Vaccines Day & Business Updates | Moderna | March 27, 2024

Stephen Hoge, M.D.:

Good morning everyone. Thank you for those who've joined in person and for those who've joined online. My name's Stephen Hoge, I'm the president of Moderna, and it's my pleasure to welcome you to our fourth annual Vaccines Day where we're going to cover a tremendous amount of data as well as a lot of the progress we've made across the business in building out our infectious disease vaccines franchise, one that we're incredibly proud of. Just a brief moment to remind you that during the day we'll be making forward-looking statements that are subject to the safe harbor provisions. For more information as well as the detail on the disclaimer, please visit the investor relations portion of our website.

So, where are we on our fourth infectious disease vaccines day? We have a pretty remarkable portfolio of something we're really proud of. There are 28 different vaccines going against different populations and different viruses, as well as some proteins from bacteria. Those include respiratory, latent, and other pathogens, as I said. It's far more than we could hope to cover given the progress we've made over the last number of years, and so we're going to focus today's discussion really on our latent and other vaccines portfolio and our respiratory vaccines portfolio. And in particular, focus on the programs that are highlighted on the right here, our CMV vaccine, HSV vaccine, our norovirus, VZV, and EBV vaccines, many of which we'll be presenting some exciting new clinical data on today. And on the respiratory side, we'll speak briefly to our COVID vaccine spike facts, as well as seasonal flu and our flu COVID, just the progress we're making there, and share some additional updates on our RSV vaccine and our next-gen COVID vaccine, mRNA-1283, which just had a successful phase three readout as we announced yesterday. And we're looking forward to sharing that data with you today.

So a little bit on that portfolio and maybe highlighting a few of those programs that we will be speaking about. We have made great progress expanding our mRNA platform into latent and other pathogens, something of a lot of pride for us, because these were much more complicated vaccines to initially create and development often had multiple mRNAs making multivalent protein antigens. And all of those are now making great progress in clinical trials. CMV, which we've talked about numerous times, is the most common infectious cause of birth defects in the United States. Actually, one in 200 babies born in the United States are exposed to a congenital CMV infection. It's been a number one priority for the Institute of Medicine to develop a vaccine against for over a decade. And we're in phase three now and we're looking forward to providing an update on that.

EBV, which is a major cause of infectious mononucleosis. It's also one of the primary causes we believe ultimately of multiple sclerosis, as well as countless other diseases including cancer. And it has obviously got a large burden of disease associated with those sequelae. We are excited to share our clinical updates in the progress there. We're working hard against HSV, that's a herpes simplex vaccine, a leading cause of genital herpes lesions. VZV, which is a disease of declining immunity in older adults that leads to a disease called shingles, and we're quite pleased by the data we'll look forward to providing an

update on. And the norovirus, a very complicated family of viruses that's a leading cause of diarrheal deaths globally and a huge burden of disease as well in developed economies, particularly among the very young and the very old.

In the respiratory space, we've made great progress against the big three. We've been talking about this for a while. The big three leading causes of respiratory disease. COVID-19, where we're going to share some updates on how we're addressing emerging variants, as well as, as I said, our next-generation vaccine, our phase three results that were announced just recently. Our RSV vaccine, we're in the process of preparing for the launch of that product this year. And we're also going to provide a little bit of updated work we're doing to expand indications into additional age cohorts. And then our flu vaccine where our first-generation, second-generation flu vaccines are making great progress in phase three, and we have next-generation programs in flight. And then of course across these three respiratory viruses and families, we're looking to do combinations both first and second generation combinations that will decrease the burden on healthcare systems for administration and actually we think.

Improve compliance and ultimately public health outcomes. Okay, so a little bit of an update on the agenda before I turn it over. So we will start out led by Jacqui Miller, our Head of Infectious Disease Development, who will join me in just a moment and walk through most of our latent virus vaccine portfolio. She'll be joined in that exercise by Sumana Chandramouli, who will come up and present some of the really exciting data that we're doing, particularly in EBV. Jacqui will then close out with some of the other latent viruses. We'll have a brief break, a coffee break, and then come back and move to that respiratory portfolio, as I talked about. Jacqui will be joined in that exercise by Christy Shaw and Raffael Nachbagauer who will both be presenting in the respiratory franchise. And we'll turn it over to Stéphane in his capacity as the Chief Commercial Officer, not CEO, who'll come up and talk a bit about the commercial opportunity, before being joined by Jerh Collins, who run through some of the really important manufacturing technologies and innovations in our network that have made possible this incredible pipeline.

