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EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc R&D Day

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PRESENTATION

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

Good morning, and welcome. Thank you for joining us on Moderna's Fifth Annual R&D Day. Today, you will be hearing from members of our executive team and from Moderna's therapeutic area heads, highlighting the progress to date on a select number of clinical programs. In addition, we have a key opinion leader in the immuno-oncology space presenting today as well.

Following the formal presentations, we will take your questions during the Q&A session. You can access the press release highlighting the progress and updates announced this morning as well as the presentation slides by going to the Investors section of our website.

On today's call are Stephane Bancel, our Chief Executive Officer; Stephen Hoge, our President; Paul Burton, our Chief Medical Officer; Jackie Miller, Senior Vice President and Therapeutic Area Head of Infectious Diseases; Praveen Aanur, Vice President and Therapeutic Area Head of Oncology; and Ruchira Glaser, Senior Vice President and Therapeutic Area Head of Rare Diseases, Cardiovascular Disease and Autoimmune Diseases.

Before we begin, please note that today's presentation will include forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Please see Slide 2 of the accompanying presentation and our SEC filings for important risk factors that could cause our actual performance and results to differ materially from those expressed or implied in these forward-looking statements. We undertake no obligation to update or revise the information provided on this call as a result of new information or future results or developments.

On Slide 3, please see the important indication and safety information of our COVID-19 vaccine, which has been authorized for emergency use in the United States and in many countries around the world. Now without further ado, I will turn the call over to Stephane to kick off the event.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina. Good morning or good afternoon. Thank you very much for joining us today for the Fifth Moderna Annual R&D Day.

As you all know, software uses a binary system made of 0s and 1s. And as most of you know, life uses a quaternary system, uses 4 letters to code any protein under the living kingdom, which is what makes mRNA an information molecule.

mRNA is a new class of medicines. We got very excited 10 years ago about building an mRNA company because, first, a very large product opportunity. We believe that in addition to secreted protein that you see in green here, which is what the biotech industry can do, we could do that but we could also make transmembrane protein in blue or intracellular protein as well. We could also do, of course, combination, and we can also do proteins coming from viruses, as we showed. We believe that the drugs coming out of the Moderna platform will have a higher probability of technical success because we use the same 4 letters to code any message, coding any protein we want and because for every family or modalities of drug, we use a semi-lipid technology.

Now the world knows that mRNA accelerates research and development time lines. And we also believe that mRNA allows a greater capital efficiency on the manufacturing front of things that is going to be very powerful to deliver value to health care system.

Since the beginning, the vision that we have was that because mRNA is an information molecule, if we invest in science to invent novel delivery system to bring the mRNA into different cell type, there will be new applications, which we call modalities. And the vision was to say that if we invest in science and are able to get mRNA into the lung or into the liver or into a different cell type, we create a new family of drugs, a new modality. And what will be really hard is to figure out how to make that new modality work. But once you will have one drug working in that modality, you will have many, and that's the whole beauty of Moderna as a platform company.

So if you think about where we are today in 2021, we have a commercial modality, prophylactic vaccine, that everybody knows us for. But in development, we have actually 5 modality. One in pink on the left is a core modality, meaning we have clinical data that we believe that modality has been derisked. And that's injecting mRNA beyond IV injection as a systemic, secreted and cell surface protein. This is a very exciting application the team is going to talk to you about in a few minutes.

And then we have 4 modalities that you see in the middle of the slide that are in development. They are all in clinical studies right now, but we don't know yet if they'll work in the clinic. And so we are really looking forward to this clinical data as potential proof of concept for the technology. And if we have good clinical data, we'll move that modality onto the left as co-modalities, and like we've done in the 2 modalities at our core, we will scale with many, many more drugs because it's exactly the same technology that we use.

We're also, of course, investing in the future. And there are 2 modalities that we are very excited about for which we have shown already a proof of concept in the preclinical, in the research phase in nonhuman primates. We've shown this in the lung with our partner vertex and also in stem cell at our Science Day back last spring.

A lot of people believe Moderna is a COVID-19 vaccine company. But as I just explained and if you look at the world picture, Moderna has a wonderful COVID-19 vaccine as the team will show you in a minute real-world evidence, but what is really important for us is Moderna is an information medicine-based platform company. And that's really what differentiates us from traditional pharmaceutical companies.

So if you look at this platform, which is how we build the company, then how do you layer product strategy on top of this? Well, our #1 priority as a company right now is to bring to market a pan-respiratory annual booster vaccine, which we plan to always customize and upgrade. Our priority #2 is to bring to market first-in-class vaccines for complex viruses. Our priority #3 is to bring to market therapeutics, treatments based on mRNA-encoded proteins, proteins that we encode in our mRNA. And priority #4 is to bring to market therapeutics, treatments based on enzymes -- editing enzymes that are coded in our mRNA.

So there, we have a 4 pillars of growth that we really see a lot of growth coming in the years to come for Moderna. Because the team has so many product, there are already 37 development programs across the company. And the research team is working to bring even more into the clinic to articulate this product strategy.

So let me spend a minute on the vision that we have for the pan-respiratory annual booster vaccine. Our goal is to have a single-dose annual booster that you can get at your GP or your CVS or your pediatrician that has the following features. The first one is that we're going to adapt the product, we're going to customize it over time; meaning as the virus evolve, our product that we give you will evolve so that you have the best protection at that moment. Sometimes, there might be years where we might need to do 2 upgrades of a product in the same year, and we will do so to protect you.

The second piece is around age, which, as you can imagine, a 2-year-old, a 30-year-old and a 70-year-old do not necessarily need the same vaccine because in those different age groups, you have different viruses that are at risk from a respiratory standpoint. And what we want to do is to basically build a toolbox of different mRNAs that we can mix and match based on age group.

And the third dimension is geography, which is, as we just announced recently our partnership with the government of Canada, there might be a year for which it makes sense in Canada for the 65 and above to adopt the strain of flu or the strain of COVID and want to be able to do that in partnership with those governments.

So our goal and our vision is to update our product based on time, where are the different viruses over time, on age group and on geography. And so we can see a world moving forward where we start from a COVID booster that is currently being reviewed by the FDA, to then add flu as a COVID booster plus flu booster, to then add RSV, COVID booster, flu booster, RSV booster. And you get the point. We want to keep adding more and more viruses of concern in the respiratory space.

I won't spend too much time on this slide, but it's just to illustrate to you that there are many more respiratory viruses that create hospitalization and deaths around the world that we need to have protection against. Everybody, of course, is very familiar with flu, created by influenza virus. But a few people are aware of RSV, respiratory syncytial virus. There is no vaccine today against RSV. And as many of you know, we have a very strong product that is in the clinic right now for which we shared data, and the team is going to share new data today with you, that we are already preparing Phase II, III, IV.

OC43, we presented that coronavirus at our Vaccine Day earlier this year. And we believe the elderly requires a protection against OC43 because many hospitalization every year, you can see here the number, are caused by OC43. A lot of times, they are confused by flu because it's the same clinical manifestation. But when you look at the molecular biology signature of those viruses, they are very different. And then there is also hMPV, PIV3. So there's a lot of viruses that our vision is to bring in a single dose to different age groups.

We think this is a very big opportunity for the company, and I think there are 3 big questions that we're spending a lot of time working on as a team. First is how big will the market be for pan-respiratory annual booster vaccine? How much share could Moderna own? And what value could we create in this market?

So if you look at where we are today, the flu market in 2019 was a little bit over 500 million doses. How big do you believe this market will be if we're able to bring to market a multivalent, pan-respiratory annual booster vaccine? I personally believe that this crisis, this trauma we're all going through is going to be remembered for decades to come. I often said I believe this is like how the 1929 financial crisis left people being very scared of death for many decades after the crisis. I believe the trauma we're all going through right now is going to have long-lasting consequences.

So then the question is how does that -- big that market become. Does it become a 800 million doses a year, 1 billion, 1.5 billion? We believe this is a very large opportunity that is ahead of us if we could bring to market a high-efficacy pan-respiratory annual booster that has high efficacy like we showed for COVID-19 across many strides.

The second question is how much share could Moderna own of that market? And it's important to know, from a technology standpoint, you could not create such a vaccine with recombinant technology. But mRNA technology, we've already shown in the clinic, we can mix and match, where

the team will show you new data of combination in a minute, is really important. So we believe we could be first to market with a COVID booster plus flu booster plus RSV booster vaccine in a single dose.

And why do we believe that? First, because we already have a quadrivalent seasonal flu candidate, mRNA-1010, in the clinic. We're going to have the data very soon. And the team is already preparing for Phase II/III to get this product to approval.

We also have an RSV vaccine, mRNA-1345, which had positive Phase I results with a very significant increase in neutralizing antibody against RSV versus pre-vaccination. And the team is also preparing a Phase II/III. So as you can see, our goal is to combine those products together. And we are announcing actually today a new candidate for COVID booster plus flu booster. So we believe Moderna could be first to market in this important new opportunity.

Now let's talk about value. We believe we can create a lot of value and should be able to capture a significant amount of value for the following reason. First is sum of the parts, which is if you could have a single vaccine that covers 2 or 3 or 4 viruses that you can buy individual vaccine against those things, is how much will you pay for a portfolio of vaccines versus one. That's the sum-of-the-parts analysis.

The second piece that we hear a lot as we talk to payers, both private payers in the U.S. as well as governments around the world, is the value of compliance to the payers. If you have 3 vaccination required, let's say, flu booster, COVID booster and RSV booster, to an elderly 65 and above who has a very high chance if he gets infected to get disease and to get hospitalized, what is the value of compliance if you know that elderly got 1 shot and that they got protected against 3 or 4 or 5, over time, viruses? They say that they are putting a lot of value on that compliance element.

The other piece, of course, that drive preference at the consumer level is number of injection. Nobody likes to get an injection in their arm. And so we believe that the consumer, especially thanks to the strong brand that Moderna enjoys today, thanks to the role we've had and we are having every day on the fight against COVID-19, has a preference toward the Moderna brand if you have a pan-respiratory vaccine available.

And the other piece that is also very important for the payers is the cost of administration. As you might realize today, it is more expensive to administer a vaccine of Moderna than to buy a COVID-19 vaccine. And so we believe, when you look at those 4 elements on value, that we're going to drive a lot of value to the health care system and we should be able to capture a lot of that value in retail.

If you look at the Moderna pipeline, we now have it on 3 different slides because of 37 development programs. So the first slide that you see here is basically Moderna's respiratory vaccines portfolio. On the top part of the slide, you see the adult vaccine, and the bottom, you see adolescent and pediatrics. So there are 2 new vaccine candidates we're announcing today: the COVID plus flu vaccine, mRNA-1073; and the RSV plus hMPV pediatric vaccine, which we are very excited about. As you look at the right hand of the slide, you will see that we own global commercial rights to all of those products.

The second piece of our strategy is developing vaccine against complex viruses. And as you can see here, we have soon to be in Phase III a CMV vaccine for which we are very excited about the increase of neutralizing antibody in Phase I and Phase II for that vaccine. And I remind you, there is no commercial vaccine against CMV.

As many of you are aware, we are progressing a prophylactic vaccine against EBV, Epstein-Barr virus, the virus that cause mononucleosis disease. And we are now announcing today a new exciting vaccine. As a therapeutic vaccine -- it's the first vaccine in infectious disease that we are bringing to the clinic as a therapeutic vaccine for EBV. The team will tell you more. So another new exciting program there.

And then if you look at our therapeutic-based medicines, you see the portfolio in autoimmune disease; in cancer, both cancer vaccine and cancer intratumoral; our localized therapeutics; and our rare disease program. Two other news I want to insist on today is, first, that on GSD1a, we got a safe to proceed to the clinic by the FDA. So following PA and MMA, which are already testing in patients, we're going to soon bring a third rare disease program into the clinic.

And then we made announcement this week on Tuesday, which I think is very important for Moderna long term. It's around Crigler-Najjar Syndrome Type 1, also called CN-1. This is an ultrarare disease. And with the team, we've been spending quite some time wondering how do we bring to market important medicines that have very small opportunity in terms of number of patients when you talk hundreds of patients around the world.

As we run the math and as we thought about it, we said, geez, if you just have to recover development costs -- clinical development costs, you might have to charge millions of dollars per treatment to each of those families, which is not us. Didn't make any sense. And so we went actually the other way, 180 degrees the other direction to say, look, we have a platform, it's a kind of sunk investment because we developed the platform. So is there a novel way for Moderna to bring important medicine to those families, to those children by giving the drug away?

And so we thought long and hard about setting a public-private partnership where basically Moderna has given free of charge, meaning there is no upfront fee payment, there is no milestone for success, there is no royalty. And we even said, look, we will provide the mRNA product for free of charge from a manufacturing standpoint. And we are very pleased to announce this week the partnership we've had with Jim Wilson to be able to do that.

As many of you know, there are several thousands of rare genetic disease in the liver that use exactly the same technology that you can see on the slide in orange that have too small of a market to make sense for us to bring commercially, and I look forward to Moderna team finding more partners to bring more of those products. We think it's totally aligned with our values, totally aligned with our mission and totally aligned with our vision that we want to be a good corporate citizen, and CSR is really important for the long-term of the company.

So today, I'm very pleased to be presenting the speakers that will be joining me. In addition to Dr. Hoge that many of you know, who is the President of the company and currently runs R&D, I'm really happy to have Paul Burton, our new Chief Medical Officer, present you some real-world evidence around the COVID-19 vaccine; Dr. Jackie Miller, who leads our infectious disease development; Praveen, who leads our oncology development; and Ruchira, who leads our autoimmune, cardiology and rare disease development.

And in terms of the agenda, what we plan to do is Stephen is going to follow me right away to give you a bit of an overview on the platform modalities and therapeutic area. Then Paul will share with you some real-time, real-world evidence around COVID-19. Jackie will walk you through infectious disease data and strategy. We'll take a small break. And then Praveen will be joined with Dr. Melero to talk about oncology. Stephen will come back to talk about LNP delivery and Moderna Genomics, this foray we are doing in gene editing before Ruchira presenting rare disease, autoimmune disease, cardiovascular. I'll come back for a quick conclusion before then we move into Q&A with the team.

With this, I turn over to Stephen.

Stephen Hoge - Moderna, Inc. - President

Thank you. My name is Stephen Hoge, and it's my pleasure to walk you through our approach to building platform technologies, modalities and advancing our portfolio of medicines.

Now as we laid out at our first R&D Day 4 or 5 years ago, there are 3 key components to our platform. The first is messenger RNA technologies; the second, our delivery technologies around our lipid nanoparticles; and the third and equally important is the process by which we make our mRNA and LNPs and pull them together into our medicines. Our platform incorporates advancements across all 3 of these areas as we advance our medicines. Now it's the integration of these 3 areas across messenger RNA, delivery and process technology that allows us to make our medicines, and we combine different versions of mRNA delivery and process into each of our medicines.

Now there are common features between groups of medicines, and we call these modalities. Moderna's modalities are really just the applications of our platform. The groupings have common features in mRNA or delivery technology or in the process by which they're made, and it allows us to manage the risk of those programs as well as understand in cases of success where we can rapidly expand and build upon that success with common programs using similar technologies. This is core to understanding our approach and strategy.

Now across all of our programs, Moderna has clinical studies ongoing in 5 therapeutic areas. We're best known for our work in infectious disease with vaccines, but we have programs in oncology, cardiovascular disease, rare disease and autoimmune diseases. In fact, we have 37 development programs, comprising 34 different development candidates. This is a dramatic expansion from 23 just 1 year ago.

Now these 34 development programs and candidates are comprised in 6 different modalities or combinations of technology, as I was speaking to a moment ago. Again, the most well known for us is our prophylactic vaccines modality, which we use in infectious diseases. But we have modalities in systemic secreted and cell surface therapeutics, cancer vaccines, intratumoral immuno-oncology, local regenerative therapeutics, systemic intracellular therapeutics and others. In fact, we continue to advance programs in new modalities that are not yet in clinical development, including the lung and the hematopoietic stem cell system.

Now looking across the modalities, you can get a sense of the history of Moderna. We started 10 years ago with the idea that we could make messenger RNA medicines. The idea was that we could use the information containing mRNA molecule to treat or prevent disease. And the very first manifestation of that was our prophylactic vaccines modality, where we advanced into the clinic over 5 years ago. Based on those early signals and successes, we advanced 3 more modalities into clinical development: first, cancer vaccines; immuno-oncology -- intratumoral immuno-oncology; and localized regenerative therapeutics, aiming at regrowing tissues, particularly the myocardium in the heart.

Following those successes, we moved to systemic modalities into clinical development: first, systemic secreted and cell surface therapeutics; and then, systemic intracellular therapeutics, both with multiple programs advancing that we hope to update you on today. And as I mentioned, we continue to advance new modalities, including the lung and HSPC system, and we look forward to providing updates on those in future R&D days.

Now the most important thing to recognize is that every time we add a modality and a new medicine to our portfolio, we develop a network effect because each incremental program, all 34 of them, help us learn something about all of the programs we're advancing. And we can take those learnings given our platform technology and rapidly apply the best of them across all programs. That network effect, each -- with that network effect, each incremental program increases the value of our science, our platform and allows us through our modalities to expand and add new medicines over time.

I'd like to take a moment and give you a sense of how we do that expansion with our modalities. We have 2 modalities, prophylactic vaccines and systemic secreted and cell surface therapeutics, which we declared as core modalities in 2019. What that meant to us is that we've seen sufficient clinical data, first, in the case of CMV as a vaccine; and the other -- and the second, in the case of chikungunya antibody program. We've seen enough clinical success and signals that we came to believe that both were substantially derisked and it was time to bring forward many new medicines.

Now the best example of that was in our prophylactic vaccines field where, as you all know, we've advanced quite a large portfolio of programs. In fact, given the initial proof of concept of CMV vaccines, we started advancing even ahead of COVID-19. But obviously, the success of our COVID vaccine work has dramatically expanded that effort as well.

In our prophylactic vaccines modality, we have a number of ongoing programs in COVID-19, including looking at pediatrics and combinations. We're also advancing a flu and RSV combination vaccine towards a Phase II. And Phase II/III programs are being prepared for both flu and RSV independently. CMV is moving forward towards its Phase III this year. Our Zika vaccine is in Phase II.

