants.

So if this pace continues, and we expect it will, as we even open more sites that we think we can complete enrollment of the study this year. And because RSV epidemiology is quite disrupted during the COVID pandemic, we are closely monitoring the RSV disease and incidents in the world using global surveillance method. And we feel like we're positioned quite well to capture RSV cases that will start to accrue rapidly, hopefully, in the Northern Hemisphere in this coming fall winter season.

So here, digging in a little deeper to where we're conducting the study. It's global. And right now, we're in 20 countries enrolling actively in more than 200 sites in those countries. So you can see from the map, the countries we're conducting are in blue that we have sites spanning all over the globe, Northern Hemisphere, Southern Hemisphere and in 6 continents, we just don't have Antarctica, and so we are well distributed to hopefully find RSV where it happens. And like many of our vaccine studies at Moderna, we care about, including people in the study that are perhaps more at risk for the disease and that we are equally representing our population in the study. So we have set diversity and inclusion criteria upfront.

And this study in the United States, our target is to enroll at least 30% persons of color, pleased to say we are above that right now, at least in the study at 35%. So we have good progress there as well.

So in this -- now moving a little bit to the endpoints of the study. We are measuring clinical disease in a spectrum of different endpoints with different severities. And some of them are listed here, specifically, one thing that we're very interested in is RSV-associated lower respiratory tract disease and this is defined as having 2 or more signs or symptoms from a list of predefined signs and symptoms.

We are also looking at an endpoint of RSV [LRTD] with 3 or more signs or symptoms. This would be a more severe disease, more symptoms associated with it. We also have endpoints against hospitalization, as well as acute respiratory disease, which does not require a lower respiratory component. In all of these endpoints, we begin to accrue cases that count towards our endpoint, starting 14 days after vaccination. And the study is designed empowered so that we should be able to accrue enough cases in a single year to reach your endpoint, assuming we have an efficacious vaccine and RSV circulates as we expect.

And we have, in fact, begun accruing cases on the study. So we do have cases across some of the participants enrolled. And we soon will be approaching a milestone where we have enough safety data to support a regulatory filing for licensure approval. Specifically, what I mean by that is that we will -- in November of this year, have at least 6 months safety follow-up data for the 6,000 participants, the first 6,000 participants, we enrolled in the study. And that means 3,000 that got the vaccine, 3,000 that got placebo.

So I want to now spend a little time talking through the statistical endpoints and how we're going to achieve success in the study. So in an efficacy study, there's a number of variables that contribute to the success of the study. Such as the sample size, the attack rate, the power that we designed the efficacy of the study. And so these are all interplay. And we are looking at efficacy at a number of points in our study. We've predefined interim analysis so we can look and see how our vaccine is doing. That's what's shown here on the left side of the slide. In this study, we've predefined 3 different analyses that are triggered by a specific number of cases.

The first interim analysis was triggered at 403 cases, the second at 75 and the primary analysis at 106. So what do I mean by a case in this slide. A case here is defined in the asterisk on the bottom as an RSV-associated lower respiratory tract disease with 2 or more signs or symptoms. However, we will be poised to look at also RSV/LRTD with 3 or more signs or symptoms at these interims. So we'll be looking at different severities of disease as we evaluate efficacy.

And I want to illustrate more closely kind of the interplay between these different study variables and how they contribute to the success of and probability of success on the study. So I'll turn your attention to the graph on the right here. And here, we're showing on the y-axis, the statistical power of the study as a function of the efficacy on the x-axis for each of the planned analyses, which are the curbs on the graph. And I'm going to walk you through 2 examples.

These are hypothetical. At this point, we do not have efficacy data for the study. But our vaccine is 65% efficacious. Perhaps a relevant number, given that another company has released data recently showing efficacy around this percentage with a similar endpoint of LRTD , again, with 2 or more signs or symptoms of disease. So if we are achieving 65% efficacy, we will reach, at some point, 43 cases in our study, will trigger analysis or first interim. And at that point, if you follow the bottom blue line, we have about a 10% probability of success, achieving success at that case interim cut point.

However, as the study increase in size and we enroll more participants and their power increases, we reach our second interim analysis, which would be triggered at 75 cases. And at that point, we have about 60% probability of achieving the statistical success. And then continue the study, more participants, more sample size, we reach the primary analysis of 106 cases. And now we have a 90% probability of achieving success in the study. So this study is very well powered to show -- if we have 65% efficacy -- to show success at our primary analysis.

But we hope we have even higher efficacy than 65%. We will see. But let's illustrate what would happen there. And this is exactly why we have those interim analyses planned so that we can look earlier and if we are quite efficacious, we'll be able to see that sooner and potentially close the study earlier and get this vaccine out to the patients that need it.

So if we have 75% efficacy, this is 10% higher than the example I just showed you. I just moved the curves on the graph. You can see that we still come to the first interim at 43 cases. But now we have a 40% probability of success, before it was 10%. And then we move on to the second interim, still 75 cases, but now the probability of success is 90%. So if we had a 75% efficacious vaccine, the study is very well powered to show success at

the second interim analysis. And of course, you could go through the other scenarios where we have higher efficacy and higher chances of success at earlier in terms. Hopefully, it makes sense to walk through how we're thinking about it.

And if we do continue to accrue cases on the study, and we've actually seen a little bit of uptick in the [number] of cases that are accruing in the study to date, we hope to be able to reach enough cases to trigger these interims this Northern Hemisphere RSV season. So it is not too far in the future.

All right. So that brings me to the summary for the RSV section. So we will be continuing to enroll, open phase, getting ourselves ready for this Northern Hemisphere surge we anticipate. We hope to complete enrollment in the study this year, as I already mentioned. And if we have cases that come across this Northern Hemisphere season and if we have an efficacious vaccine, we are ready, and we will likely initiate these interim analysis or our analyses this winter in the coming months, hopefully. We already have, by November, enough safety data to support a filing. It's really we're getting to be close to this position where we may have enough data to conclude on the study in the coming months to season.

I want to lastly point out, as noted by Jackie earlier, we do have a pediatric program. In this case, we have a monovalent RSV vaccine that we are currently evaluating in Phase I in kids that are 1 to 5 years old. It's an early Phase I study, but yet very exciting. And we hope to share data with this program soon as there's quite a large burden of RSV, as you may know, in young children as well.

So with that, I'd like to stop on RSV and pass it back to Jackie to cover CMV.

Jacqueline Miller - *Moderna, Inc. - SVP of Infectious Disease Development*

So now let's switch gears and speak about the latent vaccine portfolio. So this is our late-stage development candidate for cytomegalovirus, mRNA-1647. So just a reminder about congenital cytomegalovirus. So cytomegalovirus actually is a ubiquitous infection. So most of us have already been infected in this room. When a woman is infected during pregnancy, she can pass that infection through the placenta to her baby. About 1 in 200 babies in the U.S. are born with a congenital CMV infection. Now CMV infection doesn't necessarily mean infant will develop CMV disease. But when CMV disease does develop, it can be quite severe. So it is the most common cause -- most common infectious cause of congenital sensory neural deafness. So the only more common cause of being deaf at birth are genetic causes aggregated together.

