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PRESENTATION

Operator

Good morning and welcome to Moderna's Annual R&D Day. (Operator Instructions) Please be advised that this call is being recorded. At this time, I'd like to turn the call over to Lavina Talukdar, Head of Investor Relations at Moderna. Please proceed.

Lavina Talukdar - Moderna, Inc. - Head of IR

Thank you, Catherine. Good morning, everyone. Thank you for joining Moderna's R&D Day. Today, we will present new data and updates of many of our pipeline candidates. You will hear from Moderna's management and clinical team leads as well as from key opinion leaders. You can access the press release issued this morning as well as the slides that we'll be reviewing by going to the Investors section of our website. Presenting today from Moderna are Stéphane Bancel, our Chief Executive Officer; Tal Zaks, our Chief Medical Officer; Stephen Hoge, our President; Juan Andres, Chief Technical Operations and Quality Officer; Jacqueline Miller, Senior Vice President, Infectious Diseases; Lori Panther, Senior Director, Clinical Development, Infectious Diseases; and Allison August, Senior Director, Clinical Development, Infectious Diseases.

Before we begin, please note that this presentation will include forward-looking statements made pursuant to the safe harbor provision 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.

With that, let me turn it over to Stéphane to open.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina. Good morning, or good afternoon, everyone. Welcome to Moderna 2020 R&D Day. Happy to review today the important progress our team has executed over the last 12 months.

On Slide 3. As many of you know, our vision since day 1 has been that mRNA could create a new class of medicine and impact the lives of millions. We never thought it will be a one drug company. We thought it could be a very powerful platform. With a very large product opportunity, being able to make medicines that are not doable using existing small molecule or large molecule technology, having a higher probability of technical success because mRNA is an information molecule, having the ability for investment in science, in manufacturing process, in IT, in robotics to accelerate research and development time lines (inaudible) medicines. And the greater capital efficiency over time versus recombinant technology. That's the vision we have.

On Slide 4, we shared that slide earlier this year to show kind of a development of a company. In the first few years, we focused on the science, manufacturing to be able to enter the clinic safely, which we did in December 2015. Over the last few years, we focused to understand through clinical signal, what technology was working better, and we explored 6 different modalities in parallel which was an unprecedented endeavor.

Towards the end of last year and early this year, in 2020 at the JPMorgan Conference, we announced that due to the positive clinical data that were generated by our teams in 2019, we decided to nominate 2 of our modalities as core modalities, infectious disease vaccine and IV systemic delivery.

And we decided to double down in these modalities because in our opinion, we believe that these modalities will be at risk from a technology standpoint. We announced 5 new development candidates in the January-February time frame. And we said that we thought it will take us 3 to 4 years to get to filing our first BLAs before scaling up the organization from a commercial standpoint.

Of course, SARS-CoV-2 virus changed everything. We believe that COVID-19 vaccine, or mRNA-1273 has the opportunity to accelerate the company transition to a commercial company by 3 to 4 years. As we'll discuss today, there is a scenario where we could file an emergency use approval this year in 2020, just months from now, and we could receive a BLA approval in 2021.

On Slide 6, let me share with you a couple of high-level numbers of all the progress the company has done in the last 12 months since R&D Day 2019 in New York. We have, of course, one programming Phase III now, mRNA-1273, where we had no Phase III program last year. And we'll talk about it later.

Our teams are working very aggressively to prepare the launch of a potential launch of the product. Last year, we had 2 Phase II candidates. And this year now, we have 4, which is doubling the size of our mid stage pipeline. And the early stage development is still at 18, showing that we have a rich diversified pipeline when you add the one (inaudible) programs.

We are still very active in infectious disease, immuno-oncology, cardiovascular, rare disease. And we added this year, autoimmune disease, as we think, a very important therapeutic areas where we believe mRNA could significantly impact a patient's life. We had a transformation in a number of patients and healthy participants who have been enrolling in our studies from just above 1,000 people last year at the same time to more than 27,000 people today.

We've doubled the cash balance compared to 12 months ago, and we have added significant team members to the team to be able to beef up late-stage clinical development and regulatory, manufacturing, of course, to be ready to manufacture in case of a success of 1273, at least 500 million doses up to 1 billion dose of 1273. And of course, starting to build since the spring, commercial teams.

I would like to thank and congratulate the Moderna team. They did all that and much more during a very complicated pandemic. We believe that Moderna has the most advanced mRNA platform in the industry. The scale of investment in science and the manufacturing process development that we have done over the last 10 years, we believe, is unique based on the ability we had to set up partnerships with large pharmaceutical companies as well as the capital that we have been entrusted by our shareholders over the years.

Moderna has now one of the most advanced COVID-19 vaccine development. But Moderna is not only a COVID-19 vaccine company. It is a very large platform. Moderna has today, 23 development candidates across a range of infectious disease and therapeutic areas.

On Slide 8, you see an update on the pipeline. For our long-term shareholder, I will draw them to the right of the slide, where for the first time, we're adding a commercial column, which is an important milestone in the company development because the teams, as we said, are preparing very actively for the potential launch of a COVID-19 vaccine. We are very happy to report today that the Phase II of CMV is positive, and we picked up the dose, and we are preparing actively for the start of Phase III next year. We're also happy to announce today that the OX40 ligand program is now enrolling the patient in Phase II.

On next slide, you'll see the 2 big news over there. The first one is, of course, on CMV. The team will be sharing with you in detail the data of our Phase II study, which we had anticipated having a readout in Q3 of this year. And we're also announcing that our teams, after consulting with our scientific advisory board has picked up the dose of (inaudible) Phase III at 100-microgram per dose of a vaccine. The very important clinical data we're going to share with you today is around the antibody against chikungunya virus mRNA-1944, for which, as you know, we've enrolled additional cohorts in the Phase I study. We have a very important new data set to share with you, is that our 2-dose regimen of chikungunya antibody demonstrates the platform's ability to safely repeat dosing. The data is quite interesting, as you will see.

And a very important advancement in the company today is that we are announcing that Moderna is going to enter the seasonal flu vaccine business. And the reason is very simple, if you go to Slide 11, is we believe there's still a very high unmet medical need in seasonal flu despite of course, commercial vaccines being available. But it's this gap in unmet medical need that is driving our decision. As many of you know, as reported by WHO, there are 3 million to 5 million severe case of flu each year around the world, leading between 300,000 and 600,000 deaths. Just in the U.S., we have between 140,000 and 800,000 hospitalization a year, leading to between 12,000 and 61,000 deaths per year. We believe we have a chance to change that. We believe we have a chance to bring flu vaccine that could be more effective than the current vaccines in the light of the elderly data we have been able to generate so far across the platform with COVID-19 versus (inaudible) RSV. And in face of the significant challenge, we're matching the strength with the mutation of flu which we think mRNA is very well adapted for.

So if you think about us entering the flu business and the other respiratory virus as on Slide 12, we believe that we have a potential to create a very powerful combination, especially for older adults. If you look at it, we have already demonstrated in the clinic that we can have a vaccine that includes several mRNA coding for antigens of different viruses.

We've shown that with the hMPV and PIV3 combination, mRNA-1653. We have also shown that from a process development standpoint, we are able to even go higher, put more mRNA in a single dose. And as you know, in the CMV vaccine, we have 6 mRNA molecules in every vial. So this ability that mRNA is a unique competitive advantage.

And if you think about a few of the most deadly respiratory viruses, COVID-19, flu, RSV, hMPV, to start with the most important ones, we have actually shown positive human data of neutralizing antibody titer in all of those 4 pathogens. COVID-19, obviously, we did flu twice for pandemic flu, H10 and H7, this has been published and showed very high level of neutralizing antibodies, RSV and hMPV.

So what if one day, we could get a seasonal flu vaccine to market, and we could combine it with a COVID-19 vaccine in a single shot to protect the elderly. What if we could combine it with RSV. You understand what we could do with different combinations.

We also announced last night after the close of the U.S. market, 2 new collaborations with industry players. The first one is with Vertex. As most of you know, this is our second collaboration with Vertex. Our first collaboration, which was signed a few years ago, the goal of that collaboration was to use mRNA technology and that takes deep scientific and clinical expertise in here to develop a drug to bring into the lungs of patients to express the CFTR protein coded in the messenger RNA.

That work is advancing very nicely as we've updated you over the last few quarters. But following the progress around that program, the Vertex team and the Moderna team have been discussing quite a lot and become quite intrigued about the possibility to use mRNA technology and our delivery technologies into the lungs to go into a new field to perform gene editing.

And so we are very pleased last night to announce this second collaboration with Vertex, aiming that using our technology and Vertex expertise and Vertex massive investment over the years in gene technology, to try to bring together a very innovative treatment for patients. This deal came with a \$75 million upfront payment and as the typical milestone, regulatory and commercial going up to \$380 million.

Stephen will come back later this morning to walk you through that partnership in more detail. The second partnership we announced last night was a partnership with Italian pharmaceutical company, Chiesi. Chiesi is a commercial company, and I think this partnership goes exactly in line with what we are trying to do, which is to bring using our technology, as many impactful medicines to patients as we can. Some drugs like CMV, like COVID-19, we will do by ourselves. But there are a lot of medicines for which we believe partnering makes more sense to bring a better solution faster to patients because we're combining Moderna's mRNA technology. We have another company, expertise in the disease from both a scientific and a clinical standpoint. And so with Chiesi, we are going back to pulmonary arterial hypertension, which is a rare disease. The deal financials are \$25 million upfront and up to \$400 million in the typical development, regulatory and commercial milestones.

So this is where I'm going to stop my few words of introduction to start the day. I'm going to leave you in the good hands of the team until closing the meeting later this morning. We've decided to set up the agenda in the following way this year: We're going to start to talk about therapeutics. We have talked a lot about vaccines in the last few months. And so we thought it would be good to start with therapeutics this morning. We will take a break after we've discussed systemic therapeutic, intracellular therapeutic and intratumoral immuno-oncology therapeutics. To come back and to discuss about vaccines, obviously, we'll talk about the world portfolio first, the non COVID, and then we will finish the morning by giving you some updates on COVID-19 vaccine.

After that, Stephen will briefly talk about the collaboration I just mentioned. And then I'll say a few words for closing. We'll take your questions.

With that, let me turn it over to Tal.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Stéphane, and good morning, everybody. It's a real pleasure to be here today and start the deep dive into our programs with the antibody program against the chikungunya virus. This is mRNA-1944, and this is really the first of our systemic secreted and cell surface therapeutics. This is a proof-of-concept program that we showed the initial data last year and really a follow-up of the final cohort today that will demonstrate the ability to repeat dose with our platform.

On the next slide, as a reminder of what this medicine is about, this therapeutic, what we have here is really mRNA that is encoding for a monoclonal antibody. So we have in the LNP, 2 mRNA molecules, one encoding for the heavy chain and one encoding for the light chain. And the idea is that when these go into cells, then they will translate into proteins. There is translation that is occurring in close proximity, which allows these -- the heavy chain and the light chain to find each other in the appropriate manner as biology has designed it. And so we have the formation of a monoclonal antibody and then secretion into the blood stream. And so for us to be able to measure the antibodies in the blood stream, the mRNA has to get into the cells, they have to get translated. This is not a simple protein in the sense that 2 chains have to come together, which is, I think, an inherent strength of our platform, you'll actually see us do this with 5 different mRNAs when we come to CMV. But the salient point here is that we're measuring a secreted protein in the blood stream that has the potential for a therapeutic benefit.

So on the next slide, if -- just to remind people of the design, we started with 3 dose levels as predicted from our translational pharmacology at 0.1, 0.3 and finally 0.6 mg per kg. We described the initial results from those cohorts here last year, and we followed up then with 2 additional dose cohorts. One, with the addition of steroids to see whether they would blunt some of the adverse events that we had described and test for their influence on the pharmacology. And finally, to see whether we could take -- administer 0.6 instead of in one bolus, as a repeat dose, so 0.3 once and then a second time a week later. And we chose a week of interval because when we did see adverse events, they were your typical infusion related reactions, and they were all transient. And so it made sense that a week later would be a good initial interval to demonstrate the ability of this platform to repeat dose.

The utility of this protein as a proof-of-concept is actually that the protein is functional, we can measure the activity of the protein because it's a passive transfer. I think in the year since then, the world has come to understand much easier what a passive transfer monoclonal antibody is. In this case, it's the ability to transiently protect against chikungunya virus.

So on the next slide, let me start with the safety data, you will see here the same charts that we described last year for 0.1, 0.3 and 0.6 mg per kg. We saw very minimal adverse events until we got to the 0.6 mg per kg. And there, we started to see grade 1s and grade 2s infusion-related reactions such as headaches, nausea, myalgias. These were all transient. They all spontaneously resolved without treatment. We did see one subject have a couple of grade 3 events, notably sinus tachycardia and an increase in their white count, we did not see any meaningful change in any other laboratory abnormalities, i.e., liver, kidney function test. And so what you see here is that when we added steroids, there is perhaps a bit of blunting. It's hard to say, because, of course, these are very small numbers. We did not see any more grade 3 events across the entirety of the trial beyond that one case I described last year. We continue to see some infusion-related reaction. They are mostly mild to moderate. They are all transient, and they are all of the same type of events that we had initially described.

Notably, on the next slide, if you take a deeper look at the cohort that received 0.3 repeatedly, a week later, if you come back and you readminister it, you basically get the same thing, either nothing or you get some grade 1s and the occasional grade 2. These are nothing new. And I think the salient point here is that none of these adverse events were exacerbated in any subject that experienced them in the first week. So from a safety profile, I think this bodes well to our expectation to be able to deliver potentially therapeutic doses at the range of up to at least 0.3 mg per kg repeatedly.

Now let's talk about the pharmacology. On the next slide are the data, as we had disclosed them last year. As a reminder, we saw nice dose-dependent pharmacology. Importantly, the doses of 0.3 and 0.6, we see quite remarkable concentrations of potentially therapeutic levels of protein, these are now in the 6 to 10-microgram per ml in the blood at the 0.3 mg per kg.

And this is a monoclonal antibody. So the therapeutic concentrations from monoclonal antibodies obviously are well-known and depend on the application, but it's certainly within the range of what other therapeutic monoclonal antibodies have demonstrated. Specifically to the application of passive immunity, we had extrapolated that one would need a dose -- a trough concentration of at least 1 microgram per ml.

And what you can see here is following that initial bolus of translation, if you look at the inset, in the first 2 days is really where you see the buildup of protein, because it takes time for the mRNA to get into cells and then you get translation, the mRNA degrades, you're left with a protein.

And so the half-life curve on the right part of that graph post the peak is really a function of the protein half-life, not the mRNA or the lipid. I'll come back to the point of the lipid. And so what you see here is that at the 0.3 mg per kg or above, we maintain trough concentrations above our target for at least 4 months or so.

Now let's take a look at the effect of steroids. They don't really do much. There's a little bit of a blunting of the Cmax. You can see the curves then come together and maintain a very nice and respectable half level above the trough. And so the data are up there with steroids. The really interesting part comes when you look at the repeat dose pharmacology, and this is on Slide 23.

What you can see here are the first 3 curves, as I had described them initially the 0.1, 0.3, 0.6. And now look at the green curve of 0.3 mg per kg. So the total dose is 0.6, but we've given it now repeatedly. And what you can see is at the second dose, protein translation starts again, as if completely a fresh, which from the sense of the body it is.

And you can see the rise in protein on the second week is the same as the rise in protein after the first week given this protein has a very nice half-life, what you really see is the buildup of the pharmacology. And now we're actually achieving Cmax concentrations of up to 8 to 16 microgram per ml.

And if you just let the eyeball followed what happens a week later, I would anticipate that if we were to come with a third dose the next week, you would continue to see buildup of that protein pharmacology. For the purpose of this target product profile, I think we're clearly there, and we anticipate to have very long concentrations of a potentially protective antibody.

So it may have relevance for this target product profile, but the salient point, I think, for us, is the ability to show repeat dose in a tolerable manner, no adverse safety findings in the sense of no serious adverse events, nothing unexpected. It's all transient, no laboratory abnormalities in liver, kidney function tests and very nice dose-dependent stackable pharmacology, if you will.

On the next slide is a look at what happens to the lipid, the lipid nanoparticle itself because what I've showed you is the protein that gets translated, well, what about the drug? Well, the drug practically disappears. We have engineered and invented this lipid and the entire lipid nanoparticle for this modality specifically to have a short half-life. It is biodegradable relatively rapidly. And so what you see here are the lipid that we've invented, looking at the accumulation of it over time. And what you can see is you come back a week later, there's practically nothing of that lipid left, and you basically start from baseline again. Because you can think of what would happen with repeat dose pharmacology, I would expect that there is no lipid accumulation. I would expect that whatever transient adverse events happen, they are infusion. When they do happen, they're gone by then. And so I think this bodes well for our ability to have repeat dosing in this modality in the future.

So to summarize, I think this, for us, as a proof-of-concept, has demonstrated the ability of our platform, the technology of our lipid nanoparticles when delivery needs systemically a messenger RNA to lead to potentially therapeutic levels of protein in the blood, to do so safely, at least as demonstrated by this Phase I trial. And we've shown that the property of the protein are exactly what you would expect in this case, a long half-life IgG, a complex protein that requires 2 subunits to come together and be secreted. And importantly, to be able to repeat dose and build up pharmacology, in the case of this application, without building up any accumulation of lipid or drug or adverse event signals.

With that, let me turn it over to my colleague, Stephen Hoge, to walk us through the rare disease portfolio. Thank you.

Stephen Hoge - Moderna, Inc. - President

Thank you, Tal, and good morning and good afternoon, everyone. Before launching into a bit of a discussion about our systemic intracellular therapeutics, I did want to remind everyone that Tal has walked through an example of 1 of our core modalities, the secreted and cell surface therapeutics. And that there are 3 other programs that we won't be speaking of today, IL-2, PD-L1 and relaxin in that core modality. The modality I'll briefly update you on today, where we do have some news is the systemic intracellular therapeutics. This remains an exploratory modality, where we're looking for the first proof-of-concept in the clinic in the near term.