Jamey Mock will come up and talk about how do we think about allocating capital and how do we think about investment decisions? We have an incredible blessing of opportunities, and so what is our strategy for managing that as well as some of the ways that we're sourcing capital in the announcements made today. And then Stéphane will come up in his capacity as our Chief Executive Officer and share his update and perspective on the overall day. We're happy then to do some Q&A with everybody and we will pull the team back up here to do that. So with that, we'll get to the most important part of the day and I'll invite Dr. Jacqui Miller to come up and provide an overview of our portfolio on latent and other vaccines. Jacqui. You got it.

Jacqueline Miller, M.D.:

All right. Thank you, Stephen. Good morning everyone. It's good to see you again and I'm really thrilled this year to do something a little bit different, so to start with our latent portfolio. Every year we always talk about the respiratory portfolio first, but this year I hope you'll agree by the end of the presentation that our emerging phase one data are quite exciting.

Okay, so an overview of our latent virus portfolio and why we believe our platform in particular is well suited to these viruses. So latent viruses are a family of viruses that cause two distinct phases of infection. First phase of infection is the acute infection, and that often is accompanied by signs and symptoms that are maybe shared with other kinds of acute infections. Where these viruses, and they're almost always herpes viruses, really differ from other kinds of infectious diseases is in the latent stage. So these viruses can actually hide out inside different cells in your body for long periods of times, years, decades, then reactivate when the biological environment is favorable and cause then many longer-

term sequelae. And these longer-term sequelae can look quite different than the original infection and they can, unlike the original infection, have symptoms that can last months, years, and even lifelong.

So, why is our platform so well-suited to these particular viruses? Well, these viruses, because they hide out in cells, actually, antibodies are not always enough to be able to control the infection. T-cell responses are absolutely critical for these viruses and we'll talk about a few examples as we move forward this morning. In addition, these viruses actually, I mentioned they can hide in multiple cells in your body, so they often infect more than one kind of cell type. Unlike our respiratory portfolio where we're really targeting respiratory epithelium, here, there's a much broader range of cells we need to target. And so being able to put multiple antigens into the same vaccine to create synergy in terms of how we prevent infection and transmission from cell to cell, that's really critical for success we believe.

And then finally, we are able to include quite complicated antigens in their natural conformation. So these are viruses that often have quite large genomes. CMV actually has one of the largest genomes of all viruses, and that means that they can elaborate proteins that are really quite complicated in their structure. So being able to naturally mimic that we think really will give our platform the edge. So, what viruses will I be discussing with you this morning? Well, you know about cytomegalovirus, and we actually talked quite a bit last year about the impact of cytomegalovirus, but just to say that it is the most common infectious cause of birth defects worldwide.

And it's called the troll of transplantation. That's actually a published paper. And the reason it's the troll of transplantation is because when you suppress someone's immune system, their pre-existing latent CMV infection can reactivate and that actually can cause a number of symptoms. Severe illness, but then also graft loss, which is obviously one of the worst outcomes in those patients. Epstein-Barr also is a virus. It causes what you think of as infectious mononucleosis. So high school students who are out of school for weeks, a few months, that's their primary infection. About 3% of people will have that kind of presentation of primary Epstein-Barr. But it also is a major driver of multiple sclerosis, so it leads to a greater than 30% increase once you've had that primary EBV infection.

Herpes simplex, as Stephen was mentioning, is a lifelong scourge as well. In addition to painful lesions, there's the social stigma that's associated with reactivated herpes infection. Overall, 13% of the global population between ages 18 and 49 are HSV serotype two positive. And then finally, varicella zoster virus. This is the cause of chickenpox in childhood, but once you've had your chickenpox infection, that virus hides in basal nerve ganglia, and when it reactivates, it causes a painful rash and it can cause postherpetic neuralgia, which can last for months or even years. It's incredibly common. So by the time we're 80 years of age, one in three of us will have experienced a shingles reactivation.