This leads to about $1 billion annually in health care costs, along with the other symptoms of congenital CMV. And 1 in 5 of those 1 in 200 infants born each year will go on to develop some of these long-term complications, which include primarily neurologic disabilities, including microcephaly, chorioretinitis, which can lead to blindness, seizure disorders, encephalitis.

And the hearing loss I really want to take a pause on because it's the most common long-term complication. It seems like it might be not obvious because you would say, well, you could treat with a hearing aid or cochlear implant or other kinds of interventions. It's actually so much more insidious than that. So babies really depend on hearing the voices of their parents to develop their language. And hearing a language for infants is also important for their ultimate verbal cognitive development. So when these infants have a subtle presentation and they go a number of years without being diagnosed, their future learning can be quite substantially impacted, not because of neurological deficits, but because they simply haven't been exposed to spoken language at the right age. So in summary, this is a really impactful disease for the babies and their families that suffer with it.

So our CMV vaccine is a hexavalent vaccine. It has 6 separate mRNA sequences. 5 of them naturally assemble into something called the pentameric complex, and then 1 of them is expressed separately as glycoprotein B. The pentameric complex is important for entering epithelial cells and the gB antigen is important for the entry into fibroblast. And that's really how we measure the impact of these 2 different antigens immunologically.

Now we entered Phase III on the basis of neutralizing antibody responses to both of those different types of cells. So we knew going into Phase III that we had the ability to neutralize infection that were discrete to both of the antigens contained in the vaccine. This is now looking towards an infectious outcome, primary infection in women who are initially seronegative. And why primary infection? Because the highest risk to transfer CMV to your baby is in a woman who is initially seronegative and having her primary response. If we are able to prevent a woman from getting

infected, it follows that we would be able to prevent congenital CMV. So it's a strategy not unlike that used to license human papilloma virus vaccines, where an earlier cancer marker, CIM2, was used to infer protection against cancer.

Now just like with HPV vaccines, future real-world evidence studies have gone on to demonstrate that those vaccines prevent more advanced forms of cancer. Our vaccine will also be studied in real-world evidence to demonstrate the direct impact to congenital CMV disease.

So this is a randomized, observer-blind and placebo-controlled trial. It's evaluating the efficacy as well as safety and immunogenicity of the vaccine as compared to placebo. And it will enroll nearly 7,000 women in the U.S. and internationally. These are women who are of childbearing age down to age 16. We've seen success with implementing vaccination programs in 16-year-olds, including Meningococcal Group B vaccination. And we have approximately 150 sites globally. Why? Because unlike with respiratory vaccines where we -- people are well aware of the impact that a respiratory virus can have after the COVID-19 pandemic, it takes a little bit more education and effort on the part of our CMV investigators to explain the impact of congenital CMV.

We're also asking that women who are above 20 years of age have direct exposure to young children. The reason for that is young children actually are the primary infectious transmission individual in people's lives. So turning from seronegative to seropositive often happens in the home where there are already young children.

So our goal is to also enroll an incredibly diverse group of women, and I will show you our targets and where we are currently in subsequent slides. And like with RSV, as Christie just explained, our efficacy is based on a case-triggered analysis.

Okay. So these now are the countries in which we're enrolling our trial. And you can see not quite 6 continents, but 3 continents have sites currently activated. We're also enrolling a cohort of seropositive women to demonstrate that the vaccine is both safe and immunogenic in those women as well. And that cohort is now fully enrolled. You can also see on the left-hand side of the slide, the targeted diversity requests and then where we currently are in terms of enrollment. So we have nearly 50% of the trial enrolled from communities of (technical difficulty) and we're quite proud of that statistic.

So I'd like to also show you the statistics that Christie just reviewed for you for RSV for CMV. So in this case, we've planned 2 interim analyses, 1 when we have accumulated 81 cases of primary CMV infection after the third vaccination; and then the second final analysis after 112 cases have been accumulated. And on the right-hand side, like with the RSV slide, you see the primary interim analysis or the primary analysis, excuse me, in the dotted line. And then you see the end-of-study analysis in the solid line. We use slightly different terminology here because knowing that CMV would be a more difficult target to reach, knowing that this is really our proof of concept in the latent virus portfolio, we have actually planned to take a look at efficacy with a bit more statistical power.

So let me show you what we intend to do. If you look between 60 and 80 on the X axis, halfway between is a true vaccine efficacy of 70%. And this trial was actually designed to read out with 90% power on the dotted line at the 81 case mark. If we wait until the end of the study and the true efficacy is 70%, we actually are approaching 99% power to read out. Now it's possible that we would also be able to be successful at lower efficacies. And so for example, 60% efficacy. For a vaccine, by the way, for which there is no other licensed vaccine for this unmet need, we would have approximately 60% power at the primary analysis and then close to 90% power at the end-of-study analysis. So you can see we've kind of taken into consideration what would be desirable from the vaccine product in designing our clinical trial, so that at the end, we have labels that will be (technical difficulty) for use in the health care setting.

Okay. So now I'm really pleased to announce to you, we're also going to be taking our CMV vaccine into immunocompromised populations who suffer from CMV disease. So unlike in a healthy individual who may experience some symptoms of mononucleosis or mono when they get CMV infection, but most of whom will be asymptomatic. In the immunocompromised population, this can be quite devastating. So not only does this disease cause pneumonia, gastroenteritis, it can cause hepatitis, encephalitis and retinitis also leading to blindness, they also can impact transplanted organs. And this is what makes it a particular scourge in the transplant community.

So about 30 years ago, Dr. Hank Balfour wrote a paper where he called CMV the troll of transplantation. We now treat patients prophylactically against CMV disease when they have had solid organ and hematologic transplants. However, patients can develop resistance to CMV viruses by

being on constant prophylaxis. And those drugs are not entirely benign in their own right. So we are hoping that on top of prophylaxis, we can demonstrate added benefit of vaccination. And the greatest risk to these patients actually comes if you have a solid organ transplant as a patient who is initially negative because when you transplant an organ, you not only are transplanting the organ, you're transplanting a lot of the latent viruses that are contained in that organ. So many patients become seropositive only once they've been transplanted. And then we blast them with immunosuppression, and that infection can really reactivate.

In hematologic transplants, the primary problem is from individuals who are initially seropositive. Why? Because they start their transplant typically with the vaccine being latent -- or the virus, excuse me, being latent. Then you transplant them. They take a while to reconstitute their immune system. And while they don't have an active immune system, that virus can then reactivate. In both cases, it's problematic, particularly in the solid organ transplant population where they can actually lose their graft from CMV reactivation. Some of these patients have waited 10 years or more for their organs. So that really is an outcome we want to contribute to avoid.