And we're exploring pediatric respiratory combination vaccines, first, with our hMPV/PIV3 program, which is in Phase II in toddlers as we speak. As I mentioned a moment ago, there's a large number of respiratory combinations that we've spoken about before and that are moving forward rapidly into clinical development. And then, of course, we continue to add new viral pathogens outside of the respiratory space, including EBV, a vaccine against HIV and a vaccine against Nipah. There are many, many more pathogens that we intend to address over time, and we believe, given the derisked nature of our prophylactic vaccines modality, that we can do so with the appropriate level of aggression to try and address these dramatic unmet needs.

Now at the other end of the extreme, there are modalities that are not so derisked as prophylactic vaccines. And one example is our systemic and intracellular therapeutics modality, which we continue to call an exploratory modality. While we pulled together technologies for different modalities,

we combine a view on the disease biology, the target tissue and cell type and the required concentration of the protein as well as other features like the underlying pathology of that disease.

We'll often design a novel lipid nanoparticle if it's necessary to try and address that specific tissue in these diseases. And in the systemic and intracellular therapeutics modality, we have focused much of our early work on rare metabolic diseases. That has caused us to advance a portfolio of different lipid nanoparticles, each trying to address the respective diseases in their areas.

In fact, as illustrated on this slide, you can see that we have 3 different lipid nanoparticles within the same modality. IV-LNP 1 is targeting against propionic acidemia and MMA, both dosing in the clinic as we speak. We have a second slightly different lipid nanoparticle, which we're advancing for GSD1a, a different liver disease with different pathology; and a third lipid nanoparticle, IV-LNP 3, that we're advancing for PKU.

Now we believe that each of these different lipid nanoparticles are appropriately targeted for these rare diseases, and we're very optimistic that we'll be seeing strong clinical signals in the months and years ahead. But if in any way, any of these lipid nanoparticles looks dramatically superior, we won't hesitate to take that learning in this modality and bring forward medicines against all these diseases in that lipid nanoparticle. In that way, we are able to advance programs against all these diseases but learn -- again, that network effect, learn from individual programs and bring the best of our technology in the modality to the patients who need it the most.

Now as we advance our program -- our platform, we will continue to bring new modalities to bear and continue to bring those forward as medicines to address diseases in all of our core therapeutic areas. And in certain cases, we'll create completely novel approaches to modalities. In fact, today, we're pleased to announce that the Moderna Genomics team has continued to advance and grow, and our vision is to be a leader in the large complex genomic editing space. MGX, for short, will leverage Moderna's existing technologies in mRNA and lipid nanoparticles as well as new technologies and capabilities in biology to bring forward novel nucleic acid editing capabilities. This will be a completely new approach for Moderna and a dramatic expansion of our modality strategy.

We've identified a leader for this team, somebody who's been with us for over 10 years. Dr. Eric Huang will be the Chief Scientific Officer of Moderna Genomics and has led many of our expansion areas over time, including our expansion into the autoimmune disease space. I'd like to congratulate Eric and thank his team, and we look forward to providing updates on their efforts in the months and years ahead.

Now I'd like to hand it over to our Chief Medical Officer, Paul Burton, to provide you a little bit of context on the real-world evidence around our COVID-19 vaccine. Paul?

Paul Burton - Moderna, Inc. - Chief Medical Officer

Thank you, Stephen. Good morning, everybody. My name is Paul Burton, and I am the Chief Medical Officer here at Moderna. And it's my pleasure today to be able to review with you some of the real-world data around the use of our mRNA-1273 vaccine.

I'm going to review these data with you, and I want to just point out that these data have been generated entirely independently of Moderna. We have not been involved in the design or the execution or publication of these studies. I'm only going to comment on the mRNA-1273 data. And I would also note that while many of the studies have been published in peer-reviewed journals, just given the pace with which this field is moving, some of them have actually been published online on preprint service and they have not yet been peer-reviewed.

Before I begin, I want to just take a moment and remember the toll that this pandemic has taken on people around the world, those individuals who have been infected, the families of those people, the families of the 4.5 million people who have lost their lives to COVID-19. And I also want to take a moment and give a tremendous global shout-out to those individuals on the frontline. Health care workers, the teachers, people staffing the vaccine clinics around the world, all of you who have done everything possible to keep us all safe. Thank you for everything that you have done and that you have done for over 1.5 years now.

When we first presented these results that you see here from our Phase III program, we had a median follow-up time of about 9 weeks, and we saw a vaccine effectiveness of just over 94%. We have recently shown these data and discussed them, and we have submitted them for publication.

And the results now of follow-up in that study, with a median follow-up of 5.1 months. And what you can see is vaccine effectiveness of 93%. This is consistent across different endpoints, showing different severity of diseases and also across different demographics of individuals enrolled in the study.

I want to review now some of the real-world evidence data that we have seen published and on preprint service. I'm going to show you some data in hard-to-treat populations, people with transplantation, people with malignancy, people with end-stage renal disease, but what I'd like to start with is to show you some of the real-world evidence in general populations.

So let's turn now to an analysis of the Mayo Clinic database here in the United States. The graph on the left shows the rate of COVID-19 infection over time in people who were either unvaccinated, in the top line in gray, or in pink, those people who received the Moderna mRNA-1273 vaccine. And you can see that risk of infection is substantially reduced.

If you look now at the table on the right, you'll see that here, particularly in the month of July across the entire Mayo Clinic network, we look at the risk of infection. And again, you can see that those individuals who received mRNA-1273 has a substantially reduced risk of getting COVID-19. And this is consistent across those different states and in a month when we know that the dominant variant of COVID-19 was Delta. And additionally, as you see there in the title, the study was able to estimate that overall, the COVID-19 vaccine effectiveness of mRNA-1273 was estimated at approximately 76% protection.

In the next slide, we see the results of another large study, this time conducted in Qatar. Looking at protection, again, against infection due primarily to the Delta variant. And here, you can see that mRNA-1273 provides an estimated vaccine effectiveness of approximately 85% even in the face of Delta variant infection. So taken together, these data with those from the Mayo Clinic system, we can see robust vaccine effectiveness of mRNA-1273, even in the last few weeks when the Delta variant has really come to the fore and in 2 different geographical areas.

Let's think as well now for a moment about those residents in nursing homes. Here, you see data from a study in 289 nursing home residents by Breznik from McMaster University. And it shows the ability of mRNA-1273 to induce high antibody titers to both the spike protein as well as the receptor-binding domain, RBD, in these individuals. We know that they are at particularly high risk of infection, and they are also a particularly high risk of the consequences if they do get infected. So being able to see these high titers in those individuals is reassuring.

I want to turn now and look at some illustrative data examining the effect of mRNA-1273 in immunocompromised patients, and I would like to start here by looking at multiple myeloma patients. In the next 2 slides, we'll look at patients with hematological malignancy and then look at these patients who have been treated with mRNA-1273. The first study here is, as I say, in multiple myeloma, and it's by Stampfer and colleagues from Emory University. These investigators found that 67% of those patients who were immunized with mRNA-1273 were able to mount an immune response with titers above 250 units, a level that the authors considered to be clinically relevant.

In this study, now by Greenberger and colleagues, these investigators looked at a broader population of hematological malignancy patients as with lymphoma, leukemia as well as multiple myeloma. And they found that in a multivariate analysis controlling for a wide variety of baseline risk factors and other univariate risk factors, the use of mRNA-1273 was found to be independently associated with the likelihood of mounting an immune response following vaccination.

In the next few slides, I would like to look at and share with you data in patients with organ transplantation and then end-stage renal disease. Clearly, these are a difficult group of patients to treat. But as you can see here, 22% of these patients who had undergone organ transplantation for either kidney transplant, liver, heart or lung were able to generate an immune response following one dose of mRNA-1273. Giving 2 doses of our vaccine increased at seroconversion rate to 30 -- by 38% after 2 doses. But that meant that there was still 40% of individuals who did not seroconvert and mount an immune response.

So the question is, is there anything we can do to try and increase that rate of those individuals who will not seroconvert. And the data in this slide, I think, may provide some clues to answer that question. These data come from Hall and colleagues in Toronto. These individuals randomized 120 transplant patients who had been vaccinated with mRNA-1273 and then randomized them one-to-one to receive either placebo or an additional third dose of mRNA-1273. And what you can see here is that 55% of those patients who did receive the Moderna vaccine were able to generate

antibodies against the RBD following that additional dose. So these data clearly support the recommendations currently for additional vaccination in immunocompromised individuals.

In my final slide, I'd like to draw your attention not only to renal transplant patients but also to those patients with end-stage renal disease who are undergoing dialysis, again, a very difficult patient group to treat. So you see here that 49% of the patients who had undergone a renal transplant here were able to mount an immune response following vaccination with mRNA-1273. It's very consistent and reassuring. But importantly, if you look now at the dialysis patients who not only represent a hard-to-treat group of individuals but also hard to immunize population, 97% of those people were also able to mount an immune response when vaccinated with mRNA-1273.

So in summary, let me tell you what I think I've been able to show you today. First of all, in randomized controlled trial settings, use of mRNA-1273 provides a robust and sustained protection against infection by COVID-19. In the real-world setting, that effectiveness and protection is upheld, and that is true both in the face of a strong pressure from the Delta variant and also in different geographical regions. And finally, in those hard-to-treat populations, people with hematological malignancy, with organ transplantation and with dialysis, mRNA-1273 again is able to induce robust immune responses.

So thank you for your attention. And it's now my pleasure to hand over to Dr. Jacqueline Miller.

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

Thank you, Paul. Good morning, everyone. My name is Jacqueline Miller, and I'm the therapeutic area head for infectious diseases. And it's my pleasure today to review our development progress for our vaccine assets at Moderna.

So today, we're going to start by talking about COVID-19 and mRNA-1273, a vaccine I know you all know quite a bit about. But what you'll see is that we've actually now started to invest in next-generation formulations of the vaccine, including formulations designed to address variants of concern. We've also made progress in our pediatric and adolescent development programs, which we'll discuss in the next few slides. And then finally, we'll also speak a bit on emerging data with booster doses to be administered to increase neutralizing immunity.

So let's take a brief reminder of the time line up until this point. Back in November of 2020, we reported on the primary efficacy analysis of mRNA-1273, where vaccine efficacy was observed to be 94%. This led to emergency use authorization of our vaccine shortly thereafter, in December of 2020. Then by March of 2021, we had a database cutoff and completed an additional analysis in July of 2021, which resulted in our BLA submission on August 25. And so now we continue to answer to questions on our BLA as it is under review.

So an update of the efficacy analysis is available, and I'm pleased to tell you that the vaccine efficacy remains high and durable with 2 doses of mRNA-1273. So what we saw in the subjects who were followed after receiving either 2 doses of mRNA-1273, 100 micrograms, or 2 doses of saline placebo was that vaccine efficacy in total for cases occurring 14 days after dose 2 remained 93.1%.

And as you can see on the slide, when increments were further broken down, we see that in less than 2 months, we have 91.8% between 2; and 4 months after that second dose, 94%; and more than 4 months, 92.4%. As I mentioned, these data were followed through the end of March 2021, which was the time during which subjects were in the process of crossing over if they were in the placebo group to receive mRNA-1273. The predominant circulating strains at that time were the ancestral strain and the Alpha variant.

So now I'd like to talk a little bit about some of the special subpopulations that we've been investigating. As Dr. Burton reviewed for you, we have seen that the immune response in those who are immunocompromised is not as robust in those with healthy immune systems. So in multiple myeloma, we have seen that mRNA-1273 can induce antibody titers and CD4 cell activation. And mRNA-1273 was also associated with robust immune responses in other types of hematological cancers.

A third dose of mRNA-1273 enhanced the anti-COVID-19 immune response in subjects with solid organ transplant. And this was particularly true for subjects who take mycophenolate or other antimetabolite pharmaceuticals. And therefore, we submitted for and received a third dose indication in subjects who are immunocompromised. And so patients are out now receiving their third dose of 100 micrograms of mRNA-1273. We continue

to study the impact of a third dose in our COVE Transplant study, where patients with renal or liver transplants are being followed with 3 doses of 100 micrograms.

We also have an ongoing pediatric development program. And we have recently reported data in the New England Journal of Medicine regarding the use of mRNA-1273 in adolescent subjects 12 to 18 years of age. This was a Phase II/III clinical trial in which we studied the safety, the efficacy and the immunogenicity. And in particular, the immunogenicity was used as a bridge to establish the effectiveness of 100 micrograms of mRNA-1273 in adolescents versus saline placebo.

Importantly, subjects were also compared to those young adult subjects that we investigated in the COVE study. So subjects 18 to 25 years of age in COVE, which, as you recall, established the efficacy of our vaccine at 94% in the primary analysis, were used as the benchmark to demonstrate that at least equivalent immune responses could be achieved in adolescents.

The primary immunogenicity endpoint was met and immunogenicity was found to be non-inferior in these adolescent subjects. No cases of COVID-19 were observed in the adolescent population after 2 doses of vaccine, resulting in vaccine efficacy consistent with 100%. And the safety and tolerability profile was generally consistent with that observed in the young adult subjects of COVE.

So currently, the vaccine is authorized for use in adolescents in the United Kingdom, European Union, Japan, Canada, Switzerland, Taiwan, Saudi Arabia, Australia and the Philippines. And we continue to submit those data in other countries. Overall, nearly 2,500 adolescents received mRNA-1273 in this clinical trial.

We have an ongoing study in pediatric participants who are 6 months to 11 years of age, and we have recently completed enrollment in the 6-year-old to 11-year-old cohort. This slide depicts for you the study design, which is a bit complicated so I'm going to review it in some detail. Children have been divided into 3 age cohorts: 6 to 11 years of age; 2 to 5 years of age; and then 6 months up to 24 months of age. And in each of these age cohorts, dose ranging has been performed to find the optimal dose in that age of children.

Taking the 6 to less than 12-year-of-age subjects, we first investigated 50 micrograms and 100 micrograms and compared the 2 dose levels to assess the appropriate dose. Ultimately, we then enrolled the larger stage cohort of 50-microgram subjects, up to 3,000 vaccine recipients. And you'll see that we plan to enroll 3,000 vaccine recipients in each age cohort for a total of 12,000 vaccine recipients -- 9,000 vaccine recipients, 12,000 total number of subjects.

We currently have the dose-ranging phases of the study ongoing in the 2 to less than 6 years of age and 6 months to less than 2 years of age. And we'll report on the dose selection in those arms when those data are available. We hope to report final data on the 6- to 11-year-olds by the end of the year.

So now I'd like to shift gears and talk about what happens in terms of longer-term antibody persistence and efficacy in the COVE trial, using that as a lead-in to discuss the third dose boosters. This slide depicts antibody persistence against the Wuhan strain and the D614G mutation, so the ancestral strains, in gray versus various variants of concern in the colored lines. And these are the subjects from our Phase I study, which was originally sponsored by the NIH. And importantly, what we see is that while antibody levels to the ancestral strain diminish as is expected in the first year after vaccination, those antibody titers really remain well above the limit of detection, which is shown in the dotted line on the graph.

However, depending on the specific variant of concern under discussion, the antibody titers do reduce to a greater degree. And in particular, we see the lowest level of antibody titers against the Beta variant. The Delta variant is somewhat in between but still lower than the antibody titers against the ancestral strain. So this decreasing of antibody titers means that while the vaccine efficacy remains high and durable through the period of follow-up so far, we can expect that we may begin to see more breakthrough disease, particularly with the Delta strain so predominant.

So now let's talk about the booster studies where we've been investigating whether we can restore the immunity by giving a third dose. At the time that we unblinded our Phase II study around the time of emergency use authorization to enable those placebo recipients to also get vaccinated with mRNA-1273, we made the decision to offer a booster dose to those that had been primarily vaccinated with mRNA-1273. And you may

remember in that study, subjects received either 50 micrograms or 100 micrograms because we were still in the dose-ranging phase of our development program.

All subjects were offered a 50-microgram boost. And the reason for that was because, one, we know that fractional doses can be quite immunogenic, particularly with vaccines that give a strong primary series response. And secondly, we knew that the world would need as many available doses of COVID-19 vaccines as possible, and this was a dose-sparing strategy that we were investigating. So you can see that the original recipients of the primary series, 173 of whom received 50 micrograms and 171 of whom received 100 micrograms, were offered a 50-microgram booster. All of these subjects had received their original primary series at least 6 months prior to receiving the third dose booster.

We compared these subjects again to an immunogenicity subset in COVE. And the reason for that is COVE is the safety and efficacy study that was linked to the 94% efficacy. So if we can demonstrate that the immune responses is at least as good or better, we have a strong link back to the potential efficacy of this third dose booster.

So what you see on this slide are the immune responses that we observed. All of these immune responses are in terms of the neutralization assay. And they're given, first, in the left-hand column, for the entire study cohort, so 18 to above 55 years of age; and then broken down by 2 different age groups: first, 18 to 55 years of age -- or 65 years of age in the middle and then over 65 years of age in the right-hand column. And what you can see is that the pre-booster antibody titers in the top row actually remained quite robust in the overall age group and even in the oldest age stratum. So the cutoff of the assay is about 9.6, and that's where all of the subjects in COVE were found to be. Recall that we enrolled subjects in COVE who did not have a history of COVID-19 disease, so they're absolutely seronegative, and then had antibody titers ranging in the 2 age strata between 83 and 146.

After the boost, subjects reached antibody titers around 1,900 and nearly comparable results in both of the age strata and importantly, higher than those antibody results that we observed in the COVE study. So overall, approximately 1.7 fold higher than observed in COVE, ranging from 1.6 fold higher to 2.0 fold higher in the 2 age strata. So we're seeing that we can get an excellent boost not just in the younger subjects but also in the older age cohort.

And importantly, we see sero response rates that were at least 89% overall. So the sero response rate is measured in terms of a fourfold rise in antibody. And I would note that these high response rates were observed despite the fact that the pre-booster antibody titers were so much higher than the seronegative subjects in COVE.

The safety profile of giving this third dose booster was observed to be similar to the second dose in the COVE study, very similar pattern of reported adverse reactions with the majority being mild to moderate and lasting in the median of less than 3 days. We have injection site pain as the most commonly reported local adverse reaction and headache, fatigue and myalgia as the most commonly reported systemic reactions. And no deaths, severe AEs or SAEs were reported in this study.

So now let's look at the immunogenicity of these subjects to the variants of concern. And I want to highlight that this is a smaller subset of subjects who received a 50-microgram booster, approximately 11 to 20 subjects depending on which variant was tested. This is also in the research-grade assay and was tested 14 days after the booster dose as compared to 29 days for the primary analysis.

