Moderna Inc Corporate Analyst Meeting

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PRESENTATION

Stéphane Bancel, Moderna, Inc. - CEO & Director

Good morning. Welcome to Moderna's third annual R&D meeting. Thank you for joining us in person in the room. And for those of you joining us via webcast, thanks for joining in. We're very pleased to host you today and to share some interesting new data about Moderna's platform that are important for patients.

Before we start, let me remind you, we'll be making forward-looking statements that make mRNA to be a risky endeavor. And I invite you to check our risk factors on the SEC website or on the Moderna website.

As many of you know, since we started the company, we thought that mRNA could be a very powerful new potential class of medicine. What excited us is the possibility of doing not only secreted protein but also intracellular and transmembrane. And when you think that the majority of a protein encoded in the human genome are coded for transmembrane and intracellular protein, there could be a very large possibility to help patients.

We believe because mRNA is an information molecule that we'll have a full platform. The abilities we learn from one product into the next product, which is very unique in our industry. We believe that if we invest in this technology, in robotics, in IT, in manufacturing capabilities, we'd be able to go much faster into the clinic by speeding up the research process in the labs but also going faster into the clinic because we don't have every time to reinvent how to make mRNA.

And we proved that over time there'll be a very interesting CapEx advantage with mRNA because mRNA manufacturing is very efficient. We do not need cells to make the mRNA with very large reactors like the [SI] biotech industry. We make our mRNA in a small reactor, in the liquid-phase reaction.

So it's very important to know about how is the company. Is there some -- it made no scientific sense to any of us that this could be a one-drug company. Because of the information nature of mRNA, it was very clear that either we're not going to be successful and we could not launch an mRNA drug or there would be many.

Because there is a possibility to help patients and to change their world, we spend a lot of time thinking about risk management, the obvious financing risk, execution risk, which are true to any company. But for Moderna, we spend a lot of time thinking -- and (inaudible) is there. Thinking about technology risk, so mRNA technology and biology risk.

And so the way we build our company is to build it across modalities. Think about modalities as different applications of mRNA technology, where we use different routes of administration and/or delayed resistance. That's what is really unique about how we are building this company.

And to manage biology risk and to keep out technology risk and biology risk, we try where we can to start in a new application, in a new modality with a program that has low biology risk. And why is that? It is because if you run a clinical trial for new technology that has never been tried by man and you have a failure, you cannot see a path. These are drugs failed in the clinic because the technology didn't work or because the hypothesis around the biology was incorrect.

And because we care so deeply about learning, we try to keep those things apart as we start. So if you think about it, when we started, we started with vaccine because we thought vaccine was less risky from a technology standpoint. When -- what Tal is going to show you later injecting IV when we're going to do a rare disease for potentially a lifetime drug protein.

So we started with vaccine. And when we started with vaccine, we didn't start with CMV because that would have been a very high risk. We started with flu. Why? Because there's an easy approvable endpoint for flu. It is used for seasonal flu every year. And so by having this benchmark, we could know after the first Phase I are we home, from a technology performance standpoint? Or do we need to go back to the labs to improve our technology because we are not there yet?

We're very, very happy because the great science of (inaudible) at our first Phase I that was ran in Germany was successful. 100% of the subjects at the 100 microgram dose showed more than 40:1 sero conversion. That was a great milestone for us that enabled us from there to go into things like CMV and personal cancer vaccine.

The other thing it enabled us to do is to invest in Norwood. We'll come back to it later with Juan. Norwood is a very important part of Moderna's story and the business model we have centered around this core unique technology.

So today, as some of you have just seen the press release, we're extremely pleased and proud to announce 2 very important new clinical milestones. The first one is, of course, around the CMV vaccine. We will talk a lot about CMV this morning. But we are very pleased to announce positive interim Phase I from a vaccine that we successfully immunized seronegative above the seropositive level. We boosted the seropositive subject in the study. The vaccine was generally well tolerated. We will share with you the details of why we think we can, in the near term, start the Phase II and are already preparing for Phase III and whether we'll have discussions with the FDA. I want to remind you that Moderna owns 100% of the rights of this vaccine. And we think it will be a very important product for the company.

The second news that we shared this morning is a positive Phase I data from a chikungunya antibody, which is the first time in the world that an mRNA has been injected by IV route to make a systemic protein. That is a big scientific milestone. And if you think about this, we made humans produce antibodies in their livers. So when you think about that, this is just (inaudible) cells, usually B cell-like antibodies. I think my liver has never made antibodies so far. And that's really something really remarkable. That speaks loudly about the possibilities over time of what we can do with this technology.

The important thing about the antibody program as well, which was a big question in our mind, is how well will it translate from nonhuman primates. And as Tal will show you, it translates pretty well.

Before moving on, I will have to pause for a minute and to just acknowledge the scientific accomplishment of the Moderna team: CMV comping 6 mRNA in 1 valve, 6 mRNA molecules in each valve. This is borderline transfusion, but the team made it happen.

The chikungunya antibody is 2 mRNA in a valve that have to get into the same set of cells, make both protein correctly, they then have to surplus their body to an antibody and then to get it secreting into the blood. If you just count how many "if" I said in my sentence, a lot of things have to happen right in tiny little cells and in the body so you can see the result we're going to show you today. It's just remarkable.

And there's only one thing that I think already differentiates Moderna. It's the commitment we have to doing amazing science. And I would like to take a moment to really acknowledge not only the dozens and dozens of people that work in our labs but the leadership of the science committee at Moderna: Stephen, of course; Melissa, [Carrie], [JJ], Joe, Eric, Josh, Paolo, [Andrea]. And in one organization, it's technical development because it's one thing when Stephen and the gang invents this new technology.

Then you have to be able to make it with high purity of clinical grade to go on a clinical experiment. And for me, this is not easy. So Juan, I will see; Don, Hugh, Peter, and so -- [Nadine], Scott and also Jim. Thank you so much for the remarkable -- you guys keep amazing me and I think -- one of them, yes.

So what have we learned in the last few years about Moderna's mRNA platform? So first, we learned that we invested a lot in science. We tend to publish a lot of scientific papers. We share with the world of science. We've built Norwood. Norwood is up and running, and Juan will give you a bit of an update.

But if you think about it, in the last 3.5 years, the team has put 16 different molecules in clinical trials, 16. Remember, 4 years ago, in September 2015, we have not been in the clinic yet. I think we had 1 or 2 primary focus. That was it. That was Moderna. And that speaks loudly of the team, the platform and the investments we have made when it was early and everybody thought this was too cute of an idea.

The team has dosed so far 1,300 humans around the world, healthy subjects and patients. When you have a body of 2 or 3 patients or subjects in 1 study, it's already a very big body of data. We saw already many times over repeated

injection in the personal cancer vaccine in OX40 the patient subject to many, many dose of mRNA. Not one dose; many, many dose over time.

What I'm very excited about is that now if you think about it with CHIK map data this morning. For the first 5 modalities of Moderna, we have consistently shown that, first, our mRNA is well tolerated in humans across the globe. We have shown that the protein we encoded is active, which was not obvious. The only case it did not happen is the Zika vaccine, the first Zika vaccine. And Tal will tell you a little bit about why. And the other thing that is really profound is the translation from preclinical species as you will see today again with CHIK antibody.

So we are very, very pleased of the progress of the company. Now it's 5 out of 5 that we tried in the clinic that had positive results. So yes, there's still a lot of work ahead of us. But we are very, very pleased with the progress we have made as a company and what it could mean for patients over the mid- to long term.

Last December, we IPOed the company. And this was the state of the pipeline of the company: 1 product in Phase II, a few in Phase I and a lot in open IND or GMP cost setting. If you look at just what happened in the last 9 months, we now have 2 products in Phase II, 2 programs that are applying for Phase II, CMV and OX40 for ovarian. There's a long stack of products in Phase I. The IND for MMA is open, and we are working hard to recruit our first patient. And we have GSD1a as our latest product that we moved from the labs into development.

Just in the last 9 months, a lot of progress. And as we've shared many times on the quarterly calls, the company number 1 priority is to move those products as fast as we can to the market. That is really the priority number 1 of the team.

So where are we as of September 2019? So 4 products in Phase II or prepared for Phase II; 12, Phase I. And now we have a very strong body of data, 10 positive Phase I studies, 6 vaccines. Personal cancer vaccine, as we shared in our last call. VEGF that AZ published in one of the major journals and chikungunya antibody.

We have 4 vaccines for large unmet medical need for which there is no vaccine on the market. Think about the impact we can have to have so many people around the world as we get those products moving forward: CMV, hMPV, PIV, RSV and Zika.

For a small biotech company that had no product in the clinic 4 years ago, we now have 5 immuno-oncology programs in the clinic. We have 1 in Phase II and 1 in Phase II very soon. And we are partnering, as you know, with Merck and AZ, who are some of the leaders in the IO field.

And we have 5 important rare disease that the chikungunya antibody technology -- human data we're going to share with you today is a very important derisking. We talked about these 1,300 humans who have been dosed. The team is strong. Between Norwood and Cambridge, more than 800 members of the team. Norwood is a key asset for Moderna and a strong balance sheet of $1.44 billion as of the end of June.

So with this framing, I'm going to invite Tal in a minute. Let me share with you what we propose for the agenda this morning. As you can imagine, we want to spend a breadth of time on CMV. We have several guests that I will introduce in a minute to talk about CMV, talk about the virus, the medical need. And we're, of course, going to share with you the human data we announced this morning.

And I'll do something that I have not done yet in Moderna history. I'll go back on stage to talk about commercial and how we're thinking about launching this product, which is quite different from talking about mice only, which was where we were a few years ago with Stephen, when we did our first collaboration.

Then we'll do a Q&A just on CMV because we think there's a lot of things to talk about. We'll take a small break. We'll come back to talk about immuno-oncology. And then Tal, for the main dish of the day, will share with you the CHIK antibody data. We'll talk about MMA. And then I'll do a brief conclusion. We'll do a Q&A for the second part of the presentation.

So with this, Tal, it's all yours.

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Thank you, Stéphane. Good morning, everybody. Truly an honor and a pleasure to be here this morning to start the agenda. We will start this morning talking about vaccines. We'll do a deep dive on CMV, cytomegalovirus. And I promise you if there's nothing else you take from this morning, you will understand CMV.

We're fortunate to be joined here by 3 of the world's leading experts on CMV: Dr. Permar, Dr. Schleiss and Dr. Riley. And I've asked them to come and give you a sense of context for the disease, the unmet need and throughout we'll weave in the actual data that we have.

So I'm going to start just by a brief overview on our prophylactic infectious disease pipeline. This pipeline really, we think of it as divided in 2 big buckets: One is the opportunity to go after real unmet needs as they exist today, things like cytomegalovirus where people are getting infected every day and there's no vaccine out there in the market. And there are clear significant unmet needs. And you can see in our portfolio different vaccines going after them.

And the other bucket is those of -- I'm going to be [Disco Dan]. The other bucket is those diseases which are pandemic threats and so of obvious concern for global preparedness. We think our platform can actually do good in that domain. That's obviously dependent on public-private partnerships. And we've been fortunate to date to have the strong support of both DARPA and BARDA on these endeavors.

So why would you use an mRNA technology for vaccines? There's a number of answers, but let me give you sort of the top ones that, as I joined the company almost 5 years ago, were sort of self-evident in potential. And the first is that our platform is essentially an mRNA and a lipid nanoparticle.

On first principle, you've got a 4 nucleic acid within a lipid. It kind of looks like a virus. So it's not a far technological leap to say, "Well, if we injected IM and we get some protein made, we could teach the immune system to then amplify that signal just like a vaccine does."

And in fact, because we're making the protein from within the cell, we're mimicking the way a natural infection would make proteins. And that's important because it not only activates the immune system, it ensures that you activate both the antibody arm and the T cell arm. And you'll see examples from our platform that actually prove the point now in the clinic of the ability of this platform to both generate antibodies and T cells.

We can do a combination products. We can put more than 1 mRNA in a vaccine. We started with hMPV and PIV3, 2 viruses that cause very similar respiratory illness. So we said, "Well, it makes sense that you would put the vaccine against both together because you're trying to immunize 2 causes of the same disease." And then we took it a step further with CMV. And as Stéphane said, we've got 6 mRNAs here in one vial, and I'll get to that in a minute.

We've got -- because of the, I think, the foundation nature of synthetic biology and how we make mRNA, and frankly, I think because of our lean-forward culture from the get-go, we have a faster discovery time than anything I've ever seen in pharmaceutical industry. In fact, I joke with Stephen that he needs 1/5 the number of people that anybody else needs because every one of those people is 5x as effective just because it takes them 5x shorter to do discovery.

That has translated for us the ability to actually go from an idea on a whiteboard to filing an IND in 12 to 18 months routinely. Trust me, I can't hire the people fast enough in development to catch up with the opportunities we have there. And that has been truly remarkable.

And finally, the fact that you've got a single process and a similar way of doing all these diverse applications means that from a manufacturing standpoint, you have an agility and efficiency that is truly remarkable. And if any of you have visited Norwood or you haven't, on behalf of Juan, I invite you to. And I'll tell you, I'm a clinician. I'm a drug developer. You don't see people like me get excited about manufacturing almost ever. Come to Norwood. It is something different.

And if you understand what that means in terms of the ability then to launch and commercialize products and have the agility in the manufacturing space, not have that capital hurdle of needing to build a new plant every time you launch a new drug, I think that's a tremendous efficiency that still ahead of us.

So with that, how have we done in the vaccine? This gives you an overview of where we are today. We started, as Stéphane said, with those that are relatively simple: 2 cases of influenza vaccines, where we understand the antigen. We know how high we need to hit it in terms of immunogenicity. And we've done that. We've now published that paper, both age 10 and age 7.

We then took on additional higher unmet needs. We went after RSV with Merck, and that's worked. We may even have a better one. We -- in 2016, in collaboration with BARDA in the big public health emergency that we all felt at the time, we went after Zika. And we did that with really not even putting the 12 months into discovery. We basically took the last sequence that CDC had described and put it into vaccine and ran with it in the clinic. And where we came up short was the level of immunogenicity as the dose that we tested wasn't quite strong enough.

But at the same time, as we were doing that, we put in the right 12 to 18 months preclinically and figured out, "No, no. There's actually a much better way of doing that, that preclinically is at least 20x as potent." Not only we think so, BARDA agrees with us, we retained that collaboration. We pushed that back up forward. And in fact, within a relatively short time, we're back in the clinic in a Phase I with an improved version. Anybody who has ever done drug discovery knows that it's very rare to be able to rescue a drug a year, 18 months later because you just changed the sequence when you figured out what was wrong with it. And I can't wait to see the results of that Phase I.

We went after more complicated antigens. Now both chikungunya and Zika are examples of viral-like protein. So you need to make a much more complex protein that's got to be secreted. And that's the antigen. We've proven we can do

this with chikungunya as a vaccine. We've disclosed those data. Further development there again depends on some sort of a public partnership.

And finally, the 2 greatest unmet needs for vaccines that are wholly owned products for us are: respiratory viruses, hMPV and PIV 3, that worked in Phase I. We've disclosed the data earlier this year; and CMV, which we're here to talk about this morning. These are more complicated applications. And you see the vaccine continues to perform as expected. In fact, if you step back and ask yourself, "Well, what have you learned about the safety profile of the platform?" We've now dosed well over 1,000 subjects across all these clinical trials in Phase I vaccines.

And the adverse event profile that we've seen is exactly what you would have anticipated from any active vaccine, whether it's a live attenuated, recombinant subunit, adjuvant, et cetera, et cetera. You see the anticipated local reactogenicity. You see some systemic flu-like symptoms, and that's it. There's nothing magic about this being a platform. As soon as you get into the cells, you're making proteins. The rest depends on the pharmacology of those proteins.

And so those 3 fundamental questions, you'll hear me refer to them again. Can we do it safely? Do we make proteins -- the protein active for our vaccine modality? Starting with flu, we've now shown time and again that indeed, that is the case.

So without further ado, let's talk about CMV this morning. I'd like to invite Dr. Permar, one of the world's experts on this to set the stage for us in terms of what we're looking for here. Thanks.

Sallie Permar,

Thank you. I'm excited to come and speak today about one of the diseases that I think is the most important of our time to solve. And that's to prevent CMV and especially the congenital transition of CMV.

I'm an infectious disease pediatrician. And when I was in clinical training, it's when I really came upon this. And I'm not on...

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Yes. You...

Sallie Permar,

Okay. Am I on now? Am I on now?

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Tap it. Try it.

Sallie Permar,

Okay now?

Stéphane Bancel, Moderna, Inc. - CEO & Director

No.

Tal Zaks, Moderna, Inc. - Chief Medical Officer

You're still -- you guys still haven't even...

Sallie Permar,

I think I'm on. Yes?

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Yes.

Sallie Permar,

Okay now, unless you want to give it. So what I was saying is that I'm really excited to be here today because CMV is a disease that's very near to my heart as an infectious disease pediatrician. I am constantly bombarded with problems with children that we see in the hospital with this virus.

And it is something that when I was in my clinical training, something (inaudible) that was affected by the CMV. And I have an HIV (inaudible) and I thought who's working on this side. And I was disappointed by what the level of -- activity level at the time. I think things are going to change. And I think (inaudible) this disease. So that kind of gives you (inaudible) the vaccine.

So I'm going to go ahead and give you some of the basics about CMV and (inaudible) but starting from the viewpoint of a virologist. So CMV is in terms of the virus segment (inaudible) Salmonella. In comparison to a small RNA virus like influenza or HIV, that only have (inaudible) CMV has (inaudible). It's almost the size of the cell itself. And it's a DNA virus as opposed to RNA virus (inaudible) going to talk about that.

Its cousins are other (inaudible) virus family. So that includes herpes simplex virus, EBV that causes mono infection, and chickenpox virus.

And these are viruses that have been evolving in [human] population for millions of years. And so as they evolve with the human host, they evolve to evade the immune response and to be able to spread very easily from person to person. In fact, well over half the humans don't even know they have this virus. You wouldn't know it because generally when you get infected, it's an asymptomatic infection.

But in the (inaudible) once you get this virus (inaudible) organ transplant or HIV patients before we had good HIV therapy had major problems with CMV disease and then if you are a fetus. If you become infected with the virus as a fetus, then you are apt to have lifelong brain damage from that infection.

So the congenital CMV disease burden is one of the major causes of long-term disability in children. It is extremely common. So it happens in 1 out of every 150 live births. That's just under 1% of all babies born. And this is globally, not just in the U.S.

It is the most common form of infectious causes of birth defects. When infected, when this -- about 0.7% of babies are infected. 20% of them will go on to have lifelong disabilities because of the infection, the most common being hearing loss. But there can be other major effects, including neurodevelopmental delay, motor delay. There are children who can't walk, can't talk, have seizures and just general learning disabilities.

And so again, this is a virus that is contributing to the ongoing issues of neurodevelopmental delays in children, problems with learning. And it happens more in populations of poverty than it does in populations that are of higher socioeconomic status. So to me, it's really continuing some of the disparities that we're seeing in our economy and our society.

What -- a remarkable stat to me is that it is the cause of 25% of all of infant hearing loss. And so this is not a rare genetic disease that is only contributing a small proportion to infant hearing loss. This is 1/4 of all infant hearing loss. And with one vaccine, you can make that many babies hear again.

And the annual U.S. burden is estimated at $4 billion. And that would include things like cochlear implants, all of the social care that children who are -- have neurodevelopmental delays that have been dependent on long-term care as well as learning disabilities that we work through in school. These are some of the costs already in that $4 billion, and some are hard to measure.

And if you look over here at the causes of pediatric long-term disabilities, CMV really rates at the top. This is the list for the U.S. It comes above fetal alcohol syndrome. It comes above things that you've heard more about: Down syndrome, spina bifida.

And then come the things that we've done well at preventing, like preventing pediatric HIV. When moms take the antiretroviral, we can prevent that. Haemophilus influenzae, which is one of the major causes of bacterial meningitis that did lead to a lot of hearing loss before we had a vaccine, and congenital rubella syndrome, which we have a very successful vaccine that has eliminated that congenital infection in every country where that vaccine is used.

So I hope we have convinced you that we need a vaccine for CMV. But we need a vaccine that can provide protective immune responses prior to pregnancy in order to eliminate this infection. So this would be targeted at the adolescent time frame. This has been a top priority for over 20 years made by the National Academy of Medicine. Yet we are still without even a lot of products that have been to late-phase trials.