So we're going to investigate a proof-of-concept trial, and this is going to be conducted in collaboration with some of the hospitals here in Boston, the Dana-Farber Institute. We are using mRNA-1647 as an adjunct to standard of care. And we will be investigating the safety in these hematologic stem cell transplant patients as well as the ability to induce an immune response. So these individuals will be transplanted, and they'll start their vaccination schedule approximately 6 weeks after vaccination and get an accelerated schedule while their immune system is reconstituting and while they're getting other CMV prophylaxis. We're also looking into possibilities to investigate 1647 in the solid organ transplant population.

So in conclusion, CMV is a large unmet medical need, yes, in women of child-bearing age, but in particular in their unborn infants. It's also a large health care burden in the transplant population, and we are really looking forward to starting our proof-of-concept studies soon.

Our CMV Victory trial, the Phase III trial in healthy women of child-bearing age, is now over 40% enrolled, and we're on track to meet our diversity and inclusion targets.

And finally, we will be reporting in future events our vaccine efficacy once the primary analysis has been reached. And again, this is based on accrual of our primary infection cases.

So now I'm going to hand the podium over to Arpa Garay, our Chief Commercial Officer.

Arpa Garay - *Moderna, Inc. - Chief Commercial Officer*

Good morning. So as Jackie just mentioned, Arpa Garay. I recently joined Moderna as the Chief Commercial Officer. And what's really exciting about all the R&D updates that you heard this morning, is we now have a pretty diverse and broad set of products that we're gearing up on the commercial side to launch.

From a priority perspective, we're focused on 4 things. First and foremost, and I'll talk a little more about this in the context of COVID. We are getting prepared for an endemic phase. So for the last 2 years, we've been really living in more of a pandemic phase, and I'll talk about what that means from a commercial perspective, and we're now spending a lot of our time thinking about what does this mean as we move into endemic.

Our second key priority is gearing up for all of the respiratory launches that you heard about from Jackie and the team and making sure that we're set up for commercial success around the world.

The third, from a CMV perspective, right, in an area where there currently is no approved vaccine, we're looking at really building this market and understanding, helping to educate both consumers as well as physicians to prepare the market for a future launch. And then last but not least, as you heard this morning, we are also, in parallel, looking at getting prepared and creating the markets in rare diseases.

So from a commercial perspective, all 4 of these are actually fairly different business models, which really reflects the diversity and the breadth of the portfolio that's coming soon.

I won't go through this in detail as you've already seen a lot of the time line. But really, the key message here is as early as next year, we could be expanding beyond COVID into flu, and very soon afterwards, over the next couple of years, launching a number of vaccines.

And in 2023, so as I mentioned sort of this transition to endemic, what we are expecting in some countries is that we are going to be switching from the current state, which is primarily central procurement. So for example, today, in the United States, the government is our customer. They secure the sales, they're distributing the product, and it is a very sort of concentrated base of business. As we head into 2023, we are now heading into a new state where the government, many of them, starting with the U.S. government, are actually going to go back into a more traditional commercial model. So what that means for us is we're going to see more fragmentation around the world. We're going to be contracting with a significant larger population of providers, health care systems and payers as well as pharmacies. And our commercial model is going to have to look very different from the way that we're set up today.

What we're also expecting from market dynamic is that the COVID market is going to start reflecting more like the flu market. So what I mean by that is typically -- and this is what we're hearing from many national institutions around the world. There is a very good likelihood that the COVID boosters will become annual and likely at the same time as the flu vaccine. So this is going to turn into more of a seasonal type of pattern where we're going to see most of the purchases, the contract signed early in the year, and all of the actual vaccinations and deliveries and doses shipped later in the year, again, very similar to the flu dynamic.

Now if you look at the commercial model and the presence that we have today, you see in the blue, this is where we have direct presence and Moderna leading the business. And in the yellow, we've got partnerships established with other companies to help us distribute our vaccines. As we look at this footprint, it actually covers about 90% of the current revenue for other similar respiratory vaccines like flu and pneumococcal. So we've got a fairly large coverage of the current global business as we head into flu, continue with COVID and then build out for the rest of our portfolio.

What's not reflected here, obviously, are some key markets that we're continuing to assess in terms of future opportunity and how to build out sort of globally the Moderna presence.

So how does COVID change the respiratory vaccine market? As you all know, COVID has really brought vaccination to the forefront of consumers around the world. It has really created more of an urgency and an interest in getting vaccinated to get back to normal life. It has (technical difficulty) to bring a little bit more awareness around some of the burden of illness that the team talked about across not just COVID but also flu and other respiratory diseases. And with the mRNA technology, in particular, as we saw, over the last year or so, it's also created a much deeper consumer interest in terms of how effective are my vaccines, what is going to get me the best coverage and how do I get more engaged and actually asking for specifics ground.

So as we go ahead into the endemic market, obviously, we are expecting changes versus what we've seen over the last couple of years. But in just the high income countries, if we look only at the eligible high-risk population, so these are 65-plus or adults with risk factors, there is a tremendous population around the world of 340 million people that will continue to be motivated and encouraged by governments to get vaccinated.

If you look beyond that, in markets like the U.S. that we're already seeing, we do anticipate, similar to flu, that these age groups will be fairly broad. So in this fall, the U.S. government has recommended 12-plus get their boosters. This likely will continue over time, potentially expanding the population for COVID boosters going forward.

And the chart on the right here is just to give sort of a picture of 2 things. As we think about the size of the COVID market going forward, there's 2 key levers moving forward. One is how many people actually choose to get vaccinated. So that's the vaccine coverage rate. And then the second is really around pricing. So our current pricing approach, again, is with government, it was in a pandemic setting. As we head into more of the commercial markets, we will be looking at more value-based pricing that's more appropriate for the commercial market.

And just as a point of reference in 2021, CMS actually did their cost-effective analysis, and said the original, the 1273 vaccines were valued at about $64. So I think as we see different governments around the world doing their own cost-effectiveness analysis, we're seeing they are recognizing the value of these vaccines.

Now with flu, as Jackie talked about earlier and Christie, we had a real opportunity here with what we're calling potentially more effective or premium vaccines in flu. Today, there are a significant number of consumers who are opting not to get vaccinated because they don't believe that the vaccine is going to work for them. And specifically in the high-risk populations, we're seeing more and more recommendations for these populations to get the enhanced flu vaccines. So if you just look at the chart on the right, what you can see is the enhanced vaccines that have higher effectiveness have really grown the flu market, both in terms of broadening populations, but also in terms of price and the ability to get premium pricing.

In the RSV market, this is a market that will be, again, created as there is no vaccine available today, we see a huge unmet need in the older population but also in the future in the pediatric population. And this is a market where there's been a lot of estimates around this could be bigger than the pneumococcal market, and it could be $10-plus billion in sales.