So with that, I want to focus on 2 programs today on Slide 27. The first are mRNA-3927, our mRNA against propionic acidemia and 3705 against methylmalonyl-CoA mutase, so MMA for short. We have 2 other programs in this modality, a program for PKU and GSD1a, for which we're not providing updates today.

So first, on the organic acidemias on Slide 28. As a reminder for those who are new to the story, organic acidemias are a set of metabolic rare diseases that have to do with the breakdown of amino acids and fatty acids in the mitochondria, the energy factories in every cell. These components are broken down and fed into the Krebs cycle by the pathway illustrated on the slide in front of you.

There are a series of enzymes in that pathway, which are related to that metabolism, specifically propionic acidemia, PCC, enzyme complex and methylmalonyl-CoA mutase for MMA. Both of these enzymes are associated with rare genetic diseases, which lead to deficiencies in the ability of the body to break down those components and feed them into the Krebs cycle.

And unfortunately, there are approximately 1,000 to 2,000 patients in the United States for each of those disease. Now there's a lot in common between these diseases as organic acidemias because they're in that same metabolic pathway. And that includes both the biology and pathology of the disease, but also the treating clinicians and the centers of excellence for addressing their disease.

We've developed 2 different programs that I'll speak about briefly, one against each of those diseases, MMA and PA. We believe messenger RNA has specific advantages in trying to address the organic acidemias. One is the ability to encode for intracellular proteins. These are proteins that are actually even inside the mitochondria within the cell, and we previously published and demonstrated our ability to deliver the enzymes to the right place in the cells in vivo.

Another is our ability to combine multiple different subunits, for instance, in a propionic acidemia context, and I'll speak more about that in a minute. And then last is the ability to titrate the dose response. And therefore, perhaps address acute metabolic decompensations, which are a feature of both of these diseases.

So double-clicking on propionic acidemia on the next slide. Just to give you a little bit of an overview of this disease, the PCC enzyme is actually a dodecamer complex, made up of 6 PCCA and 6 PCCB subunits, and in fact, is 2 different genetic diseases or mutations, one arising from deficiencies in PCCA and the other from PCCB. As you can see, the prevalence is about 1 in a couple of hundred thousand births, and there's approximately 1,000 to 2,000 patients in the United States. It is primarily a pediatric disease that presents early in life with significant morbidity and mortality. Often, the metabolic decompensations that result from the inability to clear out those organic acids, amino acids and fatty acids, lead to neurologic complications, growth retardation, heart challenges and even life-threatening metabolic crises. So it's a terrible disease with significant unmet need. Unfortunately, there are no approved therapies for propionic acidemia, and the standard of care so far has been dietary restrictions and palliative measures. However, liver transplants have, in some rare cases, been shown to improve the biochemical and clinical outcomes. And it's that basis, that gives us some opportunity to proceed here.

So on the next slide, our program is mRNA-3927 in propionic acidemia, with the goal of replacing both the PCCA and PCCB subunits show the full dodecamer complex for propionic acidemia. mRNA-3927 has received an FDA Fast Track Designation, an FDA orphan drug designation and rare pediatric disease designation as well as an EMA orphan drug designation and has an open IND.

Now earlier this year, as we were preparing to initiate clinical work on propionic acidemia, the COVID-19 pandemic led to a decision that we previously announced to pause ongoing enrollment and recruitment in the study for the purposes of protecting the health of those patients and their caregivers and not bringing them into clinical settings during this time. We've actually announced today that we've restarted some of that effort. But we've used the time during that pause to make some important improvements that we think will help advance the program more quickly as we reinitiate. The first has been that we focused on amending our protocol to a novel dose-optimization clinical trial design I'll speak to in a minute. We think it will help us identify and judge more quickly.

The second is we've looked at the protocol, taking feedback from sites and from the patient and their families and caregivers to understand how we make the overall protocol less burdensome on patients. And I'll speak to that in just a minute. We are looking now also to launch an extension study, which we had always intended to do, but now we've had a chance to formally prepare, it will allow for the continued dosing of patients as well upon a positive risk/benefit for them in the Phase I/II trial, which is an absolutely important commitment in these rare and ultra-rare disease conditions.

So on the next slide, I just want to spend a minute describing the revised protocol, the updated novel dose-optimization design that we're taking forward for mRNA-3927. And this Phase I/II study has still the objective of evaluating safety and pharmacology in patients 1 year in age and up with propionic acidemia. The primary endpoints as before, are safety, PK and PD, with secondary endpoints looking at the incidence and severity of adverse events or changes in biomarkers.

As I said, we initially earlier this year, paused activities around the trial, given COVID-19 disruptions, but those efforts have subsequently restarted, and we're looking forward at the moment. Now the change has been in the dose optimization stage. While the prior design had been a standard dose escalation study, what we had realized in reviewing our clinical experience with the programs like the mRNA-1944 chikungunya antibody

program that Tal just described, is that there are a number of different ways to think about optimizing the correct dose for individuals with metabolic diseases.

And the design, as shown here, is going to be more iterative as an approach. Patients will be enrolled, and following a 21-day DLT observation window for each participant, we will take a cohort's worth of data and do innovative PK and PD modeling as well as safety data review, to select the optimal dose for the next cohort to come into the study.

That could include dose escalation or changing the dose frequency in which we'll be treating subjects for that next cohort. That will continue until such time as we identify a dose that we think is optimal for the majority of subjects, and then we'll move into a dose expansion phase, enrolling a further 4 to 6 participants at that dose level, including a minimum of 2 participants from each subtype of the PC propionic acidemia disease, 2 with PCCA deficiencies and 2 with PCCB deficiencies.

We believe this approach to optimization will actually help us to identify most efficiently, the optimal dose for treating this terrible disease.

I want to move on to briefly give an update also on MMA, where we provided some news today as well and focus on our new program there, mRNA-3705 against methylmalonic acidemia.

So quickly on Slide 33. Just an overview of the disease. It is also a rare autosomal recessive organic acidemia, as I said before. It is a progressive disease that leads to multiple organ systems failing and ultimately can lead to life-threatening metabolic decompensation episodes. The prevalence is similar to what we described in propionic acidemia, approximately 1 in 100,000, except in the Middle East, where it's even higher, maybe 5 to 6 fold higher. During the neonatal period, there can be quite severe complications from this disease, including neurologic complications, high mortality due to life-threatening metabolic crisis and other disease manifestations. There are currently no approved therapies for MMA despite this incredible unmet need. And majority of the current interventions are dietary restriction, cofactor therapy, and palliative support. However, liver and/or kidney transplants have been shown to be effective when they've been pursued even in infants as young as 1 year of age. Unfortunately, transplant has not been curative today.

So our program on the next slide, methylmalonic acidemia, was originally an mRNA-3704, but has been updated for the news today to mRNA-3705. It is a chronic treatment for patients with MMA that replaces the faulty enzyme by putting the mutase enzyme or MUT for short, back into the mitochondria of the patients suffering from disease. Due to COVID-19, as I said before, we paused enrollment in new site initiation for MMA earlier this year in the early spring. And specifically, that was for the program that we previously published on, which is mRNA-3704. Now the update today that I'll give a little bit more information on in a moment, is that we've leveraged that pause in these last few months rather than waiting to make some important improvements that we think will help accelerate the MMA program. The first have been improvements to the clinical trial design that are similar to the ones that I described previously with PA, specifically looking to make the initial experiences more friendly for patients and more operationally successful at the sites. And the second is we've identified a next-generation product, an improvement in mRNA-3705 that given the delay, we have decided to advance into the clinic instead of 3704.

So Slide 35 briefly summarizes some of that data around the next-generation MMA candidate that we're announcing today. mRNA-3705 is a superior mRNA. Specifically, it is a new messenger RNA that otherwise uses the same lipid nanoparticle. And importantly, the same lipid nanoparticle for 3704 as well as propionic acidemia, but also the same lipid nanoparticle that was used and described previously by Tal, mRNA -- for mRNA-1944, the chikungunya antibody program, for which we believe we are building substantial evidence of the safety tolerability and pharmacology.

As you can see on the graph on the right, mRNA-3705, the next-generation product, produces significantly higher levels of the human mutase enzyme in the liver of rats in the red versus the black at the top graph, and that translates into greater potency and more prolonged lowering of the toxic metabolite MMA in the mut- mice, as you can see, either comparing the red line versus the black line at the 0.5 mpk dose in the lower right-hand side.

That improved pharmacology, we think, is an important reason for why we've decided to make the change and bring forward 3705 in place of 3704. Now those aren't the only changes we've made over the last number of months, we've also taken the opportunity to revise the clinical protocol as I described, primarily to improve the patient experience and ensure the operational feasibility of the study is at the utmost.

Now next steps for this program, we will be filing a new IND because it is a new messenger RNA and new CTA applications for 3705, and we'll provide those updates at the appropriate time.

A closing on our rare disease pipeline on Slide 36. We have -- we believe there are a number of advantages to mRNA and rare diseases, and we are strategically committed, not just for the organic acidemia programs but for the other programs on our pipeline to advance them to try and help people with these debilitating diseases. The advantages for mRNA, we think are the ability to target intracellular proteins and the ability to target protein complexes with multiple subjects as best illustrated by both the MMA and PA programs that I just described. We also think the ability of mRNA as a drug with drug-like pharmacology will allow us to tailor dosing to clinical response with repeat dosing, increased dosing or increased dosing frequency as is required to meet the needs of individual patients and their diseases. And importantly, mRNA, again, does not require entry to the nucleus or do anything to modify their genes, which we think is an advantage.

The next steps in rare diseases, we'll be looking for the propionic acidemia study with its new revised protocol under existing INDs to have the first patient dose. MMA, the 3705 program, we'll be filing the IND and CTAs for that, building on the successful filings of 3704. And then we're looking for the IND filings of our 2 other rare disease programs GSD1a and PKU, as previously described. We're looking forward to hopefully clinically derisking this systemic intracellular modality with proof-of-concept in any of those studies which would move this from an exploratory modality in our mind to a core modality and cause us to double down as we have in other therapeutic areas and continue to build our commitment in rare diseases. We'll then, of course, continue to develop new development candidates and new modalities in the rare disease space and look forward to providing updates at the appropriate time.

And with that, I'm going to be handing it back to Tal Zaks to begin discussion on our oncology pipeline. Tal?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Stephen. So let's talk about oncology. Our pipeline, as you can see on Slide 38, is really composed of vaccine approaches and intratumoral injections. And what they share is a basic scientific hypothesis that says that if you can translate proteins into the human body, which we now know we can, and we've shown it time and again, then the question is, how do you leverage that ability to make a dent in patients -- in cancer and improve the lives of people living with cancer. And what we've learned over the past several years is that our immune system is potentially capable of recognizing it. In fact, if you can unleash it with checkpoint inhibitors, then you can mediate cancer regressions, and in some cases, very long-term remissions, perhaps even cures, but that's still only in a minority of patients. And so our goal has been, whether it's through personally vaccinating people with a personalized cancer vaccine or through intratumoral approaches to try and spur the immune system so that in combination with checkpoint inhibitors, we will have a higher benefit.

In the cancer vaccines, which I won't be discussing today, suffice to say that we are in a randomized Phase II for the treatment of adjuvant melanoma in combination with KEYTRUDA. And given that KEYTRUDA has a proven benefit in that setting, of course, a randomized Phase II is the right way to demonstrate proof-of-concept, and that trial is enrolling. As in all the randomized trials, you can only talk about results when you really get to the end game here.

In terms of our intratumoral approaches, the OX40 ligand program, which is the one we've started with first, I'm happy to say today, has started dosing its first -- the first patient with ovarian in the Phase II component of that trial, and behind that, in completing the Phase I dose escalation, again, in combination with checkpoint inhibitor, we have the triplet of OX40 ligand interleukin-23 and interleukin-36 gamma. Our collaborators, AstraZeneca are progressing in mRNA encoding for IL-12 with durvalumab also in Phase I. In these approaches, really, we've shown that as expected, we can translate protein. The question is, can you really translate the biology of the protein expression into useful pharmacology, i.e., an effect on the immune system and then translate it into clinical benefit. And to discuss that, we've invited somebody who is much more facile and is actually treating patients and translating that science into clinical research at the University of Colorado Cancer Center, Professor, Jimeno, and it's a real pleasure to introduce him to the audience, and I will invite him to discuss the findings that we've had and where we are in the clinical development of our intratumoral immuno-oncology programs. Dr. Jimeno?

Antonio Jimeno

Good morning. Hi, Tal and everyone. Thank you for the invitation to be the external scientist presenting this very important research and disclosures. My institution does receive research support from the NCI and our 20 sponsors for research, I am the principal investigator of, including Moderna, but I have received no personal remuneration or support from Moderna for this or any other activity. There have been -- major advances have been made in the -- with the advent of checkpoint inhibitors, and in particular, PD-1 and PDL-1 inhibitors over the last 5, 10 years, as witnessed by the multiple tumor types that are sensitive to them. However, the -- overall, it's estimated that only about 18%, 20% of all patients that receive benefit from PD-1 inhibitors or PD-L1 inhibitors do actually derive an objective benefit. And most of these patients eventually develop acquired resistance. So a major question and unmet need by cancer researchers is, what can we do to improve patient responsiveness to PD-1, PD-L1 axis inhibitors.

Next slide. According to the seminal papers describing the cancer-immunity cycle by Chen and Mellman, there are 3 essential elements that are key for successful adaptive response to cancer as exemplified by the response of tumors to checkpoint inhibitors. So the 3 things that need to happen are -- we need to have presence of immunogenic neoantigens. Needs to be presence and proper function of dendritic cells that will present the antigens to other immune cells. And we need to have active function of T cells. So functional or absolute deficiencies in any of these steps or components can result in primary or acquired resistance to PD-1, PD-L1 inhibitors.

The next slide very nicely summarizes the stimulatory and inhibitory factors that can enhance or inhibit the adaptive immune response to cancer at every stage of the cancer immunity cycle. By administering agents, either systemically or intratumorally, one can supply missing factors or inhibit -- inhibitory factors to elicit the desired immune response. It is also evident that one can -- if one supplies multiple targets and one can interrupt or interference in multiple of these processes across a variety of mechanisms of resistance, that is going to lead, like in classic chemotherapy from the 70s and 80s, that is going to increase the chance of success when giving a backbone of effective inhibitors such PD-L1 inhibitors across a wide variety of tumor types and/or individual immune phenotypes.

Next slide. Intratumoral therapy can get single or multiple modes of this cancer-immunity cycle as seen in the cartoon, depending on how many components are contained within the investigational product. And in the case of the Moderna portfolio and intratumoral therapies, they are evaluating both individual and multiplexed or multiple combinations of components of the cancer-immunity cycle to come up with 2 products that are currently under active development. First one is mRNA-2416. We will refer to it as 2416 thereafter, which encodes the OX40 ligand. The second one is mRNA-2752 that encodes both the OX40 ligand as well as IL-23 and IL-36. With the introduction of OX40 ligand alone, 4 of the 7 key notes in the cancer immunity cycle are opened up. With the addition of the other 2 cytokines, we had an additional note. And the 3 synergies substantially compared to individual or even doublet combinations, as we will show in the data a few slides below.

We go to slide -- the next slide, Slide 45 summarizes the principle behind -- or the rationale behind intratumoral therapy. As opposed to systemic therapy, where the principle is to achieve a systemic effect, intratumoral aims at focusing or eliciting an immune response in a specific area of our patient, in this case, in one of the tumors available for injection. With systemic therapy, evidently, the toxicity can be multi-organ and can be substantial. Immune therapies are better tolerated than cytotoxic agents but still can lead to significant and sometimes devastating autoimmune processes, whereas local administration should minimize the toxicity and exposure by eliciting a more focused immune response. There are also differences in who can access these drugs. Evidently, for systemic therapy, the only limitation is intravenous access. Whereas for intratumoral, we need to have a tumor that is detectable, either by physical exam or radiology and injectable. And there are less differences in terms of -- I mean, we can now safely combine multiple targets with both systemic and intratumoral therapy, although the overlap of systemic toxicities can be more limited in the former than in the latter.

If we go to the next slide. In oncology, multiple intratumoral agents are approved for in development. And in general, they have -- one of the most best known examples is the T-VEC, which is the oncolytic virus for melanoma, now approved or several immune agonists in development, including OX40, cytokines, TLR, STING and RIG-1 agonists. But if you look at this more from an internist rather than specifically an oncologist, I mean, essentially, we -- this is how we've been doing -- we have been giving vaccines with localized for viruses -- using localized injections rather than giving vaccines by systemic or parenteral administration and the toxicity premise holds in that field, too.

So in the next slide, you can see that the first agent that we will be discussing is 2416. That is an intratumorally administered mRNA encoding OX40 ligand.

Next slide. Generating optimal T cell responses requires T cell receptor activation and co-stimulation as seen in the cartoon here on the left, which can be provided via a ligation or binding of tumor necrosis factor receptor family member such as OX40. And as you can see in the cartoon on the right, 2416 encodes for the ligand of OX40 that is a homotrimeric protein regularly presented on APCs. Upon binding of OX40 to the ligand, in the presence of a tumor neoantigen, there is an expansion of both CD4 and CD8 T cells, and in printing of T cell memory and also a secondary inhibition of T regulatory cells, which have a pro tumor -- maintain a pro tumor microenvironment. Local expression of a native membrane bound form of OX40 would allow to achieve this activation.