It really can build on the success of the rubella vaccine as the example. And this is a graph of what happened to rubella infection at the time that the rubella vaccine was introduced. And rubella vaccine was not developed to prevent the infection, which is a mild supplemented infection in children. It was really developed to eliminate the congenital infection which caused heart defects, hearing loss, vision loss. And so the red line is the number of rubella cases in the U.S. after implementation of this very successful vaccine. The blue line is the congenital rubella cases that went down in a related fashion.

And so I am lucky to get to work with one of the developers of the measles vaccine. The measles vaccine was soon followed on by the rubella vaccine being related viruses. Dr. Sam Katz, he said something to me that I always remember and is kind of my mantra for what we can achieve with the CMV vaccine, is that when the rubella vaccine was implemented and so successful that the need for the schools of the deaf and blind decreased so much that those schools had to close because there weren't enough children to fill them anymore. And that's what we can achieve with the CMV vaccine.

So -- but the CMV immunology, unfortunately, is not quite as simple as rubella. Otherwise, we would have that vaccine already. So unlike rubella, the CMV immunity is not completely protective. It's not protective against acquisition of a new virus, a new strain of CMV. And it's also not completely protective against the congenital transmission. And that makes vaccine development complicated.

And what has really been complicated to the field and to -- and really, what's first identified about 20 years ago, that mothers with prior immunity to CMV could still pass the virus onto the baby. And the majority of adults have -- and women of childbearing age have CMV. That means actually the majority of the transmission is happening in that seropositive population throughout the world.

And this is just a comparison of the cases of CMV if you had 1,000 pregnant women who were seronegative, meaning they've never been infected with the virus, or 1,000 pregnant women who have been infected with the virus previous -- prior to pregnancy, so were seropositive. The rate of acquisition in a woman who is seronegative that comes into pregnancy is somewhere between 1% and 3%. A lot of those women are women who have older children, who are toddlers and especially in daycare because that is where a lot of the CMV transmission happens. With the saliva and urine shedding of the virus, that virus is very good at getting around a daycare room.

So that 1% to 3% of new infections would lead to 10 to 30 primary infections in this 1,000 women. That is -- then leads to a very high rate of transmission. 30% to 40% of those newly infected women will pass the virus onto the baby. And so this leads to somewhere between 3 and 12 women out of 1,000 passing CMV onto the baby, about 1/4 of which will go on to have defects and many of those will be long term.

Now if we look on the other side, what's really interesting is that, that number at the bottom is almost the same. And that's confusing because if you have some immunity, shouldn't it be protective, at least partially? And so this is breaking down the numbers that when you have CMV previous -- prior to pregnancy, you carry the virus in your body because you don't get rid of it. And so there is some risk that you'll reactivate the virus. Maybe some virus is replicating in the blood. And then you transfer it across the placenta to the fetus.

So we don't know what that rate is. We aren't able to measure that. And so we don't know the contribution of reactivation to a congenital transmission that happens in people that are previously infected.

However, what has been measured is how many times does a woman who has immunity to CMV prior to pregnancy become reinfected during pregnancy because, again, the immunity -- natural immunity is not protective against reinfection and because the populations who have CMV cohort together, where CMV is very geographically distributed, racially distributed, differentially with the Caucasian population have a lot lower seropositivity rate than Latino or African American population. So there's actually a lot of transmission that happens in a seropositive person probably because of the other people that they live their lives with.

And so that leads to somewhere between 200 and 300 maternal infections out of 1,000 women, reinfections. And we know that when we measure CMV in the baby afterwards, which we can do with a simple test of virus in the saliva, that's actually only a small proportion of those women who are reinfected during pregnancy or passing the virus onto the baby, somewhere in the order of 3% to 5%.

And what's notable is that these numbers are tenfold different. Mark Schleiss and I wrote an article that laid this out because it is complicated to understand that even though we see the same number of infections in 1,000 seronegative versus seropositive women, that -- the number still reflects that there is partial protection from that natural immunity.

So what all this is saying is that while natural immunity may provide some partial protection against CMV congenital transmission, it's not completely protective. And so therefore, a vaccine has to be different than the immunity that's afforded by the virus infection itself.

So the most successful CMV vaccine tested today is a glycoprotein B subunit vaccine. So that's a vaccine, that platform that came about after live attenuated vaccines and [kill] vaccines. Examples of subunit vaccines would be the HPV vaccine, would be the new shingles vaccine. Those are subunit vaccines.

So that approach was tried with one of the proteins that's included in the Moderna vaccines, which is the glycoprotein B. That's the main receptor that the virus uses to enter a host cell. And so that seems like an appropriate target.

So the subunit vaccine made by Sanofi was added with an adjuvant, which is something that makes the immune response higher. It brings in the immune cells. They added an adjuvant that's a fairly potent adjuvant and gave 3

doses to women who were postpartum -- recently postpartum from their delivery.

And the reason why they chose that population is because, like I said, women who have a toddler are much more likely to become infected. And so that was the way to increase the potential risk of acquisition.

There were about 400 women who went into the study, and they were split by placebo or a vaccine. And the results were showing some protection by the vaccine. It was about 50%, just reached significant. But this was a big win but not quite high enough to go on to the next phase of clinical translation.

But at the same time, the same vaccine was given to a separate population, the adolescent population because this may be the true target of the vaccine, where you want to catch women before they go into pregnancy. And so the same vaccine schedule on the same vaccine was given to about 400 adolescent women, half of which got the vaccine and half got placebo. And remarkably to me is the same results were achieved. And while it didn't quite reach significant of that p-value less than 0.05, those of you who know statistics, but it still reached that right around 50% protection.

And actually, a third trial that I'm not even going to show you data on is this vaccine was given to transplant patients. And the transplant patients went on to have about 50% protection against reactivation of their virus. So pretty consistent results from this one protein. Again, just 1 of the 2 proteins that are targeted by the Moderna vaccine.

So we -- in thinking about why the -- why other vaccine platforms may have failed. So the virus -- again, we talked about how it has coevolved with the human immune system for so long that it has the ability to evade the immune response with several different mechanisms. There is this frequent exposure to high levels of virus when children are shedding the virus. In particular, they shed high amounts of virus in their saliva and in their urine. And then subsequent attempts or previous attempts to the subunit vaccine were live attenuated vaccine because that would follow from the work that was done with the measles vaccine, rubella vaccine. That type of approach was not protective against new acquisition and, of course, has concerns that, that type of approach would have the ability to traverse the placenta as well and then those subunit vaccines that were only partially protective.

So there are some things that we know about immune correlates of protection, but this work is still going on. And this is the type of benchmark that you really need to know whether your Phase I or your Phase II trial is looking on target to have a surrogate endpoint of protection. And that doesn't yet exist for CMV. But there is continued work going into how we can establish that.

Some of the things that have been established is neutralizing antibodies, which you'll hear about from the data from the vaccine. This has been the gold standard for virus vaccine since the beginning of vaccine. That's how measles vaccine was developed, how chickenpox vaccine was developed, polio vaccine, et cetera.

So neutralizing antibodies, this is going to be very important. And we know it's the way that you basically prevent the virus from infecting the next cell. So neutralizing antibodies have been associated with protection against congenital transmission as well as how well your antibody binds to its target. Some more finer -- refined data said that prevention of the virus infection of a certain type of cell, which is the epithelial cell and the pentamer is required for entry into that type of cell.

But also the glycoprotein B vaccines are different from the subunit trials. The glycoprotein B vaccines have been associated with protection, just in natural immunity. In a study that we did last year looking at breastfeeding babies who are exposed to the virus that's present in breast milk -- because, again, this virus is very good at getting onto mucosal fluid. That then is the way that it's spread. And so breast milk of CMV-positive women often has CMV in it. And so we studied in babies that were receiving CMV positive-breast milk from their moms, what were the antibody responses in those babies that prevented the acquisition. And the glycoprotein B antibodies came up as potentially protective. And then a definite T cell response that we do think of as a potential important component. And that's because we know that people with T cell immune deficiencies like transplant patients, like AIDS patients are the ones that go on to have problems with CMV disease.

So just a little bit of data that we've generated from looking back at those subunit vaccines that I talked about that were partially protective. It's actually the perfect setting in which to see what predicted -- if half of the vaccines were protected, what predicted who was going to become infected versus remain uninfected.

And with -- between the 2 trials, the adolescent and postpartum trials, we had enough vaccines who became infected versus didn't become infected to run a whole bunch of immunoassays to figure out which one actually was different between the vaccines who become infected versus didn't become infected. And so this is the type of work towards an immune correlate that's really needed to guide vaccine designs.

And we had a finding of an unexpected antibody response that was predictive of protection in those glycoprotein B vaccine trials. And here's a depiction of it, that the glycoprotein B protein of the virus expressed on the surface of a cell was higher magnitude in the women who were protected that received the vaccine versus the women who received the vaccine but were not protected.

And this was not the same result if you just looked at the binding to the vaccine itself. So if we showed you the data from the binding to the vaccine itself, it would look the same between those 2 groups.

So this was the differentiating antibody response. And in thinking about what that really means, these really just say surrogate for what the -- what an infected cell would look like, the glycoprotein B on an infected cell. And so we did that assay to see if we could repeat the same results and did, in fact, see the similar results where the uninfected vaccines were protected when they had higher magnitude of that binding antibody response to the cell-associated form of gB. So this is the type of work that will help to guide endpoints for vaccine for the future.

But why would the mRNA vaccine platform be very good for CMV? I think that for one, there have been several studies now that have shown that the high-magnitude responses that are elicited with mRNA as well as durable antibody responses. And that's very important because we're going to be immunizing women likely in adolescenthood, around the time they're getting their HPV vaccine because pregnancy can happen in a wide range of ages. And so the vaccine response needs to be durable. And mRNA has proven to be a durable platform.

Also what I just showed you that it seems important that the antibody responses are able to recognize the cell-associated form of the glycoprotein rather than the soluble form of glycoprotein. MRNA would be very good at that because mRNA is relying on the human cell to express the glycoprotein. And so that also fits with what we've seen from our basic research.

And then another piece that I didn't have time to show you is we've seen -- there maybe, have been some distracting epitopes on that soluble gB protein that was partially protective, where a lot of the binding antibody response went to the cytosolic portion of the glycoprotein, which is the portion of the protein inside the cell. And that's not going to be useful in preventing -- infecting the next cell or preventing infection of the placenta, et cetera. And this type of approach, that the cytosolic portion of the protein will be inside the cell, like it is in a natural infection. So these are the reasons why I think the mRNA vaccine is a very promising approach for CMV.

So in summary, I hope I convinced you that the CMV vaccine is highly needed, I think the next 2 speakers will drive that home also. Natural immunity is only partially protective, but there are lessons we can learn from natural immunity, and we should keep learning. And we should keep learning from all our vaccine trials, what it's telling us about, what's protective. Novel platforms are needed for this. We've ran through the gamut of standard platforms in CMV, and they haven't been effective enough. And so novel platforms like RNA are needed. And I think it's really important that mRNA vaccine will express the glycoproteins on the surface of the cell instead of in a soluble form. So that will induce the type of immune responses that we've been able to show now, seems to be protective.

So thank you very much.

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Keep it on for just a minute, please. Thank you, Sallie. So with that, let's talk about our vaccine and introduce the data. The actual vaccine that we have, as Dr. Permar had said, will encode for these proteins from within the cell, and so will express them on the cell surface. And we're really talking about encoding the 2 receptors, the 2 hooks that the virus need to enter cells. One is gB, which we saw on its own, can already give us 50% protection; and the other one, and I think this has been a learning of more recent years, is the pentameric complex. This is a complicated protein that the virus requires to attach to epithelial cells. These are the cells that line our [cuboidal] surfaces. These are the cells, the first port of entry, if you will, for any viral infection. And so teaching the immune system to recognize that receptor, that hook, we believe is likely a critical component, and in fact, it's one of the components that has been missing from the history of attenuated vaccines. The ability to package all 6 mRNAs here in one lipid nanoparticle is really what allows us to effectively introduce a vaccine that will then code simultaneously for these 2 antigens.

So let's talk about the trial design. And I have to give a shout out here to Dr. Lori Panther, from my team. Everything I'm telling you here, I'm just the privileged speaker to actually represent the work of a large team. Dr. Panther was a Harvard investigator for many years. And when I met her, I actually convinced her rather than running clinical trials out there in the real world, come and help me do some of these work. And so we're -- I'm really grateful for that.

The trial that Lori and my team designed was essentially a Phase I, typical Phase I for vaccine. As you've heard, we need to think differently about the seropositives and seronegatives. They have different levels of preexisting immunity and what we -- what the vaccine will accomplish is different in both of these. And so we've got cohorts that are either seropositives or seronegative, and what we've done here is your traditional dose escalation. The dose range that we started here was quite wide, 30, 100 -- 30, 90, and 180 microgram. But not surprising if you step back and think of the dose ranges that I've showed you data with -- for our platform. Today, we've studied anywhere from 10 to 300 microgram, writ large, in our vaccine portfolio. And at about 100 microgram is where, typically, an mRNA vaccine reaches its peak efficiency for most of the vaccines that we've described.

This trial launched about 18 months ago. And today, we're here to describe the first interim results. The trial is actually doing 02 in 6 months of immunization. What I'm going to show you is the first of the data, the majority of which is after the second dose, so at months 3, a month after the second dose, okay?

So these are the data. And as a way to think about this, these are the seronegative subjects. So these are the people who had no preexisting immunity. And you can see the initial baselines are pretty close to 0, it's sort of below the limit of detection. And what -- where seropositives are in these numbers is around the 5,000. And what does that mean? It means you can dilute the serum of a seropositive person about 5,000 times and you'll still retain neutralizing activity against the virus. And so that's the benchmark because we know seropositives already have some immunity to the virus. And so can we take the seronegatives who have got none and get them to that level? That was the goal of this vaccine. That's how you benchmark. There is no yet correlated protection. So what you're trying to do is bring those who've never seen the virus to have an immune response that's similar or above to those that -- who have already seen the virus. And we know based on the work that's been shared in others, that it is -- the neutralizing activity against both epithelial cells and fibroblast is the likely correlate that's meaningful to be able to protect these people.

And so how do we do if you look at the seronegatives? We actually got them to the level and above those of the seropositive. In fact, 3 to 5 folds higher than the seronegatives after 2 doses. And you can see here the prime and boost, that 30,000 is about 5 fold or higher versus the 5,000 I've described. So that's how we did against this complex antigen, the protein. How did we do against gB? We got them there as well. We got them to the level of the seropositives. And that's the component that we already know, in and of itself, has 50% of protection. So this is really the primary goal here: to show that we can take the people who are seronegative and boost their immune response to the level at or above that of a seropositive subject.

How did we do on the seropositives? Well, this was really reassuring because if you think about it, seropositives, they've already got immunity. They've seen the virus, they're relatively protected, and yet, with these, we can further boost their immune response. Now if you think of other vaccines, we typically, as soon as those are immunized or infected -- we typically think of a 2 to 4-fold increase of that basic immunization as significant. And yet this vaccine as measured by neutralizing titers against the epithelial cells at a process where these titers are (inaudible). And at the epithelial cells, we got to the 2 to 4 range, clearly, against the gB. So even in subjects who already been infected and have some preexisting immunity, this vaccine that encodes for these 2 epitopes can further boost their immune response, and the ability there in their blood to have neutralizing activity against CMV.

How do we do in terms of safety profile? No big surprises, I think, is the bottom line. We collect safety here the way you do in all typical Phase I vaccines. There's an FDA guidance of how you send up the questionnaires. You typically look for injection-related reactions pain at the site. You look for systemic flu-like symptoms, they are coded, they are graded according to a known scale. And what you see here in general is consistent with what we've seen today in the rest of our vaccine portfolio.

Now I'm showing you the results after the second vaccination. Typically, after the first vaccination, they were milder. And so I'm showing you data that already encompasses that. And the other thing that's worth noting is it seems that the frequency and severity of the adverse events is a tad higher in the seropositives than it is in the seronegatives. Now that's not a surprise. If you remember the numbers I've showed you in the previous graph or chart, right, if somebody's already got an immune response that's primed and ready to see this virus, in fact that they've been cohabitating with this virus for decades, and suddenly they get a boost of titers above that, I've just woken up the immune system. And so it's not a surprise that, that waking up is a manifest, not just as a lab assay on the titers, but actually, in some transient flu-like symptoms. We saw nothing that was unexpected. There were no vaccine-related serious adverse events. And typical to vaccine-related adverse events, these come on, on the evening and then by a day or 2 later, they're gone. And so that's the safety profile that we've seen for this vaccine.

Now here's another interesting data point. When we started this trial, we actually started a group of sentinels with an initial process. We then took a 4-month hit and had a better manufacturing process. Along the way, what it meant was we were actually accumulating some data in the sentinels of the very first batch that we did. And that's this -- the dotted line here. The data I've just showed you is the solid lines on this graph, and you can see the 2 processes are by and large the same. But for the dotted line, these are 4 subjects per group. We've actually now treat -- vaccinated them again. We've given them the 6-months boost, and we followed them out to a year. And so while these are small ends, what you can see here is that not only do we get to the levels I described at 3 months after the second vaccination, we can actually further boost them later and maintain those levels at least out to a year, at or above the levels of immune response of somebody who is seropositive. So we've gotten our data for persistence of the immune response.

Now if you step back, there's not a big surprise here. First of all, this is what you'd expect from a vaccine that fundamentally mimics a natural infection and how it primes the immune response. Second, we've actually already described data for persistence for our influenza vaccine, for our chikungunya vaccine, so these are not new data. But for the application that we're talking about for this unmet need, the ability to protect the women for a long time, is actually a critical feature of being successful for the endgame here. So it's very reassuring that we can maintain those levels of protective antibody levels of seropositives out to at least a year with this vaccine.

The last piece I'd say is that it's hard to tell, but this graph is actually a log scale. And so if you look at the dose response there, that's actually a significant difference even out to 6 months and a year, the difference between the blue and yellow dot is still at least a twofold difference.

So we demonstrated a nice dose-response growth, we've demonstrated persistence, we've demonstrated that we can actually achieve levels of immunogenicity that are at or higher where the seropositives are. And we've demonstrated that seropositives, we can even further boost them by about tenfold where they live. And we're boosting them against the specific receptors that the cell needs to then attach to other cells. And so if you think the CMV genome that has all these other 250 genes, some of them wreak havoc with your immune system and actually dampening your immune response, we're actually going after the specific required antigen and are further boosting that.

So what's next? This was really exciting and reassuring just to see the result of the Phase I. Of course the question is, okay, how do you get to the endgame here? I think the immediate next step for us is to go and confirm the dose and confirm our pivotal manufacturing process in Phase II study. And so you'll see us in the near term launch a Phase II study that's really honing in on the dose range, that's testing that pivotal process that Juan will talk about in a minute. We're already well underway. We've submitted this protocol for review to the agency. We've picked the sites, and I look forward to this trial study shortly. This is also designed to give us a relatively rapid readout. We'll make decisions based on the immunogenicity. We will see at the 3 months' time point, again, a month after the second dose.

So what's the endgame here? Well, if you want to get to the ability to improve this unmet need, to protect babies from infection, from women who get infected when they're pregnant, maybe even have a benefit in the seropositives, the question is how do you design that pivotal trial? And I think this is another area where we're fortunate that there has been some movements in recent years. So historically, if you read the literature, there's been a lot of discussion on -- well, if you want to say that you're preventing congenital infection, you have to go prove it. And to go prove it, you actually have to go immunize tens of thousands of women and wait for them to get pregnant and collect enough cases, et cetera. And where, I think, we're in a fortunate place is after having -- talking about this for a number of years, we recently asked FDA for pretty specific guidance and a Type C meeting, how -- what do you think about the approvable endpoint? And the advice back was, that you should consider the endpoint of preventing infection. Just preventing primary infection in women of child-bearing age. If you can show that, you can show that with a safe and tolerable profile, that could be the basis for licensure.

And so that's really a game changer for us because now, if you step back and think about it, okay, yes, the endgame is ultimately shown, we prevent congenital infection. And we'll probably go do that, but we can do that in the post-licensure setting with real world evidence. But we can actually, in the Phase III, just show prevention of infection. And that means that the Phase III can probably be done with about 8,000 subjects or maybe even less, if you do the math, but we're still in the planning stages of here. But it's a Phase III trial that now looks feasible for a company like us. And so we're super excited that we actually have a way forward, all the way to licensure here and a basis for that. We've actually started the prep work to understand what the feasibility for that trial would look like.

As part of that prep work, let me invite my colleague, Juan, to talk about where we are in terms of manufacturing.