The real game changer, I think, for us, is the combination vaccines. So in pediatric populations, you see a significant use of combination vaccines. And over the years, what we've seen is as we got more and more combinations in pediatric populations, you actually got higher compliance rates and you've got more people vaccinated with their primary series. We don't have that today in the adult market. And in the adult marketplace, you see vaccination rates are actually quite low. And there are also a lot of concerns around convenience, around scheduling. And the combination market for vaccines for adults could be a real game changer.

We're hearing a lot of feedback from payers as well as consumers that this helps them get to better protection rates and coverage rates. We also hear very often that a lot of adults actually drop off of their vaccination just because of convenience. I didn't have time to get that second shot. And we saw that even last year with the flu and the COVID vaccine series, many adults got one or the other or not both. So the combination opportunity here with flu, COVID and RSV all combined into one, it could be -- is something we're really, really excited about, from a commercial perspective. And we will be the first company to be really launching into the space and establishing what this market could look like.

CMV. You heard the devastating impact of CMV for children. This is, again, another brand-new market. We are currently spending time on the commercial side, really just trying to understand the awareness with consumers, which is currently extremely low as well as with physicians and payers around the world. So the focus in the short term for us is really around how do we build the awareness and the understanding so that when we have our vaccine, we're able to get to appropriate vaccination rates to protect more women and children going forward.

And then last but not least, rare diseases. As you heard, there is a potential that we'll be launching into rare diseases as early as 2024. Again, this is a very different business model from the seasonal vaccines and then the CMV latent vaccines, which is more sort of constant demand over the year and then now with the rare diseases.

And as you heard earlier, even from the physician speaker who was talking to these patients, there is a huge unmet need, and there is a significant amount of interest and motivation from parents and from patients to want to get these products. It is a very concentrated group of customers that you generally work with in academic setting. And this is another area that we're beginning to prepare for in terms of the commercial capabilities that would be required that looks very different from the vaccine side.

So with that, just in summary, a lot of preparation happening on the commercial side. We're really excited about the diversity of the launches that are coming. And we are ready to start launching as early as next year globally with our current presence as well as our partnerships with other companies around the world.

I'm going to ask Stephane to close this out.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

Thank you, Arpa. Thanks, Arpa, and thank you, everybody, who presented today. So I'm going to be pretty brief. I want to (technical difficulty) to close. The first piece I want to share with you is how the company has transformed and why 11 years into the story of making mRNA, I'm more optimistic than ever. For the last 10 years, pre (technical difficulty) Spikevax approval, we believed that mRNA might work, and we were trying to figure out (technical difficulty) how to make it work safely in humans. And what was driving us is this belief that if we could make mRNA work, the

impact of medicine on people around the world will be changed forever because we could do medicines that are technically impossible to do using small molecule or large molecule.

And we are very capital constrained. As many of you know, because you funded us through those years. We had no revenues, and we didn't know when we make an (inaudible) product and if we might (inaudible) product. So the way we build the business was in a certain way because of those constraints, the unknown about the technology and the risk we are trying to manage on biology and technology and the capital constraint that we have.

But we are, today in, a very different world, a very different world. We now know that mRNA can work safely. And we have a unique balance sheet for a 10-year-old biotech company. I'm not aware of any biotech company 10 years into the making that had $18 billion of cash to invest in science and drug development.

I've talked with our employees in early 2021 that I wish we could change the company name. That's one of a (inaudible). And why did I say that? We just have Spikevax conditional approval in December of 2020. And I talk to our employee because I wanted people to understand we're going to change pace. We're going to change scale because it was a very different situation to be assuming or believing that it might work versus knowing it works and having no cash versus having a lot of capital to deploy to create value. And that's what we've been doing. And if you look at the expansion of the pipeline that the team described, it's the beginning of a translation of that. We're investing for a lot of launches. We're investing for scale.

Just to give you a sense. A few years before COVID, we invested $400 million per year in the company. Just this year, we're going to invest $300 million just in IT to be able to scale, to scale research, to scale development, to file BLA faster, to scale commercial, to scale manufacturing. Because with the pipeline coming, it's really important that we do that to maximize our impact on patients, and as a consequence, to maximize value. So I'm really excited about where we're heading.

And the next couple of quarters are going to be really, really interesting. You saw this morning the exciting early PA and GSD1a data. As you think about it and you look at the time line and the little triangles that Ruchira shared with you, we should be able pretty soon to pick a dose we think the frequency we might have and going to pivotal. We are very pleased that the regulators indicated that MDs seems to be a good endpoint for the pivotal registration studies.

And because mRNA is like software, we're going to do a lot more rare disease now. We have 6, which a lot of biotech companies would love to have 6 drugs in development in 1 application. We're going to do more now.

And the PCV is coming soon. And then flu. One thing I think that is lost by some people around flu is how potentially mRNA-approved vaccines are going to change the game with public health and regulators. Why do I say that? We are told by FDA on June 28, we'll have to make a BA.4/BA.5 variant for Labor Day weekend. We have no plasmid as raw material to make the mRNA. And people this weekend started to get vaccinated against COVID BA.4/BA.5.

As you know, the way the flu market works today is WHO guesses based on the Southern Hemisphere (technical difficulty) strain for the Northern Hemisphere in February of the year before. And as we know some years, because of new mutation of flu strains, the flu vaccine don't really work very well. A lot of people end up sick, hospitalized and dying because we guessed wrong the strain.

Why? I'm sure regulators have noticed that we can do that in tumors. How we change the flu market is going to be a very interesting question. I personally think that there's going to be a big change, and mRNA is going to end up being the game in town for flu as we can provide an adapted vaccines but more to see in the quarters to come. And then of course, as the team said, RSV Phase III, the readout event base could happen this winter. So that's very exciting.

And when you figure about Moderna, the thing that is really exciting is how the team has built and keeps on building optionality. We don't claim we know the best use of mRNA in the next 20 years because we don't. But you can know from us, we're going to be interrogating biology and science nonstop.

Think about the opportunity of flu and RSV and CMV and PA enabling all the rare disease. Vertex is on in a clinic soon with cystic fibrosis straight into patients, trying to test for us the ability to deliver safely in human and the fully driving impact efficacy wise in the lung. We've not talked about science today, but the team in the labs is working on many, many more candidates. You guys only see what is in the clinic or in development, but there's many more in the labs coming because we know the technology works. So why will not do more vaccines. More than 200 viruses are hurting humans every day around the planet. There's only a vaccine against around 20 of those viruses. So there's a huge opportunity for us to impact society in a very profound way because the best medicine in life is not to get sick. It's prevention. And all the players know it.

So we're very excited about the vaccines coming, more optionality. We don't talk about gene editing, but the team are working on Moderna Genomics, as you know. And then we have a team in the platform literally hundreds of scientists and engineers working to expand the possibility of doing new applications using mRNA to help patients. So this is what really gets me really excited about the future of the company.

So with this, I would like to thank our employees, of course, but also all of our collaborators, the participants in the clinical studies, the PIs, all of our partners because it literally takes a village to do what we do and a lot of people taking the risk of getting their kids and their family and loved ones into clinical trial, and we are always very thankful for that. So with this, I would love to get the team on, and we're going to be happy to take questions. I'm happy to stand.