Next slide. In preclinical models, the efficacy of the surrogate mouse OX40 was tested intratumorally in a syngeneic mouse model for hepatic carcinoma H22 shown here on your left. The spider plots show tumor volume in mice above and the survival graphs are below. And this shows that 3 weekly doses injected in the tumor resulted in reduced tumor growth in most animals and about a 50% complete response rate.

On the right, OX40 ligand was tested in ID8, which is an intraperitoneal model of ovarian carcinoma. And a single dose of mouse OX40 ligand dose IP combined with concurrent systemic anti-PD-1. And whereas neither single agents demonstrated any meaningful efficacy in this mice, combination resulted in an over 80% response rate.

This pretty striking preclinical proof-of-concept experiments prompted in next slide, the launch of the first-in-human program with 2416, and this is a first part that we'll be discussing today. This first-in-human study evaluated this investigational product in incurable solid cancer patients including dose escalation phase with cohorts of 3 to 6 patients based on toxicity as well as a confirmation cohort as needed in patients with tumors accessible to injection. Primary objectives included determining the safety and tolerability of escalating intratumoral 2416 in patients with said solid tumors and to define the maximum tolerated dose and subsequent dose for expansion.

Exploratory objectives included assessing the correlation of other investigational serum based proteins, such as ADAs with PK, efficacy and safety endpoints and to test the biomarkers of immunological response to 2416 in tumor and blood.

Next slide. A total of 39 patients have been enrolled in this protocol, 38 in dose escalation, 1 in dose confirmation. Patients were heavily pretreated and the most common tumor types were head and neck and ovarian cancer, with breast cancer melanoma and sarcoma being also represented, as you can see in the chart on the left. Treatment was overall well tolerated with 7 Grade 3 toxicities, mainly of fatigue, nausea, myalgia and injection and local reaction observed. Mild 1 to 2 local I mean systemic injection reactions were the most common toxicities observed in 7 patients each. Of 39 evaluable patients, 14 patients had stable disease as best response.

The next slide, as you can see, shows a swimmer plot of time on study which ranged between 6 to 24 weeks with several patients on study long term. Time on study did not seem to be associated with dose level, which is not an unusual event in immunotherapies.

The next slide shows an interesting distinction that this study design allowed since patients had some, but not all of their lesions injected. So we were able to dissect where we were seeing efficacy. In this bar graph, we're seeing the percentage growth or response of tumors. And we can see that injected and uninjected lesions that are plotted separately, in the 14 patients that had an overall response by RECIST, there were 4 patients that had tumor shrinkage in injected lesions and 5 patients that had some degree of tumor shrinkage in uninjected lesions. And there was an interesting mix because there were patients with tumor shrinkage in both injected and uninjected patients with shrinkage in injected lesions only and even patients with shrinkage in uninjected lesions only throwing in a number of very thought-provoking hypothesis. But overall, this shows that 2416 was able to induce both a direct immune response and a digital systemic effect. Of note, the 4 beige arrows are those 4 patients with ovarian cancer that have stable disease.

In the next slide, we can see the schemata of the biopsy and biomarker translational analysis that were carried on a subset of patients, where paired biopsies were collected pre and post therapy from the same lesion, either from injected lesions on the second day of therapy, from injected lesions on the second cycle of therapy or from uninjected lesions at the end of cycle 1, so that we will be able to address those hypothesis separately. Biomarkers from biopsies included the evaluation of OX40 protein expression, which is proof-of-concept that the drug is doing what it's supposed to be doing and T-cell abundance by multiplexed quantitative immunofluorescence analysis and changes in inflammatory markers by RNAseq.

The next slide shows that in injected lesions, there was an increase in OX40 ligand documented, as you can see in the plot on the left. The case with the most marked increase was an ovarian cancer patient that had stable disease shown here in the left, in which the post-treatment biopsy was collected 48 hours after injection. Her OX40 score went from 558 to 7,050 in just 24 hours. So that was approximately a 14 fold increase in expression of the protein. In a separate panel, T cells were also evaluated using cytokeratin staining. And it was documented that CD3+ cells significantly increased post-treatment in injected lesion, both within the tumor, and in the surrounding stroma components, indicating an engagement and trafficking of an adaptive immune response in the TME of these tumors.

We can go to the next slide, we can see that in both treatment biopsies, and this was a strikingly relevant finding, there was an increase in the levels of PD-L1 mRNA in these post-treatment biopsies with the greatest fold change observed in a sarcoma case who had stable disease and was actually the patient that was longest on the study. Both an ovarian and a breast cancer patient, also with a degree of tumor shrinkage that did not meet criteria for partial response, but that had objectively strong had amongst the greatest increases in PD-L1 transcripts. And this is important because this can be hypothesized as a consequence of an influx of T cells into the tumor. PDL-1 levels were compared with levels across the TCGA, the tumor -- The Cancer Genome Atlas study. And by this analysis, the majority of patients increased their PD-L1 scores post treatment.

Next slide, lastly, in these tumors, a general inflammation or inflammatory states index was calculated, called GEP scores, T cell-inflamed gene expression signature that has been shown to be predictive to PD-1 inhibition in some settings. So in this analysis, out of the 9 cases that were analyzed, there were increased ranked scores in 6 out of those 9s where the biopsies were taken from injected lesions. The 3 patients with the greatest increase in this inflammation score were the 3 patients that had shown the greatest clinical benefit on study, which again is an indication that good things are happening in the (inaudible) of these tumors.

The next slide shows the conclusions from this first study that are -- that 2416 was in our population, well tolerated when given as monotherapy with no DLT reported. 14 out of 39 patients achieved stable disease as best response and 6 patients had stable disease for over 14 weeks. 4 out of 6 ovarian cancer patients achieved stable disease along with clinically significant tumor regression in both injected and uninjected lesions, supporting further investigations in this tumor type.

In patients treated with 2416, had increased OX40 protein and T cell infiltration in the tumor microenvironment as well as upregulation of PD-L1 transcripts and activation of a pro-inflammatory gene expression response suggestive of an antitumor immune response. These observations together with the preclinical data support the evaluation of 2416 with anti PDL-1 inhibitors in solid tumors, which is right now, as discussed earlier, ongoing in Part B, with the focus on advanced ovarian carcinoma of which one of my patients will be dosing soon.

In the next slide, we can -- we are showing the second protocol that we will be briefly discussing and summarizes the OX40 ligands IL-23 and IL-36 study with products called 2752, which we will refer to as triplet in subsequent slides.

Next slide. So triplet or 2752 is a therapeutic mRNA based that encodes both OX40L as we discussed before, but also proinflammatory cytokines 23 and 36 because it was hypothesized, as was discussed before and we will not go over the table again that inducing these proinflammatory cytokines, along with the T cell co stimulation, would not -- would include T cell activation, but also would promote a TME that would shift from pro tumor to antitumor and induce a better response.

Next slide. This mRNA encodes these 3 components, and as discussed before, it is injected directly into the tumor, which can be done directly in clinic as we've done many of the patients or guided by imaging, ultrasound or CT, which is straightforward as well nowadays and which takes the mRNA inside of the tumors and upregulates these 3 proteins.

Next slide. Prior preclinical studies showed robust anti-tumor activity in mouse using this triplet product where introduction of these components was more effective in an immunologically sensitive model, as we can see by the 100% survival rate in the plot below compared to either of the components alone in both injected and non injected lesions in this very elegant science translational medicine article.

Next slide. Even in the difficult to treat immunologically barren B16F10 model, combination treatment of triplet with a PD-L1 antibody was synergistic and effective, as we can see here where PD-1 alone had no effect individually, the triplet had also no effect individually, but a 40% complete response rate in this mice in the left panel, the purple panel with the combined triplet plus PD-L1.

So these preclinical data and this body of immune knowledge led to the translation, next slide, of this concept into a clinical trial that is also ongoing. And that it's a dose escalation study using 2752 plus/minus the PD-L1 inhibitor, durvalumab proved for a wide array of cancers. And this is a study that is currently ongoing and actively enrolling at multiple institutions, including Colorado.

The objectives of this clinical trial is to evaluate safety and tolerability, determine the maximum tolerated dose for subsequent Phase II studies and also intends to assess anti-tumor efficacy, protein expression in tumors and the pharmacokinetics of these drugs. The dose escalation arm of the monotherapy is complete. And currently, it is a combination dose that is ongoing which will be anticipated to expand into 4 different cancer subtype indications in 5 arms once those finding of the combination is completed.

In the next slide, we will go over briefly the data that was presented at earlier in the year at ASCO. As of the cutoff data for that report, I will say, around April 2020. And of course, the enrollment to some of these programs has been impacted like everything else by the COVID-19 epidemic. So in that sense, some of testing centers, we had to come up with different approaches to continue seamlessly our service to this purpose and these patients. But as of the spring of 2020, 29 solid tumor patients have been treated with either 2072 -- 2752 alone or in combination, which has been well tolerated with no DLTs or Grade 4 or 5 toxicities.

As you can see in the plot on the table on the right, out of 23 patients with full anti-tumor valuation per RECIST and iRECIST, a patient had a partial response, 9 patients had stable disease and 13 patients had progressive disease as best response for an overall disease control rate of around 40%. Tumor shrinkage was observed in 7 patients in both injected and uninjected lesions in both monotherapy and combination. So to not repeat the discussion that we had before, showing that this not only elicits a local immune response, but that immune response that expands and can reach other tumors that were not injected just as in many other areas of immunology and vaccine biology. The patient that showed the largest -- the most -- the deepest response to say, squamous cell carcinoma of the bladder that received this combination and showed a 81% reduction of target lesion, which is remarkable. In the next slide, you can see the swimmer plot for the data as tabulated where you can see in the upper half, the Part A of the study, which is single agent and the lower half, or the Part B, which is a combination where longer diamond study is suggestive of more sustained antitumor effect of the combination.

Next slide. This is a waterfall plot. And again, injected and uninjected lesions were plotted separately for T cell that different biology questions, and the overall response is indicated at the bottom. You can see that the greatest reduction in injected and uninjected tumors occurred in the patient with the partial response, where both were in sync and shrunk by about 70% to 80%.

Next slide. The slide shows a schemata of the very complex and involved biopsy and biomarker collection schedule during this study, which was similar to the prior OX40 ligand-alone study and included measurement of IL-23, 36 that are the target of the product as well as indirect proinflammatory cytokine proteins in both pre and post treatment tumor biopsies and plasma. Immunohistochemistry for PD-L1 and T cell markers was also used to further characterize the baseline status and changes to the tumor microenvironment with treatment.

Next slide. As we can see here in this busy slide, in both mono and combo therapies, 2752 enhanced the percent of PD-L1 positive cells, particularly of tumor-associated immune cells or intratumoral cells and sustained increases were seeing throughout cycle 1. And a notable case, with the partial response highlighted here, the blood cancer patient showed that PD-L1 levels in both tumors and immune cells posttreatment increased significantly with immune cells shifting from negative expression at baseline to 25% expression after treatment in just a few days. And a subsequent accumulation of proliferating T cells, not just resident or passing-through T cells but active and proliferating T cells, CD8+ was observed post treatment which again suggests a shift from a immune barren -- immune pro tumor to an antitumor microenvironment profile.

The next slide shows that IL-23 and IL-36 gamma were elevated in a dose-dependent manner in both tumor and plasma and in figure -- in plot A, which is in the upper left corner, post treatment, which again, it's nice to see you put the mRNA, and you actually do see the protein. And associated to this, there were other proinflammatory cytokines with anti-tumor activity, including interferon gamma and TNF alpha that also increased 24 hours and 1 week post treatment, both in parallel inside the tumor and then in the plasmas circulating indicating that this local effect then gets -- it's made systemic by the circulation, which does support the approach. Most importantly, all post-treatment plasma cytokine levels evaluated were well below what has been or what we know or interpret as toxic levels when given systemically, supporting the hypothesis that when you give something intratumorally, the cytokines can achieve effective levels locally, percolate systemically, but without reaching levels that could be construed as clinically dangerous or significant for our patients.

Next slide. Here, we summarize the conclusions of this earlier combination study, mRNA 2752 given as monotherapy as well as in combination with durvalumab was tolerable at all dose levels studied with no DLTs, no limiting toxicities reported. And the majority of related adverse events were grades 1 and 2. The administration of intratumoral 2752 was associated with tumor shrinkage in injected and non-injected lesions in both monotherapy and in combination with a partial response in a PD-L1 low squamous-cell bladder cancer patient. Increased IL-23 and 36 protein expression were seen both in tumor and in plasma and an analysis of biomarkers suggested a sustained anti-cancer immunomodulatory effect of treatment that includes elevated PD-L1, interferon-gamma, TNF-alpha levels. These levels of cytokines systemically were documented, but were below what is considered to be clinically toxic, and this data support the ongoing testing of the combination of 2752 and durvalumab in arm B of the Phase I study.

With that, I want to thank you for your attention, and I will pass it on to the next speaker. Thank you.

Lavina Talukdar - Moderna, Inc. - Head of IR

Thank you, Dr. Jimeno for that very in-depth review of both the OX40 ligand and triplet program. We are running at 10 minutes ahead of schedule. So why don't we go ahead and take our 10-minute break starting now, and we will get back on -- at 9:30 a.m. Operator?

(Break)

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Hello, everybody. Welcome back, everybody. This is Tal Zaks here. Again, it's a real pleasure for me to kick off our section on prophylactic vaccines, infectious disease vaccines. This is an area where, clearly, I think, there's been a lot of focus around COVID. But importantly, we have been advancing our lead vaccine here, CMV and have promised you some news as it regards to our ability to dose select. And we're happy to share with you today the interim data from the Phase II that points to the continued progress of this. And it will be followed by the progress in other of our vaccines. And at the end, we'll come back and talk about COVID as well.

With that, let me hand over the microphone to Lori Panther, who leads our CMV program. Lori?

Lori Panther

Thanks very much, Tal, and good morning, everyone. I'm Lori Panther, Senior Director of Clinical Development at Moderna, and I'm the medical lead for our CMV program, and it's been pretty busy and exciting for the CMV team lately.

Now developing a CMV vaccine is a journey that not many have attempted. And at the end of our journey, we want to be telling the world that we're improving the health of our kids, preventing birth effects, preventing hearing loss and giving these kids the opportunity to have a normal life. So in these next minutes, I'm going to be updating you on our progress toward that goal. Next slide, please.

We now have 2 trials ongoing, and we're preparing for Phase III. I'll be talking this morning about the results of a recent interim analysis from our Phase I trial. And in addition, I'm very excited to be sharing with you the first interim analysis results from our Phase II trial. Next slide, please.

Now cytomegalovirus is a pretty common infection. I'll bet about 2/3 of the people on this call have been infected with CMV, and I'll bet almost all of us don't know it because it never made it stick. So why would we pursue a vaccine against it? Well, it's all in the timing of when that infection occurs. If a pregnant mom has CMV infection, she can transmit it to her developing baby, and it can be at a crucial time when that baby's brain, vision and hearing are developing.

About 3 out of 10 moms were infected with CMV during pregnancy will have a child with congenital CMV infection. And about 10% to 15% of those kids will be extremely sick in the labor and delivery room. Some won't even survive to see their first birthday. And those who do survive, the majority of these sick babies will invariably struggle with lifelong physical and developmental disabilities. (inaudible) kids with congenital CMV infection

who look fine in labor and delivery can be at risk for developing hearing loss and cognitive delays in childhood. Our team thinks of these kids every day. And to have a safe and effective vaccine and to prevent some of this hardship, this is a huge opportunity for us.

Next slide. So a bit of a reminder about our CMV vaccine. It contains 6 mRNAs, which encode for 2 crucial CMV antigens. One of these 6 mRNAs encode the gB antigen, and this is a protein on the virus that helps it infect many different cell types in our body, including cells called fibroblast. The other 5 mRNAs accomplish an amazing task because they encode 5 proteins that make this complex antigen on the virus called the pentamer.

Now pentamer is important because it's crucial for entry into our epithelial cells and is really good at stimulating the human immune response against the virus, but it's also really, really difficult to make outside cell and needs the cell to process it and to hold it just so in order for it to function. It's hard to whip it up in a lab and give it as a vaccine in that way. Really, the best way to make it is to have our own cells make it, which is exactly what mRNA vaccines do.

Lastly, it's important to note that the only CMV vaccine to complete an efficacy trial has been a vaccine that has included only the gB antigen, and those trials showed a vaccine efficacy of around 50%, and 50% is not bad, but the problem was that the durability of the immune response was not optimal. So with the addition of pentamer antigen to the gB antigen, we're expecting a better immune response that translates into effective protection against CMV infection.

Next slide. So here's the news on the status of the ongoing trials. For the Phase I trial, last month, we reached our 12-month analysis, which gave us some early indication of the persistence of the immune response. And for the Phase II trial, we began enrollment shortly after the first of the year, and it went quite quickly. We were fully enrolled by early March, and we've now reached our 3-month interim analysis of safety immunogenicity through those first 2 vaccinations at all of the dose levels. Now it's important to note that our challenge here was that the second vaccinations were scheduled at about the same time that the COVID pandemic was hitting the U.S. And the team quickly made adjustments so we could complete those second vaccinations but also keep our participants and our study personnel safe. Bottom line is that we were able to include approximately 65% of the total study enrollment for this 3-month interim analysis.

Next slide. Now note that the overall aim of our Phase II trial is to prepare for our Phase III trial. We aimed for this Phase II trial to provide the information we need to choose a final dose for that Phase III trial. And with the vaccine preparation that we'll be using in the -- and with the same preparation that we'll be using in the Phase III trial. There were some changes implemented to get from the Phase I to the Phase II presentation, namely the ratio of the 6 mRNAs in the vaccine will optimize for improved immunogenicity, the manufacturing process was optimized to improve tolerability of the vaccine, and the vaccine is not in liquid form anymore. It's lyophilized for implementation in Phase III and beyond. All of that said, our Phase I trial continues to teach us about the performance of this vaccine.