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

Thank you, Tal. Okay. Thanks very much. Good morning, everyone. My name is Juan Andres. I have the responsibility for clinical development, manufacturing and quality fulfillment. I've been in the industry for over -- a little over 30 years. I've worked with a different company for 18 years in a number of different countries and locations around the world and 12 years for Novartis based in Basel, in Switzerland. By just last year, I've joined the system with what I'm doing in Moderna. I lead clinical development for the clinical treatment there. Also, had quality reforms significantly for all the divisions of the company. And the last job was in manufacturing operations with 72 manufacturing sites all around the world, 35,000 people.

So for the last 2 years, I've been in Moderna. Why I'm here? The reason is very simple. I fell in love with the company. I fell in love with the technology, I fell in love with the idea that we were attempting to do. We are trying to go and do something that has not been done before and the opportunity to do save lives, that opportunity is what drives me here.

So the reason I'm here today is to talk about the CMV vaccine and how we are planning to take the CMV vaccine to Phase II to Phase III and then to commercial, okay? So in order to do that, let me start with Norwood. So Norwood manufacturing site is along the countryside. It is located in Norwood, Massachusetts, for those of you that are already familiar in the area, 30 to 45 minutes away from downtown Boston. So we're very, very close to the location of where we are currently. The facility was built and operationalized in 22 months. And believe me, I was involved in the making of manufacturing sites for a number of different years. That is a brief period of time. That is a very, very small period of time to make a facility that can make lots of noises. And we have 3 research. We don't only produce the clinical trials like the CMV and the number of projects that become the pipeline for the clinic, but we also produce for research. We produce for the clinics team and we make around 500 bottle of [product] made every month, okay? And so the facility was finishing in July. Last year, we produced our first GMP clinical batch in August. And since then, we produced around 70 batches to date. That is more in 1 year than we have produced in previous years altogether. So that gives you an idea on how much we are accelerating and the opportunity that Norwood site provides.

Here are a few pictures of the site. We wanted to design for quality, for speed and with tremendous flexibility. We wanted to do it from scratch and it's completely digitized, it is paperless, and it is designed in a way that fosters a lot of

collaboration across different people. Some of you have had the opportunity to go there. For those of you that haven't, as Tal said, you're invited to come, just let me know.

We finished the facility a year ago, and only a few months after, we were surprised by ISPE, the International Society of Pharmaceutical Engineering, I am sure many of you are familiar with them. And basically, we were awarded with Facility of the Future award, just a few months after. And we're going to be -- we are one of the finalists for the Facility of the Year Award that is going to be awarded in a few weeks in Las Vegas. So we are waiting for that. We are very proud of the site. The site is really working hard, including the personalized cancer vaccine area, that it is personalized medicine even inside the site. Very proud of the team and what they have accomplished.

So how did we arrive into Norwood? Because we didn't have it at the beginning. And of course, in the earliest phases, you don't need clinical, you don't need GMP. And -- so just start operationalizing all the areas as you move your pipeline. And one of the things that we realize is we started to rely on CMOs in third parties. But they were all over the world. They were analytical in the Pacific Coast, aseptic filling in Massachusetts or in Europe, [DNA] plasmid in another place, mRNA in another place. We had realized that integrating a number of different CMOs with the type of ambitions that we have was going to be very, very tricky. And this is the idea that led us into building the site. And at this moment in time, we are pulling all our growing pipeline in there.

We believe that Norwood is a competitive advantage, not only for CMV but for the rest of our platform. And the reason I'm stating that is, we are making all the different products, and as a platform, all the products are made in a very, very similar way. So think about it. We have made 70 clinical vaccines. It's 7-0 clinical vaccines in the same facility. What we learned about 1 product in terms of positive improvements, we can immediately apply to the next product. When we had scaled up -- so for instance, when we go from a batch of 10 grams mRNA because in the beginning you need small quantities, and you need to go and scale to 50 grams, we don't need to be doing everything in terms of a scale up. We do it for one product, and then we replicate that across the different products. That gives us a tremendous amount of flexibility but also a tremendous amount of speed.

It has been highlighted before as well that yes, we produce large molecules, but we are not traditional biotech in that sense. I have built, all over the world, facilities for biotech with 10,000-, 12,000-liter bioreactors. They are big monsters, only the diameters are as big as this thing, and they go 2 or 3 stories high. Then you have several of them that is immensely capital-intensive, but at the same time, it takes a lot of time to be able to go and operationalize a facility like this. We are a cell-free manufacturing operation. We have a bioreactor in the site, and we call it the largest scale bioreactor at this size. Okay, so that gives you an idea on how we -- how fast we can scale up. And to put it into perspective with the CMV vaccine, we are anticipating, with existing innovative vaccine, pricing that are already in the market of taking that into consideration, that we can produce the CMV vaccine with gross margins above 90%, okay? So that is something that it would be very, very important for us.

So are we ready? Are we ready for Phase II? Are we ready for subsequent phases? Yes, we are. The vials that you see in the screen are not taken from an image bank of lyophilized vials. These vials are real CMV vials. They are ready to go, we have produced them. And we just got all the -- the quality control we saw, slides proceeding, this is specific batch, this is ready, okay? So this lyophilized image is going to be the one that we take to Phase II, and it is the one that we intend to take to Phase III, and subsequently, to commercialization. So Norwood site can support making that mRNA and making those LNPs. And as we get ready, probably, we are going to lean on partners to produce aseptic filling and finishing as we move forward.

So how much capacity would we have? So how much capacity do you need? So the question is -- we can produce 10-plus million if we take into consideration that we need to make many other products. But if we dedicate a site only to our 100-microgram dose vaccine, like CMV could be, we could be producing 100 million doses just in the site, okay? So Tal, Stéphane, we are ready to go. I mean tell me when and how much, and we will go for it, okay?

So this is it. Let me introduce the next presenter. Dr. Mark Schleiss is coming to do the next presentation. Thank you very much.

Mark Schleiss,

Thank you. So this is great, this image. I mean I'm excited, we are ready to go. There it is. That is fantastic. I want to talk a little bit about cytomegalovirus vaccine. To put it in a little context for the audience, and one of the take-home points I want to make is that the subunit approach that selects key CMV genes is fundamentally different than some of the vaccines we use in the clinic every day. MMR vaccine, the varicella vaccine, chickenpox vaccine. These are whole virus vaccines that, at some level, attenuates a natural pathogen to a point where it induces immune responses that doesn't cause the disease. Now there's a whole category of CMV vaccines that does that, too. And that was alluded, too, a little bit earlier this morning, so I'll kind of review those differences as we move forward. But I think that's a key take-home point because one of the key things is safety. A vaccine that goes out into the market, into clinical care, has to be widely perceived as, let's say, particularly if you're talking about adolescent population. We live in a culture and a society where there is so much anti-vaccine pushback and so much skepticism and vaccine hesitancy that I think that's a key message that we have to have, moving forward.

Well, we've heard about congenital CMV infection and how important it is as a cause of disability. I won't belabor these points. This is the classic photo from decades ago now, the baby with microcephaly, small head, and the CAT scan of the baby's brain showing the calcium deposit. That's one of the classic and tragic findings of congenital CMV when it involves the brain. And this is the kind of thing we're trying to prevent. One of the really exciting things about this project, in my opinion, is that from the beginning, it's been targeted at preventing congenital CMV. So many pharmaceutical ventures into the cytomegalovirus workspace have started out by saying, "Let's see if we can do something about CMV in transplant recipients." Important if you're a solid organ or bone marrow transplant recipient that get CMV disease, that's very devastating. But the requirements of the vaccine and the endpoint of a vaccine program, I think, they're probably very different in healthy women than they are in transplant recipient. And so I love the fact that this is a program devoted to congenital CMV.

Sallie Permar talked about how the chief vaccine preventable causes of brain injury, neurologic damage, deafness, have been resolved in the past by vaccination. I remember, when my daughter was an infant, the Haemophilus influenza type b vaccines had literally just been licensed days before she was born and how anxious I was as a clinician, seeing invasive haemophilus disease every day, sort of find that pediatric practice in Seattle, where I lived at the time, to actually have the vaccine. I was calling all over town, "Do you have it yet? Do you have it yet?" And that vaccine really changed pediatric care profoundly, as the rubella vaccine as we've already heard. And I'm hopeful that the CMV vaccine will have the same impact. The total number of babies that are insured in the United States and Europe, from cytomegalovirus every year, is in the many thousands. And it's probably much higher than this actually in the developing world. We just don't have good data, but as we learn more about CMV in the developing world where the prevalence of disease is actually going to be higher than the United States and Europe, and we'll come back to that point in a couple of minutes. I think globally, this could have a huge impact on child's health.

So does immunity protect the fetus? And we've heard about this already this morning. This idea that if you get CMV and you recover from it, and you go on with your life, well, you're not really quite completely protected. You reactivate the virus during the course of your lifetime. You get reinfected with new strains of the virus. That's really different. Really different conceptually than the measles, which, if you recover from it, you don't get it again, you're immune. And so this is one of the underlying complexities of this crazy, crazy virus. It has all of these immune modulation genes, these immune evasion genes that allow people to get reinfected. If you haven't sensed it already, I think one of the take-home messages is that eventually, to protect babies against congenital CMV, we will need to give a vaccine to all women, whether they had CMV in the past or not. And that's why the data that we saw from Tal about boosting antibodies titers in people who are already immune is really, really important, much more so than it would be for other traditional infectious disease pathogens.

So there is evidence, as Sallie alluded to, that immunity does provide some protection. It provides a big reduction in transmission, and it probably provides a decreased severity of disease if transmission does occur. And we've already heard about what the economic benefits of CMV vaccination and how important those are.

So I'll just sort of lay out 4 points that I think are important in CMV vaccine, why don't we have one yet, why it has been so difficult. The first one is we don't really know what the correlate of protection is for the fetus -- the developing baby, and the maternal circulation, the placenta, that whole maternal-placental-fetal unit. What protects that from CMV if a woman gets an infection or is exposed? Or reactivates the CMV that she's had for decades? Is it antibody? Is it T cells? We know that both are important. You've seen various versions of this slide already. But the viral particle is very, very complex and has a lot of glycoproteins, as we've heard, studding the surface. These are the important signals or hooks as we learned -- heard earlier. I love that metaphor. Hooking the virus to the cell surface. CMV sets out to infect cells of very different types in the human body: respiratory epithelial cells, brain cells, the cochlea. And so these cells that we call epithelial, endothelial, fibroblast, require different hooks for the virus to hook into them. The virus also has all of these proteins that are sort of under the surface in this region that we call the tegument of the virus particle. And these are targets of T cell immunity. T cell immune responses to CMV have been the cornerstone of many failed vaccine platforms that have come and gone in the last decade. And so I think we still don't really know the overall importance of those antibodies -- or those T cell responses in protection of the fetus. Clearly, this platform focuses on the outer protein for ones that are the so-called glycoproteins that involve the initial steps of infection.

And so these are some of the proteins of emphasis. And we've heard a lot already about the glycoprotein B. Sallie nicely reviewed the efficacy studies from past, and Bernstein looking at adjuvanted glycoprotein B. So it was pretty good. I'm from Minnesota, so we like to talk about how things there are generally pretty good. But we need something better than pretty good for a vaccine that will protect against congenital CMV infection. And so that's where all of these other platforms and expression approaches have been used. And I won't belabor all of these points. I'll just mention that a lot of these are in clinical trials. A vector known as MVA vector, and this has been an interesting body of work performed by Professor Donald Diamond at the City of Hope oncology center in Duarte, California; some virus-like particle worked on by (inaudible) in Germany; polyepitope vaccines; soluble pentamer vaccine that's actually being developed by GSK; and then we've just heard about the Moderna messenger RNA platform.

And so all of these vaccines, I think, it's very exciting to see them move forward in the clinic. But the pentamer, that group of 5 proteins, hence a pentamer, that's involved in binding of virus particles to epithelial cells, I think is emerging as a key milestone -- a cornerstone of vaccine development. So I'll segue into just some comments about these live

virus vaccines. Again, these are different than the messenger RNA vaccine platform or the purified protein platform because these vaccines are all generated against the backbone of the entire virus genome. And so many decades ago, highly passaged strains of CMV went into human volunteers. These had a really minimal efficacy, fortunately, not much reactogenicity. However, it turned out that, that pentamer that we heard about earlier, wasn't really expressed naturally or normally in those attenuated vaccines. And so that led to a number of trials to try to optimize these vaccines to express that pentamer but still retain safety. And so that pentamer, again in this cartoon, shows the complexity of how this protein, this pentameric complex, or PC, right? That doesn't stand for political correctness, it stands for pentameric complex, that 5 proteins that bind together to allow binding of the virus particle to these epithelial cells. This is kind of the key addition that the Moderna platform has, that hasn't been in the adjuvanted gB vaccines that we heard about earlier. gB, as shown over here, is important in binding to fibroblast. But given the complexity of cytomegalovirus biology, it really need to block both of these binding steps to prevent infection. And so that's really, in a nutshell, what this vaccine is trying to do.

Now at the Merck vaccine, V160, is different conceptually because it expresses the pentamer. That's a big selling point of these trials of the Merck product. But it does it against the backbone of the entire viral genome. So every gene in the virus is present. The genome is modified in a way that allows the virus to not replicate. And so sometimes in the field, we call these DISC vaccines. That acronym stands for disabled single cycle, DISC vaccine. The hypothesis is that you'll generate broad immune responses to all of the gene products that are in that virus particle that I alluded to earlier, including those T cell targets in the tegument of the virus. But in fact, we don't know that those are necessary for protection against congenital CMV. So this cartoon shows how the Merck vaccine is made. It's done with sort of a poison pill that's built into the virus that can only be overcome using the synthetic ligand called SHIELD-1. It doesn't even exist in nature, and so that's why the vaccine is considered to be safe enough for use in clinical practice. So in the laboratory, where the vaccine is manufactured, you can generate these disabled particles, but you can only see these particles replicate for 1 round after inoculation into a subject. They're disabled. And the idea then is that they'll make -- they'll induce antibodies to the pentamer along with another -- a lot of other gene products.

I love in the presentation how this idea of the cell-free workplace, a cell-free GMP facility. It's really very elegant because the Merck vaccine still very much depends on that, upon having cells, cellular production lines where you can make this virus particles. So well, how does this virus -- how does this vaccine work? It's gone into a lot of people. It's published now. And so this paper came out earlier this summer from Journal of Infectious Diseases, from Stuart Adler et al. And what Merck did was they did -- again, as we've heard about already this morning, they have a dose escalation study where different amounts or different quantities of the vaccine were administered to volunteers. One of the arms of the study also included an adjuvant, an immune stimulation molecule. We use adjuvants all the time in clinical practice, in your primary care clinicians' office for many vaccines. And so the best response is, for this V160 vaccine were seen with the adjuvanted form of the vaccine. And using natural immunity as a benchmark, as you see in the dotted line here, the vaccines at highest doses with adjuvant were as good as natural immunity. Well, that's great if the goal is to try to protect the women who's never had CMV. And you can at least can confer, for her, the equivalent of her neighbors who's had CMV in the past. We know that, that doesn't completely protect against infection, but it does reduce the risk, reduce the severity. But I think what we really need for a CMV vaccine program is something that's better than natural immunity. And think about that for a moment. You need a vaccine that's actually better than Mother Nature, and that's a big challenge. But if we're going to prevent reinfections and transmissions to the fetus, that's the goal.

And so this is where the preliminary data that we heard about from Tal is, again, very exciting because here is your benchmark of natural immunity, and we can see that the mRNA platform is actually better. So different laboratories, different manufacturers, different experimental conditions, wouldn't it be exciting to see these run side by side and head to head in the same lab? But at least, based on the published data and the data we've heard today, it suggests that the mRNA platform is superior to the V160 platform in inducing neutralizing antibody responses against that pentamer at that epithelial cell surface, which seems to be emerging as sort of a key parameter for CMV vaccines.

So what's the population that we need to immunize? And how do we deal with this problem of transmission from reinfection? This idea that even if you've had CMV decades ago, that it never really goes away. It's a latent herpes virus that reactivates, you can get reinfected with new strains. Of course, we face this with flu every year, don't we? A flu shot every year because new strains of influenza virus form that our immune systems don't have experience with. This slide makes the point that the prevalence of congenital CMV in the population is actually directly, not inversely, but directly proportional to the seroprevalence of CMV antibodies in women who live in that population. And so this, again, is what some authorities, some authors have called the enigma of CMV immunity, the paradox of CMV immunity. If you Google those phrases, you can find a lot of interesting papers that are pointing this problem out. This is one of the major issues of CMV vaccination.

Why do reinfections occur? This is a very highly cited paper by Boppana and colleagues from the New England Journal some years ago now, in which they looked at the acquisition of new peptide epitopes and use this to define the presence of a new infection in the women who already had immunity. These new reinfecting strains can then be transmitted to the fetus. Now they don't tend to cause much -- as much severe disease as a primary infection in pregnancy. But 10% to 15% of those babies may still go on to have hearing loss. And so an asymptomatic baby at birth that looks healthy and normal, if that baby has CMV, there's still a substantial risk. We don't recognize those

babies, as clinicians, because how can you make an asymptomatic baby better? This becomes a very powerful driving force for newborn CMV screening. That's a whole other conversation in its own right and an interesting one. New York State passed a bill this year that now has opened the door to screening some newborn infants for congenital CMV. And that might be a very exciting part of the post-vaccine licensure surveillance program if these vaccines move forward in clinical practice.

We heard earlier about the power calculations that would be required if the endpoint is disease in the newborn infants or transmissions to the fetus that Moderna has nicely laid out the rationale for, in their conversations with FDA, how an endpoint of preventing infection in the woman may be sufficient for moving a product forward to the licensure phase. And I think that would be very exciting and will be justifiable, scientifically.

And this, to summarize some of the issues with CMV vaccination and as they relate to who you would immunize. And so we've had some discussions earlier today about how the adolescent would probably be the key target. And that makes a certain amount of sense, giving to young women before they enter their childbearing age. Waning immunity for vaccination could be a problem, though, if you immunize a 12 year old. And that immunity needs to last until she's in her -- into her 20s or 30s or even 40s, during her childbearing years. So how many boosters would be required? Would there be -- would it be better to have a strategy of immunizing women within the context of obstetrical practices? There's even been some discussion about how immunizing all toddlers in group daycare might be the best target population. Let's get this virus at its source because toddlers in group daycare centers are often the vehicle that brings CMV home to their mothers, who is becoming pregnant, are then at risk. And so I think this will be an interesting discussion moving forward, who should be immunized?

And so these are again just some of the other populations. Universal vaccination of all children, seronegative women. We'd probably need to immunize seropositives as well, although the Phase III studies will, I think, most likely be done in seronegative. And these are important issues moving forward.

I'll just finish then by mentioning a little bit of the last challenge as I see it with congenital CMV vaccine, which is nobody knows about congenital CMV. I've had hundreds and hundreds and hundreds of babies over the years with congenital CMV that I've seen in my clinical practice or in the context of clinical research studies. And almost without exception, I've never -- maybe I can count on one hand the number of times a woman or a family have told me that they have ever heard of this before it happened to them. And that's a problem.

Many of us in the audience with gray hair remember the public service announcements back in the '60s, I remember the '60s, for rubella, right? If you're pregnant, you should be careful. If you're around a child with German measles, you should get immunized. We don't have that same sort of media awareness, media savvy and knowledge of. And that's a problem. And so one of the things I love about democracy is that when it works well, it comes from the people and win as voted with their feet. They've talked to their representatives.

A mom, who I worked with in Portland, Oregon who had a child with CMV, actually met her representatives at Starbucks in Sellwood, if anyone knows where that is, and this is not an advertisement for Starbucks, but that's how they initiated the conversation. It went from that to a bill in the Oregon legislature to a debate on the floor to success. And so they had legislation now that tells the state health department that, "Hey, you've got to fund programs to tell women about CMV and inform them."

And of course, when the medical school found out about this, they were a little bit mad because they weren't included in the discussion. But a lot of states have done this now. And we have a similar bill in Minnesota that we're trying to get through. I've mentioned the legislation in New York. These bills have a com -- a number of unique flavors that vary from state-to-state. Some of them are, the best ones I think, are the ones that are done in past with the collaboration and cooperation with the state health departments. It's hard to get a fiscal note for a lot of these. But the best bills are the ones that are funded to provide resources to increase education and awareness.

Some of these bills are linked to a mandate that says if a baby in the newborn nursery fails their newborn hearing screen, which about 1% of all babies do, they just don't pass their newborn hearing screening, that baby should be tested for CMV. The first bill in the country actually had this mandate in Utah. And that's led to a lot of interesting data. So this is a big challenge, I think, of the CMV vaccine field. I think any program of CMV vaccine, any Phase III studies that move forward, really ought to be done in conjunction with resources earmarked for knowledge and awareness to help put this on the landscape.