Okay, so let's talk a little bit about CMV. CMV, as I mentioned, is the most common cause of infectious birth defects in the US and it leads to, in its sequelae from those congenital infections, to several billion dollars in annual healthcare costs. It can have symptoms that lead to microcephaly, choruretinitis and other neurologic defects, most predominantly sensory neural hearing loss, so it's one of the most common causes of needing a cochlear implant. And in the long term, there are other cognitive impairments that can be associated. One in 200 babies are born with a congenital CMV infection, so they're getting their initial CMV infection in utero. And while a fetus is developing, this virus can really wreak havoc on developing cells, particularly developing cells in the nervous system. Of those babies who are born with a congenital infection, one in five will have one or more of these severe life-altering problems. Okay, so our vaccine, just to review its composition, it includes six mRNA sequences. Five of them encode a very large and complex antigen called pentamer, so you see pentamer on the left of the screen. Pentamer actually is the most immunodominant antigen in a CMV immune response in humans. Unfortunately, it's very difficult to synthetically generate pentamer in the right conformation, and this is where we think the mRNA can really add the edge because these five components, the amino acids

naturally assemble into the natural conformation. And then glycoprotein B is an antigen actually that was used in a successful proof of concept demonstration. So there was a previous CMV vaccine, it included a glycoprotein B antigen, and it led to 50% efficacy in infection. So we think we already are giving ourselves a great shot at having positive vaccine efficacy by taking a known efficacious antigen and then adding that immunodominant pentamer on top.

Our CMV trial is currently ongoing. We finished enrollment and we're now in the follow-up phase where we're waiting to accrue primary CMV cases. We have 50 cases which have accrued and now are undergoing additional conformation. The randomized observer blind and placebo-controlled trial is really designed to demonstrate the efficacy but also the safety and immunogenicity of the vaccine. We completed our enrollment across 290 sites globally. This was actually our first global clinical trial, and now are in the follow-up phase of these women and adolescents, 16 years of age to 40 years of age. We have enriched our clinical study in order to ensure that we are capturing cases. We've done that by asking that we enroll women who are above 20 years of age. We ask that they have contact frequently with young children. Why? Young children are the major vector to transmit infection. So typically what happens is a mom has a baby, that baby goes to daycare, acquires its primary CMV infection, comes home and then gives a seronegative mother her primary CMV infection which she passes to her unborn child. So we think that really focusing on this population is going to be important to demonstrating the success of the vaccine. And then primary efficacy analysis will be triggered on the basis of the accrual of these primary cases. So all in all, we have about 7,300 women that have been enrolled.

And so just a refresher on what it means to accrue cases and then trigger an interim analysis. We have designed our study to be able to take two looks at our data. The first, when about 70% of the total number of cases have been enrolled or have been accrued, so that would be at 81 cases. We're anticipating that we will confirm we have 81 cases as early as later this year. The entire study is powered on 112 cases. If we're not successful with that first data, look, we still have the opportunity to look at the end-of-study analysis and demonstrate efficacy. And so what does that mean? If you look at the graph, you see that if the true vaccine efficacy, which is on the X-axis, is 60%, when we get to this interim analysis, we would have about a 60% chance of being successful.

However, if the true vaccine efficacy is closer to 80%, now we have about a 90% chance to be successful, and that's shown by the dotted line. The solid line is what it looks like at the end of study analysis, and there, if our vaccine efficacy is 60%, now we are really close to 90% power to demonstrate success. So we're very confident that we've designed the study very well and given the vaccine the best possible opportunity to be successful. Okay, so in summary, this is the most common cause of congenital infections worldwide and our vaccine has two target antigens. And again, we think this is really facilitated by the flexibility and the biologic nature of the mRNA platform. Our phase three trial is fully enrolled and we are awaiting that 81 cases in order to be able to have our DSMB look at the first interim analysis. Our potential for the vaccine efficacy readout could be as early as towards the end of this year.