So what you can see in the pink bars at month 1 post dose 2 are the boost -- or the primary series responses to the wild-type vaccine as well as the initial responses against the Beta and Gamma variants. And what you can see is that while most subjects were seropositive after vaccination, a few remains seronegative. And the overall GMTs were lower with the variants of concern. This was previously reported.

Approximately 6 to 8 months after vaccination, we now see that if you look in the bars for Beta, Gamma and Delta, approximately half of the subjects at this time point no longer retain neutralizing antibody titers. And that's particularly concerning for us with respect to the Delta variant, which is the variant that is circulating most widely in the U.S. and in other countries. However, once we give that third dose booster, you see that all subjects with all of the variants are now above the lower limit of detection for the assay. So we are able to restore that immunity.

The highest antibody responses are observed against the wild-type ancestral strain, but we're able to increase that neutralizing antibody to about the post dose 2 level against ancestral strain for all 3 of the variants tested. And that's despite the fact that initially to the Beta variant, for example, antibody titers were up to eightfold lower.

So in summary, the 50-microgram third dose booster induced neutralizing antibodies that are significantly higher at day 29 at then -- after dose 2 in the Phase III COVE study. The 50-microgram dose resulted in approximately a 17-fold increase over pre-booster titers and a 1.7-fold increase over the antibody titers observed in COVE. The third dose booster was also found to be comparable between the younger and older adult cohorts.

The safety and tolerability profile was clinically acceptable and similar to that observed with the second dose in the COVE study. Therefore, we have submitted these 50-microgram third dose booster data for emergency use authorization and conditional marketing approval within the European Medicines Agency. And we have approved in the U.S. the third dose 100-microgram for those immunocompromised subjects we think about as being in a different category as other adults with healthy immune systems.

So before leaving COVID-19, I just want to touch on our plans for the future. And what I've described for you is a strategy to cope with the continuing pandemic as we move into the 2021, 2022 winter respiratory season. But we know that nothing about this pandemic has been predictable, and so at Moderna, we continue to generate data to help us decide how to manage vaccination against SARS-CoV-2 in the future.

And to this end, we've put a number of mRNA booster vaccine candidates into the clinic with different sequences of mRNA. So first, we have 2 monovalent candidates. One is called 1273.351 that really is replacing all of the ancestral strain formulation with a sequence against the Beta variant. And why the Beta variant? Because, at the time we decided to manufacture, that was the variant against which we had the lowest neutralizing capability after vaccination with Moderna's 1273 vaccine.

Now that we see Delta surging and circulating worldwide, we've also manufactured a 617 100-microgram dose. And we are in the process of evaluating that booster vaccine candidate in the clinic. We also are investigating multivalent candidates: 211, which contains a 50%-50% mix of the ancestral strain and Beta variant; and then most recently, the 213 candidate, which contains a 50%-50% mix of Beta variant and Delta variant.

And so why are we continuing to invest this way? Because it may turn out that the best way to handle the pandemic in the future is to swap in the sequences that are currently circulating. And just as I explained with the 1273 third dose, we intend to evaluate these vaccines against all of the variants of concern and against the criterion that have been set forth in regulatory guidance. So looking forward to reporting on the first of these variant assessments in the coming months and hope to report those data to you soon.

And now I'd like to move on to talk about another critically important respiratory virus, influenza virus. So our mRNA platform, we believe, will represent important benefits over existing influenza virus vaccine manufacturer.

One, we may observe improved efficacy. Why? Because the mRNA vaccine, unlike influenza vaccine, allows the body to manufacture its own protein and then package that protein and present it on the cell surface the way our immune systems really evolved to do. But secondly, our ability to swap out sequences and deliver novel vaccine candidates with increased speed of manufacture means that we may no longer be constrained to waiting up to 6 months between when we believe the influenza season will start and picking a strain versus waiting until we see what antigenic drift looks like and selecting the strain closer to when we actually need to administer the booster dose.

We currently have mRNA-1010, a seasonal influenza vaccine, which includes 4 hemagglutinin antigens in the clinic. And that's a vaccine designed to really mimic existing quadrivalent seasonal vaccines that will help us make mRNA vaccines available as quickly as possible. It targets existing WHO recommendations. mRNA-1020 and mRNA-1030 are designed to add additional mRNA sequences coding for further influenza antigens, including neuraminidase. And these vaccines will be going into the clinic later this year -- excuse me, early next year, 1010 and 1030 will be going into the clinic.

Our quadrivalent seasonal flu vaccine, mRNA-1010, as I mentioned, contains 4 hemagglutinin antigens, and these are the existing 4 hemagglutinin antigens in licensed influenza vaccines. The sequences are inserted into the vaccine in a 1:1:1:1 ratio, so all 4 of the virus strains are represented.

As you know, worldwide influenza is an annual challenge for the medical system. There are 3 million to 5 million severe cases of flu and up to 650,000 influenza deaths annually. In the U.S., the estimated economic burden is approximately \$11 billion each year.

500 million doses of influenza vaccine were administered in 2019, so clearly, there is a need for a substantial influenza vaccine supply. But the currently approved vaccines are only approximately 40% to 60% effective each year. And that effectiveness largely depends on the degree of match between the influenza strains that are recommended by WHO, up to 6 months prior to when the influenza boosters are given. And in years where the mismatch is poor, those are the years when we see lower influenza vaccine effectiveness. An improvement has the potential to increase the current \$5 billion to \$8 billion influenza market.

So I mentioned that we were enrolling mRNA-1010. We recently completed enrollment in the Phase I portion of that study and are awaiting the clinical data readout. That study enrolled 3 different dose levels of influenza vaccine. All 4 of those formulations are quadrivalent. And it compared to a placebo control group. These were subjects who are both 18 to 49 years of age as well as over 50 years of age, so we will be able to observe in the Phase I study the immunogenicity of the vaccine in the oldest age cohort.

So I mentioned mRNA-1020 and 1030. And we will be adding further influenza antigens such as neuraminidase in order to provide the broadest possible coverage, all in the hopes of further increasing vaccine efficacy against influenza. And as I mentioned, we also aim to leverage the manufacturing speed and scale so that we can deliver our vaccines just in time for the season. What do I mean by that? That we can hopefully wait a bit longer to see what happens with antigenic drift before committing to which flu vaccine we manufacture. And that will hopefully lead to a reduction in the years of vaccine mismatch, thus a second line of defense and hopefully improving influenza vaccine efficacy. We would intend to work with WHO on surveillance techniques to potentially choose strains closer to when we have to deliver the flu vaccine.

So now I'd like to shift gears a bit and talk about another respiratory virus, respiratory syncytial virus, where we have ongoing programs in both older adults, women of childbearing age and young children. So our mRNA-1345 vaccine contains the F-protein of the RSV antigen. The F-protein is really important for virus entry. It's a single mRNA sequence that we are testing across the age strata. And it contains in its pre-fusion formulation and confirmation all of the important neutralizing antibody epitopes.

So respiratory syncytial virus is a leading cause of respiratory illness at the extremes of age, so both in younger children and older adults. In children, the hospitalization rate of children less than 5 is 3 per 1,000. And annually, there are over 2 million medically attended RSV infections in the U.S., with 86,000 children hospitalized each year. Pediatric RSV results in about \$2 billion of annual medical costs. And almost all children will have had their RSV infection -- first RSV infection by their second birthday. So this truly is a ubiquitous virus.

There's a less appreciated disease burden in older adults, but we continue to get infected with RSV throughout life. And as T cell immunity wanes in older adults and immunosenescence sets in, these infections start to become more symptomatic and more severe. There are approximately 177,000 hospitalizations in adults over 65 years of age due to RSV and 14,000 deaths occur. It's estimated globally that there are 1.5 million episodes of acute respiratory tract infection and over 300,000 hospitalizations due to RSV in older adults. And this results in an estimated \$3 billion annual medical cost in the U.S. each year.

So let's talk for a moment about our ongoing Phase I clinical study with our RSV vaccine. And as I mentioned, we're studying this vaccine across the age range because RSV is a virus that impacts across age ranges. So we have cohorts in younger adults, cohorts in RSV seropositive children, and this is part of an age de-escalation and derisking scheme before we investigate in the target population of seronegative babies. We also have fully enrolled an older adult cohort, 65 to 79 years of age. And then we're also looking at women of childbearing age because we believe mRNA vaccines can be an important maternal immunization platform.

Since this is a Phase I study, we're investigating the safety and tolerability of these vaccines as well as the immunogenicity as compared to placebo. And the only ongoing cohorts at this moment are the seropositive toddlers. So let me share some of those data with you now. So now let's review the data from the Phase I trial in younger adults. And you'll recall that I presented these data at Vaccines Day in April earlier this year, but I thought I would review them again for your awareness.

So in this study, we gave a single dose of 50 or 100 micrograms of mRNA-1345. And you'll see the responses graph in the bar graph on the right, with 50 micrograms in red and 100 micrograms in blue. We observed that, comparable to what is observed with other mRNA vaccines in our platform, the most common local reaction is injection site pain and the most common systemic solicited reactions were headache, fatigue and myalgia with the majority occurring within 1 to 3 days after vaccination.

After 1 month, to RSV serotype A, we observed approximately a twentyfold increase with both the 50-microgram and 100-microgram dose. And against RSV-B, we observed at least an 11-fold increase in neutralizing antibody titers. This was really encouraging to us and resulted in our initiation of the older adult cohort.

So on this slide, you now see the older adult cohorts, where we gave 3 groups of older adults either 50, 100 or 200 micrograms of mRNA-1345. And in the bar graph on the left, we've combined the results of the 50-, 100- and 200-microgram group because there weren't significant differences between them. So what you see is that the antibody responses to RSV-A increased 14-fold and to RSV-B increased 11-fold. What's particularly encouraging about that is that the increases are relatively comparable, particularly in terms of RSV-B, to what was seen in younger adults. And so we will be taking RSV 1345 forward into a Phase IIb/III clinical trial in older adults later this year.

So in summary, we're aiming to start that Phase IIb/III clinical trial in older adults by the end of 2021. It's going to be a global trial, and the locations are going to be influenced by the ongoing epidemiology of RSV. This is similar to how we managed our clinical trial enrollment with mRNA-1273. And you may recall that being able to enroll your trial in an area that has high attack rates means that you more rapidly accumulate cases for comparison and are able to more readily come to a conclusion about the efficacy of the vaccine.

Similar to the mRNA-1273 program, this is a placebo-controlled study and a case-driven design. The primary endpoints will be safety and vaccine efficacy and will be conducted in adults 60 years of age and older. And we expect to enroll at least 34,000 participants, subject to agreement with regulatory authorities.

So now let's switch gears to talk about one of our ongoing combination vaccine developments. This is a pediatric respiratory vaccine combining human metapneumovirus and parainfluenza virus type 3, and this is mRNA-1653. So with mRNA-1653, we have mRNA sequences for the F-proteins of human metapneumovirus and parainfluenza virus serotype 3, both of which are presented on the cell surface.

Similar to other respiratory viruses, human metapneumovirus in particular has its clinical impact at the extremes of age and in particular, in younger pediatric patients that have not yet had their first infection. Parainfluenza is the virus responsible for croup. So if you've ever heard a child with that barksy seal-like cough, very likely that child is infected with parainfluenza virus. The incidence rates of these viruses are about 1.2 per 1,000 for human metapneumovirus and approximately 0.5 per 1,000 for parainfluenza virus.

And the symptoms are actually relatively similar to some of the other respiratory viruses, including high fever and nasal discharge. With parainfluenza virus, children can get that croupy cough, more commonly wheezing with children who have human metapneumovirus, but both of which can lead children to be hospitalized due to difficulty in breathing.

So we have another Phase I trial that has been ongoing with this combination vaccine. The first cohort for which we've already shared data in the past, that was in the initial adult cohort. And now we continue to enroll in a dose-escalation fashion for the pediatric cohort. And the primary objective, as in all of our first time in human studies, is to assess the safety and tolerability profile. But we will also be looking at the immune responses.

And we're encouraged because in adults for whom it should be noted this is a booster vaccine because we have multiple human metapneumovirus and parainfluenza virus infections throughout life, we observed neutralizing titers that were sixfold and threefold higher than baseline titers. And then our interim data in seropositive children also demonstrates increases, and we're going to be presenting those data in an upcoming medical conference.

So now let's talk about some of the combination vaccines that we haven't really spoken about before. Starting with a COVID and influenza virus combination vaccine and then ending with RSV and human metapneumovirus for children. So as we presented at Vaccines Day in April, one of the

pillars of our vaccine strategy is to deliver respiratory combination vaccines. And why? Because these are vaccines that infect us -- or these are viruses that infect us over and over again throughout life. And vaccines to prevent that annual winter occurrence could really reduce not only symptoms, time off of work and school, but in the very old and very young in particular can help keep patients out of the hospital.

So what you see here first is the description of our vaccine targeted against COVID-19 and influenza. And so why develop a COVID-19 and influenza booster? Because these are both respiratory viruses that we have observed really increase in incidence over the winter months, particularly when we're driven indoors. And should COVID-19 become an endemic disease, it would increase both convenience and compliance for patients if they were able to get those boosters in a single shot.

So the vaccine is intended to include both the spike protein for COVID-19, the same spike protein that's currently in mRNA-1273 or Spikevax; and then the 4 hemagglutinin antigens that we spoke about earlier in mRNA-1010 seasonal influenza vaccine. There is always the possibility to add additional antigens such as neuraminidase should we find that to be successful in the 1010 or 1020, 1030 Phase I study that we will be conducting early next year.

And in terms of the pediatric booster, we know that RSV and human metapneumovirus are both important respiratory infections. And again, this is for children who have not yet experienced their primary infections. The idea would be to vaccinate against both of these respiratory pathogens that lead to wheezing, potential hospitalization and have also been associated with longer-term respiratory complications such as reactive airway disease.

So as I had mentioned a bit earlier, respiratory virus disease is greatest in the 2 extremes of age, the very old and very young. And we believe that starting to investigate these boosters is really an important longer-term strategy for us. The other benefit of the mRNA platform is that it allows a lot of manufacturing flexibility and adaptability; meaning that should we see the emergence of some viruses or some of the viruses become less important in years to come as we follow the epidemiology, we will be able to follow the science and create the right vaccine booster and right vaccine priming regimen for younger children to really match the epidemiology that's out there.

So this is really illustrating what I mentioned on the previous slide. Our goal is really to manufacture vaccines that are going to have the greatest public health impact. Combination vaccines can really help make sure that people are fully vaccinated by ensuring higher compliance and better uptake. And that really can result in a longer-term benefit to health care systems.

So let's talk a little bit about the development in the preclinical space of these vaccines. And we have observed in our preclinical data that flu, RSV and COVID-19 can be combined together to result in immune responses to all 6 antigens. And so these data which you see on the slide in blue to the influenza antigens, in orange to the RSV antigens and in red to the SARS-CoV-2 antigen, that we are able to induce robust immune responses to the antigen alone but then also the antigen in combination with the other RSV sequences.

And so now I'd like to shift gears and talk about some of the vaccines targeting more complex antigens. And in particular, I'd like to review our cytomegalovirus or CMV program as well as our Epstein-Barr virus or EBV program.

So CMV is a complicated virus that actually can lead to lifelong medical conditions. It starts out as a milder mono-like type of syndrome that can lead to congenital cytomegalovirus as well as other longer-term complications, particularly in transplant patients. This virus has been very difficult to target with vaccines. And therefore, our vaccine candidate involves 6 different mRNA sequences that result in 2 cell surface-expressed antigens.

The first is gB. And then 5 of the mRNA sequences self-assemble to create the pentamer antigen. And pentamer is incredibly important because it's known that it's the most immunodominant antigen and also results in the highest immune responses in humans.

So what is CMV? It's the most common -- it's a common infection and the leading cause of congenital birth defects in the U.S. About 1 out of every 200 babies in the U.S. are born with congenital CMV. And that results in approximately 20,000 to 30,000 infants born with this challenge each year. There can be a significant impact to children with congenital CMV, and that impact actually also extends to their families and loved ones.

So of those 1 in 200 babies that are born, approximately 10% to 15% of those are severely ill at birth with problems ranging from growth retardation, shock and jaundice and liver complications to longer-term complications that result in 4% to 12% of those who are symptomatic at birth. And in particular, children who don't appear severely impacted at birth can end up with longer-term complications, most commonly hearing loss. And it is actually the most common cause of nongenetic hearing loss in children in the U.S. There currently is no approved CMV vaccine in the U.S. or anywhere.

The Phase III CMV trial is targeted to start later this year, and we're waiting for final approval from the FDA to begin our enrollment. We expect to enroll 8,000 participants at 150 study centers in the U.S., Europe and Asia Pacific. And we will be testing 3 doses of the 100-microgram level. Our primary objective is to demonstrate vaccine efficacy in terms of preventing primary infection. And this is important because if moms never become infected, they can't pass the virus on to their newborn infants.

Similar to what I described for the RSV study and similar to what we've previously discussed in the COVE study, this is going to be a case-driven analysis. So we will count cases of seroconversions, and then trigger both an interim analysis to allow for early efficacy and then a final analysis for which the study is powered.

And the way that this primary infection will be determined is by seroconversion to non-vaccine antigens. The reason for that is that the primary CMV infection can often be asymptomatic and that's really what leads to so much trouble. Women who are pregnant may be affected, not have symptoms and not realize that that's posing a risk to their unborn child.

So now let's switch gears and talk about Epstein-Barr virus. And we'll actually talk about 2 programs: mRNA-1189, which is intended to be a vaccine to prevent infectious mononucleosis. And then possibly, we're planning for a second-generation vaccine, mRNA-1195, to treat more complicated cases of Epstein-Barr vaccine, thinking about post-transplant lymphoproliferative disorder as a test case.

So the first vaccine, mRNA-1189, encodes for 4 vaccine antigens. And again, here, we have the gp220 antigen and then 3 other antigens which self-assemble into a more complex glycoprotein. And importantly, with this vaccine, we have targeted the lytic antigens, so really a vaccine intended to be prophylactic primarily in nature, where the target population will be adolescents and young adults for the prevention of mononucleosis.

Epstein-Barr virus, as I mentioned, not only causes infectious mononucleosis but can also lead to associated risks with other long-term medical conditions. Like CMV, it's a herpes virus, and it's spread through body fluids, contracted primarily by young children who tend to be asymptomatic, but also adolescents. And when adolescents become infected, they develop -- they can develop the symptomatic mononucleosis syndrome.