Unidentified Company Representative

It will feel unnatural.

QUESTIONS AND ANSWERS

Stephane Bancel - *Moderna, Inc. - CEO & Director*

Good. So Lavina, you'll be moderating in a room and online? Good. What's up, Max?

Stephen Hoge - *Moderna, Inc. - President*

We're just introducing Praveen, who you've seen before, who leads our oncology therapeutic area developers.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

We're good.

Jessica Macomber Fye - *JPMorgan Chase & Co, Research Division - Analyst*

Good. Sorry about that. Jess Fye, JPMorgan. A couple of questions on your rare disease effort. How do you prioritize which rare diseases to pursue first? And maybe conversely, are there any that you've identified as not near-term priorities, for example, if they may be better served with existing products in the conditions you described? And second, can you talk about the potential path to approval for your products for PA and MMA by the end of 2024?

Stephen Hoge - *Moderna, Inc. - President*

Sure. I will -- I'll try and take both and then I'll ask Ruchira to fill in with anything I missed. So first on the strategic question, how we prioritize. We start with unmet need, where do we believe the standard of care where it exists is insufficient. And in the case of PA and MMA, there is no standard of care, unfortunately, as you heard Dr. Corson described, other than dietary restrictions and unfortunately, just watchful waiting. So we start there.

And most of our portfolio is constructed that way. There are a few examples of programs where there maybe are emerging standards of care or incomplete standards of care, one that was referenced earlier was PKU, where we do think there's still opportunities to improve for -- particularly for certain patient populations. And that's it.

With that, we then look at the pharmacology of what our platform can do. What have we shown what we can do. And there's a very wide range of rare diseases in terms of what needs to be accomplished, the amount of protein you need to place and whether or not you'll be able to demonstrate rapidly in the clinical study that you can provide a fit to those patients. And so -- and of course, there's also the target tissue, I should say.

And because the current modality that we feel like is increasingly derisked is liver targeted in its activity, most of the work we're doing right now in terms of prioritization is in liver-directed rare metabolic diseases, but there's no standard of care.

When we see the CF data, the counterpoint to that, we will be rapidly looking if we see derisking in that program with Vertex to expand our work in the lung and there are additional rare diseases and actually not so Rare disease where there's opportunities to do replacement there. But again, we'll wait for that pharmacology to unlock that modality. For now, we're really moving down and prioritizing our work in liver rare metabolic disease.

In terms of the pipeline for approval or the time line for approval, it's unprecedented what we're doing. And so everything I'm about to say is unprecedented. We don't -- we haven't done it yet. But we do see the early clinical signs both in biomarker and in terms of reduction of MDEs that we think create an opportunity for the PA program specifically as the first instance to move into a pivotal study. Now the duration of that pivotal study will be subject to what do we want to accomplish in negotiations with regulators.

But you could imagine a slightly larger version of what we've done here with [now] participants starting to show statistical significance in the reduction of metabolic compensation events. And because those events are associated with hospitalization, unfortunately, sometimes death, long-term disability, but real also expense for the systems, it's probably not surprising that the initial feedback we've been receiving is that, that's probably a good primary endpoint for those studies.

And because many patients are having many of those events every year, it is an opportunity to do that in a relatively short term. And that would be, let's say, starting a pivotal study in the coming year if we were able to find a dose for that, which we have not yet, agreeing with regulators what that study scope would look like and then perhaps, within a year or 2 of initiating that study, depending upon enrollment, being able to demonstrate that benefit and moving rapidly forward with filing.

So that is one way that can look. But again, that's the best case. We always aim at the best case. We'll have to have conversations. We'll have to follow the data. And we're not yet ready to (technical difficulty) dose or dosing regimens as Stephane and Ruchira said and that may take us a little bit longer than what I just described. I don't know, Ruchira, anything you'd add to that?

Ruchira Glaser

Yes. No, I think you covered that beautifully. The only thing I would say is that we've talked to clinicians and the scientific community, and even a 25% reduction in MDE is deemed very clinically significant.

Right now, small numbers, so we're seeing a 48% reduction. Could that be greater? Could that be less? We'll find out. But the degree of MDE benefit that we see could also help drive the time line. And I think you spoke to that by saying the data will drive what we do.

Tyler Martin Van Buren - *Cowen and Company, LLC, Research Division - Analyst*

Tyler Van Buren from Cowen. Thanks very much for the presentations. With the bivalent boosters becoming available now, what are your latest thoughts regarding the [piece] of boosting through the end of the winter? And it'd be helpful if you could discuss that in the context of the original -- the consumption of the original 70 million doses contracted with the U.S. government and when we might see those consumed.

The second question is on RSV. Can you provide your latest thoughts and observations regarding the learnings from the Glaxo and Pfizer trials and what you believe you need to show in the ongoing Phase II/III study when we see the data this year to be -- or this winter to be competitive.

Ruchira Glaser

So I can take the first one. In terms of the 70 million doses, in conversations with the U.S. government, they expect to consume them within about 5 months. So probably leading a little bit into early next year, but they will be primarily just focused at this winter season, at which point they will stop engaging in procurement and move to the commercial market. Globally, as we look at what the demand might look like, we will start -- we've already started seeing some uptake in September, but the vast majority of the demand and the uptick will be in the fourth quarter.

Stephen Hoge - *Moderna, Inc. - President*

And I don't know, Jackie, do you want to take the RSV question?

Jacqueline Miller - *Moderna, Inc. - SVP of Infectious Disease Development*

Sure. So number 12. We turn it on?

Stephen Hoge - *Moderna, Inc. - President*

You got it. You're on.

Jacqueline Miller - *Moderna, Inc. - SVP of Infectious Disease Development*

It's on. Okay. Good. Yes. So I think, taking GlaxoSmithKline first, it's a little bit difficult to comment on exceptional efficacy and hard to know what that means in terms of our trial. So maybe I'll focus on Pfizer. So they also have the 2-dose and 3-dose symptoms. Our primary endpoint currently is focused on 2-dose symptomatology. As I mentioned, or as Christie mentioned, we were looking at 65% efficacy. Actually, that's how we powered the study. So we feel like we're right on target there to be competitive. We are also now looking to promote the 3-plus symptoms to a primary endpoint as well. That's also a conversation we need to have with regulatory agencies, but we are very carefully looking at competitor data and seeing how we can adapt our trial to ensure that the efficacy readouts that we get are actually translated into label claims ultimately.

Stephen Hoge - *Moderna, Inc. - President*

I mean, I might editorialize and just say I think we're even more optimistic in the face of the data that's come out recently that it really does validate the potential of an RSV vaccine to provide benefit, which is critically needed. And I think optimistic because if we've learned something about our platform it's that we think we can produce the best respiratory vaccines. We certainly see very strong titers against RSV A and B, and we've shared those data previously.