And so just talking a little bit about how we're already looking to expand our CMV vaccine to other indications, so first, we'll talk a little bit about adolescents. You'll see in the next slide the age at which you get your primary infection. Every year, more and more primary infections happen, so really the younger you vaccinate, the more benefits you're likely to have to those seronegative individuals. And then we'll talk a little bit about our transplant program, which is ongoing. So this slide shows you, on the right, NHANES data looking at CMV seroprevalence across different genders and different racial groups. And so what you can see is that while some racial groups have more frequent and younger CMV primary infection, particularly those that are Mexican American as well as non-Hispanic Black Americans, in all gender and racial groups, the infection rate increases with age. So again, the younger that we're able to vaccinate, the more primary infection cases we can prevent and the more potential benefit we can deliver.

The CMV adolescent study has actually started its phase 1/2 enrollment, and so similar as with COVID and with RSV, we are looking to confirm the appropriate dose in adolescent patients. This is going to include both males and females because we believe that males also could benefit from not acquiring this latent infection, and it will include 770 participants. It's really powered to be the phase two portion of the study, so we can move directly into phase three across 70 sites worldwide. And immunogenicity is going to be assessed against epithelial cell infections and fibroblast cell infections. So remember, I told you latent viruses are notorious for infecting multiple kinds of cells, so we check multiple kinds of cells to make sure we can neutralize infection.

In terms of our transplant program, we know CMV is a major burden in this population. It's associated not only with graft rejection, but a lot of other end organ disease ranging from retinitis to gastroenteritis to pneumonitis. There currently are no approved vaccines for CMV, actually for anyone, not just people post-transplant, but there's a great need post-transplant. And there's a high cost and there's also some toxicities to antiviral prophylaxis. So right now, every transplant patient, depending on which center they're transplanted in, receives some degree of antiviral prophylaxis. The problem is when you pull them off their prophylaxis, they still are immunosuppressed, so their risk for reactivation really increases. So all transplant patients we believe could benefit from CMV vaccination.

There are approximately 70,000 transplants of solid organ and hematologic in the United States every year, so we think that this is really a sizable population that's worthwhile vaccinating. The risk also is lifelong, so there are whole cohorts of other transplant patients who could benefit. What are we doing? We are looking at hematopoietic stem cell transplant patients and we are waiting until after their stem cell transplant until that bone marrow has engrafted and they're starting to create new antibodies. That happens around about day 50 or so. Now, these patients then get vaccinated on an accelerated schedule, so they get all three doses, but they're getting them quite rapidly to try to bring their protection on board, so that by the time they finish their CMV prophylaxis, which in this population is for a hundred days after transplant, they now hopefully have antibodies on board to prevent reactivation and T-cell responses to prevent reactivation of their infection.

So our primary outcome measure is on clinically significant CMV viremia. So what does clinically significant mean? It means that it's sustained because these CMV levels can actually waver in transplant patients. They don't all get treated immediately. So we work with the oncologists to really define when it becomes significant enough that we would start antiviral prophylaxis. That antiviral prophylaxis is really the end point we measure. We're recruiting approximately 224 patients. It's actually quite a large phase-two study in oncology patients, and we will have an interim analysis hopefully sometime later this year.

So, now for something completely different. I want to talk to you a little bit about the work that my team is doing to incorporate artificial intelligence into the development work that we do. And I really have to say this is the result of a collaboration between someone on my team who is one of the clinical physicians. Worked on CMV, now is working on Norovirus. And one of our medical writers who worked with our clinician on CMV. And McLeet and Lee got together and really thought about how could we make our development work easier over time, so I'm going to take you through this case that really I think reflects the innovation from the very talented people that we bring into the company.

So they developed a GPT called Dose ID. What does Dose ID do? Well, it looks at all of the data that we generate out of our phase one studies. And when I present to you and I talk about these 35 subject per group studies, it doesn't sound like a lot, but we generate statistical reports with hundreds of pages of tabular data because you can slice your data in so many different ways. There's a lot to really synthesize and analyze there. And what this GPT allows us to do is leverage the available data, really synthesize it, to help our team make the available dose. And I say help, that's really important. So we don't just allow

the AI to go off and do it on its own. We clearly apply our own human and clinical judgment. But what it can help us do is maybe see patterns where we don't necessarily see those patterns in hundreds of hundreds of pages of data.