The CDC has done a good job in recent years of increasing awareness. And the web page there has a lot of valuable information. And it's been a much, much more highly emphasized part of the CDC mission in recent years. This is [Kelly Fenton], who's a state senator of Minnesota, and introduced legislation. And actually one of my patients is right here. I won't play the video. You can look at it if you'd like on YouTube.

But I'll conclude and just say there is a major public health need for congenital CMV vaccine. There are a variety of vaccines in the clinic. I hope I've made the point about the importance of the pentameric complex and antibody responses to that and gB presumably working in synergy to block binding of the virus to the cell and prevent infection.

We've also talked about how live attenuated vaccines probably have some safety concerns that subunit vaccines based on individual cloned genes don't have and these 4 areas of knowledge and awareness that I think are needed as the vaccine field moves forward.

So thank you all for your attention. I look forward to the question-and-answer period.

Laura Riley,

So good morning. My name is Laura Riley, and I'm a high-risk obstetrician here in New York now, but now I was at Mass General for 23 years. Not only am I high-risk obstetrician, but I also did a fellowship in infectious disease. So I've spent pretty much my entire clinical career, unfortunately, taking care of moms with this disease and then helping to follow them through pregnancy.

So I think you've heard a ton already. Probably everything I was going to say, you've already heard for 2 or 3 speakers. So I'm going to tell a story and then sort of explain why I think, from an OB standpoint, why I think the vaccine is absolutely critical and why I think we haven't made very much progress in the last -- over my entire career for these children.

So the story I'm going to tell, I can tell because it's already been published. It was a case reported in New England Journal and it was a patient of mine. A woman who is 42 years old, 41, 42 years old, she had years and years of infertility. And she had tried everything known to mankind to get pregnant. She and her husband were unable to get pregnant, so they decided to go to Ethiopia and they were going to adopt a baby.

And so they sort of went through that whole process. She goes off to Ethiopia. She has to spend, I think, it was like 2 or 3 weeks in the adoption agency just getting used to the baby and doing everything that you need to do to get all prepared. She did all of that. She's a totally healthy woman. She did all of that. She stayed for 2 or 3 weeks. And when she came back to the U.S., she had a low-grade fever. She didn't feel herself. And so she went off to her PCP. And essentially, she had mono-like illness and so they screened her for CMV.

It took a little while to get there. But on top of it, this is someone with years of infertility, she was pregnant. So -- and she wasn't using birth control because she didn't think she could get pregnant. And so it was just like a perfect storm, it was horrible. So I've actually met her at 14 weeks gestation. She was probably 9 or 10 weeks when she got this mono-like illness. It turned out -- long story short, it turned out to be CMV. For this woman, it turned out to be probably primary CMV. And it was a difficult diagnosis to make. The CMV, we didn't catch, which is what we all rely on to tell us sort of the general timing, led me astray actually, didn't give me the information that I really needed to do a good -- to do good counseling in this patient.

Long story short, we ended up doing -- because it looked like she had primary CMV, looks like she probably had it sometime in the first trimester. And I'll show you some data why we are concerned about the timing. She decided to do an amniocentesis. So now she's home with her 2 Ethiopian children that she has adopted. She's newly pregnant. She's incredibly excited. And we have this discussion. I say, "Look, you need to have amniocentesis." We do an ultrasound. The baby looks pristine. Everything looks totally perfect. And I'll explain to you why that was important. And we do an amniocentesis. And within 12 hours of doing the amnio, the lab called me to say, "This baby has CMV everywhere. Like this is the fastest we've ever seen this strep." I'm thinking, "Oh, my God, PCR positive, everything."

So I have this long conversation with the patient. I tell her what we know. And given the timing and given all the possibilities, this woman, this couple is devastating. And to this day, I have goosebumps sort of over this conversation. Here's a couple that's wanted nothing more than a baby for 10 or 12 years. They finally get there, and I tell them this devastating news. And they decide, "Well, we've got 2 kids, we can't take any chances." And so then we have to do a pregnancy termination. And now we're doing a pregnancy termination at like 18 weeks or -- no, actually it was beyond that because we waited awhile to do her amnio. And so she was maybe 21 weeks gestation. This is not a good situation for any couple to ever have to be in. It is uncomfortable for the person doing the counseling at not being sure about what you're saying and you're steering people in a direction maybe, maybe not. You're putting them in difficult situation. So this is kind of where I see it all as one of those people who's stuck in that small consult room trying to help people make these difficult decisions.

So I'm going to show just a little bit of data. This is the OB's perspective. So you've heard this before. I think these are the epidemiologic factors that we're concerned about. I think one of the speakers said early on, I think it's really important to understand that this is a disease or CMV, I should say, seropositivity is much more common in patients with lower socioeconomic status. It's seen much more commonly in black versus white patients or patients with Mexican ethnicity. And it's seen obviously in those with higher parity as well as residence in developing countries. And so if you think about it, the people who have highest risk for becoming seropositive with CMV are usually the ones with the least resources to actually take care of these children that are now devastated.

The other thing that's really obviously very tricky, and you've heard a lot about this, is the fact that there's multiple routes of transmission. And so when we talked about how do you counsel pregnant women? Well, there's a million things you're telling them that they can't touch the candies, they can't do this, they can't do that. It really is not

practical, which I think is the other thing that's really important here. So what are the annual seroconversion rates? So let me just state the background piece of information, just to think about the U.S. alone, there are 4 million births in this country a year. And so we're talking very large numbers. And when you look worldwide, we're talking about a lot of children who have the potential to be devastated.

So if you look at just pregnant women in general, this is just one study in the literature, but it's the one that most of us use in our thinking about this. Looking at all pregnant women, the seroconversion rate per pregnancy is about 2.3%. I think what is more important or equally important and becomes a counseling issue is those that are daycare providers, those that are stuck sort of with the kids slobbering all over everything and it lives on the surface of every toy and then they give it to each other child, including their daycare provider, that's really important. And then as you can see, the parents of children who are either shedding or not, not shedding actually, is also an important vector.

And so in terms of maternal disease, these are the things I think about as an obstetrician and become important when we're trying to counsel patients about what may or may not happen. You've heard primary CMV. It maybe symptomatic, but for the vast majority of people, it's asymptomatic. This patient sort of came in with a placard saying, "I have CMV." She had the mono-like illness. But the vast majority that I've seen in my career didn't have anything going on. And so we figured out the CMV from their children rather than from them. Reactivation again may have -- of latent CMV may have absolutely no symptoms. So it's hard for us as OBs to know that this is something we should be worried about. And then obviously, reinfection with a different strain, maybe you have symptoms, maybe you don't, most don't.

So here's where we're left in obstetrics. So the current recommendations -- because of all of the things that you've heard this morning, the current recommendations are really only to test pregnant women who have that mono-like illness because you need to understand that. The second biggest group that gets tested during pregnancy are going to be those women who are carrying fetuses that have anomalies or findings that could be consistent with CMV. And it can be quite the hunt.

This first ultrasound on the right, this baby has calcification, which is something that we're always concerned about. The second one is hyperechoic bowel. So the bowel is bright like bone. The problem with that one is that you end up doing a lot of CMV screening for kids that have a whole bunch of other things. So if the baby swallows blood, it has echogenic bowel. If the baby has Down syndrome, it could have echogenic bowel. So it usually isn't CMV, but we have to look for it. And then the last one is again -- I'm sorry, so the first one had large ventricles, so ventriculomegaly. The last one is calcifications in the brain. Any of those things that we see will prompt us to look for CMV and other viral infections.

So in terms of transmission rates, this is the data that we use to sort of counsel patients once we figure that they have primary CMV. And we -- the transmission rate, I should say, also depends in some ways on the gestational age at which we're doing the counseling and guessing on the timing of the infection. And so you can see that there is some transmission even if they get the infection just prior to pregnancy. The reason this becomes an important issue is because what we see not infrequently these days is that people doing IVF actually will test for CMV.

And when they do that, every now and then, they get someone who's going to be CMV positive and then we try to figure out when was it. Was it far enough prior to getting your blood drawn that we can still do your transfer? You can just imagine, you take in a bajillion drugs, spent $20,000, ready to have your IVF transfer. And they come see me and I say, "Ugh, it's probably not a good idea, you should wait 3 months." That doesn't go really well either. And then the other issue obviously is these other trimesters. I think the main point about this in terms of transmission rate is that transmission happens all through pregnancy. So there's no safe time. And that's very disconcerting for patients as well.

And then the timing of the infection is important for a whole bunch of reasons. But certainly important when you're talking about the level of damage potentially to children, right? So when everything is being formed, when all those organs are being formed in the first half of the second trimester as well, that's when we see the most damage. But the brain is developing all through pregnancy right until the end and kid's out and first year of life, in which case anything that can affect that is going to affect the brain, hence, the neuro developmental delays that we see.

The other reason that the timing is important is because in most states in the U.S., you can only terminate pregnancy up until 24 weeks gestation. And in some places, you can't terminate at all. So that's its own conversation. But it's an important one because that's really all we have to offer patients, when they find out that they have that diagnosis and they decide they don't want to continue the pregnancy. So we sort of have this time frame that we're working in as well.

So this has come up a couple times. I think it's important obviously to recognize that women will have reactivated disease as well as infection with a new strain. That's important. I think what's controversial is the severity of disease. It's very much less likely to happen. Is it less severe? I think it's kind of all over the board. But at any rate, thankfully, it's far less likely to lead to what you see on the right. This baby has microcephaly.

So in terms of reactivated and reinfection, I think the reason to even focus on it is because we know that, that's probably the genesis of most these kids with congenital infection. The true impact, I think this is a statement that is very true, I think we don't really understand 100%. And part of the reason we don't understand 100% is because we are strapped with just making the diagnosis during pregnancy, the only things that we have to make the diagnosis during pregnancy are CMV-IgG, CMV-IgM and then CMV avidity helping us try to figure out the timing.

The problem is that those tests, like if you were to test most people, you're going to get IgG-positive, IgM-positive, you don't know when the infection happened. And then you're stuck to kind of guess when it happened and try and make some decision on telling this poor couple, "You should do X versus X," very difficult.

So the current prevention strategies, I've gone over this, there is no routine screening. And the reason there is no routine screening is because quite frankly right now, there is not much we can do about it. And we're very concerned that the screening could lead us in the wrong direction in both ways. We'll miss people who are infected, who could have a devastated baby and also there may be people who we say, "Well, we think there's something bad is going to happen," and then they end up terminating a totally normal pregnancy. So it's not a good situation.

In terms of what should we be doing? Well, right now, the push is on education. As you just heard from our last speaker, trying to educate women about personal hygiene and kissing children less than 6 years old. I mean really like do you really think that works? I say all these things. But I can tell you, people just look at me like, "Okay, Dr. Riley," and they move on to the next thing.

The breastfeeding situation, we know that it is in breast milk. And I think this does come up occasionally. People will say, "Is it safe to breastfeed?" In general, people feel as though the benefits of breastfeeding outweigh the risks associated with there being CMV in the breast milk. And if there's a recent infection, wait 6 months. So I write that down there because I see a lot of patients, this thing in New York is to get pregnant at 50, I have found. And so when we're -- when we're doing all these consultations for the IVF crowd and they get this new CMV infection or it's the first time anyone tested for it, that's really the issue, I have to tell them, "Yes, save your money and wait until you're 6 months before they -- 6 months out before they do your transfer."

This is the public awareness that our last speaker so nicely went through. So I'm not going to belabor it. There is -- I think that the public does know about it. I think that, unfortunately, it's the public that's already got the baby that's been infected. They're the people that know about it. And everybody else is kind of like, "I never heard of that. What are you talking about? And it's all quite scary."

So what are the current treatment strategies? So there aren't any basically. We got very excited when a paper came out in the New England Journal all about CMV IVIG. There was so much excitement. And we went from that to, "We're going to give it to everybody who we think has it," and does it work, right? So another paper came out, a really well-done randomized trial came out, which suggested that it just doesn't work. So we don't have anything. The only thing that is going to help us prevent congenital CMV is going to be your vaccine, that's it. That's all we got. And antiviral medications seems like a great idea, except that most of those when used in the feed -- used in the mother are actually toxic to the fetus. So we're sort of left with what you can do once the baby is out, not what we can do during pregnancy.

So this OB's perspective. So here's the thing, these are the things I worry about and these are the things that are going to keep me up at night when you launch this. So is it really safe? And I think that you guys have convinced me that you will do all that needs to be done to tell me that it's safe. Is it efficacious? Clear that it's going to work. And is it going to be durable for all the reasons that we talked about already? When are we really going to give this? And when people say childbearing, well, don't wait until 15, forget it, because there's the 13-year-olds out there. And then when you say, "Is it going to work if you give it at 13," when I see all my IVF ladies and they're 48, I hope so. So we're going to have to think about that. And then obviously, it's a much-needed intervention. Look at the numbers, right? So, so much can be done.

So with that, I will close.

Stéphane Bancel, Moderna, Inc. - CEO & Director

Well, I would like to thank our 3 speakers for those very nice lectures. Thank Tal and Juan and their teams for the work done over the years. And as I said, I'm already happy that for the first time since 2011 (inaudible) in commercial.

So as Tal earlier described to you, our plans for CMV is the following. We want to go to a Phase III looking at CMV in connection with CMV infection in healthy women. To get there, we're going to run and start in a near-term Phase II that we think is going to be very rapid, 252 healthy subjects and we'll use a 3-month interim data point to trigger the Phase III start.

So how do we think about this vaccine? So we obviously think that CMV has a blockbuster commercial opportunity, as you heard today, an extremely large medical need, no approved vaccine on the market. If you think about the product

lifecycle, which we think is very important, and if you look CREB now with Pfizer and HPV with Merck, it's a very important part of already maximizing the impact we can have with our vaccine.

We want to start with women of childbearing age because we think it's a very motivated population as where the medical need is obviously and want to start there. Then with what we've seen with HPV, you want to go down to adolescents to broaden the protection in the population. And as we have alluded this morning, we have a possibility because I think most people don't appreciate that the reservoir of CMV are humans. Flu is birds and pigs. Zika is mosquitoes. The humans are the reservoir. So we have an opportunity to have a massive impact on public health if we're able to have a vaccine that's durable and that is given to infants.

And so if you think about that opportunity, if we think the addressable market is extremely large and if you just take a few different assumptions that you could have on what you could do after starting from the base of healthy women to go into adolescents and to go into children, you could have very, very large numbers. Just to give you an order of magnitude, the MMR vaccines have sold 200 million vials in 2018, just last year, 200 million vials around the world. So we think this is a very large opportunity for us.

We think from a commercial standpoint, the bigger part is going to be around OB/GYN and then pediatricians. And we think there's a great opportunity, both for the Phase III enrollment and for the commercial uptake to use social media and to be able to really educate about the disease. And what we spent quite some time doing already over the summer is to think about what activities are we going to start to do from 2020 to really accelerate the uptake of the Phase III because, of course, the fastest you can enroll those subjects in your Phase III, the sooner you can file your BLA to the FDA. So it's critical for time to launch.

And all the activity that you do once you get to prelaunch are very important for the ramp of a product obviously. So we're going to start partnering with all the associations, both regional and national and around the world that care deeply about CMV. We think there's great work to be done to partner across the board. We want to really start educating, starting initially from today that now the data is public, the team is going to publish the data and going to start to go through several OB/GYN conference, medical conference around the world. So the team is going to start spreading the data to educate about mRNA vaccine or product and the data you've seen today with much more details.

On the education front, there are 2 things. Both work inside the offices of the clinicians with pamphlets and information, so people understand the disease. As you heard today, we do not talk about this virus a lot because there's nothing that can be done and worrying a pregnant woman or woman who wants to be pregnant is not a very good idea when you can do nothing about it. And so we think that is a great opportunity to educate about the virus.

We have seen the CMV Foundation already having pamphlets trying to use Zika because Zika, even what happened in Latin America, has been really described a lot in the media. And so because of the similarities between Zika and CMV, it's a great opportunity to use the understanding of Zika to educate around CMV. So we want to do a lot around that. And of course, driving the awareness of the product.

If you think about pricing, and I'll come back to it in my conclusion later, just to give you an order of magnitude. GARDASIL, the HPV vaccine in the U.S., has an average selling price of around $450 per treatment. So for a few doses, $450. And as we've seen with vaccines, vaccines have very, very long life cycles. And we believe this is a great opportunity for us to have an impact. And if you think about what Juan said is the fact that we believe, given our cost structure at this type of a GARDASIL price point, this product could be with a 90 margin -- gross margin product that will provide a 50% EBIT margin opportunity. So we think it's really, really exciting opportunity.

We care deeply about the fact that we own the global rights to this vaccine. And so we're already in the driver's seat. And we believe that the best way to have a great launch and a great impact on patients and public health is to really start working from now to educate about the virus; to educate about the data that we have from the Phase I and soon sharing the Phase II data; to be able to really uptake from a Phase III and have a quick launch and then a good, big commercial update.

So that's the current plan. We will give you more details as we continue to polish that plan. But we're going to be spending a lot of time with the team in the coming months and quarters to really sweat all the details to make sure we give justice to this vaccine as we impact as many women and as many families as we can for the long term.

So with this, what I would like to do is to get onstage all the speakers for the CMV section of the agenda, so we can take a section of Q&A before we go into a little break. So Tal, Juan, Mark, Laura, Sallie, if you don't mind joining us? Thank you. Sallie, do you want to (inaudible) questions. So if you have questions, we have a couple of mics going around. You just raise your hand, we're going to start here just in a second.

QUESTIONS AND ANSWERS

Answer – Alec Warren Stranahan: Alec Stranahan from Bank of America. Just a couple of questions from me. My first question is on the dose collection in the Phase II. In the Phase I, you dosed up to 180 micrograms. Then in the

Phase II, it looks like the top dose is 150 and no real indication of anything higher like a 300 dose up. So does this mean you're satisfied with the neutralizing antibody induction of (inaudible) in the Phase I? Sort of what's the rationale for the dose collection in Phase II?

Answer – Tal Zaks: Yes, so let me take that. I think we are very happy with the immunogenicity that we've seen so far. There's not much, if you look at the data, to distinguish the 90 from the 180. There does seem to be a little bit more action on the dose. The safety profile overall is similar. But when you go into a Phase III, you want to be sure that you've got the right dose. And so what we've done is hone in a little bit on the dose range. The 300 is still ongoing. We will be -- have the opportunity to see data from it just before we launch. So if we need a course correct we'll be able to. We've enrolled everybody there. We've seen safety through the second dose and we don't see any surprises there. So if I look at this level of immunogenicity, it feels like we're there. We just need to confirm that we've got the right dose with some bracketing around it to go into a pivotal trial.

Answer – Alec Warren Stranahan: And then my second question is on durability that you'd want to be seeing in the Phase II and probably in the Phase III. So through your interactions with the FDA, what sort of length of follow-ups do you think you'll need? Obviously, it sounds like (inaudible) rate might be the registrational endpoint of that study. So just wondering if that follow-up would need to be a year or something before you submit or if that would be sort of closest to commercial launch, that follow-up study.

Answer – Tal Zaks: I don't have an answer for that yet. What we've had in our initial discussion with the agency is to understand the endpoints. I think we'll go through the usual process of an end of Phase II discussion and aligning with them on exactly the pivotal trial design and duration and endpoints before we launch it. So I can't comment on that. In terms of -- I expect that -- if you look at the history, I expect that within a year, we expect to collect the rates that would be required to actually demonstrate that significance, so your point is valid. In terms of the durability, by the time we get there, we will have even more data on the entirety of the study in Phase I. Over time, we'll have more data emerging on the Phase II. So we'll get wiser over time in terms of those numbers.

Answer – Stéphane Bancel: Matthew?

Analyst: Unidentified Participant,

Question – Unidentified Participant: Two questions for me. I guess one on the Phase I on the sentinel patients, you have here the epithelial cells, so we have an idea against the pentamer but not gB. Can you just give us an idea of durability against gB. And then second question is can you be clear of what was discussed at the type C meeting? Was it just primary endpoint and then your ability to think about what this study needs to look like after that, or what other factors? I guess you mentioned durability, right? But maybe be clear about what other factors.

Answer – Tal Zaks: Yes. So let me answer both. First, in terms of durability, we see similar data on gB just like you can get to the levels of seropositive in gB and the seronegative, you can maintain those out to 12 months. We think the relevant point here is pentamer and that's why we've shown it. And these are early days. Once we have the full durability for the entire study, we'll show you both against pentamer and gB. Look, the type C meeting, there's a whole bunch of questions as there usually is. Some of them have to do with our manufacturing. Some of them have to do with the study design. I think the salient one for us was an understanding on the endpoint in terms of how you eventually get there. That was, I think, the one that was the most important for us. And that's why we're showing it.