Next slide. So some Phase I data. As I mentioned, in August, we reached our 12-month interim analysis for this trial. And this trial is testing dose levels of 30, 90, 180 and 300 micrograms. The safety outputs revealed no surprises over all 4 dose levels, and there were no serious adverse events related to the vaccine. It was well tolerated and noted that the 2 highest dose levels, 180 and 300 micrograms had similar safety profiles. The exciting news is the immunogenicity data 6 months out from that third vaccination in the 30-, 90- and 180-microgram dose levels. And as a reminder, because I'll be using these terms a lot, neutralizing antibodies against epithelial cell infection is the measure we used to look at immune response to our pentamer antigen and utilizing antibodies against fibroblast infection is a measure we used to look at the immune response to our gB antigen.

What we saw was in our seronegative folks at the 90- and 180-microgram dose levels, at 6 months after that third vaccination, the titers against our pentamer were very encouraging with GMTs 3.6 fold and 3.9 fold higher than the benchmark of a naturally infected seropositive population. And the titers to our gB antigen remains around the -- remained around the natural infection benchmark titer. And the seropositive group, the immune boost to both pentamer and gB remained pretty robust, with geometric mean ratios between 14 to 31 fold for the immune response to our pentamer and 6 to 8 fold for the immune response to our gB antigen. So the summary here is that our Phase I trial recently gave us pretty encouraging news showing early immune persistence to this vaccine, just as our Phase II trial was taking off.

Next slide, please. So on to our Phase II trial. This trial has enrolled 252 participants, both seropositive and seronegative. The dose levels being tested are 50, 100 and 150 micrograms. And this range was chosen after a detailed analysis and modeling of what we might expect in this lyophilize

presentation was all of the optimizations I mentioned. And also, as I mentioned a few slides back, the COVID pandemic has been a challenge for all of us, and this trial was no exception. And we amended the protocol to widen the second vaccination window so this vaccination could happen safely for everyone involved. And as a result, we were able to include 65% of the total enrolled for the 3-month interim analysis.

First, the safety data. This table shows the frequency of solicited adverse reactions after the first vaccination for both the seronegative and seropositive groups. As a reminder, when we collect solicited adverse reactions, it's when we have each participant fill out a symptom diary every day for the first 7 days after each vaccination. And the symptoms we ask about are pretty much the same across all vaccine trials, that are listed on the left-hand side of the table. They're divided into local adverse reactions. So any symptoms in the arm that was vaccinated and systemic adverse reactions. So any more general whole body type symptoms. And what we saw was that the most common local adverse reaction was injection-site pain and the most common systemic adverse reactions were headache, fatigue and myalgia. And this is essentially the same profile we saw in our Phase I trial. And also important to point out, there were no serious adverse events reported, and there are no participants who discontinued the trial due to an unsolicited adverse events.

Next slide, please. This next table has the same layout and shows the frequency of solicited adverse reactions after the second vaccination for both seronegative and seropositive groups. Here, we're seeing the same profile for the most frequently reported adverse reactions that we did after the first vaccination. And 2 things to note: Number one, there wasn't a distinction between dose level and adverse reaction rates; and number two, there wasn't a notable difference between the adverse reaction rates in the seronegative group and the adverse reaction rates in the seropositive group.

So -- and also and this isn't shown on the slide here is that fever was much less frequent in the Phase II vaccine product compared to the Phase I product. And in general, the observed reported frequencies of systemic solicited adverse reactions are lower in the Phase II trial compared to the Phase I trial thus far. So these are gratifying observations because one of our aims with the modifications to the Phase II vaccine product was to do just that, to improve tolerability.

Next slide. Moving on to immunogenicity. This table shows immune response to the vaccine in our seronegative group. The top half of the table shows the immune response to our pentamer antigen. And after the second vaccination, we're seeing GMTs between 49,000 to 57,000 across those 3 dose levels. In the blue circles, we're comparing these titers as a ratio to the base line titer of a seropositive group. Now this seropositive benchmark is kind of the goal we set for seronegative. It represents the antibody level of people who have had CMV infection in the past, and this is important. What we know about pregnant women who have had CMV infection in the past is that they have about a 10x [loop] for chance of passing CMV onto their babies.

So the hypothetical question we can pose here is, could our vaccine give us seronegative person the protection of a seropositive person? And the answer is, again in the blue circles, yes, yes, by at least twelvefold -- with this 3-month IA data. The bottom half of this table shows the response to our gB antigen. And after the second vaccination, so the 3-month time point, GMT is generally hit at or a bit above the seropositive benchmark over all 3 dose levels. So this is very encouraging news.

Next slide. This table shows our results for our seropositive group. Same layout, except that the comparison here is against each group's own base line titers in seropositive to start with. And what we can see here is a robust boosting response across all those levels. With GMRs ranging 20 to 32 for response to the pentamer antigen in the blue circles and GMRs of at least 2.5 for response to our gB antigen. So also very encouraging.

Next slide. These next 2 slides are graphic depictions of the immune response tables you just saw. This one shows the progression of immune response to the pentamer antigen, so neutralizing antibodies against epithelial cells. The dotted lines represent seropositive group. The solid lines represent the seronegative group. And that black cores on a line is our seropositive benchmark value. And so also note that the Y-axis is logarithmic axis. The main focus here are the data points at the far right of the figure. We see a clustering of the seropositive and seronegative GMTs at month 3, so one month after that second vaccination. So the immune response in the seronegative folks was similar to the boosting response from the seropositive group. And again, focusing on the solid line, seronegative dose levels, we don't see a distinction between dose level and immune response at that 3-month time point.

Next slide. And this one shows the progression of neutralizing antibodies against fibroblast infection, which is our immune response to our gB antigen and the same layout here. And again, the far right side -- at the far right side of the figure, focusing on the solid line, the seronegative groups, we're not seeing a dose level distinction, and we are seeing these GMTs cluster around our seropositive benchmark level. So very encouraging observations that we're seeing.

So these Phase II interim results were key data that informed our choice to take the 100-microgram dose -- I'm sorry, next slide, please, into our Phase III trial. And to further prepare for the Phase III, we're amending the Phase II protocol to add more participants to achieve a robust safety data package at that 100-microgram dose level. We're planning our Phase III to begin next year, 2021, with a primary endpoint of vaccine efficacy against primary CMV infection in women aged 16 to 40. And we're planning to carry this out in a study population of less than 8,000 participants. We've sought and received very constructive feedback from a joint national scientific advice meeting earlier this year, and we're deep into operational preparations for this pivotal trial.

Next slide, please. Lastly, we're preparing for the launch of our vaccine in a broader sense. We've been focusing on and supporting efforts to really amplify public awareness of CMV and its impact on the health of our kids. There's certainly work to do here, and we have a tremendous team at Moderna focused on this effort.

So in summary, the CMV update here is that there's a lot of exciting news. Our Phase I trial is showing some early indication of immune persistence. Our Phase II trial is telling us that our intended Phase III vaccine product is well tolerated and immunogenic, and we've been able to select the dose going forward. And our Phase III trial preparations are keeping us very, very busy.

So thanks for your attention this morning, and I'll hand the screen over to Allison.

Allison August

Thank you, Dr. Panther. If we could move to the next set of slides, the pediatric respiratory vaccine slides. Good morning, good afternoon, everyone. I'm Allison August, and I'm a Senior Director of Clinical Development in the Infectious Diseases Division. I'm the medical lead responsible for the pediatric respiratory vaccine programs. And I'll share a brief update with you on the status of these programs.

There are several pathogens that contribute disproportionately to the burden of respiratory illness in young children. And this burden is dominated by 3 pathogens: respiratory syncytial virus, human metapneumovirus and parainfluenza virus type 3. We are very excited to be pioneering mRNA vaccines in children, through the development of vaccines targeted against these 3 dominant pathogens to address the persistent respiratory disease burden in this pediatric population. I'll now focus on a more detailed update of our ongoing pediatric programs. And I'll discuss a future vaccine option, which leverages one of the strengths of our platform, the potential for a combination pediatric respiratory vaccine.

Next slide, please. Why RSV? RSV is the largest cause globally of severe lower respiratory tract infection in young children. This has been recognized for decades, and yet it remains unaddressed by vaccine. Most children are infected at least once by the age of 2 years at an estimated annual cost of \$2 billion in the United States alone. The acute clinical presentation commonly leads to hospitalization due to severe bronchiolitis or pneumonia, and there's also evidence of an association between early trials in infection and the development of chronic sequelae, such as asthma.

Next slide, please. This slide illustrates the mRNA-1345 RSV vaccine, which is engineered for an optimal immunogenic response. Specifically, the mRNA encodes the fusion protein with modifications that enable the protein to be stable in pre-fusion combination, which is critical as it then displays the key epitopes that have already been shown to be superior antigens. Additionally, the pre-fusion F protein is anchored to the membrane, which subunit vaccines cannot do, and the formulation uses the same LNP as several of our other vaccines.

Next slide, please. This slide illustrates a high-level overview of our ongoing RSV vaccine study, which is actively screening adult participants. As with our first pediatric study, our hMPV/PIV study, the design for this pediatric study was carefully vetted with pediatric infectious disease experts, pediatric vaccine investigators and the FDA. Many of the design elements here are standard, will evaluate safety and immunogenicity with the primary endpoint being safety. As such, this study will be conducted with the oversight of both an internal safety team and an external independent DSMB.

The members of our DSMB or Data Safety Monitoring Board are all very well-seasoned pediatric vaccinologists. As outlined on the right side of this slide, this study has a small adult leading cohort. We then immediately age deescalate to the target pediatric population of children 12 to 36 months of age. Again, while the paramount goal for this pediatric study is safety, a reminder that we are already dosing children.

Next slide, please. Our second pediatric vaccine that's under development will address the 2 other major causes of respiratory illness in children, human metapneumovirus and parainfluenza virus type 3. These pathogens account for a near equivalent burden of severe respiratory illness in young children that is similarly unaddressed by vaccine. The clinical presentation with these infections can range from mild symptoms to again severe lower respiratory tract illness, including bronchiolitis and pneumonia requiring hospitalization. Of note, there's been no prior attempt to address both of the pathogen in combination vaccine.

Next slide, please. This slide illustrates our mRNA-1653 hMPV/PIV vaccine. It's notably distinct from the RSV vaccine that we just reviewed in that, this is a combination vaccine. It targets 2 diseases simultaneously. This vaccine highlights an aspect of our technology that we believe differentiates our messenger RNA approach, the ability to make combination vaccines. As detailed in the upper left-hand corner, this vaccine contains 2 mRNAs, each encoding an antigen from different virus, though formulated within a single lipid nanoparticle. It's similar to the RSV vaccine that all 3 contain mRNAs that encode with the fusion protein, all anchored to the membrane and all are formulated using the same LNP.

Next slide. This slide illustrates a high-level overview of the ongoing hMPV/PIV trial. This study (inaudible) vaccine study has an adult leading cohort, which has completed enrollment. We've also completed enrollment on the first 10 pediatric participants in cohort 1, and then had a study pause due to disruptions related to the COVID-19 pandemic. We used the path as an opportunity for an ad hoc safety monitoring committee meeting to review a preliminary data set on these small initial group of pediatric participants. The SMC, again, composed of pediatric vaccine experts recommended continuation of the study with no modification in the planned trial execution. This study is resumed. We're actively screening pediatric participants, and we look forward to updating you on our progress and the corresponding full data.

Next slide, please. So what's on the horizon for our pediatric vaccine programs? As just demonstrated by the example of our hMPV/PIV3 vaccine program and identified earlier by Stéphane this morning, we believe our platform is uniquely well positioned to enable us to formulate combination vaccines. Given the overlapping epidemiology of infection of these 3 pathogen pediatric -- 3 major pediatric respiratory pathogens, a combination vaccine would provide a substantial clinical advantage. The challenge for us is not in the scientific validity or the feasibility to execute clinically or even in the CMC rather any optimal clinical development path to a combination vaccine. We're designing a trial to integrate the endpoints against these 3 different viruses into one development path. Simultaneously, we continue to progress both the RSV and the hMPV/PIV vaccines independently, and likely through Phase II in dose selection prior to combining them.

Next slide, please. Our ultimate goal is a combination pediatric respiratory vaccine. There are clear advantages to the combination vaccine, for sure. It would enable a simple pediatric immunization schedule, happier kids, happier parents as well as help to the primary health care providers. A combination vaccine will also increase compliance and the overall uptick of and public health benefit from the vaccine.

It's now my pleasure to introduce Professor Terry Nolan from the University of Melbourne, who will share his insights on the pediatric vaccine department.

Terry Nolan

Hello, everyone, at Moderna. This is Terry Nolan from the Peter Doherty Institute for Infection and Immunity at the University of Melbourne. So pleased to be able to speak to you today. And sorry, I can't be there with you. Unfortunately, the time zone is the big killer, and we'll have to make do with this. I'm delighted to be announced today to give you some insights and perhaps a few thought-provoking observations on vaccines, particularly with respect to the prevention of children's diseases. And I've titled this brief talk, epochs and opportunities because I'm going to focus on some of the achievements that we've seen in the last 20 or 30 years, in particular, and what I believe to have been responsible for those are sort of a helicopter view and following that some opportunities that are particularly relevant to mRNA vaccines.

The advances that we've seen in disease control have been spectacular since the 1950s with polio, with diphtheria, tetanus and pertussis, with the many different organisms that can cause meningitis, I'm thinking of Hib as well as pneumococcal disease and also meningococcal diseases. Diarrheal

disease with the advent of an effective rotavirus vaccine, and then pneumonia with conjugate vaccines, in particular, conjugate pneumococcal vaccines made a massive difference to invasive pneumococcal disease and also to pneumonia. And to other conditions, which we rarely see these days in those countries who have higher rates of vaccine uptake, measles, mumps, rubella and now varicella.

I'm going to suggest there are 3 basic restraints or reasons which have contributed very substantially to these epochs with quantum shifts in disease control coming close to elimination for some, such as polio of course, and for others, very close to -- very high levels of disease control, such as meningococcal disease, for example, Hib and many others.

So the first of these is advances in vaccine science or vaccinology. Broadly speaking, especially since the 1990s, the advent of conjugate bacterial vaccines, which in the beginning were simple, such as with Hib, for example, but then with more complex multiple serotype vaccines, the conjugate pneumococcal vaccines have been wonderful examples of new technology that was previously not available.

Reverse vaccinology was an important new step that resulted in the first effective meningococcal B vaccine, a completely different approach to understand the genome of the organism and its protein structure, which in turn allowed rational vaccine design based on identifying and targeting specific areas of the bacteria, which were important for prevention of disease.

And then finally now, the era of nucleic acid vaccines, I think it's fair to say has arrived. And we are seeing that with Moderna's import in particular into the equation after many years of DNA vaccines struggling, this has been a wonderful new addition to that epoch.

The second broad thing that's happened almost unnoticeably is the advent of multiple combination vaccines. Close combinations were available in the '50s with DCP vaccine but -- and then later with measles, mumps, rubella and so forth, but it was really the large infant combination vaccines in the late '90s, early 2000s, which has really made a huge difference to accommodating the schedule to allow new vaccines to be added and to deal with issues of concern about doing too much all at once to children, something I'll come back to shortly.

Other combinations. And more recently, MMR-V, meningococcal combinations, especially some of which have come and gone as more effective combinations have appeared. I'm thinking of HibMenC HibMenCY followed by meningococcal vaccine ACYW and also in trials now and not far away, a 5 balance -- 5 sero group vaccine meningococcus ABCW and Y.

But at the same time, there's been, if you like, shifts in society, which, despite the fact there have been very significant noise attached to those who are fiercely opposed to vaccination, fortunately, in very, very small numbers, even in the U.S. and certainly elsewhere in the world. And more generally, a concern about being absolutely sure that vaccines are safe, which is now described as vaccine hesitancy or vaccine confidence. But there has been a shift in tolerance I've noticed in governments.

Certainly my own government in Australia, both federal and state governments. Shift in tolerance of freedom not to vaccinate, and this has resulted in changes in, if you like, exceptions to mandates which means that either religious objections or, in some cases, personal conscientious objections to vaccination are no longer permitted. And this has come not at the behest often of those like me, people who are involved in vaccines and promoting them, but actually has come from the politicians. And I've been surprised at how receptive they've been to the need to promote vaccination. Sometimes worried that they've gone too far. But nonetheless, it has been a shift.

There is now a view that herd immunity is everyone's responsibility and that tolerating 5% or 10% of the population does not mean to be immune because the herd will protect them is not seen any longer as a reasonable reason for them not to be vaccinated.

So this notion of combination vaccines, I want to just explore a little bit more. They have made the infant schedule feasible as new vaccines have emerged, as I mentioned. And the potential for further efficiency does exist and probably hasn't been fully realized. We've just done a review published earlier this year of the first 10 years of experience in disease control terms of a hexavalent infant vaccine, which is the anchor point of the Australian schedule. This is a GSK product, but there are other multivalent 5 and 6 valent vaccines used around the world now, and it has become the anchor point of schedules everywhere. But we're interested in just seeing what happened with the disease control as this became that anchor point. And clearly, the impact on disease control has been massively successful. It's been mediated through very high levels of uptake of

the vaccine. Obviously, having the combination in and of itself alone is not the reason, but it's permitted the promotion of vaccination in a crowded schedule to actually achieve this wonderful outcome.

And the reason why combination vaccines have been successful is obvious. It increases coverage across half a dozen conditions all at once rather than having to schedule a number of different appointments or a number of different time points in the schedule. And so if you like, those that -- for which there may not be so much enthusiasm get caught up in the overall improved coverage. There's convenience, convenience for parents and also for health care providers. The cost of materials is reduced. Storage is simpler. Marketing is also simpler rather than worrying about exactly what's in the combination vaccine. Generally speaking, the combination itself becomes known as the children's vaccine and worth getting.