And I think all of us have known adolescents who have had to be absent for school sometimes for months because of an EBV infection. It's a major cause of the infectious mononucleosis syndrome, and it's responsible for about 90% of the 1 million cases of mono each year in the U.S. And symptoms include sore throats, fever, lymphadenopathy, body aches and severe fatigue. Splenic rupture can occur in extreme cases. And interestingly, reactivation of EBV, so in its more latent formation, has been associated in some patients with long COVID syndrome.

So the lifetime risk also of multiple sclerosis is increased by about four- to tenfold if you had infectious mononucleosis as a younger adolescent. And importantly, we see almost no cases of multiple sclerosis in individuals who are negative for EBV. It's also associated with certain lymphoproliferative disorders. And particularly in immunocompromised patients and most particularly in solid organ transplants, a form of lymphoma can form when EBV gets reactivated as the patient is immunosuppressed for their transplant. And then there also is an association of developing some cancers and other autoimmune diseases.

So mRNA-1189, we intend to start our Phase I study in the fourth quarter of this year, and this vaccine includes lytic antigens, but we believe that those lytic antigens will induce protection against both B-cell infection as well as epithelial cell infection. And we aim to reduce the overall disease burden of infectious mononucleosis as our primary objective. Potential future indications may be the prevention of EBV infection and reactivation in other types of conditions like post-transplant lymphoproliferative disease. And potentially, we may study this vaccine in patients with long COVID.

And then in case the lytic antigens are not sufficient for these more challenging longer-term complications of EBV, we are also developing a formulation with latent antigens, and that's mRNA-1195. The idea would be, in this case, to prevent the longer-term sequelae of EBV, which are associated with EBV going into its latent stage after the initial infection and then reactivating over time, creating longer-term complications.

The initial target would be post-transplant lymphoproliferative disease. And why? It's because at least 80% of PTLD in transplant patients is associated with EBV, so a possibility to not only help those transplant patients but also to demonstrate the proof of principle that we can vaccinate EBV and reduce EBV-associated malignancies. There are other longer-term potential indications of this vaccine, including multiple sclerosis and long COVID. And this vaccine remains in preclinical development as we select for those latent antigens.

And so with that, I'd like to conclude and also remind you that we will now take a short break, approximately 5 minutes. Thank you so much.

(Break)

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

Welcome back, everyone. I'm Praveen Aanur, Vice President and Therapeutic Area Head in Oncology at Moderna. Today, it's my pleasure to update you all on our immuno-oncology portfolio.

As you might know, we have 2 modalities in clinic with our mRNA technology. These are the cancer vaccine programs and the intratumoral oncology programs. Today, I will update to you all on 3 of our clinical programs. I'll start with the personalized cancer vaccine program, mRNA-4157, which is partnered with Merck; our KRAS vaccine, mRNA-5671, which is ongoing 3 Phase I studies, is also in partnership with Merck.

In our intratumoral programs, I will cover mRNA-2752, also referred to as the Triplet. This is wholly owned by Moderna. I will also introduce to you all our cytokine IL-12 program, MEDI1191, which is in partnership with AZ. For this, I will invite Dr. Melero to talk us through the history of clinical development with IL-12 and a rationale for mRNA approach with this target.

Before I begin, I would like to take -- talk to you all about the status of immuno-oncology today and why we believe mRNA technology is able to address the unmet need that exists today in multiple cancer indications. Over the last few years, checkpoint inhibitors have made a significant impact in cancer treatment. However, that impact has been limited to few cancer types and a fraction of patients. That fraction has been anywhere between 20% to 50% depending upon the cancer type and stage. There is still a significant unmet need.

Our goal is to improve survival of these patients in this unmet need in combination with checkpoints and our mRNA medicines. Towards that end, our mRNA-based cancer vaccines can redirect the antitumor immunity towards the tumor with somatic mutations and thereby, enhance the antitumor efficacy of checkpoint inhibitors. Our intratumoral programs can make the tumor microenvironment more conducive for activated T-cells by checkpoint therapy, thereby having a synergistic effect with checkpoints.

Let me begin our discussion by talking about personalized cancer vaccine, mRNA-4157. As you might have heard us previously, our personalized cancer vaccine is truly personalized. We make 1 drug for 1 patient which is specific to that patient's tumor mutations. To begin the process, we take tissue samples. One is the tumor biopsy itself, and other one is a blood draw. Next, we genetically sequence both of these and compare the healthy tissue to the tumor.

We identify tumor mutations specific to the tumor. Often, we find hundreds. Out of these, using our proprietary algorithm, we identify 34 neoantigens specific to the tumor and disease used for manufacturing of mRNA vaccine. We aim to make only one lot per patient. In that way, this is truly a personalized drug design. Through this process, we have achieved high efficiency and a rapid turnaround time. In fact, our needle-to-needle time, as in time from tissue biopsy to the administration of the drug, is just in a few weeks.

Mechanistically speaking, our vaccine mRNA-4157 has just one single mRNA which encodes for neoantigens. Once inside the immune cells, this is expressed. And the protein chain is broken down by the intracellular proteosomal machinery into individual neoantigens. These neoantigens are

processed by the intracellular machinery and expressed on the cell surface in the context of MHC. This informs the T cells to act on tumor cells expressing such neoantigens, thereby to elicit an antitumor response.

In clinical development, our mRNA-4157 is currently undergoing both Phase I and Phase II trials simultaneously. Let me briefly walk you through our Phase I and Phase II studies. Our Phase I study is a typical dose-escalation study with both monotherapy and in combination in multiple tumor types. Here, we assessed the safety, tolerability and immunogenicity. We also identified a safe dose for Phase II expansions. In Phase II expansion, in one of the tumor cohorts, the head and neck squamous cell carcinoma, we observed an early positive efficacy signal, and we have expanded this cohort to 40 patients. Enrollment in this cohort is currently ongoing.

Our Phase II study is a randomized controlled study of our personalized cancer vaccine in combination with pembrolizumab. It is randomized against the monotherapy pembrolizumab alone. This targets patients with high-risk stage 3 melanoma. The primary endpoint here is recurrence-free survival at 12 months. I'm happy to inform you today that we have completely enrolled for this trial with around 150 patients.

This is a schematic of our Phase I study. It has 2 parts: part A, monotherapy dose escalation; and part B is combination dose escalation. We have completed both part A and part B. And we have right now expanded into tumor-specific cohort and currently enrolling only in HPV-negative head and neck squamous cell carcinoma.

Let me review with you all the efficacy data which was previously presented at SITC in this head and neck cancer patients. This is a table of best overall response rate. As you see, we've had patients both with complete response and partial responses. This translated into an overall response rate of around 50%. This compares favorably to monotherapy checkpoint, where overall response rate was around 15%. The disease control rate was 90% for this patient cohort.

Now looking at the swimmers plot which indicates the time on study for each patient in this cohort, and this is shown in green line. And you see some of these extends into almost 1 year. Cumulatively, this translates into a median progression-free survival of 9.8 months. Again, this compares favorably when compared to checkpoint monotherapy where median PFS was around 2 months. The median duration of response was not reached for this cohort at the time of database lock.

This is a spider plot which indicates a percentage change in tumor volume from baseline against time. As you see in the yellow-graded portion below, for patients who have had a response after starting a vaccine, the responses became deeper and durable. They are still persistent. All this indicate the efficacy of our personalized cancer vaccine in this patient population.

Moving on to our Phase II study design. This is a schematic of that study. This targets patients with high-risk melanoma who have undergone complete resection. Patients are randomized 2:1, the combination arm versus monotherapy, with the primary endpoint of recurrence-free survival. As I indicated, this is now completely enrolled.

Next, moving on to our intratumoral programs. I would now like to discuss our Triplet program, which is also referred to as mRNA-2752. Moderna's technology enables novel combination of targets. Here, we have 3 mRNAs in 2752 which encodes for different proteins. One is the OX40 ligand, which is a T-cell costimulatory protein; and the other 2 are cytokines, IL-23 and IL-36 chemo. This is administered intratumorally and either secreted or expressed locally in the tumor microenvironment, thereby avoiding the systemic toxicity that could be seen with the cytokines.

Mechanistically speaking, all 3 components of Triplet are strong immune modulators acting on different components of the immune system. OX40 ligand is a transmembrane T-cell costimulatory protein. This can enhance expansion and survival of both CD4 and CD8 T cells.

IL-23 is a pro-inflammatory cytokine of the IL-12 family, and this can cause priming of dendritic cells and also activation of other immune cells. IL-36 gamma is a pro-inflammatory cytokine of IL-1 family, and this helps in the maturation of dendritic cells. Preclinically you see all these 3 components acting synergistically in models to have an antitumor effect. That supported our expansion and ongoing Phase I study.

This is a schematic of our Phase I study. Arm A is monotherapy with 2752 alone and arm B is combination of 2752, the Triplet, with the checkpoint durvalumab. We are completely enrolled in both arm A and arm B. We have established safety both in monotherapy and in combination. We've

also established safety in superficial and deep lesions and identified a dose for expansion in combination. Currently, we have multiple dose-expansion cohorts in multiple tumor types open, including checkpoint refractory non-small cell lung cancer and melanoma.

We previously reported data from the early patients in the Phase I study at ASCO. I'll review it here briefly. The safety table is on the left-hand side. And what you see is 2752 is safe and well tolerated with only low-grade events both in monotherapy and combination. No grade 4 or grade 5 events were noted in monotherapy or in combination.

In terms of efficacy, we saw tumor shrinkage with 2752, both in local and distant lesions in this early cohort of patients which involved refractory/relapsed patient population. We saw multiple patients with stable diseases and a few encouraging early responses supporting our expansion in multiple tumor types. An update to this data will be presented at upcoming SITC in November.

As I indicated previously, that we have expanded into a cohort of checkpoint refractory melanoma in the study. This is because in this patient population, there is still a significant unmet need. The overall response rate in this population is very low and median progression-free survival is still lower. It's just in months, between 2 to 4.5 months. So with our Triplet program, we are targeting this population. And this -- we are targeting both patients with primary refractory and secondary refractory to checkpoint inhibitors. We hope to make an impact in this patient population.

In summary, with our mRNA-2752, we've established safety and tolerability of monotherapy and combination at all dose levels. We have seen early preliminary signs of efficacy supporting our expansion. An update to this data will be presented at SITC.

Now that I've covered our 2 clinical programs with 2 different mRNA modalities, I want to talk to you about the future of immuno-oncology and mRNA medicines. The future of immuno-oncology is going to be about combinations, and here, we believe our mRNA medicines will enable that combination therapies. With our mRNA technology, we are building a toolkit which can target and include each component of the cancer immune cycle, as indicated on the slide here. We hope to combine different parts of this toolkit to -- for a given patient to overcome tumor resistance and also immune resistance. With our medicines, we are hoping that we will be personalizing not just to the tumor as with our personalized cancer vaccines but also to the tumor microenvironment. Our goal is to develop mRNA-based medicines for future cancer patients which is both personalized and industrialized and which will enable a cure.

Next, I want to introduce to you all our interleukin 12 program, which is the other intratumoral oncology program. This is also called MEDI1191 and is in partnership with AZ. MEDI1191 is a single mRNA encoding for cytokine IL-12. This is expressed into the local tumor environment and avoiding the systemic toxicity that can be seen with IL-12. IL-12 is a potent immunomodulator of innate and adaptive immune system and can potentiate a strong antitumor effect.

To talk more about IL-12 and history of clinical development and the rationale for mRNA approach here, I would like to introduce to you all Dr. Melero. Dr. Melero is the Codirector and Professor of Department of Immunology and Immunotherapy at University of Navarra. He is a senior researcher at Center for Applied Medical Research. His research has included all aspects of cancer immunology and immunotherapy. He has conducted more than 40 clinical trials as a principal investigator. He has received numerous awards in this area.

With that introduction, I want to hand it over to Dr. Melero for the next part of the presentation. Thank you.

Ignacio Melero Bermejo

Hello. My name is Ignacio Melero, and I will be presenting about interleukin 12 and its exploitation for immunotherapy of cancer.

IL-12 belongs to a family of heterodimeric cytokines that control inflammation through regulating the function of T cells, in a way is a composite of heterodimers and heterodimeric receptors. Probably the most important feature that we must remember about IL-12 is that through JAK2 and TYK2, the IL-12 receptor beta 2 and beta chain transduce signals that induce the phosphorylation of STAT4 and thereby, control the function of T cells and NK cells. Other members of the family are specialized in other pro-inflammatory or anti-inflammatory functions. IL-23 drives the induction of Th17 while IL-35 is a mediator of T-cell suppression by regulatory T cells.

The main functions of IL-12 are performed through the induction of interferon gamma as a secondary cytokine mediator. NK cells, CD40 cells, either T-helper 1 cells or naive T80 cells sends interleukin 12 and produce abundant amounts of interferon gamma as well as CD8 T lymphocytes can do. And in the tumor context, interferon gamma can exert a number of distant antitumor activities. On the one hand, it induces and augments very much antigen presentation through MHC Class I and Class II pathways. It also sensitizes target cells to the subsequent attack of cytotoxic T lymphocytes.

On myeloid cells, it can switch the M2 transcriptional profile of macrophages which is pro-tumoral to a more antitumoral M1 type of a macrophage phenotype. Importantly, interferon gamma induces the expression of secondary chemokines that attract other T cells and NK cells to the tumor microenvironment. IL -- interferon gamma, either directly or also acting through the chemokine CXCL10, has powerful anti-angiogenic effects in the tumor tissue. From its very cloning, IL-12 was found to exert antitumor effects against transplantable tumor models that were found upon depletion experiments to be dependent on CD8 cells. This gave rise to early clinical research, and the group in Hoffmann-La Roche started clinical trials, testing recombinant human IL-12 at a range of concentrations and eventually defining a tolerable dose at 500 nanograms per kilogram.

There were dose-limiting toxicities, including hepatic function problems as well as pancytopenias. In any case, the toxicity seemed to correlate well with interferon gamma levels raised in these patients. And these early trials gave rise to a good number of clinical trials that spotted some levels of toxicity but very, very little antitumor activity. With the notable exception of cutaneous T-cell lymphoma mycosis fungoides, in which there was a very important, over 50%, overall response rate that could be attributed to the fact that IL-12 is highly toxic for the malignant TH2 cells of this T-cell lymphoma.

At the time, IL-12 was combined with other coexisting immunotherapy strategies that were under development, and it was combined with vaccines, softer antigens, with IL-2, with type 1 interferon or with trastuzumab. Clinical response, objective clinical response was low, and this was somehow left aside. But it must be said that systemic IL-12 has never been combined with PD-1 or PD-L1 blocking agents, something that should be considered very important because IL-12 is the main inducer of interferon gamma in the immunobiological system. And then interferon gamma is, by far, the main inducers of PD-L1 expression.

Therefore, a vicious circle can be set in motion in which IL-12 drives PD-L1 expression. And this is very important when considering combination trials. There is a molecule that is still under development using interleukin 12 in a systemic administration. In a way, it's an immunocytokine that targets IL-12 to the tumor microenvironment by means of an immunocytokine in which the antibody part recognizes extracellular DNA, recognizes nucleosomes, and these are abundant in the tumor microenvironment. And by (inaudible), it could be found that this chimeric form of NHS interleukin 12 targets to the tumor microenvironment.

In fact, in the Phase I clinical trials of such a compound pharmacodynamic activity in terms of the induction of IP-10 and interferon gamma, detectable of circulating levels was done with another feature that is common to other trials with IL-12 is that earlier doses of IL-12 given systemically desensitized to the pharmacodynamic response in terms of secondary cytokines in a subsequent administration.

These systemic delivery coincides in time with the development of local approaches based on intratumoral delivery of IL-12 that we will be combining. It must be said that this NHS IL-12 started combination trials with the anti-PD-L1 antibody, avelumab. But as you can see from clinicaltrials.gov, we know that the trial was terminated due to lack of efficacy.

So because of systemic safety problems, is interleukin 12 a case for intratumoral or localized delivery approaches such as local gene therapy? And we believe that the answer is yes. Many agents can be used to be delivered intratumorally. Most notably, pathogen-associated molecular patterns, such as DNA or bacterial characteristics or RNA as a viral mimetic, all of these compounds are being developed in that regard.

But other things such as antibodies, soluble cytokines, tumor (inaudible) cytokines, immunocytokines, and even cell therapies have been attended in that fashion. Delivering interleukin 12 or the genes encoding interleukin 12 tumors can be very active at several levels, promoting T and NK extravasation and infiltration into the tumor, enhancing antigen presentation and promoting killer activities of activated T lymphocytes.

There are numbers of pros and cons when considering intratumoral immunotherapy. Clearly, you increase bioavailability and then you minimize systemic exposure, reducing the risk for immune-mediated side effects. Clearly, to use these type of treatments, you need the proper logistics in the form of intervention radiologists and skilled personnel to perform administration in a repeated fashion.

But there are many opportunities that are being exploited by industry, all the way in Phase I and Phase III clinical trials, and importantly, pharmacodynamics can be assessed very nicely because repeated biopsies are easier to take. Clearly, we need to adjust some of the regulatory assessments of these strategies as well as we have to reconsider some of our evaluation of response considering apart the injected versus the non-injected these conditions.

We pioneered a little bit the field of IL-12 local therapy in digestive tumors, hepatocellular carcinoma and pancreatic cancer, tumors without any other amenable treatment at the metastatic state that would be efficacious with an adenovirus encoding IL-12. And it was pharmacodynamically very active but with very weak antitumor activity, if any, in that case. As a variation of that, we transduced dendritic cells with interleukin 12 to be injected intratumorally so they would [serve] themselves from tumor antigens and present them in the context of interleukin 12.

But the most potent way in animal models that we have found in our experiments is a recombinant virus named Semliki Forest virus, in which the introduction of the nonreplicative virus by the packaging in alphavirus capsids would give rise to an mRNA that eventually would express p35 and p40, the heterodimeric IL-12. And this has been extremely potent against a good number of tumor models transplantable and also growing spontaneously such as in woodchuck developing hepatocellular carcinoma.

Indeed, this treatment, because of inducing PD-L1, is highly synergistic with anti-PD-1 therapy. For example, here in B16-OVA melanoma model and the MC38 colon carcinoma syngeneic model in mice. Part of the mechanism of action is through IL-8 expression -- the IL-12 expression. But more than that, it's also the cells that are producing such large amounts of subgenomic RNA die from apoptosis and release tumor antigens for antigen (inaudible) and also this type of RNA in this type 1 interferon, which is also critical to induce antitumor immunity.