Question – Unidentified Participant: And can you -- the 8,000 patients that you referenced, can you just talk about what kind of -- I mean how you got to that number because I think one of the physicians presented, I think I saw numbers that were like 2,000 to 5,000 or something. So I'm just wondering what sort of criteria you're looking at.

Answer – Tal Zaks: So let me be very clear because I did not discuss trial numbers or faced that level of granularity with FDA. And as I said, that will happen later at the end of Phase II meeting. The numbers are a function of the incidents that you see and some preliminary extrapolation. So we may be able to do with less than 8,000. The notion here is if you find the right population where the annual incidents of cases would be 2% or so, 2 to 3%, if you can get there, then you can now calculate the math yourself and figure out what the relative power is you would need to show that. And that's how we come to that range of numbers. Of course, in a trial like this, and I've got people who have far more experience than me here onstage, but what you typically do is make sure as the study progresses, that you're actually collecting enough cases that you're appropriately powered so that if the actual incidents in your trial population is lower, you'll end up extending one larger. If you're there or higher, great, you've got that. So that's typically how I would think about the numbers.

Answer – Stéphane Bancel: Okay. Ted?

Analyst: Edward Andrew Tenthoff, Piper Jaffray Companies, Research Division - MD & Senior Research Analyst

Question – Edward Andrew Tenthoff: Just to kind of flesh out on it a little bit more because it sounds like an efficacy number. Do you have a vision that you would require a larger safety database? So would it be a single Phase III study? Or do you think even in that kind of 8,000 range and with the prior subjects says that you would have sufficient safety data?

Answer – Tal Zaks: So I -- my assessment, at this time, is I think that number should suffice in terms of a safety database as well. I also think that, that number may end up including seropositives, not just seronegatives. To the point of the power calculation, you may be able to get there with fewer subjects on purely seronegatives. You're going to need to show, overall, the safety profile for seropositives as well because we expect ultimately to get an indication that doesn't distinguish between the 2. So that's how I would come up with the numbers.

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

Question – Hartaj Singh: Hartaj Singh with Oppenheimer. Just a couple of questions. One is on just, Tal, you were talking about the background rate. You've got a lot of data presented in the United States, your Phase III will be worldwide. Is there a potential that you're looking at ex U.S. sort of the background rate of CMV infection just to see some differences there that would also affect your power? And how would you sort of approach that? And I've just got a quick follow-up.

Answer – Tal Zaks: Yes. So our work is only beginning in terms of feasibility. We are looking globally. We're looking primarily at the major places in Europe and similar geographies, similar in terms of incidence rates so that the Phase III, when we launch it, is purely homogeneous in terms of expectations.

Question – Hartaj Singh: And then just a follow-up. I believe that vaccine, the uptake is usually also driven by a lot of organizations, ACIP, et cetera, it's not just legislation, which I think helps a lot. What are some of the things you're thinking of doing going forward so that by the time, assuming the vaccine, the patient trial is successful and gets approved, that it just becomes like algorithmic-driven, right, in terms of uptake?

Answer – Tal Zaks: So my colleagues here can comment about the role of ACIP and what we need to demonstrate. We've had initial discussions with the folks down in CDC. Obviously, in order to get a recommendation, you need to show your overall benefit/risk and value proposition, which I think in this disease is going to be quite clear. I don't know if any of you want to comment on sort of from an ACIP perspective what that would look like.

Answer – Laura Riley: Well, as a former member of the ACIP, I would say that, that's exactly what we're concerned about, right? Is it going to work? Obviously, cost effectiveness is huge now. Although the absolute vote within the ACIP, we're not supposed to take into consideration cost effectiveness. But it's always presented in the workgroup. And it does -- I think it does influence in many ways what we do. And I think the deal with this vaccine is going to be CMV is the most -- congenital CMV is the most common congenital virus and so -- that we see in the U.S. and probably globally. And so I think that there's -- it's going to be an easy argument, to be quite frank, assuming it works and it's safe.

And then you bring up another point that I think is really important. I think the timing for the vaccine is critical and a good one in the sense that finally, we're at a place where I think everyone believes that vaccines during pregnancy should be done for prevention and so it's appropriate to test during pregnancy. There used to be this, you can't touch a pregnant woman because of the potential effects on the baby. And so I think with the advent of H1N1 and all these other vaccine-preventable diseases sort of wreaking havoc in the population, people are coming around to the necessity.

Answer – Tal Zaks: Thank you. I'm going to take 2 more questions and we'll have to move on.

Analyst: Unidentified Participant,

Question – Unidentified Participant: Yes. First, a comment and then a question with maybe a follow-up. This is a real moonshine vaccine. Because not only does it have 6 RNAs in it, but 5 of them encoded pentamers. So if any one of those RNAs don't work, the pentamers may, right? So it's really a complex vaccine. Now my question is about cell-mediated immunity. I mean I know you're right to focus on the antibody immunity responses because they can block virus infection, right? They're neutralizers, it's great. I mean it's a great end point. But the great thing about our vaccines is that cells take them up and they make the proteins (inaudible) and those proteins can be made into peptides and they get presented on the cell surface through MHC, so they're going to do cell-mediated immunity, which subunit vaccines can't do or they have a very hard time doing it all.

And so I'm very curious if you're getting any cell-mediated immunity. Because there are cells in the body that are producing the CMV virus. And if those cells can be killed by cell-mediated immunity, the virus titer is going to go way down and you also not only helped that person but prevent transmission to other people. So -- and the last speaker

before Stéphane spoke about shedding of virus. So obviously, you folks can measure shedding. And I wonder if we can measure either the cell-mediated immunity or the shedding in any trials or future trials?

Answer – Tal Zaks: Let me try to answer it. We're looking at shedding. And I'll ask Dr. Riley to answer that question because it's of keen interest to me especially in the seropositives. So for full disclosure here, I'm actually not a vaccinologist, I'm a cancer doctor, and I've spent most of my career being a complete T cell chauvinist and believing that's what's important. I think when I step back and look at Shingrix, which is a one subunit that's seeing -- that's had 97% efficacy against preventing reactivation of persistent infection, I think that teaches us that T cells may be important, but the ability of subunits just to generate antibodies may actually have a profound and deep effect. So I think in the context of this virus, it's unclear to me what the importance of the T cell would be.

That being said, by virtue of mRNA's ability to make proteins from within the cell, while I haven't shown you any data and we're working on measuring it, I'm pretty sure that we're able to elicit T cells because everywhere else that we've looked, we've seen the ability to generate T cells. I just don't know how important they are as the core of the protection or how to get there from a measurement as I am in terms of my confidence in the antibody levels.

Answer – Sallie Permar: So I'll just tell you from preclinical nonhuman primate standpoint, one of the things that I've took on in this field is trying to develop a nonhuman primate model of congenital transition, where we could test vaccines. But first, we didn't know if the viruses in primates that are similar to the human CMV virus actually crossed the placenta. And so we took about a strategy of immunosuppressing the moms and then infecting them with CMV to see if we could see it. And when we depleted their CD4 T cells of these pregnant [dams], we infected them with CMV. All of the fetuses got infected. And all of -- 80% of the fetuses were aborted. So we saw much more severe infection of the fetus and 100% transmission in setting of absent CD4 T cells. We don't know if that...

Question – Unidentified Participant: What's the percent of transmission when you didn't deplete the CD4 cells?

Answer – Sallie Permar: So small numbers so far. But it was at about half. So 100% versus less than half, kind of similar to the human situation, so -- but we don't know if that the T cells are needed for high good antibody responses or the T cells needed to kill infected cells. mRNA vaccines traditionally, what data is out there, induce great CD4 T cell responses. So I expect to see that.

Question – Unidentified Participant: So CD8 T cell depletion would be very interesting.

Answer – Laura Riley: We're going to do that in the new grant we just received from the NIH.

Answer – Tal Zaks: Question over here.

Question – Unidentified Participant: What plans do you have to introduce the viral challenge to confirm the fact that you're providing protection here? And then maybe a second question on whether you anticipate that a seronegative patient would need a booster at some point to remain above the seropositive level?

Answer – Tal Zaks: I don't think a challenge study is feasible here, certainly not a human challenge. I think we've agreed that animal models are available. And we've already done them and shown that it works. So the next step is really the human study. So how much higher above the levels you need? I think that's an unknown and one of the things that we are going to have to figure it over time as we measure both the durability of our vaccine and its efficacy in the real pivotal trial. I think further that, it's going to be really hard to answer that question. Bob, you had a question. I'm sorry, I just saw Bob raise his hand.

Question – Unidentified Participant: Two quick things. Very nice, awesome presentation. Two quick things. One, just -- I'm sure this is true, but these proteins are invariant across strains?

Answer – Sallie Permar: Variable strains.

Question – Unidentified Participant: Strains, or geographic variability of the antigens you've given.

Answer – Sallie Permar: They are not. There's several different genotypes that make up each of the glycoproteins. So that's one thing that we've been studying in the lab and we'll be interested to see how it plays out here. I think something that can be done in the clinical trial is sequencing the virus that is actually acquired by vaccines to see if there's a shift in the vaccines, what viruses they're acquiring versus placebo recipients to see if the vaccine -- if we see protection. Or even if you don't see protection, were they protected against the strain that the vaccine was made against? Or were they protected against all strains?

Question – Unidentified Participant: So is there already evidence in your model that only certain strains are protected against?

Answer – Sallie Permar: Very little. It's still an unknown question, I would say. We are looking at it in the old vaccine trial.

Question – Unidentified Participant: And any sense of the fraction of the U.S. population of the prevalence that would be covered by the existing sequencing?

Answer – Sallie Permar: Which is it again? Which strain again?

Question – Unidentified Participant: The prevalence -- the U.S. prevalence to CMV, what fraction of it?

Answer – Tal Zaks: So I believe this is the one that's the most prevalent, but I'll get back to you on the (inaudible).

Question – Unidentified Participant: And then one small question. The press release mentioned 1 Grade 4 elevated PTT, which I just wonder if you could say anything more about this.

Answer – Tal Zaks: Yes. It was a subject that had a somewhat abnormal baseline. It was temporarily associated with getting the first or second dose. We got the subject back for follow-up by the time we found them. And 10 days later they came back, it was back to normal. And there were no clinical (inaudible) of that whatsoever. So technically it reached the level of Grade 4...

Question – Unidentified Participant: What do you make of that? I mean what does that allow there? Or was that what you think is a real finding?

Answer – Tal Zaks: I don't think is a significant finding. It's not something we've seen anywhere else. I think it's in -- from my perspective, I don't think it's of clinical significance.

Answer – Stéphane Bancel: So can I just suggest one thing just process-wise? We have another Q&A session at the end. I just want to be careful, we have a very heavy agenda and we are already a bit behind schedule. So I guess maybe a 10-minute break. There's coffee just outside. So we will start (inaudible), okay? Thank you.

(Break)

PRESENTATION

Tal Zaks, Moderna, Inc. - Chief Medical Officer

So for the next section, we're going to be talking about immuno-oncology, and then we'll get into the rest of our programs. To sort of set the stage and give you a sense of what it is we're trying to achieve in this part of our pipeline, I'm going to start with the cancer vaccines modality. In a nutshell, what we have here is a personalized cancer vaccine that we've been talking about for a while, and we've -- we're now in the clinic. We in fact have started the randomized Phase II. And the KRAS vaccine, which is a part of a partnership with Merck, if you step back and ask yourself, okay, why does mRNA make sense in immuno-oncology? Everything I told you before is true about the ability to simulate the immune system. It is also true that we can get -- by injecting the mRNA into a tumor cell, we can actually change the local microenvironment. And that's a unique feature that's sort of taking it a step further from vaccines and into localized therapeutics in a way.

We can engineer the mRNA so that we avoid off-target effects. So if any of this mRNA finds itself in organs we don't want to, it'll actually get shut off and we've discussed that in the past. And so we think with these features of being able to do combination, being able to get into the tumor as well as induce the vaccination, it opens up the opportunity for many applications.

Now with -- always, when you have a wide opportunity, so you have to ask yourself, okay, what is it that strategically I'm trying to do? And what made sense for us from the get-go here was really to build on the ability in our modern understanding of what the immune system can do for cancer patients and our ability to modulate that and try to use our technology in ways that would further boost that. Dr. Flaherty will come up after me. We'll talk a little bit more broadly about where the field is. But for us, it's an opportune time to use mRNA technology to try and boost the inherent activity of checkpoint inhibitors. And if you think about ways in which you can do that, I've sort of already described one, which is a vaccine and if we could vaccinate against cancer as a therapeutic vaccine, that would be great. And the other obvious place to go is, can you change the local microenvironment so that you're turning -- to use oversimplification, you're turning a cold tumor hot, and in the background of checkpoint inhibitor, you're now unleashing the immune system in a more potent way.

In terms of why this should work for a T cell vaccine, just to give you the cartoon version because mRNA translates proteins from within the cell, we end up presenting the epitopes to T cells in the way they're presented naturally, in a way our immune system has been trained over eons to actually recognize peptides. And so we're leveraging that potential from basic biology in order to generate T cells, which actually tells you if you think about our CMV vaccine, all those proteins that are getting made and shuffled as proteins to make antibodies, there's a part of that protein that you would expect would get shuffled into the MHC molecules and actually lead to T cell production.

Now for a personalized cancer vaccine, this is not just a theoretical, it's actually a manufacturing tour de force because what we do here is we start with a biopsy from a patient, and we fully sequence it. And from that point on, all the information we need from that patient is up on the cloud. It's all digital. There's a bioinformatics process that happens on the cloud that actually picks the best epitopes, and then it comes back down to the manufacturing site to make a bespoke vaccine just for that one patient. We started on our first application with a concatenate of 20 neoepitopes, and we've recently increased that to 34. So our personalized cancer vaccines now pack 34 neoepitopes that are predicted to be the ones relevant for that patient's immune system to recognize cancer into every vaccine in a bespoke manner just for that patient. We've done now over 60 or 70 of these. We can consistently get this done in approximately 50 to 60 days. We're working on ways to even further shorten that.

What we do here is once the vaccine is ready, we actually start repeat immunization. So now every time, every 3 weeks, the patient will show up to get their KEYTRUDA, they actually get a vaccine. So we've now given this repeatedly, every 3 weeks, up to 6 months. We've done this now at 1-milligram dose. If you recall the dose of the infectious disease vaccines, we're talking about 90 to 180 micrograms. So -- and that was already a dose that was quite potent. In oncology, we've taken it a step higher because obviously, you want to make sure that you get the most that you can, and so we've got already a buffer from the infectious disease vaccines where we know we're already potent as an immunogen.

The side effect profile has been benign. We've seen no great 3s or 4s in the study that we've done so far. It's been fairly well tolerated. These are the data just very quick recap, this is the first subject we treated in the Phase I study at the 1-milligram dose first for which we have apheresis data, that's a procedure where we actually collect a lot of lymphocytes so you can actually do very refined measurements of the activity of the vaccine against every epitope. And the salient point here is that there were 18 epitopes that were predicted to bind to the Class I to this part of the immune system. And of those 18, we actually proved recognition in 10 of them, so a hit rate of about 60%. Now how good is that? Well, I have to tell you based on pre-existing literature and what the competition has done, I have set 60% as a benchmark for our success sort of going into this a few years ago, so we're right there. How many epitopes are required? Well, if you get just one, but it's the right one, that should be enough and we know that from adoptive cell transfer. Now the question is, are you able to generate enough of the T cells and the right kind of them to actually mediate a response? For that, we're conducting a randomized trial.

The only example that I'm aware of that has actually been proven to be a neoepitope from an oncogene that is shared between patients is KRAS. And I think Keith can talk to this a lot more eloquently than me, but KRAS is the most commonly mutated oncogene in common epithelial cancer. Then what we did here based on initial preclinical data that suggested that you should be able to generate T cells against the KRAS mutation in the right context, we went ahead and made a vaccine that's a concatenate of the 4 most prevalent mutations. They cover together between 80% and 90% of all KRAS mutations in epithelial cells. And so that trial -- when we showed this to Merck, they actually said, we want to run the trial, so let's partner up with us on the trial. We want to make sure that we actually recruit the right patients, those that have the right immune system and so it's Merck's team that's today running the trial. They've already started dosing both as monotherapy vaccine and in combination with KEYTRUDA. And the essence here is exactly the same as I've discussed. And this is where the trial is.

The other part of our portfolio here has to do with intratumor immuno-oncology. So here it's a very different approach. In a vaccine, what I'm doing is I'm figuring out what I need to stimulate the immune system against specifically for every patient and I'm injecting a vaccine into their arm in the way we've done for CMV, but I'm doing it repeatedly every 3 weeks to boost that specific immune response. With an intratumor approach, I'm waking up the immune system without knowing what I'm waking it up against. So it doesn't have the specificity of the vaccine, but what it does is it actually uses the local tumor microenvironment. So we inject a combination of cytokines to wake up the immune system and draw into T cells and change an immunosuppressive local environment into an immunopermissive one. That's the idea. And so you go into a tumor lesion, whether it's superficial on the skin or a deep-seated lesion that you need to inject, and Keith will talk a little bit to the complexities of that, but the goal here is that if you can do that, then you can sort of wake up a local microenvironment and draw in T cells, the right antigens are already there in the cancer. And so these are 2 very orthogonal approaches to build on the fundamental ability of a checkpoint inhibitor to unleash a T cell.

And so where are we here? The first one that was really the pharmacology proof of principle for us was OX40 ligand. It was just one membrane-bound protein. We've injected it now to patients repeatedly. We've gone up to 24 injections given over 6 months every 2 weeks, at doses of up to 8 milligram. By and large, it's been well tolerated, and we've shown that we can actually lead to protein production. And this was all discussed last year at SITC. And what you see here in the graph is the red field is actually standing for OX40 ligand within the biopsy of the patient that got mRNA. You can see on the left the field before they got the mRNA, there's no red there, okay? So we've shown we can lead the protein production. We've shown we can do the safety. Now the question, does this work? I don't know yet. We've seen an interesting signal in a couple of patients with ovarian cancer, where the injected lesions shrunk. It doesn't constitute a formal RECIST response. It was enough for us to go ahead and start expanding that trial into a Phase II in ovarian cancer and that cohort should start.

On top of that OX40 ligand, we then said, okay, we understand the fundamental safety profile of the delivery technology and we've proven that this delivery technology can lead to protein production in tumors. Now let's go make more proteins that have a more profound effect on the immune system. And so we did this. We combined 2 active cytokines, interleukin 23, interleukin 36 gamma, together with OX40 ligand with the same idea of now injecting tumors, ultimately, in combination with a checkpoint inhibitor. For this, we're -- we've partnered with AstraZeneca, and we're using durvalumab, their PD-L1 inhibitor. This trial -- this is a trial design. The idea here is to go both in monotherapy but then quickly get to combination dose with durvalumab. And once we do that, we will do dose expansion cohorts, testing the ability to actually mediate true RECIST responses in a variety of tumor types.

The red checkmarks, they indicate where we are. We're currently dosing at the 2-milligram level as monotherapy, and we're well ahead -- advanced in the combination with a checkpoint inhibitor.

Finally, there's one last opportunity here in this intratumor space, which is interleukin 12. Interleukin 12 has been discussed -- or has been studied for a long time as a potent -- potentially potent anticancer cytokine. You cannot give this systemically because you run into toxicity before you ever had a chance to see efficacy. But you could potentially give it locally. And in fact, there are data showing with other approaches that giving IL12 locally could actually lead to tumor regression, not just where you've given it but some abscopal effect and that's been described. And so the idea here is can you do this using a messenger RNA technology? This was one of the molecules that got AstraZeneca most excited about the opportunity set in oncology when we partnered with them several years ago. This has now progressed. They've taken it into the clinic and are actively dosing patients. I'm not going to belabor the preclinical data here. Suffice to say that for all of these molecules, the preclinical data is what you'd expect. When we use these kind of agents in the relevant preclinical models, we actually can mediate the sustained and durable remissions. Unfortunately, translating mice to humans is not as straightforward as it is with rare genetic diseases for oncology. And so you got to go run the right clinical experiment here and that's what we're in the process of doing. Let me give the floor to my mentor and colleague Keith Flaherty. Thanks, Keith.