And finally, in terms of parent acceptability, this notion of worrying about a pin cushion or antigen overload and anxiety I think paradoxically has been helped by having combination vaccines because the numbers of actual separate injections or separate vaccinations is what parents often see and are concerned about as was shown in this national survey done in the U.S. by Bruce Gellin and others. Kathy Edwards was one of the authors of this paper, A National Telephone Survey.

I just wanted to point out on the bottom line of this chart the 25% of parents who are surveyed here, these are parents of children aged 6 years and under. The 25% felt that they were concerned, had serious concerns about the children's immune system possibly being weakened by too many immunizations. Even at that time, of course, the view may be different now. I'm not sure that this particular survey has been repeated more recently. But the concern that doing more and more with the children's immune system is something which we as promoters of vaccines need to recognize that and then explain and be part of the discourse in promoting vaccination.

I want to switch now just very briefly to thinking about the future and what the next epoch might look like. And in particular, the identification of respiratory viruses as high-value targets. I believe elsewhere in the program, you'll see some of the epidemiology, which underlies the basis for, if you like, what's called off on the unmet medical need, which is demonstrable. But in summary, there's clearly a continuing case and need for better influenza vaccines. We've got good vaccines, but they're not good enough. The fact that they need to be renewed annually is an issue. And until there is something -- a technology, which is going to overcome that, we're stuck with it. But in particular, the effectiveness of those vaccines, which are given annually is not where we'd like it to be. It's in the 50% to 60% range at best rather than the 90% plus range where we'd like to see it.

Secondly, respiratory syncytial virus, or RSV, has been a more than 50-year quest now to identify effective vaccine against this nasty virus, which affects particularly very young infants with high rates of hospitalization, potentially leads to future development of asthma, which until we have a vaccine, we won't really know for sure. But that quest for the vaccine has been harmed considerably by early adverse effects in the late 1967 and '70s of a vaccine candidate with associated enhanced respiratory disease that led to death in some infant subjects because of enhanced infection once they're exposed to the wild virus after having been immunized. There is much better understanding of that phenomenon and much better technologies which can address that risk. And in fact, there are now many candidates from several platforms, both delivering to pregnant women to protect their infants once they're born and also to infants themselves. And of course, Moderna is one of those players in this field.

Other respiratory viruses, which are really important include something called parainfluenza virus type 3 or PIV3, which causes also significant and serious respiratory illness, pneumonia, and it also causes croup. And so an effective vaccine against that is a tantalizing prospect. And human metapneumovirus, so a more recently discovered virus, which does can cause significant pneumonia again and increased waste of hospitalization, another very important target.

Is there a niche for mRNA combination vaccines? I think there's some conspicuous advantages that mRNA construct or platform does offer. The first is the capacity to package more than one targeted disease in single vaccine. So in effect, the combination vaccine by having more than one type of RNA scripting a particular protein directed at a particular target disease.

What the limits for that will be remain to be seen. But in concept, the simplicity of this construct really tantalizing. There's a reduced risk of chemical or immunologic interference between components of the multivalent or a combination vaccine. This has been a problem in the development of those big combinations that I mentioned to you before. And it was overcome, but was considerable difficulty with multiple clinical trials and attempts at changing the underlying construction of those combinations.

The other advantage potentially of an mRNA combination vaccine is that it's tunable. In other words, the potential to redesign the vaccine to address antigenic drift, change in the mutation or mutation in the virus, which the vaccine is directed against. But with a simple alteration in the mRNA script, if you like, without altering the entire construct. This has enormous implications for simplicity in terms of whether further regulatory requirements might exist for further clinical trials or not and potentially is a huge advantage.

And similarly, if it does turn out that mRNA vaccines don't require adjuvants to the same extent that proteins obviously do, this is going to be a huge positive for potential new vaccine development.

This slide, regulatory touch points addresses some key issues. I'm not a former regulator, but I've had a lot to do with interacting with regulators over my career. And one of my formal colleagues -- or one of my colleagues, a former regulator, made a simple point about adjuvants that, in general, regulators don't like adjuvants. They add complexity, they add uncertainty. And by and large, it's a much simpler world without them. So obviously, adjuvant, there are good reasons for having adjuvants, and they do work and offer considerable advantages in some context. But having a situation where they were not required is obviously going to be a big advantage.

Secondly, safety. For children's vaccines, in particular, there is -- well, more generally across the whole age span this phenomenon is occurring. But especially for children, there is a tangible shift in base line on risk tolerance by regulators and increasing requirement for manufacturers and for public health authorities to monitor and provide evidence on safety for vaccines. And as far as the clinical trials that are required, increasing requirements for numbers for all sorts of other considerations to provide a higher level of safety assurance are part of the modern landscape.

The assurance of vaccine effectiveness or efficacy, VE, for drifted targets. So again, where there have been viruses that have mutated, the regulators these days are much more concerned about monitoring changes in vaccine efficacy over time. This has been very much the case with influenza recently. And if it is going to be the case that there will be important rift in SARS-CoV-2, this will be an issue for future generations of SARS-CoV-2 vaccines. And potentially other viruses, including the ones we've just been talking about.

And finally, for children, clinical trial complexity is the nature of the game. Age de-escalation, that is giving vaccine safely to all the children before we give them to younger children, is a general requirement for regulatory approval. And with that, either dose de-escalation, reducing the dose as you go down through different younger age groups also part of that requirement.

Another factor, which is important, I just want to really, as we come to the end of this talk feature is the changes in various ecology from COVID social impacts that have occurred, and we've all observed although possibly haven't observed because people haven't been looking. What I mean by this is this disruptive virus ecology can occur because through the public health measures to contain the pandemic virus, usually with very severe social restriction. I'm speaking from a city, which is now getting into nearly 2 months of very severe lockdown. And believe me, we will have enough of it. But there has been a consequence, as you expect, impact on virus circulation. That's exactly what it's designed to do targeted at the COVID virus. But in fact, it also has an impact on all other virus circulation, including influenza, including RSV.

I'll show you some data on that in a second. But the reason for mentioning this is that this has a significant potential effect on clinical trials programs, especially for respiratory viruses we've just been talking about because some of those programs depend on a proportion of early childhood participants in clinical trials being seropositive, which means that they have had to have been exposed to a virus, usually in the first year of life or so that most children become positive to RSV by time they are 2. But if the virus is not circulating, they will not be seroconverting.

And in the period when a Phase III study, an outcome study will need to be done to look at the reduction in the clinical cases of RSV, for example, this applies to other viruses. But using RSV as an example here. If there is a little in the way of circulating disease because of this social restriction is going to make doing Phase III studies harder. It will take longer, and that's going to be an issue.

Here are some data from my hospital, the Royal Children's Hospital in Melbourne, and these are not the search data, these are practice data. So the axis on these 2 is, the left panel 2019, the right panel 2020. And they show the months from January to August. Remember, our winter period is really from June through August, September. And what it shows is the number of PCRs, which were done for presentation. So these are not selected at all. This is all presentations with respiratory illness of children who have given the diagnostic PCR, whether they were admitted to hospital or whether they were just an emergency attendance irregardless.

The -- you'll see there, first of all, just the red curve on top, the proportion who are positive for RSV, you'll see a massive difference in that curve from 2019 into 2020. And the black bars are the actual numbers of positive RSV identifications that have occurred. And you'll see that in the winter months, for us, they virtually disappeared. And what we would have expected was something like what was on the 2019 panel on the left. So there's been a massive reduction in the amount of RSV disease simply because transmission has been suppressed by the public health interventions, which have been undertaken.

And just to remind you, also where we sit, so to put this in context, on this graph, which shows daily new confirmed cases of COVID-19 from one of the commercial sources of data. The Y-axis here is a logged axis. So you'll see -- this is up-to-date or relatively up-to-date, just the last few days. India has now taken over the U.S. as you can see. These graphs are also color coded to show the number of -- the test rates within those different countries. But just focusing on Australia on the bottom there, you'll see in these national numbers for Australia are almost entirely in my city in Melbourne. And we'll see we are just now emerging from our second wave, which has occurred during our winter. And we have had really horrendous time in getting control of this. It's got into aged care facilities and so forth. And we've gone into this very severe lockdown that I've just mentioned to you.

So good luck with your coming winter. I'm hoping that you guys aren't going to have anything like what we've had to live with. You've still up there with what looks to me like still in extended first wave. But I'm surely hoping that you're not going to have to go through what we've just been through, what Spain, Israel and the United Kingdom are about to go through or going through right now.

Second last slide. I just want to finish by reflecting on the fact that the objective of all of what we're doing is not to have a licensed vaccine. The objective is to have a vaccine that actually is used in a population and actually does something about reducing disease and death. The way in which we value vaccines is very important. That's what governments really are focused on. And national immunization programs, or NIPs, where they are publicly funded. A way in which that happens in the U.S. is more complex than in some other countries, including Australia, where it's a simple mechanism. But effectively, mechanisms to justify making available vaccines free to the population. The justification for those is based on public funding.

The public funding itself is really probably the most important determinant of vaccine confidence in the community and therefore uptake. It's, of course, is good to have a vaccine free of charge. But the message that is transmitted to most of the population is that if the government is prepared to pay for this, it must be worth having. And the vast majority of those who go ahead to have their children vaccinated have that underlying belief that the government isn't wasting its time here and investing public resources, it must be worth having.

So better methods for cost effectiveness evaluation is a little concern I have that we're not yet fully realizing the full value of vaccines, and I think we need improved health economic methodologies to do that. Understanding the full range of benefits across the life course of a vaccine's impact. Governments are also interested in, obviously, implementability, simplicity in both scheduling and administration. And that's why combination vaccines, as we've discussed, is also very important. But really, in summary, governments are looking for good value for money and high levels of public and health care provider demand for vaccines.

So just to finish, 3 simple points that I want to make for today, and I'm hoping that this will help inform your further more technical discussions on particular vaccines. The first is that the advances in vaccine science that we've seen have provided absolutely enormous quantum shifts in value through primary prevention of childhood diseases using an amazing array of new science and technology approaches, which is really reaping value for the community. Second is a much simpler concept, but an elegant solution is combination vaccines. We already have a proven track record, and there is significant future potential for their further exploitation. And to wrap all of this together, I do think that mRNA vaccines have a lot to offer in reflecting on all these opportunities for coming epoch.

Thanks very much. It's been wonderful to have the chance to speak to you today. And I'm hoping that soon, many of you will actually be able to come and visit us in Australia and I too can come and visit you all in the U.S. Thanks very much. Good night.

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

Thank you very much, Dr. Nolan. So my name is Jacqueline Miller, and I joined Moderna very recently to head the Infectious Diseases Development Group. And it's my privilege today to speak to you about our COVID-19 vaccine, mRNA-1273.

So on Slide 117, you'll see that this vaccine is very special for a number of reasons. But in particular, this is the first Phase III program that Moderna has embarked upon.

Next slide, please. So I don't have to tell anyone on this call about the unprecedented impact that this virus has had on the functioning of day-to-day human life and global economies. This virus was, it's hard to believe, first identified in December, so barely 9 months ago. And since that time, nearly 30 million confirmed cases have occurred worldwide and almost 1 million deaths. In the U.S. alone, we're at 6.6 million confirmed cases and nearly 200,000 deaths.

Importantly, this vaccine does not impact everyone equally. And we know that one of the greatest risk factors for severe complications includes increasing age as well as younger and older patients that have significant comorbidities, so including cardiovascular disease, diabetes, lung disease and even obesity. So fairly common conditions, particularly in the developed world. So developing a vaccine against this disease has become an urgent global health priority as currently there's no approved vaccine for COVID-19.

Next slide, please. So I'd like to review with you mRNA-1273 and the protein our single messenger RNA sequence encodes from. So this is, again, a single sequence messenger RNA. It encodes for the spike protein, which for coronavirus, is the protein utilized to enter the cytoplasm of the cell. Once inside the cell and with translation, this protein, which has 2 proline residue substituted naturally assembles into its trimeric confirmation and is presented on the cell surface in the immunodominant pre-fusion confirmation. And this is important for 2 reasons: One, we are presenting the antigen on the cell surface, in the same way that it would be presented as if there were a true viral infection without actually being a viral infection because there are no viral components in the vaccine. But secondly, that immunodominant confirmation is important because what we've learned from convalescence era is that the greatest neutralizing antibodies are to that pre-fusion confirmation.

So on Slide 120, we show a time line for the clinical development of this vaccine. And this has been an incredible effort between multiple partners and stakeholders to be able to bring development from initially knowing the sequence in January to launching our Phase III study in July of 2020, while still maintaining the checks and balances that are necessary as you proceed from one phase of clinical development to the next. And I think importantly, we have managed through close working and reviewing of data through both our partners with BARDA and NIAID as well as with the U.S. FDA, to review data at critical time points to ensure that taking the next step in development is warranted while still moving through expeditiously to address this public health crisis.

Next slide, please. So on Slide 121, I'd like to share with you the study design for the Phase I clinical trial that has been sponsored by the National Institutes of Health in the U.S. So this was our first time in human study with 1273, which started in March of this year. And the primary objectives were to assess the safety reactogenicity and immunogenicity of the vaccine in 3 different age strata: 18 to 55 years of age, 56 to 70 years of age and over 71 years of age. This was critically important because, as I shared with you earlier, increasing age is the single greatest risk factor for severe complications to COVID-19.

So this is a study that was designed to evaluate 3 dose levels: 25 micrograms, 100 micrograms and 250 micrograms in a dose escalation manner. The data were available in the 18- to 55-year-old cohort prior to moving to the older age cohorts and prior to moving to Phase II and III studies. Importantly, we saw some increased reactogenicity after the second dose with the 250-microgram dose in the 18 to 55 year olds, and we elected not to continue with that dose level in the older age cohorts. Instead, a dose at 50 micrograms was added. Another important finding from this trial through the 3 dose levels was that the 100-microgram dose was more immunogenic in terms of binding and neutralizing antibodies than the 25-microgram dose. So between the improved immunogenicity profile and the improved safety and reactogenicity profile, the 100-microgram dose has been chosen for further development. And now in the slides that follow, what I will share with you are the results across the 3 age cohorts with that 100-microgram dose.

So on Slide 122, you see a summary of the safety data we have observed in the Phase I clinical trial. This is a bar graph in each symptom, starting from top to bottom, the 3 age cohorts, youngest to oldest. We look first at the systemic symptoms as well as at the local injection-site symptoms. In gray, you see the reported rates of mild or Grade 1 adverse events; in blue, the moderate or Grade 2; and in orange, the severe or Grade 3.

So in the 3 age cohorts, after the first dose, the most commonly reported systemic symptom was fatigue and the most commonly reported injection-site symptom was pain. The vast majority of these events were mild in severity. After the second dose, we observed some increased reporting of reactogenicity. And what you will see on the slides that follow is that, that increased reported rate really corresponds with an increase in antibody responses and particularly neutralizing antibody responses. The events were mostly mild to moderate in severity. And importantly, they were self-limited in duration. So the majority of these symptoms resolved within 2 days, some persist as long as 5 days. There were no vaccine-related serious adverse events reported in this trial and no halting rules for the trial have been met.

So as we go to the next slide on 123, we start to see the immunogenicity data across the 3 age strata. And in the slides that follow, you'll see a consistent pattern of data presentation. So moving from left to right, you'll see the 18- to 55-year-olds, then the 56- to 70-year-olds and then above 71 years of age. This first slide depicts the binding antibody concentrations, and these were measured via an ELISA enzyme-linked immunosorbent assay.

Again, subjects were vaccinated with the 100-microgram dose at day 1 and day 29 or 1 month apart. What you see on the x axis are the antibody concentrations measured through area under the curve at various study day time points. So 2 weeks after dose 1 as well as 1, 2 and 4 weeks after dose 2. And in the pink, you see the middle 2 quartiles of a range of 41 convalescent sera, which were tested with this binding antibody assay. And this is important because we're now able to compare the immunogenicity results from our vaccine with patients that have had natural infection and developed an antibody response.

So after the first dose, 100% of subjects seroconvert to the spike protein, even in the oldest age stratum. And these antibody concentrations also exceed the median of those of the convalescent sera. After 2 vaccinations, we see that in all age groups, the antibody concentrations are within the range of the highest quartile of those convalescent sera.

Next slide, please. So the previous slide showed you the overall antibodies. These now are antibodies that are actually capable of virus neutralization. So these are neutralizing antibodies that have been measured in a pseudovirus lentivirus reporter assay. And again, you see the 3 age groups, moving youngest to oldest from left to right. Again, you see the convalescent sera in pink.

So after the second vaccination, the antibody responses were detected in all vaccine participants across age strata. And the levels of neutralizing antibodies were also comparable in all 3 age groups. Importantly, these neutralizing antibody titers are within the upper half of the range of convalescent sera for all 3 age groups.

Next slide, please. So on Slide 25 (sic) [125] we're transitioning from talking about the humoral or antibody responses to the cellular or T cell responses. And in this Phase I study, across the 3 age strata, we investigated CD4 T cell responses of both the Th1 and Th2 phenotype.

So why is this important? There have been some speculations that coronavirus might lead to vaccine-enhanced respiratory disease because of some similarities with previous viruses where vaccines to respiratory syncytial virus and measles virus were shown to induce the Th2 phenotype, which was hypothesized to lead to more severe disease in vaccinees. In our case, what you see are the CD1 -- or Th1 CD4 T cell responses in all 3 age groups. And what you can see is that by 1 month post dose 2, these T cells are induced in all participants. The Th2 phenotype was detected exceedingly rarely. And again, this was reassuring for us to begin a larger scale trial in Phase III as we begin to monitor for vaccine-enhanced disease.