The most advanced local therapy thus far is a strategy called tavokinogene talsaplasmid. This is a strategy in which an expression plasmid under the CMV promoter, encoding both chains of IL-12, is injected intratumorally, and then needles with electrodes are inserted that cause a discharge that electroporates the plasmid into the surrounding cells. And this has been shown to exert the tumor effects, both in directly injected tumors, for example, in this case of satellite metastases of melanoma and in non-injected ones.

This is in the clinic and as monotherapy in patients who have previously failed to PD-1 inhibitors has attained -- maintained the PD-1 inhibitor some level of efficacy that has given rise to an ongoing randomized Phase II clinical trial that intends registration. There are a number of agents based on intratumoral injection that are under development. I spoke to you about NHS IL-12 being developed by Merck Serono. I spoke to you about a plasmid that it's electroporated. But there is another form in which a lipopolymer with a plasmid encoding IL-12 is being used for ovarian cancer.

There are biotherapies based on oncolytic viruses that express interleukin 12. There is HSV herpes virus vector expressing IL-12 being developed in the clinic. And with interest for a sample for primary brain tumors, their CAR constructs that include a regulatable IL-12 gene that is expressed tight regulation of this is required because there have been toxic events, very serious toxicity with the early advent of this strategy to the clinic. And then there are strategies based on mRNA, including an mRNA mixture that includes IL-12, interleukin 15, interferon alpha and GM-CSF. And then I will be detailing about MEDI1191, which is an mRNA developed -- codeveloped by AstraZeneca and Moderna.

Another way to use these things is to use self-replicating RNAs that can be transfected. And by encoding a replicate will replicate the RNA, expanding it and also with subgenomic promoters amplify very much the RNA encoding the heterologous gene, in this case, interleukin 12. And this strategy has been applied in the laboratory of Ron Weiss by intratumoral injection formulated in the TT3 lipoparticles. And this gave rise to very interesting antitumor immunity, not only against the directly injected tumor but also in smaller tumors growing at a distant subcutaneous site in the same mouse.

In the case of Moderna Therapeutic, they optimized an IL-12 encoding mRNA that is made in a single chain by linking both chains with a linker. It's clearly optimized for expression. And not only that, but to prevent systemic toxicity because of escape of the RNA from the tumor and reaching

the liver, it has a microRNA-122. This microRNA is expressed in hepatocytes and if escaping from the tumor, this would curtail expression in the liver.

The idea is to inject this intratumorally, transfects with a very good technology for encapsulation of the mRNA in lipoparticles and get as much as possible local expression of single-chain interleukin 12. In the mouse models, this is very potent. And using an MC38 transplantable model resistant to PD-1 and PD-L1 therapies, it could be seen that intratumoral injection rescue -- had a very interesting response rate as monotherapy and also greatly synergized both for the directly treated and untreated distant tumors with anti-PD-L1 antibodies.

The mechanism. Both NK cells and CD8 cells mainly generating interferon gamma as the main secondary mediator. These induced chemokines that recruited other T-cells and enhanced the function of a number of cells. It's likely that not only tumor cells are being transfused with the IL-12 encoding mRNA but also the cells in [this trauma], including macrophages and dendritic cells. And that could be an important functional feature.

Omid Hamid in ESMO TAT presented the early clinical experience with this agent with the lipoparticle, mRNA encoding IL-12. And 2 strategies were pushed. One of them was sequential administration of the intratumoral RNA lipoparticle and then a PD-L1 blockade with durvalumab or alternate schedules in which first patients are treated with mRNA and then followed by durvalumab in combination.

Dose escalation of the levels of mRNA given intratumorally are being pushed. The trial is still ongoing. And importantly, at the first 3 dose levels tested, the treatment seemed to be highly tolerable only with some local effects and in these heavily pretreated patients. And no DLTs, no dose-limiting toxicities were identified.

Pharmacodynamically, it looked very good. It was inducing interferon gamma detectable in circulation. So that means that this was being produced as well as IL-12. And the transcriptomic data in pair biopsies obtained from some of these cases indicated that the transcriptional profile secondary to interferon gamma was being (inaudible).

There were a couple of very interesting partial responses, one of them, among these 10 patients, one of them in head and neck cancer that had previously progressed to nivolumab and that experienced a very significant response. And then in a mucosal melanoma in an anal canal melanoma in which a 63-year-old male patient had a very interesting partial response in multiple metastatic sites implanted in the peritoneum. So these are interesting data that tell us that these should be contained. It's a safe therapy. There are early signs of clinical activity and pharmacodynamic activity.

So one of the things I am not very happy with is that this trial is only ongoing in the United States. I certainly wish Europe and Spain to enter. And to finish with, I will acknowledge the patients and their families, as in every clinical trial, the core facilities, the people who actually finance my work because we are trying to build a bridge between medical research institute and a teaching hospital in Pamplona, Spain. Thank you very much for your kind attention. And now I will leave you with the next speaker.

Ruchira Glaser

Thank you. Hello. I'm Ruchira Glaser, and I'm the head of our Rare Disease, Autoimmune & Cardiovascular portfolio. And I'm really excited to present to you the progress we've made across our portfolio this past year. I am an interventional cardiologist, and I joined Moderna for the transformative potential of our medicines. And I cannot believe how quickly we have made progress entering multiple programs in the clinic in this past year.

It's incredible to see that our diverse portfolio affects -- leverages systemic intracellular therapeutics, localized regenerative therapeutics and systemic secreted and cell surface therapeutics. And I'm going to share more about that with you today.

Let me start with rare disease, where we have propionic acidemia, methylmalonic acidemia, glycogen storage disease type 1a and PKU. I won't be talking about PKU today because it's preclinical. But this leverages, as Stephen mentioned, the LNP 3 technology.

Let me talk first about propionic acidemia. Our mRNA-3927, which I'm pleased to report is now in Phase I. PA therapy encodes for an intracellular enzyme. And propionic acidemia is a rare metabolic disorder, which affects 1 in 20,000 to 1 in 250,000 people across the world. It's caused by changes in either the PCCA or PCCB gene. These genes provide instructions for making the 2 subunits of propionyl-CoA carboxylase. And changes

in these genes disrupt the function of this enzyme. This prevents the normal breakdown of these molecules. As a result, propionyl-CoA and other potentially toxic compounds can build up in the body.

Unfortunately, this leads to damage in the brain and nervous system, causing serious health problems. Our therapy has the promise for PA by encoding those 2 proteins through encoding for the PCCA and PCCB in our single lipid nanoparticle. Propionic acidemia, as I mentioned, has significant morbidity and mortality and does not have an approved therapy. It's primarily a pediatric disease with the majority of cases presenting within 3 days of life. And if untreated can lead to death and coma. There's no approved therapy as I mentioned. And as such, patients have to take dietary measures and palliation. Liver transplant which is highly morbid has been shown to improve outcomes.

A PA patient's course is marked by recurrent episodes of life-threatening metabolic decompensations, and even with that, progressive multiple organ damage. This includes the central nervous system, as I mentioned, but also includes chronic renal failure, heart failure and increased risk of stroke and bone and blood disorders.

I'm excited about our mRNA-3927 combination therapy. It goes into LNP 1, as Stephen has told you, and is administered intravenously. Once inside the cell, the 2 mRNAs are transcribed to produce the PCCA and PCCB subunit that form back the normal functional enzyme. As I mentioned, I'm really excited that our PA program has now entered the clinic with our first study whose objective is to evaluate the safety and pharmacology of mRNA-3927 in people 1 year and older with propionic acidemia.

We'll also look at pharmacokinetics and pharmacodynamics. Cheese; and plasma biomarkers, especially methylcitric acid, 2-MC; and 3-hydroxy propionic acid, 3-HP, will be really important for us to understand the potential efficacy of our drug in individual patients. The study design is an adaptive design where we can dose different levels and look at those markers along with others in order to titrate to the best dose for patients. We are recruiting in Canada, the United Kingdom and the United States, and we've dosed multiple patients.

I'm pleased to say that we've completed enrollment of our first cohort. And we're really excited to see what happens to 2-methylcitrate and 3-hydroxy propionic acid along with a host of other markers.

Next let me tell you about methylmalonic acidemia, or mRNA-3705. Our MMA therapy encodes for the MUT enzyme. And MMA refers to a rare autosomal recessive acidemia as well. It affects 1 in 100,000 patients in various parts of the world and is caused by the defective or missing MUT enzyme. The changes in MMUT gene cause methylmalonic acidemia. This gene provides similar instructions for making the enzyme methylmalonyl CoA mutase, and changes in the gene disrupt the function of the enzyme and prevent the normal breakdown of molecules.

As you can see on the right, it's just one step further in the same pathway as propionic acidemia. Just as in the case of propionic acidemia, methylmalonic acidemia has no approved therapies. It's a primarily pediatric disease with onset early in infancy as well and has significant mortality and morbidity. Similar to propionic acidemia, it's marked by recurrent episodes of life-threatening metabolic decompensations and progressive multiple organ damage. Current interventions, again, include dietary restriction as well as cofactor therapy and carnitine. Liver and/or kidney transplant can restore quite normal life in some patients.

Our MMA therapy encodes for the MUT enzyme, as I mentioned, and utilizes the IV-LNP 1 platform. Once inside the cell, this mRNA is transcribed and hMUT protein is produced, restoring normal enzyme.

I'm really excited to say that after years of hard work, the methylmalonic acidemia program has also entered the clinic and is now in Phase I/II study. We'll be looking at safety and the pharmacology of mRNA-3705 in patients greater than 1 years' old of age. We'll also look at plasma biomarkers. And again, here, we're looking at methylcitric acid, 2-MC, but also methylmalonic acid.

We've dosed our first patient, which is really exciting, and we're actively recruiting. This trial design is similarly an adaptive design, which is designed to leverage the data that we get maximally from our biomarkers and our safety and expand where we see the greatest promise. We're recruiting in the United Kingdom and Canada, and we're really excited to see what happens to methylcitric acid and methylmalonic acid.

Next I'd like to tell you about GSD1a, glycogen storage disease type 1a, another systemic intracellular therapy for rare disease. GSD1a therapy encodes for the G6Pase enzyme. The disease is a rare inherited metabolic disease that results from a deficiency in the metabolism of glucose. The mutation in the enzyme glucose 6-phosphatase leads to difficulty metabolizing glucose, as you can see on the right-hand side. And there is unfortunately no approved therapy for glycogen storage type 1 disease.

The disease burden is significant. There's life-threatening hypoglycemia, long-term liver and kidney damage and long-term hepatic complications that are observed in 75% of adult patients. In 10% of patients, this can lead to hepatocellular carcinoma. The prevalence of this rare disease is 1 in 100,000 live births. And again, there is no approved therapy for this disease. Patients are forced to have strict dietary controls and have to take uncooked cornstarch to improve their hypoglycemia. Glycosade is an approved therapy, which is a cornstarch that is a mainstay of dietary management. Patients may undergo liver and kidney transplantation. Our mRNA-3745 utilizes a different LNP, LNP-2. And once entered into the cell, the ribosome transcribes it to produce the deficient enzyme, which then can restore normal glucose production.

I'm pleased to say that we've now filed an IND that's opened in August of this year. And as such, we're preparing now for Phase I study start. Our trial design is a simple single ascending dose design in patients 18 years or older with GSD1a. We'll look primarily at safety, but we're also going to be able to see whether if we can impact changes in glucose metabolism by looking at fasting challenges and other biomarkers. Site initiation and site study start-up is under full way, and I'm excited to start this study.

Now I'd like to switch gears and talk about the systemic secreted and cell surface therapeutics and talk about IL-2 in autoimmune disease, our mRNA-6231, which I'm really pleased to report has also entered Phase I this year. IL-2-6231 autoimmune therapy uses IV LNP 1. IL-2, by way of background, is a cytokine that can stimulate the proliferation of T cells. Modified IL-2 is longer-acting and more selective for high-affinity IL-2 receptor. This is important because it's mainly expressed by regulatory T cells. These cells we know are responsible for dampening the immune response. Our mRNA-6231 encodes for this modified IL-2. It's administered subcutaneously and then transcribing the cell and secreted as long-acting IL-2 mutine. As you can see in the figure below. Once on the Treg, this expands the Treg population and modulates our immune system.

And it's important to know that IL-2 is a very well-validated target for a range of autoimmune conditions. For us, I'm particularly excited because, not only is IL-2 a validated target, but this program represents the first subcutaneous product for chronic use as a therapeutic for Moderna. The IL-2 biology promotes immune tolerance through generation and maintenance of the regulatory T cells that I just described but potentially without sacrificing the ability of our immune system to protect us from opportunistic infections. This selective Treg expansion has applications to many diseases, and this is supported by a large body of published literature. As such, there are multiple IL-2 molecules in clinical development for a range of autoimmune conditions. This includes inflammatory bowel disease, psoriasis, systemic lupus erythematosus, graft versus host, autoimmune and others. I expect to see clinical readouts across industry to give us further mechanistic insights and early clinical evidence as to the hypothesis that chronic exposure to low-dose IL-2 could be very beneficial across the spectrum of autoimmune disease.

And as for our own IL-2 program, as I mentioned, I'm really excited because we've entered Phase I in a simple Phase I dose-escalation study in healthy volunteers aged 18 to 50. The primary objectives of this study are to evaluate the safety and tolerability of these escalating doses, again, administered subcutaneously for the first time. But we'll also be looking at the Treg expansion population and see how our mRNA IL-2 can preferentially expand this important set of regulatory cells.

Let me turn now to cardiovascular disease and talk about localized regenerative therapeutics, our Vascular Endothelial Growth Factor A program, the VEGF-A program, is in development and indicated for myocardial ischemia. We've partnered with AstraZeneca and are now in Phase II.

Before I go into great detail, I'd like to share with you this brief video that will give us an overview of VEGF-A program.

(presentation)

Ruchira Glaser

Great stuff. So I'm really excited to share with you the science around VEGF-A in greater detail. As an interventional cardiologist, as I mentioned, this is something that I've followed for many years as many of us believe in the restorative power of VEGF-A. As I mentioned, Moderna and AstraZeneca

are collaborating on this. And with AZD8601, we have a locally administered mRNA that encodes for VEGF-A, and it's going -- it's a hypothesis to promote recovery of cardiac function through tissue regeneration.

VEGF-A is a potent angiogenic growth factor, and as such, promotes the growth of blood vessels. Importantly, it's the only product in our pipeline currently that's directly delivered, meaning it's not delivered in a lipid nanoparticle. Instead, it's formulated in a biocompatible citrate buffer saline and delivered directly into the myocardium to produce the VEGF-A protein locally.

We believe that mRNA medicines have the potential to address ischemic cardiovascular disease, something I'm personally super passionate about. Heart disease is the leading cause of death in the United States. Coronary disease is the primary cause of ischemic heart failure and affects the arteries that provide blood supply to the heart muscle. It's the most common type of heart disease, and nearly 1 million Americans suffer myocardial infarctions. They're often fatal and even lead to damage and arrhythmia and pathologic remodeling over time.

Over 18.2 million adults aged 20 and older have coronary disease. And 2 in 10 deaths from coronary disease happen in adults less than 65. So coronary disease leads to myocardial infarction, which can lead to heart failure. But not only that, chronic coronary disease, even without heart attack, can lead to inadequate blood supply to living part to the heart and cause the muscle to not pump effectively, creating heart failure as well.

And this is the basis for the VEGF program. coronary heart disease is caused by insufficient blood flow to the myocardium because of these atherosclerotic stenosis or blockages in these main coronary arteries. And we know that this condition can be treated and has been effectively by revascularization techniques such as coronary artery bypass grafting and percutaneous coronary intervention or angioplasty, but we also know that these approaches aren't possible for all patients. There's actually an increasing group of severe angina pectoris patients with refractory angina who can't be treated with conventional approaches or have partial benefit.

Patients who have myocardium that's alive but have insufficient blood flow can have chronic impairment in their left ventricular function. So those who can't get complete revascularization could improve their heart function potentially if that new blood flow could be restored. And heart failure is really important. The prognosis remains poor, with mortality estimated at 40% in patients at only 4 years from diagnosis, worse than several common forms of cancer. It's also tremendously expensive, representing 2% to 3% of national health expenditures in high-income countries, and this is projected to double in the next 20 years.

VEGF has established data to give us belief in our hypothesis, starting first with the pig model, where a single administration of VEGF mRNA improved cardiac function after 2 months after myocardial infarction. You can see on the right hand -- I'm sorry, on the left-hand panel, the vehicle at the top and our mRNA at the bottom, where green represents new blood vessel growth, an increase in blood vessel growth and restoration of blood vessel growth with AZD8601. In the middle panel, you can see the percent of area damage is decreased in both AZD at low dose and high dose compared to vehicle alone.

And finally, invasive hemodynamics shown on the right-hand panel show an improvement in heart function with AZD8601. So pretty exciting animal data. This led to our Phase I safety study, which looked at safety, but also suggested angiogenic potential, as I'll show you. This study was performed in men with type 2 diabetes, and they received intradermal injections of AZD8601 or placebo at randomized sites on their forearm, acting as their own controls.

In terms of safety, the only treatment-related adverse events were mild injection site reactions. And as you can see on the table here, the -- across a variety of adverse events, the placebo groups shown on the left and the placebo versus mRNA in 2 different combinations shown on the right had very similar adverse event profiles. This is really encouraging and led to the Phase II program.

The Phase I program also looked in an exploratory way of efficacy by looking at enhancements in basal skin blood flow at 4 hours and 7 days after administration by utilizing laser Doppler fluximetry and imaging techniques. As you can see in the graph on the top on the right-hand side, mean VEGF-A protein levels in mRNA-treated sites were significantly elevated after administration, as you can see most markedly in the blue line. At the bottom, you can see that there was an enhancement in basal skin blood flow, again, most markedly seen in the blue line.

This suggests that mRNA VEGF-A has the potential for regenerative angiogenesis. As such, the hypothesis is the local transient increase in VEGF-A protein levels in the heart can reduce morbidity and mortality in patients with heart failure with reduced ejection fraction by improving cardiac perfusion and left ventricular EF. We can stimulate vessel regeneration to improve cardiovascular outcome. And VEGF protein would be made locally within cells and secreted into the neighboring environment just where it's necessary to mimic the natural paracrine role of this protein. That's quite exciting.