But we also know from our COVID vaccine experience that we lead to some of the strongest cellular immune responses, and that really does impact the severity of disease in respiratory viruses, particularly for high-risk population. So we're cautiously optimistic that we're going to be on the board quickly, and maybe, because of the strength of that platform, be able to demonstrate an even better response.

Elizabeth Daniels Webster - *Goldman Sachs Group, Inc., Research Division - Associate*

This is Elizabeth Webster, I'm from Salveen Richter with Goldman Sachs. Two questions from us. One, in rare disease, could you walk us through the strategy for scaling up that vertical? And how big do you think it could get -- could become eventually?

And then second question on the COVID booster. You anticipate the uptick this fall to be indicative of demand in the endemic market on the forward?

Stephen Hoge - *Moderna, Inc. - President*

You take the second. I'll take the first. So how big can it be? Look, we believe in the mission of the company, which is to address any disease where we think our technology can help. And there's a very long list. We have to prioritize our efforts as we do that. We started with the pipeline that we've announced.

But as Stephane alluded to, you can assume there are multiples of work underneath the waterline, I guess, that are still in preclinical. And what we want to do is, as we build more and more confidence with our performance in clinic and ultimately, hopefully, into pivotal studies with the first generation programs that we will rapidly move in medicines against many of those other diseases. And so we -- I can't -- I wouldn't suggest that we will go into the hundreds or thousands of rare disease, of which there are actually incredibly large numbers, but we will work really aggressively to take -- to address as much of that unmet need as we can. And sometimes in creative ways.

I'll point to just one example on our pipeline. We have a program in CN-1, which is partnered with the University of Pennsylvania and the Institute for Life-changing Medicines, which is an extremely rare disease. It's ultra-ultra-rare 100 patients. And in that case, we chose a noncommercial path for moving that program forward, partnering and actually providing that drug to a nonprofit entity development.

And so it's on -- it's a wide range of disease between CN-1 and where we are with some of the first generation, but we will be looking to make sure that our technology has as big an impact as possible.

Arpa Garay - *Moderna, Inc. - Chief Commercial Officer*

And then just to add on the building up of the vertical, I'd say, from a commercial perspective, -- the main focus is going to be just around getting access. And then we've got a very concentrated base of institutions that we'd be partnering with. So it would be fairly small as we compare that to the rest of the portfolio.

And then I just want to make sure I remember the second one on the -- was it the size of the endemic market?

Elizabeth Daniels Webster - *Goldman Sachs Group, Inc., Research Division - Associate*

Further uptick this fall could be indicative of demand in the endemic market?

Arpa Garay - *Moderna, Inc. - Chief Commercial Officer*

Yes. Got it. So I do think the uptick this fall will be indicative of the future. But again, it is in terms of the market shares, I think that will be a little bit less predictive of the future, right, just given the central procurement and the doses that we purchased around the world.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

And I think to maybe add to Arpa's point, is going to be indicative, but it will be interesting to see people who might decide not to get a booster, how sick they're going to get this winter, then they might have a different decision the winter after. So we'll see. We'll learn a lot this winter.

Stephen Hoge - *Moderna, Inc. - President*

The other reality is that many of the high-risk populations almost already received a fourth dose even earlier in the year. So there's just a whole bunch of unique features to this year.

Michael Jonathan Yee - *Jefferies LLC, Research Division - Equity Analyst*

Michael Yee from Jefferies. On propionic acidemia, it seems like there's activity, but it's sort of hard to tease out small numbers. But in designing the pivotal program in the future, can you just talk about what the control would be? Would it be the persons on baseline? And when you look -- what's interesting is if you look at the number of events going into it, we're all over the place. So obviously, we have 0, you can't reduce from 0. So it's the trial design. Can you maybe talk a bit about that and how you would handicap that for success, some just small numbers?

And then maybe on flu, Stephane commented that the power and speed of picking the COVID strains maybe would be a more direct proposition for flu. Is that sort of the message you're telling us now is that the flu strain and the speed of picking this strain is really the proposition here? Because I think Wall Street is sort of confused how flu really matters and how that will be differentiated.

Stephen Hoge - *Moderna, Inc. - President*

Well, I'll take the first one. So it's an active -- it's a great question. And in our discussions almost on a weekly basis right now, we're wrestling with very much that same point. It's not ours alone to make. We have to talk to regulators and get aligned with that. And so those discussions are ongoing.

I will frame up the range of options, but I don't think we have a defined path yet in that pivotal. On the one hand, you could think about possibly doing a placebo control. The unfortunate reality there though is you'd be waiting for events that would lead to potentially lifelong disability in those patients, allowing MDs to recruit.

On the other extreme, you could say, well, we're just going to have every patient's history or maybe even the synthetic control based on a large group of patient's history suffice as the background rate of MDEs and then demonstrate a benefit of a significant reduction compared to that. You can imagine propensity matching populations. And in that sense, your clinical study would probably be substantially smaller because you'd really only be recruiting and enrolling subjects to receive the drug.

We're looking at those and other options. And what we would like to do is make sure that we work with regulators to get to a clinically meaningful endpoint, also one that recommending bodies that payers can be comfortable with. It shows a benefit but also does that in the most efficient way possible, the fastest way possible because these patients are suffering from lifelong disability and we do think that this medicine has the potential to help.

So we're -- as we develop a little more data, as we finalize the dosing regimen, we're very happy to see that we have not seen MDEs yet on the 2-week dosing regimen. And if that continues to hold up, it's low numbers, but if it continues to look good, it will help us feel even more confident that we can do that at a smaller study size because that affects us as we'll get, obviously, commensurately larger. And so as we firm those things up going into the winter, come to a decision about that pivotal dose that we want to carry forward into an expansion and engage with regulators on what they need to see and other HTA assessment bodies need to see, then we'll be able to come back and describe what that study looks like.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

So what we care about with respiratory vaccine is just to prevent people to get sick and hospitalized. That's our goal. The traditional way to make medicine was constrained by manufacturing and technology. So let's start with the end game. You have had the magic wand. Whatever product do we want? Multi-virus protection of respiratory. So that's why we talked about for several times, (inaudible) COVID and flu and RSV combined. And then doing the best biology that we can to protect people to get sick. So what is that? We think [it's HAs, it's NAs.] What about maybe 2 or 3

H3s? We talked about it in one of the call a couple of quarters ago. People think about Moderna trying to use their pharma framework applied to Moderna, but we believe it makes no sense because we have a very flexible technology where manufacturing is not a constraint. It's a massive asset.

We've demonstrated we can do things in 2 months from scratch. If I say that to people, go and continue doing a new vaccine from scratch in tomorrow and say, okay, here it goes again. Seriously. And so the piece we are trying to do is to play a movie backwards from if we have the magic wand and we have the perfect products so people don't get hospitalized, what is that? And so how many flu studies do we have right now?

Stephen Hoge - *Moderna, Inc. - President*

6 or 7?