So in summary, from the Phase I clinical data, the neutralizing antibody titers are observed in 100% of evaluated participants. And this is critically important because we see these antibody responses in the upper half of the range of convalescent sera in all age groups. Again, there was a live neutralization assay that was conducted. I have not shown you those data today. But importantly, they were well correlated with the pseudovirus assay, and that is the assay that we will move forward with in Phase III. And we saw at day 43, geometric mean titer levels at the selected dose of 100 micrograms, also above those seen in the reference convalescent sera.

So why are all of these observations important? While we observed similar levels of neutralizing antibodies in nonhuman primates, the rhesus macaque. And the rhesus macaque, while they don't have the same severity of disease observed in humans, they do get the same respiratory symptoms when challenged with SARS-CoV-2. So after these animals were vaccinated and then challenged both in the nose and in the lungs with SARS-CoV-2 virus, the antibodies that are induced are able to protect these animals from infection, even at the lowest doses that we believe would be subtherapeutic doses. And that's important, again, to reassure us, moving into this large-scale Phase III study about the possibility of this vaccine, not only to protect against symptomatic infection but also to prevent against enhanced disease.

So on the next slide, Slide 127. I'd now like to start talking to you about the ongoing studies in Phase II and Phase III. Moderna has sponsored a Phase II study, which is a safety and immunogenicity study that is investigating 2 dose levels, 50 and 100 micrograms, in 2 different aged strata, 18 to less than 55 years of age and greater than 55 years of age. A total of 600 subjects have been enrolled, so 300 subjects in each aged stratum. And within each age stratum, 100 subjects in each group were randomized to receive 2 doses 1 month apart of either the 50 or 100 micrograms of 1273 or placebo.

We have enrolled healthy males and females above 18 years of age. And we consider these individuals to be historically negative for COVID-19 disease. So they are queried at the start of the trial, but we do not screen subjects out for baseline SARS-CoV-2 sera status. And with an infection that can be as silent as COVID-19, that's critically important as we begin to assess our vaccine in the field in larger populations.

So the study endpoints are going to be safety, and these are going to be similar to what you see in the Phase III study. We'll look at solicited adverse reactions for 7 days after each vaccination, unsolicited adverse events, which will occur 1 month after each vaccination and serious adverse events and medically attended adverse events that occur throughout the trial.

From an immunogenicity perspective, we will be evaluating binding antibody concentrations with ELISA and neutralizing antibody titers with the pseudovirus assay. The length of follow-up time for all subjects will be 13 months or approximately 1 month after the second dose. So this study is completely enrolled, and all subjects have received both doses, so they're in their longer-term follow-up of the study.

Next slide, please. So as I mentioned, on July 27, we launched our pivotal Phase III efficacy, safety and immunogenicity study, which will enroll 30,000 participants to receive either 2 doses of 100 micrograms of 1273 or placebo. This study has been branded the COVE study, which stands for the COVID Efficacy and Safety study. And would not be possible without the partnership of BARDA, who is funding the study; NIAD who have been significant scientific collaborators for the study; and many other thought partners as we have designed and executed on the study.

So unlike the previous 2 studies, this is really the study where we are going to demonstrate that the vaccine will be useful for various populations that need protection against COVID-19 disease. At least 25% and up to 40% of subjects in this study will be at increased risk for severe complications of COVID, either because they're over 65 years of age or because they're under 65 years of age, but have one of a variety of comorbid conditions that the CDC has suggested, are associated with an increased risk against severe complications. The remaining 60% to 75% of the subjects will be less than 65 years of age and not have a particular comorbid risk. However, they will be living either in areas of the country where infection rates are high or will have an occupation that puts them at increased risk for disease.

And importantly, because minority communities have been disproportionately impacted by the burden of COVID-19 disease, we are making enrollment of a population reflective of the U.S. demography a priority for this study. And I'll speak more to that in the slides that follow.

Similarly to the Phase II study and Phase I study, while patients should not have had a history of COVID-19 disease, we are not excluding participants based on their initial sera status. There are 2 co-primary objectives of this study. One is to demonstrate the efficacy of the vaccine against symptomatic COVID-19 disease, and the second is to further evaluate the safety and reactogenicity profile. And subjects are going to be followed for approximately 2 years after the second vaccination. And while I'll be giving you some more details in the slides that follow, I'm really pleased to announce that this morning, we have posted our full study protocol on the Moderna website. So if you have curiosity after the phone call, you'll be able to look and see some of the methodologies we'll be using.

So on the next slide, I'd also like to go over an initiative that I'm particularly proud of, and this is the COVE study, Diversity and Inclusion Advisory Committee. So as I mentioned to you, we are absolutely prioritizing, ensuring that the study results that we generate are representative of the U.S. population, and therefore, we can have more confidence in the generalizability of those results to the individuals who really need to be vaccinated.

The purpose of this committee, which is comprised of various health disparity experts from various groups within the government, are to help us review our enrollment and race and ethnicity demographics on a weekly basis, to help us design outreach activities and outcomes to really engage communities that traditionally have shied away from participating in clinical research. We also want to be sure that we are making it more feasible for subjects to continue the study to completion. And so to that end, they are also supporting us in the development and implementation of retention strategies.

Next slide, please. So the study is really well underway and enrollment is closing in on completion. We've enrolled over 25,000 participants as of today, and the number of subjects that have received their second dose is nearing 10,000 subjects. You can see on the right-hand side of the slide, a pie graph depicting the current ethnic diversity. And while it's a little bit difficult to read, we're extremely proud of the fact that we have been able to get to approximately 28 of participation from ethnic minorities and diverse communities. We are now posting this information on a weekly basis to the Moderna website and the statistics are updated every Friday. So if you have interest to follow after the call, you can continue to follow on a weekly basis.

So next slide, please. Now I'd like to transition into explaining a little bit more how we're going to evaluate the efficacy against symptomatic COVID-19 disease and about how the trial will be monitored throughout its duration. So on this slide, we review the case definition for symptomatic disease. And to be considered a case of COVID-19 in this trial, subjects need to have a set of clinical symptoms, coupled with a laboratory assay, an RT-PCR, nasal swab, nasopharyngeal swab or saliva Swab, that's positive for the SARS-CoV-2 virus. These symptoms can either be systemic symptoms, in which case there must be 2 of them and these symptoms include fever, chills, myalgia, headache, sore throat and new smell and taste disorders. Or a subject can have a single respiratory sign or symptom, which include cough, shortness of breath or difficulty breathing or having clinical or radiographical evidence of pneumonia.

The primary analysis is for subjects that are seronegative at baseline. So although we are assessing all-comers, and we will certainly be looking at those subjects who are seropositive in some of our exploratory efficacy analyses. The primary endpoint is based on subjects who are initially seronegative. The cases begin to accumulate at 14 days after dose 2. And if you recall back to the immunogenicity data that I showed you in Phase I, the reason for that is because we've shown that those neutralizing antibody titers are present at that time.

So if we move to the next slide, I'm giving you an overview of how this study is going to be monitored. And I think it's important to emphasize that we have an independent Data and Safety Monitoring Board that is looking at this trial. So these are investigators that are part of the committee set up by the NIH, but independent of both NIH and Moderna. And their role really is to look at the clinical data as we progress through the trial in both blinded and unblinded fashion. They're looking for any potential safety signals as well as the opportunity to tell us that we have met our primary efficacy statistical criteria.

So what will happen during the course of this study? We meet frequently with the DSMB. These are experts in infectious diseases, epidemiology and bioethics, and they are monitoring both serious adverse events as well as cases of COVID-19 throughout the trial. Each time they meet, they make a recommendation about whether the trial should continue as planned, whether the trial should continue with some modifications or whether the trial should conclude. And the trial may be also paused if a safety event is observed, but it can also be concluded on the basis of meeting efficacy criteria. Those recommendations are communicated to an oversight group, and that oversight group is comprised of 3 individuals, 1 from the NIH, 1 from BARDA and 1 from Moderna.

So Moderna actually chairs that committee and discusses the recommendations with the oversight group, so that we can benefit from the expertise and experience of our partners. Once the oversight group has met, the decision is discussed at senior levels within Moderna. And should we hear at one of our interim analyses that we have met our efficacy criteria, Moderna will then consider the totality of the database, both safety and efficacy and make a decision about whether to submit to FDA for the emergency use authorization.

That review by FDA is also an independent regulatory review, and they themselves also seek independent advice from a committee called VRBPAC or the Vaccines and Related Biological Products Advisory Committee. So the point I would like to underscore is that throughout this process, there are independent reviews of data, both in an ongoing way and once the analyses have been concluded. And that independent review really gives confidence that the data generated in this trial are representative and can be relied upon to give confidence to implementation of a vaccine program.

So let's move to the next slide, where I'm going to speak a little bit more about the DSMB monitoring of the primary efficacy endpoint in a bit more detail. And I'm going to take a couple of minutes with this slide because it is a bit complicated. I'd like to start the graph on the right.

So what the graph on the right shows you is the cumulative boundary crossing probability on the y axis as a function of vaccine efficacy on the x axis. In any efficacy trial, the likelihood of meeting your endpoints is really based on 3 factors: the overall efficacy of the vaccine; secondly, the sample size, so larger sample sizes lead to closer refinements of point estimates to the actual efficacy; and then third, the random distribution of events as you go through a trial. So in any given trial, you don't necessarily receive cases that occur in the vaccine group and control group in an alternating fashion. They come into the trial and are reported randomly.

So how does this graph help us understand how likely we are at various interim analyses to meet the statistical criteria? Well, if we move to the next slide, what we see is a vaccine efficacy highlighted in blue at 60%. And this is important because 60% is the conservative assumption that we used when we designed the trial. Obviously, we are quite hopeful that the true vaccine efficacy will be higher. And what you see on the left-hand side of the grid is that the first efficacy interim analysis will be performed when 53 cases are accumulated. That's shown in the fine dotted line labeled interim analysis 1 on the graph. At interim analysis 1, if the vaccine efficacy is 60%, there's a 10% probability that we are able to meet the statistical criteria successfully.

But as we capture more cases, on the next slide, so now we're talking about the second interim analysis, where there are 106 cases accumulated, you see that with the higher sample size, the likelihood of meeting our statistical criteria increases to 65%. And by the time we reach the final analysis on Slide 136, at 151 cases accumulated, we have a 90% probability of successfully meeting that statistical criterion. And that's really what we're speaking about when we refer to a study having 90% power.

So the study was really designed to look at 151 cases, but because we believe that our vaccine may be more efficacious than 60%, we've designed these interim analysis to allow ourselves the opportunity to investigate the data and potentially conclude the trial earlier based on meeting those criteria.

So if we go to the next slide, now we're going to go through the same 3 different analyses, but see what happens when we land at 75% efficacy. So if we move to Slide 138, what you can see is with just a 15% increase in efficacy, at the first interim analysis, there's now a 50% probability of successfully meeting our statistical criteria.

On the next slide, 139, you see that once you get to then the second interim analysis or 106 cases of COVID-19 accumulated, the likelihood of meeting statistical criteria exceeds 95%. So I hope that that helps demystify a bit how we will be monitoring the safety and the efficacy of our data while we go through the study. And we really look forward to bringing you more updates of these data as they occur.

I'll conclude my presentation, and I'm going to hand over to my colleague, Juan Andres, who will speak to you about the manufacturing and distribution of the COVID-19 vaccine.

Juan Andres - Moderna, Inc. - Chief Technical Operations & Quality Officer

Thank you, Jackie. Good morning, good afternoon or good evening. My name is Juan Andres, and I have responsibility for clinical development, manufacturing and quality in Moderna.

Slide 141, please. As we discussed in previous meetings, we are a platform, which in manufacturing terms mean that all our products are made in a very similar way. This allows that any learning and improvements that we have had over the years can be applied across our pipeline.

Next slide. Because we know the importance of improving our platform, it has been a top company priority to invest in CM and C, chemistry, manufacturing and controls. The fundamental product understanding has allowed us to make tremendous progress in shelf life, storage temperature, safety and tolerability, potency and consistency of manufacture.

Next slide. Specifically, mRNA-1273, our COVID vaccine candidate, benefits from the progress we have made with all the other vaccines in the pipeline. On the left-hand side, you can see 3 different graphs. Each graph represents a critical quality attribute for the product. Each dot in its graph represents a real GMP batch manufactured during the development of 1273. The values show very high consistency, and you would not be able to differentiate that there are 3 different scales in each graph, small, medium and large. This level of consistency is what you want to see during the scale-up of a product.

Next, please. We presented extensively in March our manufacturing site in Massachusetts. We wanted it fully integrated, end-to-end, to ensure we mastered all parts of our process. In addition, we designed a plan with a high degree of automation and digital integration to allow rapid growth and scale. Little we knew then that this thinking was going to be essential for scaling up COVID mRNA-1273. Having produced here over 100 GMP batches, in addition to thousands of preclinical and development batches, give us a good and tremendous confidence that we can deliver on our mission to manufacture high quantities of mRNA-1273 COVID vaccine.

Next slide. As a reminder, our process is not a traditional biotech monoclonal antibody that requires huge bioreactors. We do not need cells to produce mRNA. No need for product-dedicated plant. Having our manufacturing plant and being an [ancillary] cell-free process allows us to scale very fast.

Next. Now we are producing a commercial engine. And this is in addition to the ones we have before and we will be able to produce hundreds of millions of doses in this infrastructure. Also importantly, this capacity can be used beyond the COVID vaccine for other products that we commercialize after it. We believe this experience is a competitive advantage.

Next slide. So how are we scaling up? Once we decided in our industrial scale, we are replicating units of the same equipment inside our plant and those of our partners. Having the same kit allows for easier replication, faster technical transfer and a much reduced risk of surprises among [different] plants.

Next. We have designed 2 different supply chains using this concept. One in the U.S. for the U.S. and another one in Europe for international markets. The magnitude of this effort required us to partner with very reliable companies. So let me expand about them in the next slide. So these companies have -- are very experienced commercial manufacturers, all with extensive experience launching and supplying medicines worldwide.

Lonza. Lonza will help Moderna to produce active ingredients, both in the U.S. and in Switzerland. Lonza has an impressive track record of healthy pharmaceutical companies with more than 45 BLAs, MAAs to market, commercializing in more than 80 countries and with many expedited review designations.

Catalent; for formulation, fill and finish in the U.S., definitely, one of the top aseptic manufacturing companies producing vials with isolated technology.

ROVI for formulation, fill and finish for international countries. Experienced in 65 markets including the U.S. and with a lot of vaccine experience. We are also finalizing agreements with other partners. I cannot thank enough our manufacturing partners. I have not seen in my career such a tremendous collaboration and purpose from employees of different companies.

Next slide. So how are we designing the product to be in the market? We will have multi-dose vials with 10 doses in each vial. 10 vials will go into a carton, cartons will go into a case and cases into pallets. The pallet will be stored at negative 20 degrees Celsius or negative 4 Fahrenheit, which is the normal, a standard freezing temperature. Frozen food and freezers at home target the same temperature. We all are familiar with it.

Next slide. We are designing the supply chain for COVID mRNA-1273 to be fully flexible. We expect the product to be stored at minus 20 degrees Celsius for a minimum of 6 months. As we get more real-time stability information, we may go beyond 6 months. In addition, the product can be up to 7 days in the refrigerator at positive 2 to 8 degrees Celsius. Again, this could be longer once we have more real-time stability.

In addition, the product can be up to 1 day at room temperature during administration. All of this allows to use existing market infrastructure. Finally, the product is ready-to-use as is. No dilution or special handling is required.

Next slide. By using existing infrastructure, there is flexibility to send different quantities to the different needed locations, bigger quantities to large immunization centers, or for instance, a single pack to a small nursing home or doctor's office. For immunization, just draw 0.5 mL and inject.

Next slide. COVID mRNA-1273 is a liquid vial. The other vaccines in our pipeline are designed to be lyophilized or freeze dried as you refer to call it, which could allow for 18 months or more of refrigerated conditions, positive 2 to 8 degrees Celsius. For instance, our CMV vaccine candidate is, as you can see already in lyo form.

You may be asking yourselves why we didn't go lyo for COVID 1273. While there is not enough lyo capacity in the world for a global pandemic of this nature to be produced in lyo. I can also tell you that we have an active technical development program, intended to have a stable to 2 to 8 degree liquid formulation.

Next slide. Our CM and C readiness is well advanced for a BLA and emergency use authorization. First, we count with a very experienced management team with an impressive track record in product development, BLA preparation and launch and running commercial operations. As discussed before, we are privileged to have second to none partners to help us in our mission. Third, we have validated our first commercial scale, and the next scale is well in progress.

Our manufacturing plant has produced above 100 GMP mRNA batches. And finally, we are having real-time and constructive dialogue with regulators. In the right-hand side, you can see a picture of real COVID mRNA-1273 vials intended to go to market. I have personally brought numerous products to market in my 30-year career. And I'm very confident to make this one happen, too.

Next slide. We are on target. We are bringing together the infrastructure to produce 500 million to 1 billion doses per year. We are already actively manufacturing for market use, and so far, our scale-up and documentation is on track to deliver.

Next slide. Before I hand it over to Stephen, I want to sincerely thank employees, manufacturing partners, supplier partners and regulators and government agencies for an incredible collaboration and tireless effort. This is indeed unprecedented. Stephen?

Stephen Hoge - Moderna, Inc. - President

Thank you very much, Juan. So I'd like to take the closing few minutes of our prepared remarks today and update on a couple of activities in the new research and development space.

I'll remind you that we generally do not talk about all of our preclinical research and our extensive investments there, but we have a longstanding and major strategic commitment to continue to push the boundaries of how we use our mRNA technologies and to create an expanding pipeline in all of our core and noncore therapeutic areas. But we do regularly update when we do deals. And in this case, in particular, we announced 2 partnerships today that we wanted to provide a little more context on it.