As such, as I mentioned, the AZ has performed a VEGF-A Phase IIa study, which is focused on safety in patients with chronic heart failure as well as exploratory efficacy. They randomized patients with -- undergoing coronary artery bypass surgery with reduced left ventricular ejection fraction to a series of epicardial injections at the time of surgery with either mRNA AZD8601 or placebo and follow these patients up to 6 months. We've looked at a variety of endpoints, primarily safety and tolerability, but as I mentioned, really important exploratory endpoints were examined. This included imaging endpoints such as blood flow, left ventricular function, wall motion and overall cardiac function. Also looked at clinical symptoms through established quality-of-life questionnaires and New York Heart Association functional class as well as biomarkers, importantly, troponin T and NT-proBNP, markers known to be associated tightly with cardiac prognosis. And finally, they measured concentrations of VEGF protein.

I'm really excited to see the results of this trial. And although the trial numbers are small, it's important to note that we have seen, in other therapeutics in the cardiovascular space, when there is great concordance in multiple endpoints across symptoms, imaging and biomarker, there's a suggestion of potential efficacy. The trial has completed recruitment and now is in analysis, and I can't wait personally to see the results.

What's really unique about this trial is that these epicardial injections are targeted by imaging techniques, O-PET in particular, that target the areas of myocardium that are getting insufficient blood flow. You can see on the figure here, the green area is getting less blood supply in the region of the right coronary artery compared to the less circumflex artery on the left side and the LAD where you can see that there's robust blood flow. As such, surgeons map out this area on the right coronary artery for the epicardial injections of the mRNA.

Next, I'd like to talk about our systemic secreted and cell surface therapeutic Relaxin for heart failure, mRNA-0184. Relaxin is a naturally occurring hormone. We actually know quite a bit about it through multiple studies. It's naturally occurring in both men and women, and it becomes elevated in pregnancy. It's a vasoactive peptide, which is associated with cardiovascular remodeling and protects from vascular over work, improves renal function and promote cell growth and survival. Subsequent studies have implicated Relaxin's role well beyond pregnancy through these vasodilatory antifibrotic and anti-inflammatory effects in multiple organs.

And evidence suggests that it has an impact on cardiovascular disease. It activates a variety of pathways that reduce oxidative stress, fibrosis and inflammation. And evidence suggests that it improves myocardial overload, improves renal function, as I mentioned, cell preservation and remodeling. Our Relaxin therapy, mRNA-0184, encodes for a Relaxin infusion protein, which I'll talk more about. At -- once entered the cell, it's transcribed and then released systemically.

Our Relaxin program is being developed to treat decompensated heart failure. Acute heart failure has become a substantial public health problem affecting 2% of the adult population, and it's the most frequent cause of unplanned hospital admission in patients over 65. But I wanted to talk specifically about the period after discharge with acute heart failure. This is an incredibly vulnerable phase. And it's about a 2- to 3-month phase, during which patients are at high risk for readmission to the hospital, high risk for progression of their heart failure and for mortality.

And heart variety decompensation contributes often to permanent further decline in their disease. Serelaxin has been studied previously. And despite promising early results, its pivotal Phase III trial did not meet its primary endpoint. As you can see on this figure here on the right-hand side, serelaxin had a very short half-life. In this study, it was infused for 24 hours. And as you can see, very close to after 24 hours means serelaxin concentrations dramatically declined. It's hypothesized that this was a major contributor to the failure of serelaxin to provide clinical efficacy in heart failure.

We think that a longer-duration Relaxin with repeated infusions could allow for improved efficacy compared to serelaxin. This longer-acting form of Relaxin has the potential for extended disease impact. We can also administer it more repeatedly in the acute or subchronic dosing paradigm to extend the impact on cardiovascular disease compared to the single acute dose that had to be given for serelaxin. And our design and indication strategy will reflect those advantages.

Our previous Relaxin collaboration with AstraZeneca saw protein expression, in fact, in nonhuman primates up to 10 days. So again, showing the advantage of a significantly increased half-life, without the need for a continuous intravenous infusion to maintain levels, and introducing as such the feasibility of repeat dosing. I'm excited for this one, too, because we're going to enter the clinic in chronic heart failure. We're going to introduce a product with better pharmacology compared to the one I just showed you in collaboration with AZD7970, which you can see here on the right-hand side. The green line is the enhanced mRNA-0184. And you can see the total Relaxin expression for a given dose is significantly improved compared to the AZD7970. We have additional nonhuman primate studies ongoing. And as these complete, we are now planning for our first Phase I study in participants with chronic heart failure.

Ultimately, Relaxin is envisioned to be administered after heart failure decompensation to bridge patients through that vulnerable period, a time where very few therapeutic options exist for patients who are already optimized on heart failure therapy. We're also planning to leverage the extensive knowledge we gained clinically from the serelaxin experience to accelerate our own development program.

I'm really humbled and pleased and excited by the tremendous progress across a variety of therapeutics that we've made just in this past year at Moderna. And now on the verge of our first sets of data, I'm excited with the team to take a data-driven approach to our next steps.

With that, I'm going to turn back over to Stephane for closing remarks. Thank you.

Stephane Bancel - Moderna, Inc. - CEO & Director

So team, thank you so much for these exciting presentations. So now let me close with a few slides.

As we look at the next 10 years, there are a few important things that have changed for us, which shape how we think about the future. The first one is that we know now that mRNA from Moderna works. It's very important because for the last 10 years, we believe the mRNA should work. Today, we know. And as I like to say in business, your risk appetite and your investment appetite between believing something and knowing something is quite different. And this is especially in the context of our unique cash position in the industry and the fact that it's growing pretty rapidly.

We've announced this morning that we are now at the end of August with approximately \$15 billion of cash. That is an extraordinary ability to invest and to grow the business. And you'll be pleased to know is that since the beginning, we built Moderna so that it will be highly scalable because we knew from a scientific standpoint this could not be a one-drug company. It will either be 0 because we would run out of cash before we made the science work and have our first approved product or that will be a company with a lot of products. Well, now we know which one it is.

And so when you look at this picture, it's really exciting to see that what we're spending most of our time at the company every day is to scale the company so that we can grow 10x from where we are today. We think this is just the beginning. Moderna is an information medicine-based platform company. Sometimes I hear people comparing us to big pharmaceutical companies, and I just don't understand it. They live in an analog world. We live in a digital world.

We have a platform, and the molecule we make everything from is information-based. And so I'm very excited about where this company is going and about the many medicines that the team is working on today, the 37 development programs and even more excited about what I see in the labs in research that has not been communicated yet. That's coming at the next generation of transformative medicine for patients. I'm not even talking about future modality like [lung] and stem cell, which are extremely powerful.

The product strategy is clear. Priority number one, respiratory annual booster vaccine. I believe we could be the franchise here that could sustain the growth of the company and the funding of the company growth for many years to come. I think it's going to change the world of billions of people in their daily lives and allowing them to spend winters without getting sick from respiratory viruses.

We're going to bring a lot of first-in-class vaccine against complex viruses for which there is nothing on the market, for which people are getting sick every year with a lot of burden of disease that we can prevent. I believe our mRNA medicines are going to drive new therapeutics with our first

mRNA-encoded protein and then gene editing encoded enzymes. And this is what is really exciting is the abundance of products and the ambition of this strategy.

If you look at the pipeline, which I won't go through in a minute, it's really, really large now. And we own most of those products. A very strong respiratory vaccine franchise, a franchise of novel vaccines that you can see on this slide. There is no vaccine on the market against CMV. There is none against EBV, or Zika or HIV or NPA. And this is really what Moderna is trying to do. We are not interested in me-too products. We're interested in using our platform technology company to build innovative medicine to help patients, to help families and to drive values to payers. And on the therapeutic front, you start to see what is the beginning of a very ambitious, very broad portfolio.

I believe that Moderna has its brightest year ahead of itself. And so to scale, we're investing in talent in terms of hiring better, training people to maximize their impact and growing people so that they don't even want to go work anywhere else, that this is a company of their career, and they can grow their career at Moderna. We're also totally reinventing Moderna University. We put a lot of emphasis on training for many years already. But as I look ahead, as I think about the scale-up that we have to do, I want to double down and invest more and reinvent Moderna University.

As you know, since the beginning of the company, we believe that the only way to maximize this platform, the only way in the next 10 to 20 years to build the best version of Moderna is through a strong digital and robotics tool. In only the 2019 to 2021 time frame, we're going to invest in digital \$0.25 billion. I don't know many biotech companies that are doing such an investment, and we believe it's a must. We cannot achieve the best version of Moderna without those investments. On top of this layer of digital and robotics, we are now going all in, in terms of AI. We want to make AI a part of how we run the business.

And because most senior people in most companies in the world do not really understand AI, we are launching an AI academy within Moderna. We're going to partner with best academic groups in the world to make sure that every employee, and I mean every employee, is trained in AI, understand what AI can bring to us and is proficient so that we can build AI in every function of the enterprise on the layer of clean data coming from digital and robotics enablement that we're investing so hard. I really believe this is critical to build the best version of Moderna. This is all about learning. This is a new technology. And we're not necessarily going to be the smartest, but I can guarantee to you we're going to be the company who's going to learn the fastest. And I believe in compounding, and I believe that's what is most important to build the best version of Moderna.

In terms of manufacturing now. The manufacturing process is still being improved. While we are the sixth version of a manufacturing process, we're just getting started. I have a chance regularly to see the creativity, the ingenuity of our engineers. And I can tell you that how we are improving, how we make mRNA, how we are reducing our footprint, how we are maintaining new equipment, removing steps is just extremely exciting, and I cannot wait to share those progress with you.

And then manufacturing. We just decided recently to add a fourth building to the Norwood campus. Many of you came in the summer of 2018 for the launch of what is now called MTC, Moderna Technology Center, South Building. Since then, we build the North Building and then the East building. And now we're building a fourth brand-new building on the come out of the ground on that wonderful campus to keep increasing our capabilities and to prepare for the future and the scale-up of the company.

We've also announced recently a very innovative partnership with governments. The first one was printed with the government of Canada, where we have agreed with them to build a state-of-the-art mRNA plant in Canada to be able to provide the pan-respiratory vaccine booster for many years to come. And we are in discussions with more countries around the world that have reached out to us because they realized, with the real-world evidence that Paul shared with you, that we have a very strong vaccine that has a long duration of efficacy, and they want that technology in their country.

So as I look at the next 10 years, it is a very exciting inflection point in the company. We moved from believing that mRNA was going to work to knowing Moderna's mRNA work. And as we've seen in the last year, not all mRNAs are created equal. We have an unprecedented cash position that allows us to invest in the business to build the best version of Moderna. So as I look forward -- I look forward to be able to share with you the progress of the company and to build the most impactful health care company in the world.

Thank you very much. And now with the team, we'll be delighted to take your questions. Operator?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Salveen Richter with Goldman Sachs.

Salveen Jaswal Richter - *Goldman Sachs Group, Inc., Research Division - VP*

So the first one is regarding your vision for the pan-respiratory annual booster vaccine, which you're going to customize by age and geography. What would the regulatory path look like for such a vaccine in that case?

And then secondly, with regard to the 50-microgram being used as a booster dose here for COVID, just remind us on the rationale and then how you manage the distribution and pricing aspects when some are purchasing for the boost and some are purchasing the 2- to 3-dose regimen where there's maybe a benefit to doing the latter? Just curious on both of those things.

Stephen Hoge - *Moderna, Inc. - President*

Sure. Thank you, Salveen, for the question. I may start with the second one and then pass to Jackie to talk a little bit about our overall development strategy for the pan-respiratory vaccine. So first, on a booster. I know it's an important topic. We'll just get it out of the way. We continue to believe that 50 micrograms of a third dose booster is going to be necessary this fall given the ongoing threat of the pandemic from Delta and the potential for waning immunity. And as Jackie laid out today and as we showed in the data, we feel very confident that 50 micrograms is the right dose. We significantly exceed the very high bar set by our Phase III study and our real-world evidence that Paul described. And so we think that is the right bar, and we're quite confident in that. I'm confident in it for my family, my parents.

Now what we need to do is provide all that data that we gave a preview of here to regulators, and we're working constructively with the FDA. But then once we get through that path, we'll have to provide it to public health officials. Because ultimately, the decision of when to boost and how to boost really resides with those public health officials and regulators. We will do that in a way that provides the most flexibility for governments. We're in this together fighting this pandemic. We want to make sure that we provide solutions, whether it's a first dose primary series of 100 micrograms or whether it's a booster dose for a healthy adult or whether it's a third dose 100-microgram boost for somebody's immune-compromised.

And the question of how we'll handle the price is really secondary. What we want to make sure is we get as many doses to as many people as possible to help address this pandemic. We have contracts in place with all of the governments that we've been serving that deal with how we will bring forward boosters, and we'll comply with those contracts and make sure that we provide as many doses as possible to as many people as possible.

The last thing I'd say about that is that an efficient use of a 50-microgram booster we actually think is the most prudent thing we can do both for our individuals, but also for public health. As we've said before, we think it could result in up to 1 billion doses more available for our response to the pandemic over the next year, which we think is obviously in everybody's interest. So we'll continue to work with everyone to try and provide the data to help public health officials and regulators make that decision. But as a company, we feel pretty confident that is the right one for us.

Now looking forward, Jackie, do you want to provide a little bit of the view of how we're thinking about developing pan-respiratory and maybe the question on the strategy there?

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

Yes. Absolutely. Thank you, Stephen. So great question on how we get there. And you heard today that we have programs in the clinic, not just for COVID-19, but for the first iteration of a seasonal influenza vaccine and then also RSV. And so I think about these vaccine development programs as like the LEGO blocks that we can then use to build all kinds of different configurations in the future. So you may have been seeing in the news that, in addition to surges of COVID-19, we're seeing increases in influenza and also unseasonable respiratory syncytial virus worldwide. And this really is the reason why we want to advance those respiratory programs, conduct our studies for pivotal licensure at a time when those viruses are circulating.

And then our plan would be much like with our booster strategy to really rely on immunobridging and safety demonstrations in multiple different combinations. Another important aspect to the strategy is, while we are putting this foundation in place with the monovalent antigens, we then want to also begin to develop our combinations. And so that's why we're really intending to start with COVID and flu later this year. So I need to say that we are still discussing this strategy overall with regulatory agencies, and it may evolve as time goes on. But we're really also building on the knowledge and development of previous combination vaccines, which have been licensed in the pediatric space in the past.

Stephen Hoge - Moderna, Inc. - President

I just have to add as a comment for somebody like you, Salveen, who's been following the story for a while, but we have been talking about combination vaccines as one of the key features of our platform. And we're really proud today showing how that's coming to bear. And many of the new combinations we're announcing today, they're just the beginning of where we intend to go over time. We've been talking about it for years, but it is really exciting to see that come to fruition, not just in the pediatric space, where Jackie said is well preceded, but actually in the adult space where we think it's really needed.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. And maybe if I may, just to add to Stephen's point on the pan-respiratory, which is around the investment in science, in lipid, in manufacturing processes that the team has done over the years that has allowed us, as you've seen last year, to be able to get a high dose into the clinic safely. And when you think about combination, you need to be able to have enough mass of enough components so that you can get the clinical benefit to the patient. And that's another very important differentiation that I think we're quite uniquely positioned.

Operator

Our next question comes from Michael Yee with Jefferies.

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

Can you hear me okay?

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes, Michael.

Stephen Hoge - Moderna, Inc. - President

Yes.

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

Great. Two questions for you guys. One is on respiratory infectious diseases such as RSV and flu, specifically with RSV. There are others that are having Phase III data next year. I was wondering if you could speak to how you believe you would compare and contrast or could be better. Or is it a platform power thing to combine it all that you really think is really the key long-term benefit? So that's on RSV and respiratory vaccines.

And then second is the whole segment on therapeutic vaccines, and I'll even throw in there cancer vaccines. Do you think that there is one specific data set that would really convince everyone on an aha moment that it's all working and it's truly playing out as you have predicted? Maybe just point to 1 or 2 things you think would be a real aha for us.

Stephen Hoge - Moderna, Inc. - President

Well, thank you for the question, Michael. I'll take the first stab at one and then -- and Jackie, I'll ask you to fill in a couple of places. So Jackie may be more measured, but I've been living with this for the last 10 years. So I'll say I actually think, Michael, we have a benefit on both the dimensions you listed. If you look at the experience of the last year -- or 2 years, I should say, with mRNA vaccines, I think it's quite reasonable for us to expect, particularly in the respiratory space, that we have a best-in-class platform and that we might see superior efficacy.

And I certainly think the early data that we see out of RSV says we're doing really well, maybe best, although you don't have direct head-to-head, so you have to qualify how you say that. And so we're looking forward to quickly, as Jackie described, moving into Phase II/III studies, trying to develop that efficacy data very quickly in RSV. And we're very optimistic about that stand-alone opportunity.

But the second part is definitely true, too, which is, we think an inherent benefit of messenger RNA as a technology is the facility with which we can combine things. We've been doing it from the beginning. You've seen us do it from the beginning. And we've had respiratory combination vaccines in clinic in toddlers since before COVID was a pandemic. And so we're quite excited by the chance to solve a bigger health care problem than just RSV by adding RSV to flu and COVID and other combinations in the future. And I think that is an inherent advantage over time that our respiratory vaccines platform will have.

So I'd say it's both. I'd say it's -- we actually think we're going to have really distinctive efficacy data, but we do also think we can bring better solutions forward in our partnering with public health systems. And that's going to be a part of what we do. Jackie, do you want to maybe take the question of data we might see in the therapeutic space that would have us be excited?

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

Sure. So I can talk a little bit to some of the planning we're doing for therapeutic vaccines. And the one I'm particularly excited about is EBV and post-transplant lymphoproliferative disease. So we've known for a while that viruses like EBV and CMV can have oncogenic potential, meaning that they can lead to cancers. But solid organ transplant patient population is a population that is really at increased risk for developing a lymphoma-type cancer, particularly in their first year after transplant. And the reason for that is, if they happen to be negative for EBV and they received an organ from a donor who is positive for EBV, the EBV in the white cells in that organ can reactivate. And in the setting of immunosuppression where there aren't other white cells to tamp down nascent lymphomas, it really can become a large problem and actually lead not only to the need to treat the lymphoma itself but also to graft loss. And you can imagine, in the first year after transplant, that's a tragedy.