Keith Flaherty,

Thanks, Tal. So I've been around these programs since quite a while, before the INDs were filed. I'm going probably as -- I think that's right. So I'm not going to tackle the issue of interpreting interim data or we can discuss that in Q&A, rather my task is to kind of contextualize these programs in the landscape of immuno-oncology and try to address the issue of, if successful, where would they fit in or what would they contribute. So as titled the talk as I have because really, the magnificent event of the past decade has been the introduction of antibodies that disrupt PD-1, PD-L1 interactions. That's the big moment. And really, what that has allowed us to then do is to try to understand what is the basis or the determinant of response in patients who achieved at least partial, if not complete, responses to PD-1, PD-L1. A bit more difficult do that in combination specifically with cytotoxic chemotherapy. VEGF-targeted therapy is the same. And the group that I direct at Mass General tries to tackle this problem broadly. Because melanoma has always been my focus, I'm going to use melanoma data, and it's good canary in the coal mine area as I'm sure you're well aware. But all of my comments are meant to really relate to the ramifications of these programs broadly across cancer and I'll come back to that point a couple of times.

Okay, so here's some melanoma data, but I could show any other population in which PD-1 PD-L1 antibodies have shown some monotherapy efficacy and make a very similar point, which is that we basically have 2 problems to try to overcome. We have a big problem of de novo resistance, even in a tumor like melanoma, with a 40% response rate. MSI-high colon cutaneous squamous-cell carcinoma and Merkel cell carcinoma, these have the highest response rates, 50% response rates and in some cases, to monotherapy PD-1. But you still see this rapid disease progression in a subpopulation of patients, even in those indications, a much bigger problem of course in cancers for which the response rates of PD-1, PD-L1 is 15% to 20%, sufficient to drive overall survival benefits and FDA approvals but an even bigger drop-off in terms of early progression.

I would tell you clinically that it would appear that these patients are getting no therapy whatsoever. This is -- some people call this hyper-progression. That was the term introduced by lung cancer doctors. Melanoma is a very aggressive disease, as aggressive -- we never use that term hyper-progression, we do say this is the natural issue of disease as though these patients were getting nothing. And that really is a striking phenomenon with this therapy, very different than molecular-targeted therapy, oncogene-targeted therapy where there's this varying kind of graded response to nonresponse profile across the population. Here, it's kind of black and white. Patients either just blow right through therapy. That's about 45% of the patients in this overall pembrolizumab cohort but those were a mixture of some fairly relapse refractory patients. The treatment-naive patients are on the right-hand side, and that's a better estimate. About 35% to 40% of patients have de novo resistance, they just blow right through therapy. Then you get an effect, and so there, we have stable disease, which is not a great outcome. And certainly, a PD-1 monotherapy just don't lasts very long. Partial responses, the next best thing, those are absolutely durable, but they're not permanent. Complete responses/near-complete responses, meaning like you're left with some radiographic artifact, that's what we're aiming for and that's what accounts for the tail of the curve. That is now supported by data like this. This is complete response data and the durability of that data now with subsequent years of follow-up. And there's trailing data in other tumor types that make this point. If you clear your tumor you're in great shape for the long term. If you don't clear your tumor, you're going to progress. It's just a matter of time. That was not a statement that people made

4 years ago. But starting 2 years ago, anyway, we began to get this very strong thrust of the data that partial responders, middle-of-the-road partial responders are going to progress if they've got viable tumor remaining. So deepening response will result in greater duration of response. That is my contention. So certainly, if we can help patients to achieve a complete/near-complete response, who are otherwise destined to have a partial response, that's going to be beneficial. That's going to translate in overall survival advantage. If you can overcome de novo resistance, that would be an enormous contribution. And so I'm going to harp on that point through the rest of the talk as I move more quickly.

Okay, you've all seen data like this, I just -- I like to go back to this 2014 paper because it was really the first observation in melanoma pembrolizumab-treated cohort that described the phenomenon that no, it's not PD-L1 expression on tumor cells or infiltrating immune cells that really sorts response, nonresponse very well. This is really scoring de novo resistance versus the other group. Even infiltration of CD8 to the tumor alone is not a great discriminant, but if you overlay on top of that a marker of activation, in this case, granzyme B, which is an obligate subset of the upper left-hand panel. So these -- you've to have T cells in there for them to be granzyme B-positive, those are the patients who respond. So if you have the right T cell repertoire is the point that I'm driving at here. At baseline, even though the tumor is progressing, the patient is going to die if things don't turn around and patients don't have a treatment response. It's those tumors that have infiltration of an activated T cell repertoire of sufficient quantity as this data suggests are the patients who are one drug away from at least inducing a partial response, if not a complete response.

That was the starting point for our entry into this area, about 4 or 5 years ago now I guess, where we took our serial biopsy approach, which we elaborated mostly in pre-oncogene-targeted therapies in previous years and directed it to PD-1 antibody treatment. Again, biopsy in patients with superficial manifestations of metastatic disease is the cohort of melanoma patients receiving PD-1 antibody, again, doing single-cell RNA sequencing to try to get more resolution on that data that I showed you before, which is sort of a bulk phenotyping of immune populations in tumors. At the single cell level, you get really amazing resolution and rather quickly are able to start to sort the T cell population, if its predominant, associate it with response. And if it is in the minority, nonresponse. This is a published paper from last year, so I won't go through it, but basically, we saw a much better discrimination in terms of outcome prediction, ultimately, shown here on the lower right-hand panels with these AUC curves. So.

If the majority of T cells in the tumor had the right state of activation, the right transcriptional state, that associate it with response. And it turns out that there's even a single transcription factor that we could use in that CD8-positive T cell population to denote the population that are in this proper state, but they're not just granzyme- or perforin-positive, they have to be in the right transcriptional state. And it turns out that that's a state that has stem cell-like features. This is a pool of cells that we think can basically regenerate or repopulate itself and ultimately produce the numbers needed to clear a tumor. If you have exhausted T cells as the predominant set, then basically, you're not going to get a benefit from therapy.

So can we shape this T cell population? That is ultimately the goal of these programs, which I'll shift into here in a moment. So the alignment between T cell infiltration, it's not activation, and tumor mutational burden has been shown by many groups but going back to that (inaudible) paper, to be tightly correlated. So those tumors that high -- have high tumor mutation burden have baseline high T cell infiltration. And as you well know, tumor mutation burden is tightly correlated with FDA approval. As I've suggested though, even in tumors that have overall survival benefit from PD-1 antibody, alone or in combination with other backbone treatments, 15% to 20% response rate. That's a heck of a lot of de novo resistance, even in those indicated populations. Then you move out of the zone here of not -- of insufficient response rate to translate into those -- into approvals and you've got big swabs of cancer, right? So you've got some very immediate indications including much of breast cancer, all of prostate cancer, microsatellite stable colorectal cancer untouched by PD-1 antibodies to a large degree. But again, I want to just highlight this point that this is not a met need. There's still a ton of unmet need in the PD-1 indicated tumors. I'm highlighting here in peach those indications, where trying to present the entire solution in the form of cellular therapy has been effective and I'll maybe circle back to that a little bit later.

So now you know that there are 3 programs charging forward in parallel. I'm highlighting here the academic data that, ultimately, was the foundation of Neon's entry into the space and BioNTech, as you're aware, also in the personalized cancer vaccine arena. And the approach that's been taken in common with the Moderna program as well, has been to start in settings where feasibility would be anticipated to be at the highest possible level, which is to say high-mutation-burden tumors. Where you're going to get a lot of predicted mutated new antigens to start with. So you have a pretty good menu and you can then start putting your inflammatic/immunologic MHC presentation filters on that, to say, "Okay, can we get an adequate number of peptides with which to immunize?" And as Tal said, predictively going into these study you would expect that not all would generate either CD8 or CD4 responses. So start with a large denominator, so you can start to hunt and refine your understanding of predicted immunogenic peptides to actually responsive immunogenic peptides. And so that's the approach that we've taken in this initial academic study. As you can see here, there was a mixture of both CD4 and CD8 responses. It was actually one of the surprises, I would say, of this initial study from bicoli to (inaudible) farber, that there was so many CD4 responses that was really not anticipated, certainly, based on the mouse data that preceded this human investigation.

This was adjuvant data and it was a striking degree to which patients not only were able to generate responses to immunize peptides, but also in the uncontrolled population, admittedly, the disease-free survival.

A really striking finding presented in this paper, in fact, with the 2 patients who then subsequently relapsed after receiving vaccine alone, got PD-1 antibody therapy and had complete responses. I highlight that because the proof-of-concept trials that you've seen not just from Moderna, but from the others as well, have been trying to demonstrate feasibility, safety and really workout the kinks in terms of the operational workflow in relapsed/refractory patients, generally speaking. So PD-1 antibody patients who were maybe warming up on PD-1 antibody therapy and then start receiving vaccinations.

We absolutely believe that the adjuvant setting is where we relieve the pressure in terms of the feasibility issues because you've got a lot more breathing room in terms of having a patient's vaccine degenerated then as opposed to a patient who is in the metastatic setting and already maybe several weeks into it. In a disease like melanoma, same for non-small cell lung cancer, head and neck cancer, these are aggressive tumors in the metastatic settings. So the adjuvant setting gives us that breathing room, but I just want to emphasize the point that we think is probably also the optimal sequence to be thinking about or being able to interrogate optimal sequence, I should say, in the adjuvant setting where we have a little less of that freedom to operate in the metastatic setting.

So this is ultimately where all see these vaccines ultimately taking hold, the BioNTech randomized Phase II trial as you're aware in the metastatic setting but the adjuvant trial, I hope, believe, is ultimately going to show the greatest potential impact to this approach.

It tells us there are amongst canonical driver oncogenes in cancer, there's one that shines out as being -- having human proof-of-concept data that it is immunogenic, that actually you can direct a T cell response to this epitope and that mutated KRAS proven by adopted T cell therapy. I mean this is the most powerful use of this approach. I've always politely complimented my colleagues at the NCI surgery branch in saying, "This is a fantastic research tool that you're working on here." Never going to be a scalable therapy for patients certainly not globally, but I love what you can do with this approach to show what epitopes are capable of driving a tumor-clearing effect. And as you know, they focus on cancer test antigens in years past and lineage antigens, particularly in melanoma. But this really powerful proof-of-concept results highlights the point that, in fact, that T cell actually can latch on to KRAS and being a driver and founding mutation in a great majority -- vast majority of the tumors in which KRAS mutations are found. Certainly, seems like the right substrate to direct a nonpatient specific, if you will, or shared antigen vaccine approach.

So this is just a schematic that reminds you a couple of points about where efforts have been directed in years past between lineage-specific antigens for vaccine, but also for cellular therapy. Of course, if you can afford to wipe out an entire lineage like your B cell population, if you can get away with that for at least a time, then it's okay to direct a fully locked and loaded T cell population at a tumor that otherwise lacks the relevant T cell repertoire, has a hostile tumor microenvironment as well, but that's not very many tissues, unfortunately.

Then you've got your tumor-associated antigens or tumor-specific antigens where most of the academic work in years past and some cell therapy work ongoing adopted T cell therapy not CAR T cell therapy is directed now. And as we've talked about sort of situating where does patient-specific vaccination fit in, it's ultimately got a potential and a much broader footprint in terms of the opportunity space, but it is largely nonoverlapping with those domains where cellular therapy will continue to be directed.

So let me put intratumoral therapy just kind of highlighting where there had been. I would say, to a degree -- I'm sorry go back one there. So proof-of-concept findings either with these pathogen-associated motifs, CPGs, multiple clinical trials corroborating each other that, that actually can move a needle in intratumoral context or platform, not appropriate for systemic administration. Seeing, I would say not -- still not quite there yet in terms of having clearly established proof-of-concept. But the oncolytic viruses as complex as they likely are mechanistically, they clearly established proof-of-concept in terms of the intratumoral approach. Admittedly, most of this work is in melanoma, but as you know clinical trials have now multiplied in another indication.

A nuance of tumor-injected therapy that I want to be clear to highlight, as you look down this cascade of water fall plots with T-VEC in melanoma. In a disease like melanoma we actually have a fair fraction of patients who have cutaneous, subcutaneous disease, which that can be injected. It's fairly straightforward to get a response in an injected lesion. In fact, for years, we've known that interluekin 2, interferon. In my younger days, we used to inject just about everything. BCG, and you can go through rounds of this stuff and you can get responses in injected lesions. The hard trick was what's shown here, T-VEC was really the first agent to show us noninjected lesion response. And in melanoma patients, that's usually nearby cutaneous, subcutaneous disease, sometimes regional lymph nodes. But uninjected visceral, that's a big ask based on the precedent data, interleukin 2 and interferon could never do that for any of the other therapies that I mentioned.

This is the first one that actually tipped over in terms of yielding that result and we think that's why it improved overall survival. I realize that the FDA didn't put it in the label that it improves overall survival, but all of us involved in the development of this agent truly believe this data speaks to that point particularly in lower disease burden patients. So

patients without very burdensome metastatic disease as the subset analysis here suggests. You really can alter the true natural history of this disease with just a single agent injected in therapy approach. Modest as it may be, based on this data, but it's real. And that has just caused this wave of enthusiasm. Yes, in melanoma where it's so feasible to do this, but there's a big swath of additional cancers that I'll come back to that we think this approach can be directed against.

You're aware of this data also, which ultimately prompted Phase III clinical trials, for which we're still waiting results. But the point being that on a PD-1 backbone, the same exact therapy now has a much more significant set of waterfall plots, admittedly meaning fewer patients shown here, again fairly straightforward in terms of getting injected legion responses, but if noninjected, both nonvisceral and visceral response rates are really what has prompted enthusiasm here.

Now uncontrolled data, of course has steered us in the wrong direction before ultimately randomized data is what's needed. That's an obvious point or more powerful proof-of-concept data that you actually are moving the needle, both mechanistically and in terms of altering tumor immune interactions, that had never been demonstrated with epacadostat, the IDO small molecule inhibitor. But with T-VEC, in fact, that has been demonstrated. And of course, Moderna with their programs in our discussions over the years were well aware of the need to be able to demonstrate proof of mechanism, both approximate expression of mRNA, but also immunologic proof of mechanism, which, of course, has been integrated in the early studies that we've collaborated on. But just to highlight here the point that unlike IDO, there are agents that have single-agent activity, have clear single-agent proof of mechanism and injectable platform, I think, certainly, have a basis for receiving our attention in the field.

I do just want to also quickly highlight the point that PD-1 antibody is the big gorilla because it has such widespread use in cancer, but when administering either a vaccine or for that matter in tumor injectable therapy, it remain possible that CTLA4 and CTLA4-related priming could actually be a more optimal combination partner. Just want to mention that because it's a trailing strategy, I think that one has to consider that at least spritzing in a bit of CTLA4 antibody could be an appropriate strategy. This data, I think, with really striking suggestion in that direction corroborated by a much smaller cohort with [cavitac], another oncolytic virus of a different sort, not the [GMCF]-secreting HSV, for the coxsackievirus were again, in combination with ipilimumab, admittedly a small cohort much more striking results observed.

TLR9, our CPG specifically, as I've said before, have generated recurring signals across 3 programs that they can overcome resistance in a subpopulation of patients. It just reinforces the point that injectable therapy really is the only category we have right now in next-generation I/O where we've seen recurring positive signals even in relapsed/refractory patients. As you well know in next-generation checkpoints and myeloid cell targeted therapies and other metabolic modulators beyond IDO, we have yet to see those successes. And so this is, I think, part of the reason why we feel the tension continues to be directed so firmly here. Including repurposing agents for intratumoral application, like CTLA4, which does have a therapeutic index problem, as you're well aware, both monotherapy and in combination with PD-1. And academic work at Stanford initially sort of proved the concept that this really could engender systemic response. And in fact, head-to-head comparison, modest size trial in France is being conducted to see if intratumoral CTLA4 actually could overcome or could supersede intravenous with the PD-1 backbone therapy has shown here.

So the idea of manipulating the microenvironment with multiple maneuvers, that's really what got me and colleagues subsequently excited about this platform in terms of intratumoral therapy. We know that even more simplistic manipulations actually can produce benefit to patients, but if you could pack into a single therapeutic, multiple manipulations to really shape the tumor microenvironment, so that those patients who have an adequate T cell repertoire that's elsewhere in the body not in the tumor, and it's not activate in the tumor potentially could have all of the alterations necessary to facilitate activation and entry of that T cell population. And that's the way in which I see the intratumoral platform has been so complimentary to the vaccination platform, which is really trying to boost and create the T cell repertoire, modulating the microenvironment is complimentary and different approach, which really could have very widespread ramifications in terms of using clinical practice.

I'll admit that both academics and the FDA were a little conservative about the idea of just assuming they would be safe to put a "stick of dynamite" into a patient's tumor, if you're introducing multiple manipulations in particular, there were concerns. I would say, go back maybe 3, 4 years ago that liver metastasis, for example, or relatively peripheral thoracic tumors and other abdominal sites could be safely approached with intratumoral therapy. But we've got now Phase I data that's quite mature with multiple of these platform approaches that suggest this is, in fact, not a problem. I know that many people registered a complaint that while this is going to require an event with radiologist and the community-based practices are going to be stressful. If this has efficacy, people will do what they need to do, right. So the point being that as I've said, we know what the phenotype is in terms of an immune therapy response that produces long lasting and perhaps permanent benefit, which is clearing a tumor. And if that's what's achieved with combinations like this, a few intratumoral therapies that require a trip to the [radiology] over the course of the couple months period of time, on top of a systemic therapy backbone, if that's what's needed to produce a durable remission that last for years, trust me, in practice it will be rewired to that, not just academic practice, where we've already done this for the purposes of clinical trials, but I mean even in community based and global practices well.

So I will not read these points to you, but I'll leave them up here as we transition onto the rest of the agenda, there will be Q&A coming a little later. So I'll stick around for that and happy to address questions then. Thank you.

Tal Zaks, Moderna, Inc. - Chief Medical Officer

Okay, I'm going to continue seamlessly into our systemic therapeutics. And then we've got a little bit of news today to share with you. To put it in context as we think about that x and y or the technical risk in the biology in medicine unmet need, CMV represents, I think, a new peak for us on the unmet need horizon. This one represents us extending what we can do in terms of our fundamental modalities.

Systemic secreted therapeutics was always envisioned to be a lead into the ability to do quite a large significant pipeline of medicines. The first ones that we have that are purely secreted are going to be the antibody program that I'll touch base in a minute. We have a collaboration with AstraZeneca around Relaxin, which is meant to provide a secreted hormone for the benefit of patients with congestive heart failure. And we have got a program looking at Fabry disease well to prove that we can actually supersede what a traditional enzyme replacement therapy can do.

There's also going to be intracellular programs that we'll talk about after this. So let me cut to the chase and talk about this program. Admittedly, it took me about a year to learn how to pronounce chikungunya in one flow. The virus is really, sort of, part of this show but not the entire story. What we're doing here is using the platform to teach the body how to make its own medicine in a way.

We're giving mRNA intravenously with the goal that it goes to the liver and other organs and makes a protein that then gets secreted into the blood. Now we chose a protein that happens to be an antibody for 3 simple reasons: One, it's actually a complicated protein, it's not a simple one. It's a heavy chain and a light chain that have to assemble together intracellularly and be secreted in the right form to the blood. Second, because it's a protein in the blood, it's relatively straight forward to measure and because it's an antiviral protein, it's got a neutralizing activity against the virus, we can actually measure the activity and prove that the protein that we make with this technology is functional.

Finally, this has always been of interest to DARPA, who have been funding us from the early years as a target of interest to them. And so we're using the ability to demonstrate that we can use mRNA technology to transfer passive immunity as a proof-of-principle for what this platform could potentially do for other systemic therapeutics. And so this drug mRNA-1944, is essentially encoding for the heavy chain and the light chain of an antibody. CHKV-24 is the name of the antibody. This antibody was derived from a collaboration with Jim Crowe at Vanderbilt. And it was really taken from the blood of patient that was convalescing from chikungunya. And define such that it had very potent neutralizing activity against the virus.

And so the idea here is passive immunity, but it's information transfer. So we've got the antibody sequence from 1 patient, and we know that antibody is potent and what we do here is we take the information and we encode that same antibody and have somebody else's body make that antibody in vivo for them. We don't actually have to make the recombinant antibody. We can react within a few weeks in a case of a future pandemic and just take the information from one antibody and use it to induce passive immunity in the recipient, okay? So that's the idea.

Now this was predicated on a lot of preclinical work and I'm showing you some of it is. We've published this, on the top, are the mouse models, and what you can see here's that mRNA-1944 actually encodes for a functional antibody in mice because the mice who gets the drug survive a 100%, you can see on the top right. And those who don't, all die. So mRNA can lead to the translation in a mouse of an antibody that's fully functional.