So the first on Slide 158 is a new partnership with Vertex, expanding on our multiyear collaboration with them in the field of cystic fibrosis. This new announcement that was made yesterday is aimed at expanding into gene editing and gene therapy technologies as an alternative approach to treatment of cystic fibrosis. And I'll provide in just a minute, a little more context of how these 2 different approaches to addressing this disease will operate in parallel and the difference in to do it [personally].

Initially, we're going to be focusing on continuing to use the novel lipid nanoparticle and mRNAs that we've been developing with Vertex for the first program, but expanding those into the gene therapy space and importantly, benefiting directly from Vertex's ability to bring a substantial number of gene-editing therapies and technologies they've acquired or built internally over the last number of years and bringing those payloads into our existing delivery infrastructure and platform technologies.

Moderna is going to be leading the efforts around discovering and optimizing the mRNAs and LNPs and partnering with Vertex to develop the payloads as described. There's a \$75 million upfront, as Stéphane described, and appropriate milestones in tiered royalties as we move forward.

Now, just a little bit on Slide 159 to contrast these 2 efforts for those who are perhaps asking how do we do 2 deals in cystic fibrosis at Vertex. So first, in the center, there are approximately 10% of people who suffer from cystic fibrosis who are not going to be addressable with the CFTR modulators that Vertex has been pioneering and leading in -- that have been transformational in the treatment of the disease.

Unfortunately, for those with those genetic predispositions, alternative approaches are necessary. And several years ago, we announced the partnership on the left, which will be continuing and is continuing to show progress as we announced a couple of months ago. And that is delivering a messenger RNA that itself directly encodes for the CFTR protein that is missing in people's -- missing or not functional in people who suffer from cystic fibrosis. That CFTR protein then can normalize chloride ion transport and address the disease.

We've been working incredibly hard with Vertex to advance a candidate for CFTR based on mRNA delivery of CFTR protein and providing updates in the near term, but as we have announced over the past year a couple of times, we've been making good progress towards that objective.

The deal announced yesterday, extended, the collaboration now in gene therapy, is described on the right here. This case, we'll be using the same or other delivery technologies and encoding for a gene editing or gene therapy approach. Now in the example in the cartoon on the right, we've shown a Cas9 protein, a CRISPR protein that can be used to directly edit a DNA. But it's illustrative of many different payloads that Vertex through their extensive work in the gene editing, gene therapy space can bring to bear in this partnership.

We will deliver that mRNA encoding for that protein as well as other payloads and seek to directly edit or otherwise replace or modify the gene for CFTR inside the lungs of people suffering from the disease. And therefore, instead of just expressing the 1 protein for CFTR hopefully will lead to a durable addressing of their clinical (inaudible). Both approaches are moving forward, and we're excited to continue to expand our commitment to cystic fibrosis and work with Vertex who is an unquestioned leader in both addressing the unmet need in cystic fibrosis, but increasing the leader in the gene therapy space as well.

Now Slide 160, we did announce another partnership as well yesterday with -- in this I and also dealing with a pulmonary disorder with Chiesi. The Chiesi Group is a rare disease Italian company that many of you are probably familiar with a strong commitment to innovation against rare diseases including pulmonary diseases. And in particular, this program is in the discovery and development of mRNA therapeutics against pulmonary arterial hypertension, a rare disease infects 2 to 5 people per million adults. It's a progressive and terrible disorder resulting in high blood pressure in the arteries of the lung and ultimately right-sided heart failure. There is substantial unmet need, in particular for novel treatments that could delay or reverse the progression of the disease in patients.

Now it is our first partnership with Chiesi, and we've found a great match in our commitment to addressing rare diseases and to using innovation to get there. This partnership -- under the partnership, Moderna will lead the discovery efforts, and Chiesi will be leading the development and commercialization worldwide, but it will really be a true partnership throughout.

Moderna did receive a 20 -- will receive a \$25 million upfront is eligible for development, regulatory and commercial milestones as well as royalties based on the progress of the programs we have [got to] move forward together.

And with that, I'll turn it back over to Stéphane for his concluding remarks.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thanks, Stephen. Before closing, I would like to thank our teams and our guests for their presentations today. And I would like especially to thank the Moderna team, our partners, our suppliers, all our collaborators, probably incredible last 9 months that everybody has been working so hard, trying to stop this pandemic.

mRNA could be a new class of medicines, that was our vision. This is how far we have come. As Juan told you, those are actual photos of 10 dose vials that are ready to be used and shipped if 1273 is approved. The team is working hard to make as many product as we can while ensuring high quality, and respecting, of course, all the rules of making GMP products.

On the right, you have a markup of the cardboard that the team actually has been working on a of (inaudible) version and be ready for shipping.

If you go to 164, Moderna has and will continue to expand in 2 dimensions. That has been our vision and our strategy since the beginning, and we're not slowing down. The first dimension on the x axis is time, which is going from the concept of a medicine to the commercialization of medicines, go from an idea of a drug, preclinical research, preclinical development, Phase I, Phase II, Phase III and commercial. This is very typical to pharmaceutical and biotech companies.

But the other dimension in which Moderna is expanding regularly, and we are very committed to keep expanding to maximize the potential impact that we can have on patients, is around the breadth of mRNA technology. We started it with a clinical vaccines, oncology, VEGF to inject it directly (inaudible) in into people's heart; rare disease, the work that Stephen and his team are doing with Vertex team and figure out how to deliver safe [amount] into a lung. And with last night announcement on gene editing, we just want to continue to expand exploring how we can help as many patients as we can by expanding the use of our technology.

And on Slide 161, you'll see basically the current pictogram of where we are as the pipeline as a company, trying to continue to advance the pipeline to the right to launch those important medicine and continue to advance by adding new breadth to the company.

Slide 166 is a usual slide of company update and profile, COVID-19 in Phase III, CMV, PCV, OX40 ligand to program in Phase II in cancer and VEGF in cardiovascular, 8 programs in Phase I, now 12 positive Phase I clinical readouts.

The portfolio is very strong and very diverse, 7 vaccines for major unmet needs, 5 immuno-oncology drugs that are all in clinical studies, all combined with commercial checkpoints, program, 2 autoimmune disease program. 27 (sic) [27,000] healthy volunteers and patients enrolled, more than 1,100 employees, very strong manufacturing infrastructure, partners and a strong cash balance.

As we close, let me share a few thoughts. Moderna could receive an EUA for mRNA-1273 in 2020. Moderna could receive a BLA approval for mRNA-1273 in 2021. mRNA-1273 could validate the entire vaccine portfolio because mRNA is an inflammation molecule. The Phase III success in mRNA-1273 could have implications for all the vaccines in development, all the vaccines in the research pipeline, all the vaccines that we are not yet working on in the labs. That is the power of an inflammation molecule.

I believe 1273 would transform Moderna and create a unique and historic inflection point for the company. With a manufacturing base plan of 500 million doses per year that Juan and his team are working to potentially get up to 1 billion doses per year, Moderna could have a multi-billion revenue line in 2021. That will create a very strong balance sheet by the end of 2021 because we have \$1.3 billion (sic) [\$3.1 billion] of cash as of June. And the multibillion-dollar of potential revenues will, of course, add to that balance sheet. If we can execute and achieve that, that will allow Moderna to invest in R&D, to scale the development pipeline and maximize what we can do for patients.

Our strategic priorities are very clear. Number one priority is to maximize the impact of 1273 access and thus value creation of this product between now and the end of 2021. This will allow us, priority #2, to accelerate vaccine development to accelerate as much as we can product in the pipeline, to bring new vaccines to development like through as we discuss today, and many more.

It will allow, priority #3, to generate multiple human proof-of-concept in oncology, rare disease and autoimmune diseases. And this will now allow, priority #4, to continue to invest to expand the breadth of mRNA and how we can help patients by investing in mRNA technology improvements, delivery technology, lung delivery, gene editing, and Stephen and the team have many, many more ideas.

I believe this is a historic moment for the company. I'm extremely thankful for what the teams have done to get us to this point. And we are extremely thankful to our long-term investors that have provided over the years the capital, so that we can build the best version of Moderna that we can.

With this, thank you for your attention. We'll now be very happy, operator, to move into Q&A.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Matthew Harrison with Morgan Stanley.

Maxwell Nathan Skor - Morgan Stanley, Research Division - Research Associate

This is Max Skor on for Matthew Harrison. To start off with, can you comment on the potential read-through of the repeat dosing data to the rest of the pipeline, specifically LNP clearance and pharmacology? Also, are you measuring the functionality of the antibody?

Finally, can you extrapolate anything from the CMV data to the COVID-19 vaccine? What are your thoughts around potential durability and the portion of induced neutralizing antibodies that are functional?

Paul Heath

This is Paul. Thanks, Max, for those questions. You asked me a few, I just want to make sure I don't miss any. So if I do remind me. Read-through on the platform, look, I think the repeat dose is clear to really -- or 3 critical fronts. Number one, when you do see adverse events, they're mild, they're gone within a day or 2, and there's no accumulation of any adversity, and I think that's critical point to establish. We had assumed that because of what we saw in the single dose, but it's very reassuring to see you come back again, you get the exact same profile out of nothing or Grade 1, Grade 2 relatively minor and transient effect.

Number two is the translation of the pharmacology. Do you repeat to the same extent you had, and I think the answer here is yes, and it's pretty clear. Number three is you look at the PK curves and sort of the lipid nanoparticle, it's pretty clear that clearance is rapid. Clearance is much more rapid than the protein, which is what you would expect. That's the beauty of this technology. The mRNA gets in, the LNP is rapidly degraded to all of its components, and then they're gone because we've engineered it to have up in short half-life. What you get is the stackable pharmacology. And so I think that really bodes well.

And the final point I'd say is look at the doses at which we're seeing potentially therapeutic levels of protein that 0.1, 0.3, 0.3, given repeatedly, that's the dose range at which we are -- we anticipate to have benefits for the children.

The second question you had was on durability, I think, in the read-through between CMV -- oh, I'm sorry, you also asked about the activity of that protein. Yes, it is active -- it is active, because we measure its activity based on neutralizing. We had demonstrated that in the past, but didn't -- for you again with the data, but the protein that we make is indeed functional because you can demonstrate neutralizing activity of that monoclonal antibody that gets formed.

To your question on durability and CMV readthrough, I think that you can see with CMV, the unique ability of this platform to boost. And why do I say that? Because if you fast-forward to COVID, we see some platforms like ours with mRNA that can boost repeatedly. And I think the CMV data

are proof of that versus other platforms, namely engineered recombinant viruses, the adeno vectors for one, where I think boosting is likely to be more challenging because a lot of the immune responses against the vector as opposed to the transgene.

In the case of mRNA, all we are doing is just showing the body that singular protein. The beauty of the CMV data is that you can see that, again, in functional readouts for neutralizing activity against 2 separate antigens that we can continue to boost. You've seen the confidence around selecting a dose for Phase III. I think that bodes well for durability on COVID.

I think the last point to sort of extrapolate, I think it's early days to know-how and what is a durable immune response for COVID. I think my sense is that people who've gotten sick do not get sick the second time, therefore, for the duration that we understand as far as these 6 months, the durability is there for infection. And since we can elicit the same level of antibodies or higher, then we anticipate to have durability at least as good as from wild-type infection.

I do think that if you put it all together, we see the potential down the road to also use our technology to boost the immune response further against COVID just to make sure that people remain protected.

Operator

Our next question comes from Ted Tenthoff with Piper Sandler.

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

Thank you for all this data. Really great to see the progress, not just on 1273, but on the pipeline more broadly. And I just have to say amazing what the difference a year we'll make, not just at the company, but in the world as well. I wanted to dig in a little bit more on the concept of adding the flu vaccine and even the potential for flu plus COVID-19. How would you envision and appreciating your kind of just announcing that, but how would you envision developing that? Would this be something where you would have to advance the flu vaccine itself and then ultimately combine them? Or would the whole goal be to just do flu with COVID-19 for (inaudible)?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Sure. That's a great question. Stephen, go ahead.

Stephen Hoge - Moderna, Inc. - President

No, you go ahead, Tal, please.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Well, you can tell we love answering this question because we've been thinking about it a lot internally. I think the beauty of our platform for flu is that we envision the ability to react quickly, right? And so one of the challenges with flu is that to match this year's need with a vaccine. And I think a technology that can react so quickly, and you've seen us do that in the case of COVID, I think that bodes well for our ability to provide a unique solution for flu.

Now, of course, the challenge is that with flu, we're going to need a different vaccine every year. And the question is, what will happen with COVID? And I think it's early days. So there's 2 scenarios. One is it's the same COVID, but people want to have a boost or people need to have a boost. And we'll see that over time, in which case, it's pretty straightforward to combine our vaccine, the one for COVID with whatever annual variant you have because of the ease of combining mRNAs in the same vaccine. And I think we've now demonstrated that ample times.

The second possibility is that actually, you will start to see immunological escape mutations for COVID [arise]. Now that's still not shown to be clinically relevant. People have started to describe it, but it's unclear whether that's going to be of epidemiological significance. If it is, then we would simply do the same, and we would make sure that we move quickly on both. Not having to have an egg-based sort of chicken form platform, but rather one that is digitally encoded and can move rapidly, I think, is going to be an advantage to our ability to serve the need of -- in either scenarios. Over.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes. And let me just add one piece, which I think it goes back to a medical need, which is even flu market was well-served with high efficacy vaccine, we will not bother. Because, as you know, we like to go after big medical problem, high unmet medical need. This is where we want to apply the platform, given all the things that we could do in theory with mRNA technology.

And I think the elderly data that we got just push us in that direction even more. As you know, even mRNA technologies have shown a drop from young adult to the elderly with COVID. We believe that all the investments we made in science over the years, formulation, manufacturing process, explain why the elderly data is so strong.

So between us, Tal, was saying around the [strand] in mutation, the ability to have high efficacy. If we could have a high effective flu vaccine, that we could then potentially combine it, as Tal described, we could have a big impact on reducing death, on reducing hospitalization and on reducing the time people waste by being even sick when they are likely sick and miss work and so on. So we think it's a big medical problem. We think we have a chance to make a dent on it, and we're going to go after it.

Operator

Our next question comes from Salveen Richter with Goldman Sachs.

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

Two for me. So can you help us understand your assumptions that get you to a November base case for the first interim look for the COVID-19 vaccine and then in EUA by year-end '20, given the probabilities that you mentioned today?

And then secondly, could you just provide your thoughts around rare side effects associated with vaccines particularly given the neurological safety events we saw with Astra, including transverse myelitis?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Salveen, thanks for the questions. It's Tal. Let me -- assumptions for the November base case. Well, I think that there is a likelihood that we will reach 53 cases in November. Now -- so if we -- if the vaccine is highly effective in the 80% to 90% range, as Jackie walked you through the math, then it's a question of getting lucky that we actually have the split in the sample size that we have because admittedly, 53 is a relatively small number. But if the vaccine is very effective, then there is a good likelihood that we would cross that barrier even at 53. And if that's the case, then I think that's a scenario where we have data in November to support an EUA.

I think FDA in their dialogue, I'd say 2 things, one, there's a very strong collaborative work between the agency and I think all companies, certainly ours, so that they're here where we are, and we're working hand-in-hand to ensure that it doesn't take them long to approve an EUA, once we cross the threshold, and they have the ability to query and get comfortable with our data. So I think that's the scenario here.

In terms of your second question on rare side effects, so a couple of points. Of course, the transverse myelitis that's been described, I think it's early to say to what degree it's related, but we all want to be conservative. The scientific hypothesis that I have seen and sort of make sense to me, have

probably more to do with an adeno vector platform than they do with the antigen per se or anti-spike protein immunity. I think the second point is that we've not seen a similar case nor have, so far, have we been asked to change anything in terms of the conduct on our trial.

And I think the third point is the -- I'm reasonably confident that if it were to occur we would have seen it. In other words, we have very robust safety monitoring embedded in this Phase III protocol. That's not just us, but it's the -- our NIH collaborators and any question on any case or any adverse event that people are worried about gets escalated quickly to the independent data safety monitoring board.

So it's always something you look out for vaccines. And you will never hear me say that our vaccine is safe because safety is always defined over time, and it's related to what we're trying to achieve. So we never rest on the laurels of feeling good about it in the sense that we always continue to collect the safety data. Having said that, so far, so good for where we are in terms of our vaccine. Over.

Stéphane Bancel - Moderna, Inc. - CEO & Director

And maybe to just to add a little bit to Tal, maybe Juan, if he want to add a bit of color. The other piece that's important, Salveen, to enable a potential EUA in that time frame is the CMC work that is ongoing, both within the company, where the teams have been working really hard to get us kind of BLA-ready. So that CMC is not in a critical path, that is really important. And there is a very close dialogue with the agency on the CMC side, so that everything is done before the clinical data comes out, so that the clinical data is really the bottleneck for a commercial EUA that we don't then we don't need to have meetings and data and other pieces of EUA missing. So there's a lot of work going on there that Juan and the team are leading to me that CMC is not critical part. I don't know, if Juan -- if you want to add any color?

Juan Andres - Moderna, Inc. - Chief Technical Operations & Quality Officer

Yes. So for instance, one of the strategies that we have followed this as we scaled up as soon as we completed the next cycle of scaling up, we have validated the process. So we have put together the PPQ packages. So that we are ready almost at every moment as we go forward. And obviously, these packages, this information is being shared with agencies as in real-time in a very transparent way.

Operator

We have a question from Michael Yee with Jefferies.

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

Appreciate all the details and programs today. Platform question relates to the fact that the difference between this year and last year is that you've dosed 25,000 people now for COVID and presumably could be millions of people over the next year or 2. How should we think about how much derisking of the platform or the LNP or mRNA specifically could be extrapolated to different parts of your other programs, whether that be oncology or more likely prophylactic vaccines, which I think is most derisk?