This population is really a great test case for us to demonstrate that if you can suppress EBV, you can basically suppress the development of cancer. And so the idea would be to build on that population into other populations. So really excited about moving forward to demonstrate the therapeutic potential of preventing infectious diseases for other longer-term medical conditions.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. And in addition to what Stephen said around the combination, Michael, I think there's another important point, which is the goal in this business is not to get in the clinic. The goal in this business is to be able to get a product approved and to be able to scale manufacturing. Until that point, we do not impact patient and do not generate sales.

And if I just reflect on what happened over the last 18 months, there were, what, 100 or 200 teams around the world who started chasing this virus at around the same time when it emerged. Not many made it to finish line clinically with good vaccines. Some that finished clinical development are still not authorized.

And then there's a manufacturing challenge. As we've seen, there's been quite a number of companies that I was even surprised myself because of their scale and the history and the experience of a big manufacturing program. So as I look at Moderna, for me, it's a total package. It's what Stephen said about the platform and the science. It's about the ability to drive manufacturing and scale to get things approved by the regulators and to drive sales and impact on patients. That's what I think really differentiate Moderna, it's the full package.

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

Could be better, could combine and good manufacture. Yes.

Operator

Our next question comes from Gena Wang with Barclays.

Huidong Wang - Barclays Bank PLC, Research Division - Research Analyst

I have 3 sets of questions. The first one also regarding the combo vaccine. Just wondering how many RNAs you can combine in one vaccine. And would that be due to the limitation on manufacturing or dosing? And then pricing-wise, what will be the general principle for pricing and for combo vaccine?

And the second question is regarding COVID vaccine -- giving Pfizer -- your mRNA sequence are almost identical. Could you -- like what do you think it could lead to the differences in long-term clinical benefit?

And the last set of question is regarding the cardio programs, which is very exciting. But since those candidates are not in liponanoparticles, what additional modification you need to do to increase stability? And what is the half-life of these mRNAs in tissue?

Stephen Hoge - Moderna, Inc. - President

Thank you, Gena. Great questions all. So I'll quickly take a stab at the first question on mRNA. I might turn it to Stephane on the question on pricing of our combination vaccines. I'll offer a perspective then on Pfizer and the benefits, but I'd invite Jackie to comment there. And then lastly, to Ruchira, on CV. And one of those programs actually is in a lipid nanoparticle, but more on that when she speaks.

So first, on how many mRNAs we can combine. We do not currently know the upper limit. I think that's the best way I could answer that question. I will remind you that we have taken 7 mRNAs into clinical studies. Our first CMV vaccine actually had an additional antigen in it and shown that, that works. We shared today that we've got well north of 14, I think, mRNAs working preclinically. And we've taken that to more extreme versions of experiments in some of our early research areas, and we haven't yet run into a limit. We have not yet seen dramatic interference there. So somewhere north of 10.

Stephane Bancel - Moderna, Inc. - CEO & Director

Seems like we have a technical problem with Stephen. So I think he covered most of the first question.

Paul Burton - Moderna, Inc. - Chief Medical Officer

Stephane, let me just...

Stephane Bancel - Moderna, Inc. - CEO & Director

Sure, Paul. Go ahead.

Paul Burton - Moderna, Inc. - Chief Medical Officer

Thanks, Stephane. Maybe I can just -- while Stephen's coming back. Gena, just on the platform. I think many of the publications that we talked about reference the same kind of things. We've spent 10 years investing in science to develop a really exemplary lipid nanoparticle. And we can dose a high level with that. We're also able, with our vaccine, to put 100 micrograms. And we know that 1 molecule of mRNA will make somewhere between 1,000 and 10,000 molecules of protein. So we can generate large amounts of antigen.

And then I think, finally, at least with COVID, the schedule that we have taking a 28-day dosing schedule is important. It gives the germinal centers some time to rest. It allows B cells that have same antigen to go back and to become clonal and expand. So I think those are the 3 things: a lipid nanoparticle, the ability to dose at higher levels and then the dosing schedule that we've been able to come up with.

Stephen Hoge - Moderna, Inc. - President

Couldn't agree more. Sorry that I had to step way for a second. Technical issue.

Stephane Bancel - Moderna, Inc. - CEO & Director

Let me take the pricing question, Gena. I think it's a very important question. So as I said in my introduction, we want to first think about value. And we think this pan-respiratory vaccine will deliver incredible value to health care system because, first, you have a sum of the part of how much it will cost you for a flu vaccine and RSV vaccine and a COVID booster and so on and so forth.

And as we said, our goal is to keep adding components because really all high-stretch goal is to make sure people do not get to hospitals with respiratory viruses. So we might even keep adding those that have less incidents but that hurt people because that's what we believe in as a company.

The second piece is going to be, of course, around compliance. I mentioned it briefly. But in all my discussions, the health care providers, the payers, health care ministers around the world and so on that we'll be talking to, thanks to the COVID discussions, they're all very clear. They don't believe there is a world where somebody gets 5 or 6 shots in the fall to provide against protection against all those things. Nobody likes a shot. And then it's a very high cost, as we discussed, as I said sometime, in today's pricing environment, it's more expensive to do the administration of a vaccine than for the U.S. government to buy the vaccine.

And then there is also, of course, consumer-driven preference. And so as you put all those things together and you kind of see what's already available out there on respiratory vaccine because there are a few in the markets that are more normal market forces versus pandemic situations. The other question is we want to have maximum impact on patients. If we have a long-term view, which we always do in our company, if we believe

we can keep adding components and we're going to really differentiate from competition by adding component because over -- because of the science and technology limitation, why won't we give the last component free of charge?

You keep adding components every year. We have not decided that. I'm just giving it as an example of our mindset, which is we want to drive share because we think this is how we can help the most people. So we will give you more details in the quarters to come as we refine the strategy, but I wanted to give you a bit of color on how, as a team and as a board, we're thinking about it. I think the next one is for you, Stephen, is what would we expect potentially the difference with Pfizer and Moderna on the COVID-19?

Stephen Hoge - Moderna, Inc. - President

Okay. So I think it's the difference of working on something for 10 years versus a year. We've had a tremendous amount of investment in our core technology platforms. And as Paul summarized, I think quite well a moment ago, it has allowed us to do things like provide a higher dose, which provides, we believe, higher titers. And Paul walked through some of the data that shows that. And higher neutralizing titers correlate with better immunity, we believe, and ultimately, are some of what's driving the advantage in the real-world evidence that's been reported so far.

Now it's important to say that we don't rest on our laurels. We continue to think that we need to continue to invest in technology, as you all know. And we're going to continue to try and invest the best-in-class platform over time. And so we're looking to wait for always to do ways to continue to increase that potency, improve tolerability and allow us to do more combinations in the future. But we believe it's the work that we did over the previous decade on the science that's really allowed that, and Paul covered some of the specifics there.

The last question was on CV. Ruchira, do you want to take that?

Ruchira Glaser

Yes. Happy to. Thanks for the question. So the VEGF program, as you mentioned, is not in a lipid nanoparticle. And to answer about residency, we saw in the Phase I program that actually, we still had local VEGF produced at 24 hours. And so -- and actually, this paracrine-like effect is by design. So it's really useful to have sort of make it mRNA locally injected in certain disease applications, including this particular cardiovascular disease. When we just want transient effects and that mimic sort of what in this case, VEGF does naturally in humans. And I think it's important to point out that because this is our first locally injected, without LNP, we'll find out through proof of concept that whether we can then extend this to other local mRNA applications. And we could, for example, use them in surgical applications and orthopedics and dermatology and as well as other cardiovascular disease. So that's a little bit about VEGF and the lack of LNP is an advantage rather than a disadvantage, quite deliberate.

In terms of Relaxin, actually, that is in an LNP. So it's a good counterpoint to VEGF. Because obviously, these are both used to treat cardiovascular disease. But here, we're using a similar systemic secreted approach as we did with our NAb program, which gives confidence that we will see similar expression. And the biology of Relaxin is such that we want systemic expression here. We want all the vascular effect systemically that we know Relaxin endogenously can produce. So this is an example where we do want that LNP to give systemic secretion. And it's also similar to our interleukin-2 program, which is applied to cardiovascular disease.

So I think in summary, we the 2 programs that I mentioned, the VEGF and Relaxin, are 2 different examples of how, within one disease, cardiovascular disease, we can tailor to what's the best delivery solution that fits the biology best to get the best clinical efficacy. One local paracrine effect where we don't want the LNP. Another systemic longer-term effect where we do want that to be encapsulated in the LNP.

Operator

Our next question comes from Ted Tenthoff with Piper Sandler.

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

Great. Thank you very much, and thanks for all the time today. And importantly, thanks to all of Moderna employees for all your hard work to keep us safe. I'm just really struck here by how Moderna has become a global pharmaceutical company since your last R&D day. A lot of questions on the combo respiratory vaccine, but I want to focus on working diseases. And I really want to get a sense of when we could get that initial proof-of-concept data probably from 3927 would be the first one. And based on those results, how do you anticipate scaling this effort much like you have with vaccines?

Stephen Hoge - *Moderna, Inc. - President*

Great questions, Ted. And I know you know it's something that's been a passion of ours to try and bring medicines to these patients and not just in one disease, but all of them. First, I'll say -- I'll kick it to Ruchira in just a second. But first, we won't guide on when we'll see the data, because all of it is really beyond our control, right? At the end of the day, we have to do the right thing for these patients in this study. And we depend upon people enrolling, those things proceeding operationally with the investigators. But really it's those patients that are inspiration, and we need to be respectful of their time and, ultimately, their choice. And so we can't guide on when we will have exactly that data. But I could maybe invite Ruchira to, now that we have the first cohort enrolled, what's the process that we're going to be going on without sort of covering specific time frames and how that could play out.

I'll remind you, just before I hand off to Ted -- or Dr. Ruchira, this is our first cohort. It's not intended to be the only cohort, and we are actually looking to dose-optimize here. And so we can almost anticipate we're going to be looking at a second cohort in a slightly different dose regimen, and that's the right thing to do to make sure we bring the best medicine for it. But Ruchira, do you just want to give a quick summary of the process from here?

Ruchira Glaser

Yes. Sure, I'm happy to, Stephen. Thank you, and thanks for the question. So as Stephen mentioned, this is an adaptive design for the study. So what that really means is we're going to look at this first cohort, and we'll get pharmacokinetic data. We'll get PD markers, a couple of the biomarkers in particular that I mentioned, and see how those data fit our dose prediction models in our preclinical studies and what kinds of PD are we actually getting. In addition, of course, we don't want to overlook the safety. That is the primary objective of the study. And we have an independent safety monitoring committee that will be evaluating the safety, which in this trial thus far has actually looked quite good so far.

But as Stephen mentioned, we'll take those data and see whether we can further optimize the dose. We could extend -- we could change the dosing interval as an example. That's already prespecified in the protocol. We could increase the dose. We could decrease the dose. We can make 2 changes at the same time as well. But we want to be careful because we want to learn as much as possible and do the right science, as Stephen alluded to, so that we truly come out of this trial with the optimal dose.

The only other thing I'll mention is that once we do get a dose that we think is optimized, the design of the study is such that we can expand the cohort in that dose. So once we think, yes, we've hit the optimal dose, we can enroll more patients into that dosing cohort. And we can even increase the dose or change the dose in the patients who are enrolled in our long-term safety extension study. So we'll get lots of data when we get to the proper dose.

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

Yes. And maybe I can briefly take the last question, Ted, around what happens if we have positive data. I mean, as you know, it's the world Moderna model, which is we always venture in the clinic with a few programs, not too many because if the technology is not ready yet, there will be a lot of expenses and a lot of work. And always, there's a risk to patient that we are very serious about. But we don't want to think we've won because there might be a lot of reason between the technology and the (inaudible) as we've talked about for years that you might have a false negative data set, would be, of course awful.

And so the team is working really -- Stephen's team in the labs is working really hard because there are many more rare disease out there. And so it's maybe a good opportunity to come back to what we announced on Tuesday with Jim Wilson around (inaudible) because I think also it's an important piece of who we are as a company, which is as we look for those ultra rare disease or the rare disease we will do, like a lot of biotech from our company are doing, but for those ultra rare disease, where it's exactly the same technology that we need, it's where you have literally hundreds of patients around the world. As we run the math on the back of the envelope, like this makes no sense. We cannot be as a company. This is just not who we are as people, charging millions of dollars per year per family. That is just something that we cannot do.

And so we're just -- after talking a lot about it and try to be creative, we just went the other way around by deciding those medicines that are just too small for the good investment of our shareholder return. We still want them to bring solutions to families, to those children, to those parents. And so we just gave it away. We gave 100% away. There is quite a number of ultra rare disease in the liver that I think we will want to do similar setup so that we can maximize the impact we can have on patients because that's what really drives us.

Operator

Our next question comes from Matthew Harrison with Morgan Stanley.

Unidentified Company Representative

This is Kostas on for Matthew. One question from us on the flu vaccine. Can you discuss a little bit the potential development pathway and whether you will need to run a Phase III study here?

Stephen Hoge - Moderna, Inc. - President

So I'll invite Jackie in a second. We would intend to run a Phase III study. We also intended to run combination studies in the future. Maybe Jackie can just give you a quick overview of where we're approaching it right now, but the most important thing to say is that we need to work with regulators, not just in the U.S., but globally, to find the right path. And those are ongoing discussions. And so in any event, right now, we don't have that final answer. But what maybe Jackie, you could offer is, what are the options that are laid out ahead of us?

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

Yes. Thanks for that, Stephen. So with influenza, there actually have been multiple pathways to licensure that have been defined. There's an accelerated pathway that involves demonstrating noninferiority versus immunogenicity or efficacy and then potentially demonstrating post-marketing effectiveness as well. But as Stephen mentioned, all of these are options that are on the table that we are currently discussing with regulatory agencies, and we anticipate being able to take that next step now that our Phase I trial is completely enrolled. Once we have data from that study and have selected the dose that we then put into the Phase II portion, where we're going to expand the safety database and generate additional immunogenicity, we'll be able to really refine those plans for Phase III in ultimate BLA and other registration submissions.

Operator

Our next question comes from Hartaj Singh with Oppenheimer.

Hartaj Singh - Oppenheimer & Co. Inc., Research Division - Research Analyst

Great. Just 1 question on CMD specifically. I know you had mentioned that there will be an interim and a full readout and it's case-driven. We need a certain amount of sort of follow-up data on safety before you can do that interim. Just any color around that. Would really appreciate it.

And then a second question is much more broader. One of the things I've always appreciated about Moderna, and still do, is the flat structure, Stephane, Stephen and everyone else. Very -- things are done very quickly. The company is getting larger and the modalities are filling out, that flat structure could be a little bit more on risk. Have you ever considered going the other way, which is that spinning out for your modalities? You're very well funded. You could fund them. You could participate through the upside of spinning out various modalities as independent stand-alone companies or even keep them sort of within Moderna as J&J is prone to stand-alone structure. Just any thoughts there.

Stephen Hoge - Moderna, Inc. - President

Maybe Jackie, do you want to take the first question on CMV? And then Stephane, I don't know if you want to take the second. It feels like it's more at your level.

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

Sure. So happy to discuss our plans for the Phase III CMV study. And again, that's going to be a safety and efficacy study, and it's designed to demonstrate efficacy against primary CMV infection in women who are of childbearing age. And so the design of that study is actually in some ways similar to what we've just done with the SARS-CoV-2 study. So we've powered the study both conservatively to make sure that we give ourselves the best chance of success but also built in an interim analysis based on fewer cases in case the efficacy is overwhelming and we're able to declare early success.

But to your point, there will be a minimum safety database that's needed. That was exactly the same situation that we faced with SARS-CoV-2 where for the EUA, we had a median of 9 weeks of safety follow-up. For the BLA, we had a median of 6 months of safety follow-up, and we anticipate that we would be following subjects in the trial actually in terms of following for antibody persistence multiple years.

So I think future BLA submission plans, again, a topic for discussion with regulatory agencies. But it will be a combination of when we accrue sufficient cases for that analysis, plus ensuring an adequate follow-up time of those patients so that the safety database is adequate for the registration.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thanks, Jackie. So Hartaj, let me take a stab at the other one. Stephen, given you're a part of the experiment, if you want to add, that would be great. So as you know, Hartaj, but most people on the call might not know, we actually tried. We tried in the early days of Moderna to basically have different legal entities that will have different focus. And we went back to reemerging everything because it was actually a pretty bad idea. And I have a -- it was my idea. So I'm going to own that 100%. And I was -- the idea we had at the beginning because the platform is so big, you need to decentralize management and so on to keep the speed, which is very much a part of the culture of Moderna.

But the piece that we totally misread is the fact that the platform is evolving at such a speed. We keep investing aggressively on the platform, both sides, process development. And so if you put those things into pieces, the change we saw at the time, which is why I don't want to do the experiment again, is you have a lot of friction happening between the kind of central platform team and the therapeutic area of the product companies. And we were trying to do this to kind of align with search and development by therapeutic area like traditional pharma company do. And it was a very bad idea because the most important point of integration because we have a platform, because it's information, because there's incredible correlation between products was actually between the platform research and the biology research by therapeutic area. That integration is fundamental to keep the velocity of Moderna because it's a massive network effect.

Sometimes -- it's something we observed in rare disease that the team goes and applying vaccines and vice versa. So not only there's correlation between the modalities, of course, which is why, as you know, we represent them with colors in those kind of verticals. But this is a lot of correlation. Because at the end of the day, think about mRNA as a toolbox. You can play with UTRs. You can play [optimization] with caps, with tails and manufacturing process and so on. And so every time you learn something, you can apply it and push it into the ecosystem very quickly.

So your question is still, of course, very valid, which is how do you scale the company. And so it could come out, there's a few things. It's, one, great people. I've always believed that correct people were really important. But if the last 10 years has taught me something is that great people are essential. And so every time you learn something, you can apply it and push it into vehicle system very quickly. So your question is still, of course, very valid, which is how do you scale the company? And so in a very quick manner, I think of a few things. It's one, great people. I've always believed that great people were really important. But in the last 10 years, I taught me something is that great people are essential. You cannot do great things without great people. It just doesn't work.

And if you just look at this screen, I mean, Jackie has been with us just a bit over a year. She brings fundamental experience from infectious disease vaccine. Sorry, Jackie, if I made you blush. The Ruchira has simply incredible experience in the clinic -- in clinical development and Praveen and Paul. And that's really part of the story of Moderna, which is you need to make sure where we are going as a scalable company, not where we came from. We need the right team. So great people.