Arpa Garay - *Moderna, Inc. - Chief Commercial Officer*

I have to think about it.

Stephen Hoge - *Moderna, Inc. - President*

Okay. There are 6 different candidates in clinical trials.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

Okay. Right now. We only talk about the Phase III because that's the only thing what we care about is what's in your Phase III when you launch next year. But if you think about it, what we're trying to do is to really change the game. We believe millions of people, dozens of millions of people get hospitalized every year because of flu. It's crazy. We think we can totally change that. It won't take -- it won't take a month or 2, it will take a few years, but we're going to change that by getting product where people don't get sick and hospitalized. We think we can do that, and nobody else can do with [other] technology. You cannot think about doing what we are trying to do, with recombinant. That's impossible.

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

Great. Thank you very much. Ed Tenthoff, Piper Sandler. And I got my (inaudible) based on Tuesday so thank you very much.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

You're welcome.

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

So I love the updates on the orphan disease side. I have always really appreciated the application of mRNA in those areas. And appreciate in the advance that it can be made with mRNA there. I wanted to ask kind of how things are progressing on the gene editing side with Minigenomi partnership and through other efforts kind of how that could maybe impact some of the things that you're doing on orphan diseases on the mRNA therapeutic side things?

Stephen Hoge - *Moderna, Inc. - President*

Yes. Great question. Thank you, Ed. So obviously, we have started our own efforts in genetic disease, as you said, with mGx, and that's because we see opportunities there, but it's important to contextualize those. Base editing and gene editing approaches, if you go down that path, are really site and gene specific. And many of the diseases in our pipeline, just take the PA example from today, there were 2 different mutations, 2 different organs. That would require 2 different drugs in a gene editing context. And you have to demonstrate that you could add different sites differently if that's what it was or if you were inserting a gene that you could do it well.

And so in some ways, there are diseases like these with a lot of heterogeneity in those genotypes, like PA, that might benefit more from just 1 drug. And by the way, our drug, in this case, the program we're carrying forward in propionic acidemia is treating both mutations on the PCCA gene and the PCCB gene. We showed you 8 patients today. The ninth, we didn't have the data on. But as you could see, there were responses across both. So it's not even just different genotypes that we're seeing. We're actually seeing different genes that we're able to correct based on the clinical syndrome.

Now over the long term, we see the benefit of decreasing the need for, let's say, every 2-week IV infusions for the rest of your life, which is what our current medicines being dosed at. But that will require a lot of the gene editing technologies or gene insertion technologies to catch up, right, to get to a point where they could really deal with that massive diversity in mutations. And that's a place that we are hoping to be pioneers ourselves, but I think it will take quite a long time. And in the interim, there's an opportunity for us to make , hopefully, a really significant difference in the lives of these patients. And so we'll focus that way.

Then the last thing I'd say is these things do not necessarily need to be inherently competitive in the long run. There are a lot of these things, where if we were able to do some partial gene editing and stabilization or gene insertion, there may be addressing the extreme of the disease, but still leave opportunities. I think of the way people dose multiple different types of medicines to control blood sugar today. And in those situations, it will make sense, we think, to still have the ability in the time of stress or hospitalization or when somebody is undergoing some sort of procedure to be able to give them the reserve by loading them with the enzyme that are mixing with an mRNA drug. And so as an example, even in that circumstances, we don't think it completely supplants.

Simon P. Baker - *Redburn (Europe) Limited, Research Division - Head of Pharmaceutical Research*

Simon Baker from Redburn. Thank you very much for a very comprehensive update on the whole portfolio. Just continuing with PA. I wonder if you could give us an idea of what the split is between PCCA and PCCB mediated disease. And the reason I ask is back to this point on gene therapy that if we think about classically, (inaudible)in terms of gene therapy, looks like could B less amenable than A just because of the size of the gene versus captive capacity. So that opens up a broader question of where do you see the gene therapy threat in this -- in PA and the broader area because clearly, (inaudible) is very appealing, but is it feasible because of cell turnover?

And then secondly, a question in 2 parts. Could you give us an idea on flu and 1010. How to think about the commercial opportunity between approval and before the efficacy study. And on CMV, you talked about a $2 billion to $5 billion opportunity, and you cite the example of Gardasil at 5. Sensus has that doubling by about 2028/'29. So I'm just wondering, that $2 billion to $5 billion are a little on the conservative side. Why shouldn't CMV be more like HPV given the impact that, that condition has?

Stephen Hoge - *Moderna, Inc. - President*

So I'll take a first crack at the PA program questions. So first, on the question of PCCA, PCCB and whether we think they are more amenable or not? First, in gene insertion, so the gene edit -- not gene editing, gene therapy approaches, where you're doing plasma draw, there has been a an emerging, I think, scientific understanding that those episomal genes get silenced over time, and that does lead to a period of time where you might be able to go off therapy, but ultimately, a decrease in the pharmacologic benefit. So we actually think as a function of those technologies, there's an opportunity always for, mRNA independent of the challenge of the size of the protein. Now you pointed to the size of the gene that is also a limitation of those viral vector technologies.

On the PCCA versus PCCB, in our study, it was 3 and 5, and, Ruchira, I can't remember off the top of my head, the epidemiologic breakdown between PCCA and PCCB, can you or...

Ruchira Glaser

Yes. I don't have the exact numbers, but I think the other point that people have made -- clinicians have made is that, even with newborn screening, we don't actually know with that degree of precision what the truth is. And I think that with new therapies, we'll actually really be able to hone in on it because right now, the people who -- we know that certain mutations will lead to milder phenotype than others, and that may just be skewing the numbers in certain countries about the PCCA versus PCCB.

Stephen Hoge - *Moderna, Inc. - President*

I know we have some data from our natural history study. We'll just have to follow up with it. I just can't not remember it off the top of my head. Apologies.

Unidentified Company Representative

And then I can take the question on flu, 1010. Once we get registration, the immunogenicity data will be sufficient for a commercial uptake. We're seeing that already in COVID. So I think from a flu perspective, we don't need to wait for a commercial launch for the efficacy data.

The second piece around the uptake and the timing, I think it's actually more driven by what months we launch in. Because with the seasonality of flu in the Northern Hemisphere, most of the orders are coming in, in the first quarter. So it's going to be more driven by the month, really than it is by potentially the efficacy trial.

Second question on CMV. We also hope it is a larger market opportunity given the unmet need. That being said, the HPV and the Gardasil population is inherently just larger because it covers males and females. The opportunity with the adults in CMV is really just women of childbearing age as well as a broadening as we get into the toddlers, as Jackie had referenced, which will be gender neutral. So I think the population sizes are different, but still more to learn around what that global uptick in demand will look like.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Okay. I will read out some questions coming from online. So for rare diseases, how do you differentiate from traditional modalities in advanced development stages such as recombinant enzyme replacement therapies versus mRNA therapy?