So let me explain how it works. GPT, for those of you who don't know, is generative pre-training transformer. When I first heard that, I said every single word in that phrase is English and I still don't understand what you're talking about. So this is how it has been explained to me, and I think it's really that middle column that will help explain it. So what the GPT can do, you feed into it multiple parameters, and actually, it's not a static tool. It's dynamic and you can add to it over time. So for example, if we learn that being on a certain medication is a risk factor for having lower immune responses, or we learn that having had a previous flu vaccine increases your response to your next flu vaccine, we can add and customize over time.

Then what the application does is synthesizes the data, and it does it in minutes rather than days. I'll show you a timeline in a minute, but it helps really visualize data in a way that's helpful for us to move from compiling and generating graphs to actually thinking about what the data are telling us and what we're trying to prioritize in this dose selection. And then it will recommend an optimal vaccine dose. But as I say, we don't check our brain at the door, we work with the GPT in order to think through, do we agree with that recommendation that's being made? Okay, so this is what the process flow looks like. We pre-specify metrics that we put into the GPT. So like I say, for flu vaccine, super important about when you last had your influenza vaccine. Might be completely different for one of the latent viruses where your previous seropositivity is going to be super important.

You then add in additional critical data for comprehensive analysis, and what you see from the bottom arrow. This can be an iterative step. So you can learn and then look in your data for more factors and add them in. You can say, "Hey, I want to see if knowing that CMV is going to have an impact earlier in non-white groups, I want to see what it looks like in the earlier age groups in communities of color." So it allows us to really customize how we look at this for each of the different programs. And then it provides a suggestion for optimal dose, but what I find really useful about it is it synthesizes and provides visualization in a number of different ways. So it gives me a number of different ways to think about the dose selection I want to make. It works in parallel with the human process and it has the potential therefore to accelerate dose selection timeline, because we're not spending our time generating tables. We're moving right to that discussion, that meaty discussion of how do we balance risk and benefit and select the optimal dose.

Okay, so the example that was utilized, I told you that both of my team members, McLeet and Lee, were working on CMV together. So they decided to train their model using our CMV data and they also asked the model without telling it what dose selection we had come up with to think about that. And so, inputting all of the data from all of the studies that we have conducted, what you see in the middle is the Python code. And I just got back from Greece, so it's all Greek or Python to me. But anyway, it translates to English somewhere. And actually, the GPT, in addition to giving us some different ways to think about that dose selection, also recommended the same dose that we've chosen two years ago. So that we think was a really successful pilot and we're now going to look to input this into other dose selection decisions that we're going to have to make that you see on the slide. And we can actually take this idea even further. So when we talk about in the company that we digitize everything, we're really thinking about other ways that these GPTs can be customized to help us review and understand our data. Reactogenicity is something that we really think about a lot on this platform. It's something that we're hoping as we move forward to further minimize, so a reactogenicity reviewer and generating different graphs and things is being developed. In addition, there's a lot of clinical literature out there. It's very, very difficult in this infodemic to keep track of everything that's being published on all the

programs we work on, so this is a clinical literature review assistant that helps us really pull out the main topics from papers as they're being published.

And then we're also looking at selecting the best clinical biomarkers. It's actually not always easy. I glibly talk about we measure primary infection. What I haven't told you about is how we define that primary infection, how we look at different assays and select how we're going to define this as a primary infection, that's not. And this biomarker tool is going to help us weigh our different options in the pros and cons. Okay, so with that diversion, I'm now going to introduce Sumana Chandramouli. She's our program leader for our Epstein-Barr virus programs, and she's going to tell you about two of our ongoing programs.

Sumana Chandramouli, Ph.D.:

Thank you, Jacqui.

Jacqueline Miller, M.D.:

You're welcome.