We get very nice expression levels in the mouse, you can see the red dot, at about 0.5 mg/kg or above 10 micrograms per ml and you can see the dose response curve. So we're getting pretty clear pharmacology here and this is a mouse that is -- it's got immunological defects, so actually this mouse requires a heck of a lot more protein to get that survival graph than a typical human would.

So how do we do translating from mice to nonhuman primates? And that's here on the bottom. This is taken from the GLP toxicology study for this program 1944, and what you see here is the dose response curve, the green, the blue, the red, 0.3, 1 and 3 mg/kg given to nonhuman primates. And you can see very nice dose dependent pharmacology, where we get to levels of 10 micrograms per ml or above already at the somewhere between the blue and red here. And you can see furthermore that if you come a week later you can actually give another dose, you continue to boost the pharmacology because the protein has a long half-life, right? This is an antibody. In fact, it is engineered to have a long half-life. And so this -- should it work, will transfer passive immunity that will last for a long time as long as the antibody levels are above a certain threshold. So those were the preclinical data and with a modicum of excitement and trepidation, we actually took this into the clinic. And the question is, can you get similar levels of expression safely in humans?

And so we designed this trial. And this trial -- I'll make 2 points. First, as a new trial for any modality, we care really about 3 things: Do we understand the safety profile? Is it safe? Do we make protein? And is the protein functional? We've done that in infectious disease vaccine time and again, I've shown you data in oncology, we've got data for VEGF and this is now a systemic modality for the first time. And the second thing to note as we went into this trial, this

has been a journey of many years. Getting a lipid nanoparticle deliver technology to do this is not trivial. And as we went through the tremendous effort that Steven and the team had to put in, it was really understanding the fundamental to what leads to the expression and what leads to the potential adverse events and how do we circumvent them?

Now as I've shown you the preclinical data, the toxicology profile was actually quite nice. And so what we did here after a lot of internal discussion, and I'm grateful for the leadership of Allison August here, this is not my team that's actually designed and run the study. After a lot of internal discussion, we decided that we were going to go first in man into a healthy volunteer setting, and we want to understand the full safety profile so we were going to do this with minimal premedication. We'll give antihistamines as is often used, but we're not going to use steroid premedications which are usually given with these types of medicines, and I can come back to that.

And so this is a trial design. We started 0.1 mg/kg, the dose that I've shown you in preclinical species. We went on to 0.3, 0.6 and potentially even higher. We do this very measured and safely, so we start with 3 sentinels one at a time. And if that's okay, we go on and expose another group of 5 subjects, 3 of whom are going to get the drug and 2 of whom will get placebo. So that was with the design, and as I've shared with you in the past, as we told you in our August quarterly call, we're actually at a point where we've already treated 6 of the 8 subjects all the way to dose level 3. And when we step back and look at the data, we realize we actually have a cogent body of data now that is worth sharing and that's what I'm going to walk you through.

So how did we do in terms of protein expression? And what you see here on the right are the pharmacology curves for the antibody, right? So I'm measuring the CHKV-24 antibody. That's not the drug I've given. I've given mRNA-1944 that encodes for it. What you can see in black is the 0.1. In red, is the 0.3. In blue, is the 0.6. The reason that you're seeing these graphs go out and get truncated is because these are interim data. So the 0.1, we have the longest follow-up, to 0-point red we have up to 12 weeks of data. For the blue, the 0.6.

And just by way of reference, we have predicted based on those preclinical models that I've shown you, that 1 microgram per ml in the blood should be a protective level against getting chikungunya disease. And we got there by the synthesis of 2 lines of logic. One is the preclinical data that I've shown you. The other is simply epidemiological surveys of people who have been infected with chikungunya. And the question is how much antibody do they have in the blood because we know they're protected against further disease if they get infected again.

And so we had predicted 1 microgram per ml was the level we're getting to. And what these curve show you is that everybody who got the active drug within hours already has protective levels. At 0.3 mg/kg, we maintain those protected levels projected out to at least 4 months. So for the first time, we've actually taken the sequence of an antibody and used it to generate passive transfer immunity. At the 0.6 mg/kg, we see even higher exposure. And you can see on the top right there, the actual exposures and there's one other point that I would make in terms of the exposure here.

Look at the variability. If there's anything here that surprise me, let's just say that we were all super gratified to see these numbers, but the one thing that stood out to me the first time I saw this was actually how tight these error bars are. This is a Phase I healthy volunteer subjects. We've treated people with different body habitus. We've treated men and women. We've treated people as young as 23 and as old as 50. Now when you look at our preclinical data, the error bars are always tight. But, okay, preclinical species have always kept the same and they all kind of look the same. People are very different. And yet when you look at the exposure data, the variability between the lowest and the highest, right, look at 0.3, it's 6 to 10 microgram per ml, that's as tight as you get with the injection of a monoclonal antibody. The same tightness we see at the lower dose and the higher dose. And so what that tells me, fundamentally, is 2 important things: One is that the fundamental efficiency of our platform is maintained, right? Because we're measuring at the end of the day translation of antibodies. So whatever the mRNA had to do, find its way to the liver whatever cell, get into the cells, make protein. The protein gets secreted. The end result of that is what's measured in this. And you see very tight variability. And the other thing it tells me is that with such a tight nice dose-response curve, our ability now to predict and project what it's going to take to make therapeutics in other diseases is actually quite robust.

The half-life here is about 60 days. So as you can imagine, every time I go and double the dose of the exposure, you're going to expect 2 months more. So we're already at a point where we can see 4 months or longer of protection against this vaccine and it is of interest to continue to explore this pharmacology.

So we're making protein. We're making the protein at levels that look reasonable. We've got the half-life of the protein that we completely predicted, but is the protein functional? And the question is yes. Now on first principles you would expect it to be functional because how can you make a nonfunctional protein? But the naysayers will always find reasons why? "Oh, well, if you make antibody in a liver cell maybe it isn't going to work because the T cells make antibodies." Well, actually biotech industry taught us that CHO cells make antibody. The whole variety of cells in the body can make antibody. If you can get the right sequence into the cells, evolution takes over and now you're making the right protein and so here's the proof.

This shows you the neutralization against the virus of the blood from these participants who got mRNA-1944. And what you see is that already a dose of 0.1, you're starting to see a proportion of those subject get as high as a titer of 1 to 100. It's an arbitrary number just to give you a sense of magnitude. Every one of the participants who got mRNA-1944 is making some neutralizing active antibody in their blood. And at 0.3 and higher, 100% of the participants actually have titers of 100 or greater against this virus.

So we're making protein and we're making protein that is functional. All right, so the pharmacology goals have been achieved. Now the question is, okay, what do you understand about the safety profile? So let's talk about the safety and you see here the totality of the safety data that we've had and let me take a minute to walk you through it.

At 0.1 and 0.3 mg/kg, we see no clinical significant adverse events whatsoever. Now remember, 0.3 mg/kg was the dose at which I told you, we had already surpassed our predicted pharmacology and now I'm telling you that dose subjects to that 1-hour infusion neither them nor the principal investigator could tell whether they were getting a placebo or the drug.

As we push up the dose to 0.6 mg/kg, we're starting to see infusion-related reactions. Now these were not a surprise. These were actually already predicted within the protocol. We anticipated them based on the greater literature and these were the typical infusion-related reactions, you see changes to a heart rate, blood pressure, fever and that's what we saw here.

So let's talk about this. We saw it in 3 out of the 4 patients -- subjects, I'm sorry, participants. One of them had none. The other one had some grade 1s. There was a participant that had a couple of grade 2 G.I. symptoms. In this case, it was nausea and emesis. And then we had a participant that actually tipped over to grade 3. They had a rapid heart rate. It wasn't irregular. It was just a regular sign of tachycardia, but it did dip over for about 15 minutes on the evening after the infusion into grade 3 territory, so that counts as a grade 3. Now that subject also had additional grade 2 infusion-related reactions, adverse events. Among them was fever, emesis, and on a routine EKG that we do, as a routine part of this trial, we noted some inverted T waves. There were no associated cardiac symptoms and these completely resolved. In fact, all of the adverse events we've seen on this trial have spontaneously resolved and they resolved without any medical intervention.

There was not a participant on this trial that required as much as TYLENOL. There was no serious adverse events. There were no discontinuations of infusion or discontinuation from the trial. The adverse events that we see are typical of infusion-related reactions. They come up relatively quickly within a few hours after a completion of infusion. By the time the participant goes to bed and wakes up in the next morning, they're pretty much gone. We did see one white count elevation, the next day, that tipped over to technically a grade 3 level. That too started to come down the following day and then completely resolved. And notable as well, for the first time ever, for a technology that we're giving at this doses intravenously, there were no other adverse associated laboratory abnormalities. We saw no adverse reactions in liver function tests, kidney function tests, other hematological parameters.

So where are we? This is an ongoing trial. We think the body of data was worthy of sharing. Clearly at 0.6 mg/kg, we got some work to do. The obvious next step is to go and see whether steroid premedication as we commonly use for many other medicines of this type will ameliorate and decrease the rate of adverse events of infusion-related reactions. We can also consider splitting the doses and so we're looking at all those opportunities.

The salient point here is that when you're giving a protein that you build a pharmacology over time, if you have adverse events that come up quickly over the first day and then completely resolved, that obviously gives you a window then to repeat dose. And so that's what we're going to be exploring in the next trial when we get into patient populations.

So one last point here, how do we do relative to where we predicted to be? So those of you who've been following us for years, from about 2 weeks after I joined the company, I've become infamous for drawing this curve on the whiteboard and say, well, here's where I hope to be and here's where I'm worried about, all right? And so when we started this trial I actually asked the clinical pharmacology team to go and draw out based on all the preclinical rodent and nonhuman primate data, where do we expect the human subjects to land if, indeed, we can translate this without any loss of potency. And so when we started the 0.1 mg/kg, based on the predictions in blue, you can see where we thought we would land and this is modeling. That's why you see this shaded area, that's a 90% confidence interval of where we thought we would be and the straight lines are them used. Where did the human participants land? Right there. Smack in the middle of where we predicted they were, without any loss of potency in translation. What about the 0.3? This is what our prediction was. The shaded areas appear a little bit whiter. That's an artifact of the fact that we're looking at absolute level. Percentage-wise, we're talking about the same levels of variability. The red line is the mean. The shaded areas are 90% confidence interval. Six subjects at 0.3 mg/kg, where do they end up? Right there. Exactly in this area, even a tad higher.

How do we continue to dose escalate 0.6? What did we predict? That's in green shaded area, 90% confidence interval. Where did these 4 subjects land? Right there.

For the first time in history, we've actually shown we can teach a human body to make its own medicine by just giving the information required to make that medicine. And I have to tell you, for me personal, while a passive immunity drug is perhaps not as intuitively exciting as an anti-cancer drug or a disease drug, the ability to do this from a foundational scientific perspective was really a high moment. And all of us in our careers have these moments that we won't forget. For me, that moment will forever be the data that we sat in the team -- with the executive team. We kind of looked at each other and people kind of looked at me and said, "Okay, so what are you saying?" And basically, I must have said, "It works."

What does it mean for our portfolio? Well, first, just a recap, we see dose dependent increase in levels as we dose escalate. We see that the protein we make is fully functional as predicted. We see that we have a dose, at which we have a very tolerable profile, where participants don't know if they've got placebo or they got (inaudible) drug but they're making therapeutic levels of protein. 6 to 10 micrograms per ml for anybody who cares to pull up the label of an antibody is within the therapeutic range of many monoclonal antibodies.

In this application, we've reached the ability to confer or we project conferring passive immunity for at least 16 weeks or 4 months already at that dose of 0.3 mg/kg. And we fully predicted the amount of protein that we would make without any loss of potency between preclinical species in humans. So just like a 100-microgram will immunize the monkeys and will immunize a human and a few microgram will give you VEGF in a rabbit ear and will get you a VEGF in a human skin. A 0.3 mg/kg dose will get you 10 micrograms ml of secretion of an antibody whether it's a mouse, a nonhuman primate, or a human. And so that, I think, puts us in a really good spot for where we're going next, which is this really strongly supports our ability now to get into rare diseases. To go and do protein replacement intracellularly in places where we cannot measure the protein.

So Greg, Dr. Enns, will talk about methylmalonic acidemia. That is the first one where we have the trial open, and as he'll share what we're trying to do there is actually solve for protein intracellularly. We're not going to need to measure that by doing biopsies because we already know that in the case of a secretive protein, we can achieve this pharmacology.

Thank you.

Gregory Enns,

My pleasure to be here and now for something completely different or along the same track and set up so nicely. So I'm a biochemical geneticist, and that often requires a little bit of explanation to start. I am a pediatrician by training. I trained in medical genetics at UC San Francisco, and then I further trained and specialized in biochemical genetics. So I take care primarily of children, but I do see adults as well who have inherited inborn errors of metabolism, and these individuals often, well absolutely are healthy and fine for at least a few days or a few hours if they are more severely affected. And many of the conditions that I care for are detected nowadays by newborn screening, and methylmalonic acidemia is one of these, as an example. And I am just delighted to hear that Moderna is going into this area because there is still a large unmet need for these disorders as a whole and methylmalonic acidemia as an example for sure.

So I was asked to give a bit of an overview of MMA or Methylmalonic acidemia, and I'm happy to do that. Here's my brief disclosures and moving along.

So MMA, like many of these conditions, is an autosomal recessive disorder. The -- again, like any of the genetic conditions I care for, these are not binary diseases. They're not 100% switched on or switched off if you have an enzyme difficulty or problem. There is a range of enzymatic activities so they are determined by the underlying genetics. And the more severe form of that condition is, I call, Mute 0. Chuck Venditti at NIH says Mut, but I will speak with Mute because the enzyme name is mutase. So the Mute 0 is the most severe form of the disease. A more partial form is called the Mut - where they have some residual enzyme activity and these patients are typically more mild in presentation. The enzyme we're talking about is that methylmalonyl-CoA mutase. In North America, their prevalence is about 1 in 50,000 so this is indeed a rare disease. When you lump all the rare diseases together that there is screening for in California, for example, the incidence is closer to about 1 in 1000, 1 in 800 depending on how you count them.

So like many inborn errors, you have to have a pathway site to hit you with a biochemical pathway, but this is just to show where the enzyme has its activity. It's a nuclear encoded enzyme, but it's localized in the mitochondria so it's synthesized in the cytoplasm and imported. It's a homodimer and requires a form of vitamin B12 or an activated form of vitamin B12 to work. It's in a pathway that involves the degradation of a number of amino acids, which are conveniently -- they make up the mnemonic vomits so when I'm teaching medical students, it's very easy. It's, oh, it's really you're not seeing fatty acids and finding a (inaudible) and screening. It sounds so good and so that's -- but these patients often will come to us with that problem, and that's one of the things that we see in a viral infection or viral illness, these kids will get severely ill and that catabolic illness itself is what stimulates the metabolic crisis.

So when they are coming into a hospital with a problem, it's not that they have MMA, per se, it's that they have an infection that is causing them to be catabolic, that has been really stressing that pathway.

And the pathway is involved in line with the propionic acid or propionyl-CoA carboxylase, and this is a metabolic pathway that eventually yields succinyl-CoA that can be used in the TCA cycle. And so biochemical pathways are typically listed like this. This is how we learn them, but there is such an integration with biochemistry and metabolism that it's always a little bit more nuance and little bit more complex and it's -- this is not quite PKU. In PKU, there is an enzyme deficiency, phenylalanine builds up, phenylalanine is toxic. You decrease phenylalanine, you take away the toxicity primarily. Here, there are multiple inputs in the bioenergetic system.

So what do we see? First off, although we have newborn screening, so we intend to pick up all this children nowadays because of the newborn screen. Often times they're coming in for a presentation before the newborn screening results are even back. So these are children who are coming to the neonatal intensive care units with very acid -- acidotic, their pH is typical less than 7. They have often hyperreninemia as well, and they're going into a coma. So they present with lethargy and they have a severe presentation that is dramatic and might need dialysis to correct.

If they present later, they can -- they -- or have more mild disease, still having some form of neurologic involvement is very common. Here are the sort of acute and chronic presentations of 2 common organic acidemias, propionic acidemia is included in this slide here. But it's a nonspecific neonatal sepsis like picture that is common in the neonate with the classic Mute 0 disease. Altered level of consciousness in older children having ataxia, lethargy, even mistaken for drug overdoses is relatively common as well.

GI symptomatology, pancreatitis can develop in individuals, you can have vomiting and other problems. Interestingly, for MMA in particular, there is renal tubulopathy and these patients will develop kidney disease, typically later in life, later for a pediatrician, this is in the adolescence years often but depending upon the severity of the underlying mutation, you might see kidney disease developing the first year or first few years of life as well. The things that keeps me up at night or keeps me pacing around is a fact that these children are very prone to brain injury. And we think this is in part due to the reliance upon the important parts of our brain, the basal ganglia, the gray structures on oxidative metabolism.

So even if we have a diagnosis of MMA and we are treating a child and we're going to therapy a little bit, we do again the usual medications, dietary interventions and things like that. These children can come in acutely and have acute decompensation resulting in permanent brain injury that can lead to a movement disorder or child who is walking, talking, going to school might not be able to do any of those things again after they've had a crisis. So we treat -- like many of these conditions if you have a block in a pathway, we decrease the flux through that pathway so there are special formulas that are low in amino acids that are used in methylmalonyl-CoA pathway. Every patient, every family, has an emergency letter or sick day protocol to come in just to make sure that they can contact us at all time. Carnitine is often given as a supplementation because methylmalonyl -- methylmalonic acid and other metabolites bind to carnitine and deplete the body of carnitine, which is an important part of our energy process. Some of the MMA forms, not the classic Mute 0s typically, can respond to vitamin B12. So we give a trial of active form of vitamin B12 and hope for the best, but most of the time, they do not, unfortunately, and when they're coming in, I already mentioned dialysis because their ammonia levels can be just as high as you would expect to see in a classic urea cycle defect. So we're talking about children coming in with the ammonia levels of 3000, 3500 micromoles per liter, something like that with normal being around 30 in the neonate closer to 80. Renal failure, as I said, happens later. So what we've done and one of the things that we've started to do is treat with liver or combined liver kidney transplantation. Others have used kidney transplantation alone. I'll go into a little bit of the data.

The nutshell here is that kidney transplantation alone does not restore propionate metabolism as well as liver transplantation and the combined liver, kidney transplantation does a wonderful job of restoring body in vivo propionate metabolism. So I call this gene therapy with a scalpel. We have excellent transplant surgeons who are at the ready at all time -- at all times, and they've done a wonderful job with our patients. But we've -- as I said, we've done mostly liver, or combined liver/kidney transplantation. I say we don't do kidney transplantation, although we would consider it and we are considering it in the case of an adult who has a more mild form of disease where that kidney transplantation might be little bit less invasive. So it's something just keeping back of our minds. The thought of doing the combined liver/kidney transplantation goes back to several years. This is I think the first article that I know of that reported this, is Dr. Leonard's group in the U.K. And this is from a -- now -- going back a couple of decades in our patients because we had at least a 5-year follow-up here. So these are the first 2 patients that we did a combined liver/kidney transplantation at Lucile Packard Children's Hospital and what you can see is that the MMA levels dramatically fall. You can measure blood and urine MMA levels and you're seeing -- this is in micromolar up to over 2000 micromolar in one patient and looks like over 10,000 in another and realized normal level is 0.3. So these are exceptionally high levels and we get these exceptionally high levels in children who have also have kidney failure.

The typical Mute 0 MMA patient or run levels if did not have really significant kidney involvement between 200 and maybe 700 micromoles per liter and this is sort of a paper that we presented on a group of patients. I think we had 14 or 15 reported here that underwent either liver kidney or liver transplantation. The mean age of transplantation in our group here is close to 9 years. This is again going back to when we started doing this work. Currently when we're

seeing children who need the transplantation with Mute 0, we're typically transplanting them between 6 and 9 months of age, try to get things really early and it's only going to be liver because the kidney physically working just fine at that age.

But just to give you an idea of at least this cohort, patient survival was 100% in children we transplanted. We had one liver have hepatic artery thrombosis that required a second transplantation. You can see the dramatic drop in MMA just similar to other cases I've already shown you. And the main outcome is here, it's -- we don't have that threat of hyperreninemia which is a severe condition that can permanently affect the brain as well. And none of our patients had metabolic acidosis following the transplant procedure.