Stephen Hoge - *Moderna, Inc. - President*

Thank you for that question. So look, first and foremost, we're going after diseases that require an intracellular enzyme. You'll forgive me for the molecular biology geek part of this, but that PCCA program is 2 different mRNAs. Each coding different large subunit proteins that you need to make 6 copies of each of those proteins that becomes a dodecamer, it's 12 pieces. And it has to get assembled in the mitochondria inside of a cell. There's no way anybody is pushing an enzyme replacement therapy with an IV infusion to do that, the other direction. And that's really the core of where we intend to differentiate.

We will look, over time, at therapies that might be addressable with recombinant proteins. I think that's probably where the question is coming from. Because we do see making the protein in the human does lead to, we think, differentiated pharmacology. You can imagine different glycosylation patterns and function. But for right now, most of our pipeline, you'll see us going after are diseases that have exactly that same feature I described, which is it's intracellular enzymes, many of them in mitochondria that cannot be forced in the back door, if you will, as a recombinant protein.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Questions from Gena Wang of Barclays. PA, what level of 3-HP reduction will you be aiming for?

Stephen Hoge - *Moderna, Inc. - President*

I think it's too early to say. So we're encouraged by the trajectory. I think we went to 0.45 NPK and we saw a 34% reduction, as Ruchira described. We were at 19% before that. We've already decided to go to 0.6. So we're taking that next step. And of course, we would love to see 3-HP start to normalize or you'll continue that [trajectory].

But it's important to note that 3-HP itself is not a validated biomarker in this disease. And really what we're meaning to do is prevent metabolic decompensations, the acidosis events that are ultimately life-threatening to these patients. And so in some ways, the -- while we will work to use the biomarker to help us select a dose, what really matters most is how are we are doing on those clinical endpoints that matter to those patients. And that's consistent with the feedback we received with regulators. So I wouldn't want to pick a 3HP reduction target and say that's it. I think it's more of this sense that we continue to see perhaps from the early data protection against MDEs or relative decrease, and as we dose escalate, hopefully, that persists over time. It's probably the most important signal and then 3-HP continuing to lower will be just supportive of that.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Another question from Gena on the flu vaccine mRNA 1010. Do you need to show some positive trend of events in addition to immunogenicity data for licensure?

Unidentified Company Representative

So the licensure program is really designed on the safety and immunogenicity. It's based on regulatory guidance, and it is something we have discussed with regulatory agencies and gotten some initial positive feedback. That said, we know we will need efficacy data. We intend to launch this efficacy data in what I anticipate to heavy flu season. And if we have case events that allow us to make an efficacy assessment, of course, we will submit that as supplemental information to agencies. So we don't think it's necessary, similar to what Arpa was discussing, but we do know at some point, it will be needed and it certainly would be reassuring in terms of getting flu vaccines launched in the next year. So we'll have to see how the case accrual goes.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

A question on our bivalent vaccines. In bivalent preparations, have you found the same intensity of response? Are there immunodominant effects?

Unidentified Company Representative

So that actually is something I discussed a little bit in the presentation, but maybe I can expand. So we have seen actually a consistent pattern of responses. The exact levels of antibodies we induce may vary between different variants. But overall, we see that from an immunogenicity perspective, incorporating a separate variant of concern seems to not only enhance antibody responses to the variants we're targeting, but also enhance immune responses to the original strain and other variants of concern. And this effect, at least with the 211 vaccine, has seemed to increase over time at the 6-month time point. So we've seen the day 29 effect with both 211 and 214 data containing an Omicron containing variant. And we're anxiously awaiting our 6-month antibody persistence data with 214 to confirm that finding as well. And then maybe just to comment that the reactogenicity findings were also very consistent. So both 211 as a third dose trended generally lower than mRNA as a second dose. And then 214, again, as a fourth dose also trended lower.

Stephen Hoge - *Moderna, Inc. - President*

I would just offer a view to that, too. We -- I think we presented the last vaccine data in the spring. I think Dr. (inaudible) actually presented work on germinal centers, which had demonstrated that with mRNA vaccines, including with our platform, we're really seeing a profound number of germinal centers that are being set up in patients or in recipients of the vaccines, even better than with other technologies, for instance, of recombinant protein flu vaccine.

And that is evidence of a continually evolving and learning immune response. And so if anything, the fact that those persist over time, I think, gives us some confidence that what we're seeing in these early neutralization assays, which is a great diversity, is actually hopefully expanding, and we're continuing to do better and better at educating the immune system. And I think that might play a role, to come full circle, in how we do in flu and why we're quite hopeful that we'll be able to see a different and a benefit with our efficacy study.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Thank you. We'll take 1 last question on PCV. How long is needle-to-needle for PCV? And can you share any details on that, please?

Stephen Hoge - *Moderna, Inc. - President*

Praveen, you'll fill in. So needle-to-needle for us, the target is to dose within 6 weeks from biopsy. The challenge as we'll get to as we look at that data is that, that isn't always doable in the best of circumstances, and we faced a COVID pandemic over the course of the study. And so when we get the full data, we'll look at what that distribution is. The protocol certainly allowed for people to receive their vaccine at the third cycle or the fourth cycle or whatever is necessary. But it's -- our goal is 6 weeks and even better. Anything you'd add to that, Praveen?

Praveen Aanur - *Moderna, Inc. - VP and Therapeutic Area Head of Oncology Development*

Yes. Just to add on to that, as Michelle explained earlier, the protocol allows for first 2 doses of the checkpoint inhibitor, KEYTRUDA. And then subsequently, by the time we get to a third dose is when we have to give the vaccine PCV in majority of the patients, that's what we are targeting. Yes, but it allows that flexibility beyond that. So this is going to be a detailed analysis as we get the data, more data around this.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

And maybe just to add 1 last piece, which is this is what we did for the Phase II study. So we had to make a lot of trade-off of how ready was manufacturing for starting the Phase II study. We've done a lot since that Phase II study started. We learned a lot because of COVID. We've learned a lot because we have 400-plus engineers dedicated to improving the technology and the process. And so we are very aware that those people have cancer and every day matters. And so we're going to do everything we can in technology, investments, to digital robotics investment. If the data is positive, to shrink that time line as much as we can and going to night-shift and so on, which we did not do for the clinical study. But if the data is positive, we're going to think about it in a very different manner because we need to make sure we get the vaccine as fast as we can to people, without, of course, compromising safety of making the product.

Lavina Talukdar - *Moderna, Inc. - Senior VP & Head of IR*

Great. Thank you, panel. And I'll turn it back over to Stephane for concluding remarks.

Stephane Bancel - *Moderna, Inc. - CEO & Director*

Great. Well, first of all, thank you so much for attending. I appreciate all of you that made the trip. We really appreciate some of you getting on to early shuttles from New York. We look forward to talking to you for Q2 -- Q3 results, but also we have an ESG day coming in the fall. And of course, we look forward to getting at the time sharing the PCV data in Q4. Thank you very much. Have a great day. Thank you, guys.