Most companies think -- using the past to project the future. We never use that at Moderna, I think it's irrelevant. We try to invent the best version of Moderna and then we (inaudible) (03:35:20). Okay, what do we need to get there and to build the capability? So great people is one.

Two is culture. We have had our fair share of mistakes over the years via great people that are just not a good cultural fit. We got a culture for everybody, but when people usually are a good fit to the culture, they're having a lot of fun.

And the third piece is technology. As you know, I've mentioned it in my closing remarks, I believe that if you can give high-quality data in real time where everybody has the same data, the CEO or Vice President or technician because we all use the same system. And you can use that data to make decision to decentralize decisions. I think you can keep the agility and that's where -- what we are going for.

So that's a bit how we think about it, no plans to spin out the companies.

Operator

Our next question comes from Joseph Stringer with Needham & Company.

Joseph Robert Stringer - Needham & Company, LLC, Research Division - Associate

A couple of quick ones here. One is on the systemic intracellular therapies, in particular, the rare disease. Just wanted to clarify or understand sort of the comments around some of the ultra-rare indications and whether or not they could be partnered.

So is it still the plan or the strategy for Moderna to sort of keep PA, MMA and GFP and PKU, for example, unpartnered and in-house and that's sort of separate relative to other indications such as CN-1? I guess it's my first question. And I have a follow-up.

Stephen Hoge - Moderna, Inc. - President

Sure. I can take that pretty quickly. The answer is yes. We intend very much to develop our own and commercialize our own portfolio of rare disease medicines. Stephane's distinction was situations where there might be less than 100 patients, it might not make sense for that to be something that Moderna takes on ourselves forever. And yet we want to serve those patients.

But there are many, many diseases, and you listed a couple. And if you look at our pipeline and see them like PA and MMA, where there are hundreds to thousands of patients. And we do think we are well positioned to serve them. We are committed to those communities. And so we do not want to partner those programs. We won't go forward along there. It's only in those areas where we are currently not advancing programs than the ultra-ultra rare that we think a different model might be.

Joseph Robert Stringer - *Needham & Company, LLC, Research Division - Associate*

Okay. Great. And the second one is just more broadly on capital allocation, and I suppose, maybe just outside of vaccines here, how quickly do you see the Moderna Genomics division sort of rising up and becoming a more prominent factor here relative to some of the other programs or divisions such as the rare disease and oncology and autoimmune?

Stephen Hoge - *Moderna, Inc. - President*

Great question as well. So everything we do at Moderna, we try to do it at the Moderna pace. And so you should expect -- our vision is that we will grow MGX, Moderna Genomics, efforts as fast as we grow other things. We think it's the right time for us to go aggressively in that direction.

The technologies that need to exist in genome editing on the protein side are just now becoming, we think, ready. And we obviously think we have the best platform technologies in mRNA delivery and nucleic acid delivery and design. So that is the moment we intend to capitalize on urgently. We are growing quickly with that team. We've always -- we've already got a floor in labs and we're hiring for anybody who's interested, and we look to have an impact on our pipeline quickly here. Now we want to do it responsibly and we've got some work to do to bring forward all the right combinations of technologies that use the best of our platform. But our vision is to do that quite quickly.

Operator

Our next question comes from Cory Kasimov with JPMorgan.

Cory William Kasimov - *JPMorgan Chase & Co, Research Division - Senior Biotechnology Analyst*

Two COVID-related ones for me. First, given the substantial boost in neutralizing antibodies with a third dose, how long do you anticipate protection to last relative to the initial 2-dose regimens. Is there any modeling or anything like that you're able to do on that front? And then the second question I have is I'm curious as to your thoughts on the future potential to mix vaccines, so you could potentially open the market to people who were previously vaccinated with Pfizer-BioNTech or J&J or something else they could get the Moderna vaccine. Is there work you're doing on that front? Or do you have insight into potential regulatory requirements there?

Stephen Hoge - *Moderna, Inc. - President*

So maybe I'll take a stab at the first one on durability, what we do and don't know. Invite the Jackie and Paul to comment on what we do or don't know about the development work we're doing in heterologous boosting, but also some of this is really a real-world evidence public health question. So Paul, maybe you can offer some thoughts on that.

First, on the question of durability. Obviously, we're seeing [1.72-fold] higher titers after a 50-microgram boost. That's great. You might logically say, well, does that mean that we're going to last twice as long and maybe not need a booster for a year or a little bit longer. It's really hard to know. It's hard to know for a number of reasons.

One is we have not actually given a third dose of our vaccine and followed the kinetics of what that will look like. It's possible that it will be flatter, it will last longer. And so that's good news. But it's also possible that what we'll continue to see is a line that's the same sort of decay curve that's been seen more recently that's associated with the need for boosting.

And then you might say, okay, well, then annually because we're a little bit longer, but not forever. I think we think what will drive most boosting over the long term, and this is a Moderna hypothesis, the data needs to emerge, but we think what will drive most boosting is the seasonality of respiratory infections.

We all have seen over years, and this is true for RSV, it's true for flu, it's true for the metapneumoviruses, rhinoviruses, coronaviruses, they tend to infect in the winter months, slightly different sets of months. And we do think that it's going to be in everybody's interest to have an annual booster against that full set of viruses to try and make sure that we provide the highest level of protection and the highest level of elimination of that morbidity and mortality from those viruses.

We don't think that's going to be a different answer for COVID. And we do think it's -- over time, will be the right approach. But it's also possible that we'll find that you don't need a seasonal booster, and that may be every couple of years to work too. That's just ultimately something we'll have to wait for the data to say. We don't have it now. Jackie and then maybe Paul, any thoughts on heterologous boosting and how we're trying to fill in that picture?

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

Yes. I mean -- so maybe I will just also comment that with most vaccines, you see a bimodal distribution of kinetics over time. And for each vaccine, what that looks like is slightly different, but there's typically a decline in the first year after vaccination. And then antibody titers tend to plateau.

With multiple doses of vaccine, you also see a maturation of the immune system. So not only the quantity increases over time, but the quality increases over time. And we're actually looking into collaborations to better define both the quantity and the quality of antibodies. And as we continue to extend our Phase III study, much as we offered our Phase III participants crossover if they first received placebo after our vaccine was authorized, we're also looking to offer that third dose to the people in the clinical trial and really follow them over time to better generate that data and define what you're speaking about.

And then we're currently involved in 2 collaborations, 1 with the NIH and one with the University of Oxford, where we are looking at mix and match boosting. So where Moderna booster or third dose, sometimes second dose depending on what the primary series was is given after multiple priming schedules. And so this is both on mRNA platform. So either Moderna or the Pfizer vaccine, as well as adenovector platforms, including both Johnson & Johnson in the U.S. and AstraZeneca in the U.K. And we know our partners are working to analyze and report on those data as quickly as possible. And hopefully, we'll be sharing them soon.

Paul Burton - Moderna, Inc. - Chief Medical Officer

The only thing I would just add just around there is look, I think the scale and speed with which vaccines have been deployed against COVID is just unparalleled, unprecedented. Certainly, that's true globally. I think there are a few questions certainly in COVID that we'll sustain a 3-year cycle to generate data. And we're in the fortunate position, having all of these different databases in the real world that I think we can really address those questions quickly.

We can do randomized pragmatic trials as well now. So I think if we just wait a few months, people will be getting boosted spring of next year, I think, or even I think there will be a slew of new studies coming out, really addressing exactly your question in the real world. But as Stephane says, we just have to take a little bit longer to let those data sets mature.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes, the last thing -- my discussions with different countries is that some countries are doing it pretty aggressively already and have some of them for several months. I think a lot of countries are working up to the fact that [alimony] vaccines are not the same and that it's actually a different mass. Sometimes people spending -- actually have been for us quite a while, if you don't have that much as a question there, oh, it's a different mass. Yes, it is. And then if you think about it, Cory, most people, maybe not you because you work in this business, but most people don't know which brand of booster they got last year or the year before. And even if it was even the same technology, even though the same company. And so if you think about something with tetanus and a lot of vaccine we all use in our life is the only another one you got before. So a lot of data is being generated, both in the real world as well as with the group that Jackie described.

Operator

Our next question comes from Geoff Meacham with Bank of America.

Alec Warren Stranahan - *BofA Securities, Research Division - Associate*

This is Alec on for Jeff. A couple from us. First on seasonal flu. I think 2023 has been floated as a target for submission and/or approval. What would you say is the key gating steps for approval in 2023, say -- versus, say, 2024, 2025 for 1010? And with 2023 at this point, your baseline assumption given regulatory discussions?

And on RSV, you mentioned accelerating it into late-stage studies. So I would also be interested to hear how close do you think the ultimate launch could be versus competitors? And as a follow-up on 1345, it's definitely good to see the GMT boost in older adults. But I was wondering if you had any data from these patients on T-cell response given others such as GSK have flagged this as an advantage for its adjuvanted vaccine.

Stephen Hoge - *Moderna, Inc. - President*

So I'll let Jackie take the last one, but I'll take the first couple quickly. So on 1010, we're going to go as fast as we can. And as we talked about, we're moving into, we think, Phase II/III studies very quickly here. We have not guided on when we would expect to file, when the approval would happen. And obviously, we're not going to do that here, I'm sure you can understand why.

But at a practical level, it's because we do need to agree with regulators on the path and it may be different in different geographies. And so we will -- as we get that -- now we'll have those conversations, and we get that clarity, we'll obviously offer more clarity, but today, we can't.

The second thing which was on RSV and competitive. Again, we think we're right there in that first wave, maybe just behind it, but not by very much. And given these are going to be multi-season studies when they're up and running, at least the ones that have announced have, and we would expect to do something similar, that we think we're going to be in that first wave, and it will ultimately, we think, be to the credit of our vaccine if we're able to get there right at the same time or maybe even earlier if we are fortunate in being able to catch the right epidemiology to be able to demonstrate that benefit quite quickly.

And so we don't currently imagine there's going to be a huge gap or if there is that it's not going to be a substantial commercial issue in RSV. Jackie, do you want to take the last question on RSV?

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

Sure. So with respect to T-cells, I mean just as we've done SARS-CoV-2 in a subset of subjects, certainly, we'll look into T-cells. But I want to emphasize that while T-cells certainly are an important component of the immune system and theoretically correlate to efficacy, the proof is always in the pudding from a clinician standpoint.

And so I think the real value of the vaccine will come from the efficacy trial that we're planning in older adults. And at least from a technology platform perspective, what we've seen with our SARS-CoV-2 vaccine is that this platform can lead to efficacious vaccine in older adults. So really hopeful for the data that will come out of that efficacy trial, and of course, can be supplemented with a better understanding of T-cell responses. But I think it's really the efficacy data in the end that's important.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. And just to add one thing to build on Jackie's point. We spent 6 months last year where everybody telling us, you don't have good T-cells, your vaccine is not going to work. But I think we were pretty good. And then duration looks pretty good too. So as Jackie said, in this business, clinical data and real-world evidence is what clinicians use to make clinical decision for -- the best fit for our patients.

Operator

Our next question comes from Simon Baker with Redburn.

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

Firstly, a big picture question on rare disease. As a number of you've highlighted, the opportunity set is enormous. I mean it runs into the dozens and hundreds of diseases. So I just wonder if you could give us a few more pointers on disease selection. And allied to that from a development point of view, I noticed that amongst the countries in which you're conducting clinical trials, the U.K. features perhaps higher than one might expect. And I was just wondering if there are any specific reasons like the U.K. Biobank that make it a good place to develop drugs for rare diseases.

And then a quick question on 8601 beyond cardiovascular indications. This was alluded to briefly, but I just wonder if you could give us any color on the potential elsewhere, and I was particularly thinking about diabetic foot ulcers. Any thoughts on that would be much appreciated.

Stephen Hoge - Moderna, Inc. - President

Great questions. I'll take the first pass and then maybe Ruchira, I invite you to comment both on the U.K. and on the 8601 question around AZ. So first on the strategy, look, we want to use this technology to help as many people as we can against all diseases. Now we're limited only by our capacities right now, and we used to be limited a little bit by capital, but not so much anymore.

And so what we want to do is try and responsibly, but aggressively bring forward a very large portfolio of rare disease medicines. We are waiting for some signals as per our modality strategies I talked about, out of the initial cohorts to confirm that we've got the right technology to go do that. But as soon as we get that confirmation, you can expect us to add a very large number of diseases.

And I think that, as you pointed out, there are dozens, maybe hundreds of diseases that are -- have epidemiology that is similar to those in our pipeline already, large ranges of metabolic diseases, the organic acidemias are well known, but -- urea cycle disorders and so on.

And we are -- you can rest assured that we're looking at all of them. We've actually extensively published in many of those diseases in preclinical models and we'll be looking forward to accelerating those medicines as soon as we derisk that modality and seen in the clinic a strong signal.

I don't think we have a hard and fast rule though, that we can offer about if there's not more than 300 people that we wouldn't develop it or that if there's 5,000 that we wouldn't look at it. Actually, we're focused on where do we think our technology and our platform can alleviate the burden of disease, can help people. And wherever we think that we really can do that, and we can sustain that effort in the right way, we will do so.

And only in a few cases where we say, well, there might be others that are better at sustaining that effort, like The Institute for Life Changing Medicines that Jim Wilson has set up, we partner out. But really, the majority of this work, if not all of it, we intend to do ourselves. So Ruchira, do you want to comment maybe on the U.K. and 8601?

Ruchira Glaser

Yes, happy to. Thanks so much for that question. As it relates to the U.K., yes it's behind a little bit. It really was based on good early experience strong investigators who had a passion for the science and had a passion for treating their patients in this way. It's just a great example of the strong

collaboration that it takes to conduct trials in rare disease between regulators. So in this case, obviously, the MHRA, patient advocacy groups, patients and their physicians.

But the U.K. Biobank is a really interesting question, one near and dear to me and to Moderna as well because of our interest in large data sets and the artificial intelligence. And certainly with rare disease it's -- the genetic applications, the U.K. Biobank is something that we've actively discussed trying to leverage going forward. But in general, just the guiding principles to where we do our future rare disease trials will be to go where we have these strong collaborations, but also go where the disease (inaudible) trials are feasible to do.

When it comes to the diabetic foot ulcer, a great idea and certainly something that could be a potential application. So yes, the answer is yes. I think the other thing to bear in mind is not only does proof-of-concept in our coronary artery disease studies that AstraZeneca is conducting for VEGF, give us about local injection, it also can give us some proof-of-concept to the biology of VEGF. And in that there are upstream pathways to VEGF as well that can cause local vascular regeneration and other things.

And those will be things that we are poised to take advantage of and leverage when we achieve proof-of-concept. And those can also be applied to diabetic foot ulcer. So something to watch out for in the future.

Operator

Our next question comes from Mani Foroohar with SVB Leerink.

Mani Foroohar - SVB Leerink LLC, Research Division - MD of Genetic Medicines & Senior Research Analyst

One of the topics that you brought up for the vaccine franchise more broadly is the value of compliance and getting shots (inaudible) large. Can you give us a little bit of feedback on how -- what you're seeing in terms of vaccine acceptance versus hesitance? How that might vary between booster doses versus initial vaccine doses? And how you think in terms of your development process, commercialization and communication strategy, steps you can take to combat this sort of ongoing rising tide of vaccine hesitance that we're seeing in the U.S. and elsewhere?

Paul Burton - Moderna, Inc. - Chief Medical Officer

Maybe I can just start on vaccine hesitancy and then Stephane. I mean, so it's a very interesting question you bring up. As a surge in general in this country once said that drugs don't work in those who don't take them. And it's absolutely true. We have to do everything, I think, as a company to try and encourage compliance, adherence and perseverance. There has clearly been a slowdown in vaccine uptake around the world, I think, and it's certainly something that we're interested in trying to counter and understand. Going into communities and trying to solve the situation does not work that's been shown.

I think we have to do it with data whereas everybody has said today, we're a very data-driven company. We have an unparalleled platform. We have excellent real-world efficacy data effectiveness, and we have great safety data as well. So I think on the hesitancy front, what health care leaders around the world keep saying is people should get vaccinated. And I think people who are on the fence should see the data that we have and should be very comfortable and confident in using the platform. Stephane?

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. I will maybe just add. I mean, if you look -- and I'm sure a lot of you have seen a lot of examples of people who decided not to be vaccinated 3 months, 6 months ago and have been hospitalized or their loved one hospitalized and so on. So I think as Delta is spreading with such a high earnout, we just want to get more and more people realize that there is really the world of the has been vaccinated and those that have not they don't have a quality of life. Everybody is talking about going back to normal.

A lot of us that have been vaccinated, like you on the call and this team, will live a pretty normal life. I go to restaurants indoor because I know I have a good vaccine. And so I take airplanes, I have a social life again. And so I think over time, you're going to have people that are on the fences or have been on the fences who I think by seeing their friends having a normal life and by some of our friends that have not been vaccinated getting hospitalized, that will also keep driving it.

Of course, you will always have a group of people that will be diehard and never get a vaccine in their life. Well, this, I don't think we can really do something about those. But as we talked about it, I mean, the flu market is only 500 million dose worldwide for a planet of 7 billion people. I believe that number is going to increase drastically with respiratory viruses. And as Paul said, we're going to do everything we can to get people comfortable. We also have the science and the technology innovation adjuvanting our product. The mRNA is going for (inaudible). So there's a lot of things that I think is very unique to mRNA technology that we need to do more in terms of communication.

As you know, Moderna does not have 100,000 people. We are less than 2,000 people now, so we're still building and getting those things done. But I think there's a lot of things to do and also people tend to see across the platform that, hey, I got this vaccine last year from Moderna. Here comes a better one with another boost. Here comes CMV and so. So I think that over time, too, you will have overpopulation between people wanting taking care of their children, pregnant women. I mean if you look at the spectrum of vaccines that we have, I think we have a lot of ways to cut this over time and to keep getting better use of vaccinations.

Okay. Well, I'm assuming we are done with questions. So first of all, thank you very much for spending 4 hours with us. We really appreciate it. We know we are all very busy. I would like to thank the team and everybody that is not on this video conference. That's all very hard work for many years to get us to this point. I'll say in my closing, we have not been as excited about Moderna's future as of today. And I cannot wait to see what Moderna's going to bring us in terms of the science, in terms of medicine and impact on patients over the next years to come.

So thank you so much, and we see you very soon. Stay safe. Bye-bye.

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