So just maybe make a comment about how much will have changed in the next year after dosing all these people? And then the second question relates to information yesterday from Lilly suggesting there was 6% to 8% resistance to virus, at least to that antibody. Maybe just make a comment about whether that surprises you with the fitness of what's going on with COVID, the implications as it relates to the development of a vaccine?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thanks, Michael. This is Tal. Let me take those. I absolutely agree with you that I think the increase in the safety database that we've experienced so far and -- we've gone from hundreds to thousands to tens of thousands, and hopefully, knock on wood, in the not-too-distant future we'll be able to bring benefit to millions.

That, I think, provides tremendous reassurance for everybody regarding the fundamental of mRNA vaccines. And I do think there's a read-through to the mRNA platforms. Admittedly, therapeutics are higher doses given repeatedly. But so far, what you've seen is if you follow the science, what you see is what you'd expect. In that regard, we've been -- and I think everybody has been reassured, although I'll say -- we've not been surprised. This is what we've expected based on the scientific principles that underlie what it is we're trying to do here. MRNA as a molecule is nothing new to humanity nor is it new to evolution. It's one of the oldest forms of molecules known to man.

To your point about the Lilly and resistance, I think there's a big, big difference if you're talking about a single monoclonal antibody as something that generates selection pressure during the time of an ongoing active infection and viral replication in somebody's body versus a very polyclonal response elicited by a vaccine ahead of an infection.

People have described resistant clones come up to this antibody or that. They've not yet translated into an epidemiologically relevant escape. I think if we did that, people would probably start calling SARS-CoV-3. I think it's why Regeneron, for example, has gone from the get-go with a combination of 2 antibodies. And now if they think just 2 will be enough to get over the problem, then certainly, when you have thousands, which is what I would be -- expect the case for a vaccine, and certainly, we generate a very nice broad response. Part of it is against the receptor binding domain, but clearly we have epitopes outside of that. And even within that, you've got a polyclonal response. So I don't think that, that's relevant on the first order of scientific principles to expectations of a utility for a vaccine. Over.

Operator

Our next question comes from Gena Wang with Barclays.

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

The first set of question is regarding the Phase III trial design. Just wondering, first, is there any futility embedded in the interim analysis? And also regarding the trial size, I think Pfizer increased the trial size. Do you feel comfortable -- confident that 30,000 patients will be sufficient to reflect different population. And lastly, 60% efficacy, when you mentioned that, I just want to confirm that means 60% reduction of positive COVID-19 versus placebo. And I have a quick manufacturing question, as we're just wondering, have you already started the commercial doses? And how would you split in the future between U.S. and the EU?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Gena. There were several questions embedded there. Let me take the first few on trial design, and then I'll defer to Stéphane. The -- yes, we do. There is a look for futility. It's sort of the foremost statistical look. It's handled by the independent statisticians within the data safety monitoring board because we want to make sure that things are going the right way, not the wrong way.

In terms of trial size and relevant populations, if you look at our performance on the diversity, I think, and we've been very transparent with it, what you've seen is over the past few weeks, we have continuously improved our ability to reach minority populations and ensure that the door is open wide and long for them to have the opportunity to enroll. So I expect that at the end of the day, 30,000 subjects should give us a pretty good representation across the different risk strata be it age or your comorbid conditions.

Now the truth is that, that confidence is much less a function of the trial size, and it's much more a function of how many events will you see at the time when you decide there's -- or it's apparent that there's efficacy. Because obviously, if it's -- if that efficacy is driven by a very small number of cases, then it doesn't matter whether you've got 30,000 or 100,000, it's all resting on a few dozen cases that make that determination. And that's an interplay, frankly, between how effective the vaccine is, as Jackie has described it. And the statistical rigor and analysis under which we all have to make sure that we don't unduly delay an effective vaccine for the population.

The last question you had was, yes, 60% of the calculation is done simply for vaccine efficacy. It's derived by dividing the rate that you get within the placebo versus -- I'm sorry, within the vaccinated versus the controls, and that's the reduction in the risk.

Let me hand it over to Stéphane.

Stéphane Bancel - Moderna, Inc. - CEO & Director

I think you answered everything perfectly, Tal. You need to add anything else now?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

I think there was a question on the commercial, on how we intend to distribute between U.S. and ex U.S., if I recall.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes. So on the U.S., as you know, we have an agreement with the U.S. government for 100 million doses. And so our intent is to work very closely with Operation Warp Speed with the CDC, with the U.S. Military to get the vaccine to central nodes of distribution. As you have seen, McKesson has been retained by the U.S. government to do with physical distribution. And so that's kind of how it's going to operate. The allocation in terms of population at risk, in terms of different geography and states will be decided by the government, not by Moderna. And outside the U.S., it will be done through outside the U.S. supply chain that Juan and his team have established. Lonza for making formulated products, ROVI in Spain for filling the vials. And that would be the same thing, I would say, ship directly to governments that have placed orders already or the others to come as we continue to engage with government and to figure out how we can be helpful. And this is how we are going to be -- it's going to be done. Does that make sense?

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

Yes.

Operator

We have a question from Cory Kasimov with JPMorgan.

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

And really appreciate all of your transparency around this Phase III program. So speaking of the Phase III, I'm curious how we should be thinking about infection rates in the COVE study relative to the reported SARS-CoV-2 infection rates. I get that you've selected site locations that are trying to be near COVID-19 hotspots. But interested to get your view as to whether the confirmed case rates are underreported or if there is a specific strategies to enrich your trial for events.

And then my second question is, I'm wondering if you can speak to any assumptions around the potential timing of the second interim, if it gets that far given the November commentary for the first plus the lower statistical bar you have for the second one?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Cory, it's Tal. Let me take those. Let me jump to the end game. I think it's too early for us to say whether the infection rates are exactly what we would anticipate on the zip codes where the trials are occurring. What we have done in the trial is try to ensure that we have a representation of the risk factor. And by the way to enroll everybody needs to be at higher than the usual risk, that is they have to have a risk factor, whether it's by their occupation that they're out there. They're not like me sitting at the computer all day long. They're elderly, they have co-morbid conditions or they belong to minority communities. And so with that, we've tried to enrich for the relative expectation of cases.

On the flip side, often clinical trial participation doesn't necessarily one-to-one match the demographics of any given zip code. So we've taken active strategies at every local level to try to ensure that the person who will have is most likely to get infected and most likely to get sick when he is infected. But it's too early to say whether the rates are actually on par with expectations. So we have a pretty wide range of when the cases could happen.

In terms of your question on the timing of the second interim, it's important to note that it's not a linear. It's not going to take the same time that it took from the start of the trial to get to 53 as it is going to go from 53 to 104. I think going from 53 to 104 will happen much quicker because you're now sort of at the linear part of the curve. Everybody has already been enrolled, everybody is being followed up. So you're constantly accumulating follow-up, and it's a function of the follow-up time that you expect to see cases.

So I expect the delta between those 2 to be a matter of weeks, maybe a couple of months, probably not longer based on current expectations. But again, all of this is subject to varying predictions -- we look -- and we try to project ahead. And I can tell you that every week when we look ahead the variance in projection is probably in the order of 2 weeks, but to expect sometimes earlier, sometimes later. So I think our ability to project the movement of this pandemic is too imprecise to give any more, I think, precision on when we would expect those cases to happen. Over.

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

So thank you so much. Before the next question, I just wanted to clarify 1 point that was in the previous question, which referred to lower statistical criteria at subsequent analyses. I wanted to be clear that actually the statistical criteria are the same throughout the trial. So these criteria are aligned with the guidance that FDA issued earlier in the summer, and they align with a lower band of 30%. The difference between each subsequent analysis is that we have a higher sample size of cases. And with a higher sample size, you have a closer estimate of the efficacy through 95% confidence interval. So that's really why the likelihood of meeting your criteria increases given the same vaccine efficacy assumption.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Jackie.

Operator

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

Alec Warren Stranahan - BofA Merrill Lynch, Research Division - Associate

This is Alec on for Geoff. Just 2 for me. So first on the Chikungunya antibody program. Could you just remind us as to the benefit of expressing an antibody with mRNA rather than just administering the antibody on its own, especially given what it looks like as the need for frequent repeat dosing? Is it mostly the dosing interval? Or are you also looking at the antibody quality as well?

And then my second question is on the seasonal flu program. How is your clinical experience with 1851 for H7N9 and 1440 for H10N8 influenced the way you're thinking about the continued development for flu, including the use of endpoints such as the hemagglutination inhibition titers? And would you seek to partner the flu vaccine programs out with, say, the NIH or other parties? Or are you really looking to take it forward on your own?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

So Alex, let me start. The benefit for us -- well, first of all, this was the first opportunity to demonstrate protein functionality. I think monoclonal antibodies are probably the most widely used and best understood of protein types of drug. I think it's a great proof of concept. More to the point, you can't make the wrong antibody with an mRNA technology, right? So I think the veracity of the biology that you translate and the -- once you

make the antibody, you know that antibody is going to be functional. And I think that is a potential advantage of this technology that has to do with all the effort you need to do in the recombinant space that here the body takes care of it.

I do think there's a world ahead where the potency rapidity of actually making something new and potentially even cost of goods would be would make this platform a beneficial even in the monoclonal antibody space. It's not immediate. It's not necessarily today, but I think that, that future is there.

The final piece is that there's an opportunity to do combinations that, for us, on a relative cost of goods basis would be a very significant difference than what it does in the monoclonal antibody space. There are a few examples of antibody's combinations, and they usually max out at 2 for obvious practical reasons. I think we see a future where we could leverage the part of this platform to do combination mRNAs to go even beyond that into a polyclonal or polyepitope or even a polydrug type of a product that would be based on monoclonal antibody recognition.

Seasonal flu. Let me take a first stab at that. I think we've always been excited about the potential we have for flu because if you go back to the H7 data, the rate of seroconversion that we saw was practically in everybody. And that's been a reassuring feature of our vaccines, it's true of COVID, look at the CMV data. The error reports are actually quite small. When somebody gets immunized with our platform, they mount an immune response, and it's pretty clear and it's robust and it's neutralizing.

And so we had seen that from the early days. In fact, there's no other published reports of (inaudible) H10, but for H7 there were, and proteins alone didn't do much. Proteins with an adjuvant, sometimes got there halfway, but we can consistently get there, and we can do so with a really rapid turnaround time. I think the advantage we have now is having demonstrated that, having demonstrated combinations. And now that we will have set up a manufacturing infrastructure, I think that all puts us in a well-poised position to enter that space, as Stéphane had said, and I'll defer to him for any additional comments. Over.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes. Maybe -- thank you, Tal. Maybe just 1 thing on the seasonal flu to add to Tal's Remark is that do not forget if you have a curiosity to go back after today's announcement and look at the human data and preclinical data with human data publishing vaccines for both H10 and H7 in the same paper. Remember, this was -- what Stephen will call kind of dark ages, Moderna technology reaction. This was when old standard lipids, it was not by variable, not the lipid we use now in CMV or 1273. This was done with all the mRNA potency technology. This was done with very old manufacturing process. And so I will not be surprised when we go into the clinical of the seasonal flu product that will have even a better performance to what we already saw at that time.

As Tal said, most of the participants, if not all where with a HA titer that was above the FDA-approved endpoint, which we use as a bar for assessing success of this program. So I think this is going to be quite interesting going back to the clinic with seasonal flu with the newest version of the technology and all the investments the team have done.

Operator

We have a question from George Farmer with BMO Capital Markets.

George Farmer - BMO Capital Markets Equity Research - Analyst

Can you talk a little bit more about the Th2 response that you're not seeing in the Phase I study. I mean now you're kind of referring to this as perhaps a good thing. Some of your competitors are boasting that a catalyst had a Th2 response. How should we think about that as within the context of your vaccines versus others?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

So this is Tal. Let me take it from a clinical perspective. I think the focus on the Th2 stems from the observation, that when people went back to those vaccine-enhanced respiratory diseases that were seen in the case of formalin-inactivated protein vaccines or viral vaccines with RV and measles back in the 60s, and they try to analyze the immune response in those children, it appeared that you get a more Th2 gear, and I think of Th2, broadly speaking, to sort of your allergic, antihelminthic and antiparasitic response as opposed to the Th1, which is more towards viruses and intracellular pathogens.

And so with that context, people have been trying to look at the balance of Th1, Th2 with the expectation that you really are looking to get Th1. What we've done is -- we and our collaborator is a lot of correlative preclinical work, primarily geared around the safety question, looking at aged mice as one extreme and then looking at every species, evaluating histopathology to reassure ourselves that indeed when we're preventing infection or preventing disease there's no exacerbation anywhere. And that continues to correlate -- now it's a correlate, not a causative, but it does continue to correlate with the Th1 responses as opposed to Th2 response.

And so when you put that all together, we've seen a Th1 response for our platform consistently and correlate of protection. And then we see it in the clinic. I think that's really reassuring. As I said, it would be worrisome, especially to have a protein or adjuvanted protein to the unit vaccine as more of an allergic type of an immunological profile. It's not proof, and it's not causative, but it -- that's when -- that's the reason people look at these profiles to begin with because of those correlations back -- dating back decades of what we're seeing with RV and measles. Over.

George Farmer - BMO Capital Markets Equity Research - Analyst

Okay. And then in a Phase II trial, you mentioned that you're fully enrolled, everyone received a booster. Will we be able to get a look at the neutralizing antibody responses, whether using the PRNT assay or the pseudovirus assay near-term rather than having to wait for the full 13 months of follow-up?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Well, it's not going to be 13 months, but I do think we're going to wait for the endpoint as defined, which is a couple of months. And frankly, right now, the important thing for me was in that trial was to get a sense of reassurance of safety on the way to Phase III and then over time to understand how 50 performs relative to 100. So we will share them when we have them. In terms of decision-making, stay tuned, I guess, and once we're able to show them, we will.

George Farmer - BMO Capital Markets Equity Research - Analyst

Okay. Great. And then 1 final question on the CMV vaccine. So how should we think about the market for this vaccine? Is there a market, in fact in patients or in individuals who are seropositive? Or is it -- should we just think about potential penetration in seronegative market?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

So the expectation here is that this will be irrespective. This will be utilized irrespective of sero status. Because if you had to start to test for people, it would actually end up being a real barrier to access. And so if you talk even to the FDA, certainly, the folks that we've spoken to back at the CDC, there is an expectation that this will be for everybody. And the FDA was clear in stating that they don't expect us to demonstrate benefit for the seropositives, only safety, but they do expect us to demonstrate safety for seropositives because of the expectation of a label that will be inclusive for everybody.

I will say this, I'm super curious as to whether the ability to boost even seropositives by the amounts that we are. Remember, these are people who are living every day with a virus and there is some homeostasis between their immune system and the latent virus infection. I'm super curious to see whether the effect of -- that we can focus the attention of the immune system on these antigens to the level that we sort of reset the homeostasis

for these people may have a benefit as well down the road. But admittedly, it's going to be really, really challenging to demonstrate that benefit, and I don't expect us to be able to do that prelicensure, hopefully postlicensure.

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

First of all, I'd like to echo Cory's sentiment, everybody congratulating you guys in showing tremendous transparency. And hopefully, some of your competitors in the U.S. and elsewhere will follow suit in that regard.

In terms of questions, a couple of quick ones. First of all, for you, Stephen, is the -- for the partnership with Vertex, is it reasonable to assume that both of those -- both sides of the partnership are pursuing an entailed approach to delivery for CF?

For Tal, regarding 1273, you commented, and I may have misheard it because you cut out there for a second, that you expected the 53 events perhaps in the November timeframe, which sort of explains that discussion around November. Did I hear that right? And should you not hit the stopping threshold for efficacy at those 53 events? Is it reasonable to expect the 106, 153 -- 151 events closer to, say, December, January timeline based on average event rates you're seeing right now in the study?

And then as a third question, one of the nuances around COVID -- the COVID-19 disease itself is that it appears to be materially more -- it tends to be severe more frequently in men than in women. Do you see a biological component of that based on the data you've seen in early studies and your study of the virus preclinically internally? Or do you think that's more driven the behavioral and cultural factors between the genders in the place where the majority of COVID-19 burden is being seen?

Stephen Hoge - Moderna, Inc. - President

Sure. Certainly.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Maybe take the first.

Stephen Hoge - Moderna, Inc. - President

Yes. I will take the first.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Stephen, you want to go first?

Stephen Hoge - Moderna, Inc. - President

Yes. So just very narrowly on the question on the Vertex partnerships. We haven't disclosed, but the short answer is we are looking at all sorts of delivery, including inhale delivery. And we obviously believe the fastest way to access the lung is going to be through an inhaled route. And so both of our partnerships with Vertex do look at pulmonary delivery through the inhale route.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

And on your question on events, yes, I think there is an expectation for 53 events to occur in November. Sometime in November is sort of a reasonable base case. And then the next analysis would take place at 106. The likelihood -- I think Jackie walked through, how the likelihood is a function really of the number of cases as well as the actual vaccine efficacy at any given point.

The question around more severe in men. I don't think I've got any wisdom to add here to what's out there in the field. It is possible that there are biological factors that relate to gender here. I will -- I don't think we've seen -- well, we've not seen any differential effect in any of our trials in terms of vaccine performance or antibody levels. And so I don't necessarily expect to see a gender difference in the performance in terms of preventing cases. Whether those reasons have to do with behavior, and therefore, infectious load to begin with, which seems to be 1 possible mechanism for explaining why some people get more sick than others, or whether they have to do with inherent biology, I don't think anybody knows at this point, certainly I don't. Over.

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

Great. This will be helpful. And congratulations, again, on the progress.

Operator

Thank you, and I'm showing no other questions in the queue.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Great. So thank you so much, everybody, for joining us today. The slides, of course, are available on our website. Stay safe everybody, and speak to all of you very soon. Bye-bye.

Operator

Ladies and gentlemen, this concludes today's conference call. Thank you for participating. You may now disconnect. Everyone, have a great day.

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