Renal function seemed to stabilize following transplant. But this is an ongoing question, especially because some of the transplant anti-rejection medicines will also affect renal functions. So we're following these patients. And the neurological outcomes, they don't reverse if you have permanent hits or if you have specific damage even not going to change that. But after transplantation, these children tend to at least maintain what they had before and then improve socially and functionally. They can be much more interactive, just they do better if they survive the procedure and go on.

So the complications have been described in a number of publications. Mortality being #1. Even if you transplant, some individuals have gone on to have what we call this metabolic stroke or the basal ganglia burnout. When you look closer at the data, most of the time those are patients who've been ignored or not treated aggressively following transplantation. And in these disorders, these organic acidemias, it's a little bit different than the urea cycle defects, once you've put in a new liver for urea cycle patient, they don't have hyperreninemia anymore and hyperreninemia is the main issue with those patients so they are pretty okay. We treat our post-transplant organic acidemias including MMA the same as we do pre-transplant, and then we slowly start to liberalize protein, slowly start to decrease the carnitine levels, slowly start to let them have a little bit more normal diet and things like that. And what I think it -- transplantation does is at least it increases the bandwidth of their ability to sustain an intercurrent illness because if they do come in with a vomiting illness, they are much easier to treat. We never need dialysis. We never need anything else after the transplant procedures so to speak.

So other complications listed here, immunosuppression, of course, and actual surgical complications as you would expect. So post-transplant outcomes, I already stole their thunder a little bit there. Another publication showing accumulated data shows that after the transplant, their crises go down and the body weight goes up because you can eat better and you have a more normal diet and more normal existence. There are several therapies in development. Gene therapy has -- there has been some preclinical data in gene therapy publications and of course what we were talking about today will get to as well. AAV has been the primary focus of gene therapy in preclinical models. There have been some evidence of hepatic genotoxicity and immune responses including neutralizing antibodies which is of course a concern as would be insertional mutagenesis as do some of the accumulation of data, adenovirus, AAV, and lentivirus have all been used in preclinical models, usually just mouse models to show the efficacy and you can see that there is a reduction of methylmalonic acid as well as it's an improvement in weight gain, using I think on the right, we have an AAV9 vector on the -- yes, sorry, on the right, we have AAV8, on the left, We have AAV9, but you can see that there is at least some clinical -- there is some preclinical data that shows a response. And what we're talking about today is something that is exciting for me, because although we do a lot of liver transplantations, we might be the leading place for transplantation for this specific indication for MMA. I don't like to do it. It's an involved procedure and there are some of our patients even with our outstanding transplant team, who opt not to undergo the procedure because of the risks. So when I saw this article came out, this is before, I think, really was talking a lot, I presented it at a journal club, I was very enthusiastic about it. I don't think I ever told you that part, but the mRNA therapy, of course, has a potential to change the intracellular environment, produce a normal enzyme and I look at it a little bit like enzyme replacement therapy because it actually is. We do a lot of ERT at our centers usually for lysosomal disorders of course, and we used take valuations well. So we use the injectables to treating in-born areas of metabolism, but this is quite -- it's quite exciting, there are a couple of preclinical papers that I prepare and I think just have maybe one slide here that basically shows that the improvement in metabolism, the production of protein intracellularly in the liver following the injection of the mRNA, lipid nanoparticles in a Mute - model on the left and a Mute 0 model on the right, you're seeing improvements in the MMA levels and improvements in the overall growth, very similar to what we experience and see in our patients. So I look forward to the day we can start the clinical trial at our center.

So in summary, this is a severe disease, especially that Mute 0 phenotype and it's associated with high morbidity and mortality. We have used liver or combined liver/kidney transplantation, which has improved the overall life of our patients, we -- thank you -- stabilized their metabolic crisis, et cetera, and looking forward to working further and see a crystal ball sort of waving on the side there. This is the conversation that I have with my family, and this is often the tipping point of why we even would pull the trigger on the transplantation. We might have a child look good for a period of 3, 4, 5 years and then have a crisis and not be able to walk, talk or have a permanent movement disorder. We can't predict that even with the best dietary therapy and aggressive emergency management, we still can't predict that, and that's often the tipping point of why we go ahead and do the transplantation in the first place. So that's a little bit of the background. Thanks for your attention.

Stéphane Bancel, Moderna, Inc. - CEO & Director

Thank you, doctor. So just a few slides to wrap up, and then we'll get the entire executive committee to wrap the day.

We are very proud, of course, of the announcement of this morning both for CMV and the CMV data as well as chikungunya. I want just to step back and reflect on fact that this was not easy. This required a lot of work and a lot of capital. And I would like to take this opportunity to thank our investors and to thank our partner who had faith in our ability to execute on the science back in 2013 when we were a team of 20 people, and guided us a few miles to be able to see the -- this could be possible if the right team had the right resources. We stand correctly and this is what the team has done. So I think it's very -- a usual combination of great scientific focus with the right partners and the right capital.

So it is now (inaudible) as you can see as the company continues to mature, and the clinical data that we presented today and we have over the last month just confirmed our thesis that we believe that mRNA could be a new class of drug. We have now 4 programs in Phase II or preparing for Phase II, 10 positive Phase I which is a very large number and 12 programs in a timed Phase I as we speak.

If I look across the company, we believe we have very strong vaccine mortality, 6 positive Phase I data. We have 3 vaccine, which we believe have the largest potential, the CMV vaccine we talked a lot about today, but let's not forget we have a (inaudible) vaccine, same thing, very large unmet medical need. No vaccine in the market, and the combination of the vaccine for hMPV and PIV3, 2 more respiratory viruses that are third and the fourth after flu RSV, hMPV and PIV3 that we would combining in one vaccine, 2 mRNA, one will provide protection against hMPV and one against PIV3. In IO, we have 5 programs are in clinic in Phase II or in Phase I and we're partnering with best company in the world. We want to see the data coming through and we are very, very eager for those results. And with today's news about the efficacy and the safety profile of chikungunya antibody, we're very excited and not only we can show, we can make a functional antibody, but of course the technology that we're going to be using for rare disease can be effective at the safe dose for those kids that are needing those medicines.

Let me only spend 2 minutes on vaccines because we believe at Moderna vaccines is a great business for following reasons. We think that there are 3 big buckets of vaccines in the world. There are main 2 vaccines. Those are on a intracellular focus. The innovative vaccines like Prevnar and HPV and then there are public health vaccines. Vaccines that are very important for the world, but for which one not anticipate to make a return. And the reason for that, of course, is pricing. If you look at it, the measles vaccines are very, very overpriced. You see it when you go and get them for seasonal flu shot at CVS. The innovative vaccines, we talked about it, Prevnar, the cost of treatment is around $750 in the U.S., HPV is around $450 for a course of treatment, and yellow fever in some countries sell for literally $1. And these drugs cost a big margin, very abusively. So in the measles vaccines, we have no intention to develop measles vaccine with Moderna technology. It will not be a good use of resources of balance, but of course if somebody wanted to come along and partner on the measles vaccine with their capital, we'll be happy to do that. We really want to focus on innovative vaccines. For public care vaccines, and as you know we have a few in our pipeline, we believe it's an important part of our mission and the responsibility of the company. We want to partner with foundations like we have done before. We want to partner with governments because we believe it is really important to use our technology to get those vaccines to protect millions. We will not do it with our shareholder capital, that will not be the responsible thing to do. We are already open for business like we've done with DARPA, with BARDA and Bill Gates Foundation with which we're partnering for projects that are in research. So the big focus of Moderna is on innovative vaccines.

So let me share a few examples of innovative vaccines to share with those of you that are not as familiar with vaccines, what it could look like. So Prevnar has a few interesting characteristics. So this is a vaccine that Pfizer is commercializing. The turnover in 2018 was $6 billion. It's the #1 product of Pfizer. There's no product that Pfizer has that has a bigger turnout on an annual basis and look at the launch here. Prevnar 7, the first edition of Prevnar was launched in 2000. Look at the prediction for 2024, and I can bet with you that Pfizer is going to be selling Prevnar for many, many, many years to come.

Another example is Gardasil, the vaccine that Merck has to protect against HPV. Gardasil was launched in 2006 so it's quite a number of years ago. This is a third product from Merck. The first product was KEYTRUDA, a wonderful drug. But I think that by the time KEYTRUDA goes for patent, which will happen next decade, HPV will be bigger than what it is today and what is going to be in 2024. Merck has announced that they are building additional manufacturing capacity. As you know HPV needs to be protected in children, both boys and girls because it's very proven the long-term effect in cancer. So it is very important vaccine. So we believe this vaccine has a very long life cycle and is going to generate great business for Merck.

Let me now close with Shingrix because sometimes I hear vaccines have very, very slow uptick. It takes years to get to a couple of million dollars and to a billion is almost impossible. So look at Shingrix, it was launched in 2017. First full year, $1 billion of sales in 2018. This is the fifth product of GSK today. If you look at the GSK products that on the top 5, I bet to you in a few years, Shingrix will be the #1 product of GSK, I have no doubt. So we believe that innovative vaccines are first very important for public purposes, obviously and there could be a great business for shareholder capital.

So if you think about our midterms for this year. The #1 priority of the company is to really been on the strong vaccine franchise and continue to innovate and do research on innovative vaccines. Stephen and Andrea and the team are, as we speak, working on additional new innovative vaccines that are already in a free [universal] potential. We believe [the cap] could be a couple hundred million dollar a year, this was yellow fever sales every year, and we remember yellow fever is supply constraint. Every year, people are missing doses of yellow fever so it's even possible that it's higher, and it has a pandemic you could see symptom of flu big spike that is not sustainable.

If you seeing on these really exciting immuno-oncology pipeline. We're self-paced for strategy across our 5 programs is to see can we improve a response of checkpoint monotherapy. Checkpoints have been wonderful for patients. We're saving people's lives every day, but unfortunately they do not work for everybody. So we see a massive unmet medical needs are there, and we're hoping that some of our products could help patients who are fighting cancer.

And now, of course, with chikungunya human data to grow and to really start clinical trials, which we are eager to do, not only in MMA, the PA is just behind it. We just have an objective (inaudible) of this year. So we have a very nice portfolio of 5 rare disease. And for those of you who follow or not present on the presentation, Stephen and team have a very interesting new science that they showed at Science Day in May. So we anticipate in the future that we will be able to expand into new (inaudible) area.

So to close, there is still a lot of work. We're not done. I don't think we're going to be done for a long time because we believe this technology is very powerful. We believe that by working together as a team, this company can have a big impact on patient's care, of course, many, many for us to carry on. Think about what we've shown to date now, we've shown we can code mRNA safely in a human to make a viral protein, it's called an antigen who (inaudible) 6x. We've shown we can code an mRNA to code a human protein, VEGF, OX40 have demonstrated that. And with today's news that we can create an antibody, we basically have a full toolbox of what you need to go help patients. We can do that in the secreted space. We can do that in a transmembrane space. We can do that in intracellular space. So I think we can barely imagine what the future holds for this technology and for what we can do for patients.

A few years ago, when we were not in a clinic, I had no idea that one day we will have KRAS vaccine. I had no idea until the NCI paper came out and Tal came back from NCI with a big smile on his face saying we should really do a KRAS vaccine, there is good scientific ground now. We have an enormous helping. It's called academic world. We are living a biology revolution around the world where every day we learn more at an exponential pace about what proteins do in the human body. What a wonderful time to believe this technology where we have this team that has a serious commitment to science and to invest in science for improving and expanding the technology. The ability to use -- now would be able to make quickly, high-quality GMP product and the clinical teams to put that into music into the clinic so can try with clinical research to see either hypothesis is correct or not. And as we said before and we are doing that PCV, we've randomized head to head. We care about knowing ours drugs are going to work or not. We've said this many times, we're not in a business of doing any comparative study, another in-comparative study, just to keep the product in the pipeline. We want to be very disciplined with our shareholder capitals. We want to put it on the drug that have the highest chance of getting approval and that's what we'll keep on doing.

We feel all very fortunate at Moderna of the mission that we have. We feel very lucky, we think it's a once-in-a-lifetime opportunity to be able to go to work every day with amazing people to try to do something that has never done before to help our patients. And that is what is giving us so much energy. So with this, I would like to close.

Thank you very much for attention. I would like the executive committee to please join me so we can take questions. Thank you.

QUESTIONS AND ANSWERS

Answer – Stéphane Bancel: Another one. Sorry. Lori and Megan, Stephen, who am I missing. They all have just come in.

Good. So can we have some mics please? We're going to start with questions anytime. We have. Thank you.

Analyst: Unidentified Analyst,

Question – Unidentified Analyst: Two quick questions, if I may. Tal, I'm wondering, so again congratulations. I agree with you that's a monumental achievement, really cool. I'm wondering how we should be thinking about immunogenicity for the proteins and the antibodies that you are creating and are secretive. So I'm not sure if you analyzed that but if not, maybe you can kind of walk us through sort of the thought process about what we should think about that because it is being generated by the body, but is there the potential for immunogenicity or antibody -- anti-drug antibodies?

Answer – Gregory Enns: I think I'll take that, and maybe Tal will jump in. So it is something we will naturally look for in our Phase I (inaudible) genes therapy. As relates to 1944, you see that a very long predicted clearance that certainly there hasn't been a clearance vaccine against that protein. Like -- it is something we always worry about and

we think about very specifically as we design the drug. So all of our therapeutic platforms actually are very different platforms than our vaccine platforms. We use different chemical components and lipid nanoparticles. We send them to different cell types and actually we published also we even put in microRNA sites in the mRNAs encoding our therapeutic proteins to prevent their expression in immune cells or antigen preventing cells. All of that is sort of belt suspenders and a couple of other things, but it's fair to say that as you look at our preclinical data whether that's the [GOP] toxicology work that we have done in primates multiple times or the publications even the -- some of the presenters put up there of our work have not yet seen immune response to the encoded therapeutic proteins when we do all of those things. So it's a mix of different process for mRNA, different encoding elements and very different lipid nanoparticles that we think is pretty essential to that. But we'll always be looking in the Phase I. Obviously, if we see anything, we'll let you know.

Question – Unidentified Analyst: Yes. I am thinking about that specifically for chronic dosing. So with this proof of concept in hand, if you can remind us the status of MMA 3704 and then also if this is kind of the greenlight you were waiting for to really expand and continue to invest and evaluate other opportunities for mRNA could be used to treat orphan-type diseases like this?

Answer – Stéphane Bancel: So what we want to do at this stage is to prosecute the portfolio we have. Because with 5 rare disease, we think there is plenty. We want to make sure we focus on execution. We also want to be careful about our expenses. So as we've done in the past, the strategies are with the risk with first program, chikungunya antibody, try a few programs to confirm that you're on the right path, and then we can double down. So Stephen and his team are working on even more rare diseases. But we do not anticipate right now to take more into the clinic because it's just totally correlated risk. We want to see MMA result, we want to see the PA result, but trust me they're not waiting either, that are more stuff cooking in their labs. But now we have to be cautious. Anymore questions?

Question – Unidentified Analyst: On the cancer programs, I know a lot of this is partner-driven, but I'm just wondering if there is any data that we should expect maybe over the rest of the year or early next year?

Answer – Tal Zaks: On the partner program?

Answer – Stéphane Bancel: IO...

Question – Unidentified Analyst: On the cancer [IO] data.

Answer – Tal Zaks: So yes, there's a lot to expect. The challenge is, as Keith will readily tell us, it's hard to know when it is going to come in because really what we're trying to do now with our programs in the IO phase is to seek responses, right? So at least for those Phase I programs that are open label and looking for responses, they are powered to a certain size. We are treating certain cohorts but of course you'll see the data as it matures. You'll see as we treat more patients, we'll have the opportunity to see more responses. I think we're -- that difference is in the randomized Phase II. That's how it will take time. As you can imagine from the statistics, it's powered to actually enroll everybody and then follow them for a year of them [mark] analysis. And remember these are patients in the adjuvant setting so on one hand, as Keith's alluded to, and I completely share his belief that in this space we want to go and improve the utility of something like a personalized cancer vaccine especially now with the benefit of KEYTRUDA in that space. On the flip side, you actually don't see the benefit until you accumulate enough events over time and you look at it versus the control arm. So on that aspect, that one we're going to have to be patient and let time do its thing. And the other programs -- and that's true for our partner programs with AstraZeneca as well on [IO12]. It's open label as responses come in, we have enough an opportunity to see them.

Analyst: Unidentified Company Representative,

Question – Unidentified Company Representative: We have another question in the back.

Analyst: Unidentified Analyst,

Question – Unidentified Analyst: 2 quick questions. Rosenberg selected for immuno reactivity to KRAS G12c. I don't know if you're [slogging] for that. You're just targeting it. So I wanted to hear your compare and contrast on the NCI approach versus your approach. Second question, there is a therapeutic index to the amount of LNP that you can give as defined by your results. So can you talk about the question and LNP question.

Answer – Tal Zaks: So let me try and take these in sequence. Rosenberg showed that, that 1 KRAS in the context of that 1 HLA was actually a tumor rejection antigen, if you grew the cells ex vivo and gave them back. Our vaccine is trying to expand on the mutations spectrum. So the patients enrolling in the trial are going to be patients who have any one of the 4 mutations that is in the vaccine.

And then, we will look post talk and see who did what in terms of seeing any responses or immunogenicity because immunogenicity for some of the other epitopes in terms of the other HLA is yet poorly understood. Where we are

trying to mimic Steve's approach is on selecting the HLA that people with the right allele at least at the starting point for a proof of concept so that Phase I the first dose confirmation for safety is in all-comers population immunologically that got the 4 mutations. The next phase for the trial will be focusing in at least to start with on HLA, A11 and CoA as in his case, and then, testing anybody who's got any one of these 4 mutations and then we see what we get. So that's on the KRAS. In terms of the LNPs, look, I think these are early days, in preliminary findings you're seeing our study that's ongoing. I think the fact that we're seeing infusion-related reactions at this rate at 0.6 means we got to do something different. For me the obvious next step is go from (inaudible) with steroids to the degree that, that ameliorate as it does with many other injectables then I would expect that we could be able to give even 0.6 mg per kg at a safe and well tolerated level. It depends on what premedication regiments. As an example, back when Keith and I were training, every fellow was taught that Rituxan, oh my God, this guy's infection really reaction so we will give him steroids. If you look at the label for REMICADE, you give 100 milligrams of methylprednisolone every time you give it to the mature patient you like every few weeks. So it's not a showstopper (inaudible) that got approved last year is the lipid nanoparticle with an siRNA that's given at 0.3 mg per kg already with steroids. They never actually tested it without steroids. I think for us it was important as the first step into this platform to fully characterize the safety and tolerability without it before we reported it. And I would point to the fact that the starting dose for MMA for methylmalonic acidemia is 0.2 mg per kg and that's a dose that's predicted already to have the possibility of benefit, and that's very nicely bracketed between the 0.1 and 0.3 that you see here that has absolutely no significant adverse event. So I think it's early to say that we know what the top dose is but we pretty clearly have cleared the dose at 0.3 where we achieved therapeutic level of protein and the adverse event profile is so benign that you don't know some of these are on drug or placebo.

Analyst: Unidentified Company Representative,

Question – Unidentified Company Representative: Any other questions? Yes.

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

Question – Hartaj Singh: Hartaj Singh with Oppenheimer. First of all, just amazing data on the chikungunya antibody. You have created memory for me at least seeing that, that will stay with me for the rest of my life.

Just a quick question on the -- on just you -- you can get the, I guess the primary structure of the antibody right through the [MRA] the coding structure. There is a secondary tertiary structure as to where these antibodies. Tal, can you just talk about when you think about the future antibodies trying to come up with these approaches? Does that play into how you think about if there is some kind of screen there and -- or not really you can pretty much go into sort of any antibody that's available there in the human body?

Answer – Tal Zaks: I think the right person to answer that is actually Stephen because he's pretty much smarter than me in thinking about the tertiary structure. For me, they kind of look the same when you just take the sequence and get what you expect, but...

Answer – Stephen Hoge: Well. So I think the question is the complexity of the antibody structure impacting maybe our next choice on discovering programs and the shortages. Given that we've been able to make any protein we've chosen to make so far, it does cause us to look at what are proteins that people have struggled to make in other ways because, obviously, there can be a real advantage of this sort of approach. We're not ready to guide on specific programs right now. I think we'll continue to look at that. We are also in the preclinical space where you can increase your end. We're always looking to characterize the quality of those proteins in particularly not just tertiary structure, but also glyco forms that contact constellations both intracellular -- both for liposomal and extracellular proteins. We're actively looking at those things and many of -- much of that data will probably come out in our preclinical publications where we do that work.

Analyst: Unidentified Company Representative,

Question – Unidentified Company Representative: Any other questions? We're good.