Sumana Chandramouli, Ph.D.:

Good morning everyone, and thank you, Jacqui. My name is Sumana Chandramouli and I'm a senior director and program leader in infectious disease research at Moderna. And it's my pleasure to tell you a little bit about our EBV and HSV programs today and share some early clinical data. So EBV, or Epstein-Barr Virus, is a herpes virus that has several serious health impacts, including

Including infectious mononucleosis, multiple sclerosis, and several cancers. There is no vaccine today for EBV. EBV happens to be a virus that infects nearly everyone worldwide by the time they reach adulthood, so seroprevalence ranges from 90 to 95% throughout the globe. And the age at which we get infected depends on where we live. So in low and middle income countries, which is shown in the light green in the graph on the left, this happens pretty early in childhood. But in high income countries, including the US, this seroconversion happens more gradually and reaches a peak of about 90% at age 22. And while most people acquire EBV asymptomatically and don't even realize that they've caught the virus, in early adulthood or in teenage years, that first infection can result in infectious mononucleosis or IM. And the peak vulnerable age for this IM is between 15 and 19 years of age. And IM, while it is self-resolving and a relatively mild disease, it can lead to serious complications like splenic rupture and lymphadenopathies in certain cases.

Apart from infectious mono, which is a result of primary EBV infection, EBV is also linked to several longer-term health conditions. So most recently we've heard a lot about EBV and MS. For decades, actually, we've known that EBV seropositivity is linked very strongly to a risk of developing MS. And there's nearly 1 million people living in the US today with multiple sclerosis and EBV seropositivity is nearly universal in this patient population. And this is shown in the graph on the left from a recent landmark study in 2022 that looked at millions of patient samples and data, and they found that there is nearly a 32-fold increase in risk of developing MS following EBV seroconversion.

And it's also interesting to note that the age of EBV seroconversion seems to play a slight role because the 32-fold is when EBV is contracted later in life, compared to a 26-fold when it's earlier in life. And then on top of EBV itself, there is an added risk from symptomatic infectious mononucleosis in the medical history of these patients. So if we look at the graph on the right, the center bar is now benchmarking to EBV seropositivity and MS risk, and we see that if there was symptomatic IM in the medical history, there is at least a two to three-fold increase of that risk even further. It's also interesting to note that the epidemiology of infectious mono and MS are quite similar as well.

EBV was the first human oncogenic virus to be identified in Burkitt's lymphoma in children in sub-Saharan Africa, and since then we've come to know that EBV can cause several different lymphomas, and this can be in post-transplant patients like post-transplant lymphoproliferative disorder or PTLG, nasopharyngeal carcinoma, predominantly in Southeast Asia, Hodgkin's and sporadic Burkitt's lymphoma, and a certain percent of percentage of gastric cancers and non-Hodgkin's as well. Now what's interesting is, again, just like with MS, not only is EBV the causative agent, but there is an added risk that comes from having symptomatic infectious mononucleosis to developing these cancers later in life. This can be as high as nearly six-fold for lymphoid malignancies in the years following infectious mononucleosis. Overall, globally, EBV-associated cancers are about 200,000 new cases every year, and 1 to 2% of global cancers and cancer deaths are because of EBV.

Now, what are we able to do about EBV and this unmet medical need for vaccines? At Moderna, we are developing two different vaccine candidates against this virus, given the complex mix of diseases that it causes. The first one at the top, mRNA-1189, is what we envision as our prophylactic vaccine. It is a vaccine that is composed of lytic antigens and we are gearing it to build a robust immune response in terms of an antibody response against EBV. The primary indication we are following for this vaccine is infectious mononucleosis, but given the causative link between EBV and all the other long-term conditions, we envision that if this vaccine is efficacious, we might see prophylactic prevention of all these long-term sequelae as well.

The second vaccine candidate, mRNA-1195, is designed to induce not only an antibody response, but also build up a robust cell-mediated immune response against EBV. It is composed of lytic and latent antigens, and here we are hoping that this vaccine can be helpful not only in people that don't have EBV yet, but even in people that have already acquired the infection latently. Here we are planning to test this vaccine in multiple sclerosis and in transplant patients with the idea that immune dysregulation of or by EBV may be one of the underlying mechanisms behind disease onset and progression. So today I will be sharing some of our early results from our mRNA-1189, phase 1, so mRNA-1189, just a little bit more about the antigens. So we have four antigens in this vaccine composition, gp220, gHgL, gp42. They're all surface glycoproteins on the EBV virus, and together they form the bulk of the core virus entry machinery for EBV to infect both B cells and epithelial cells. And we hope that combining all of these antigens together can help us stop the virus from attacking either of these cell types.

Furthermore, these four proteins together are pretty much the target of all of the neutralizing antibodies raised in natural infection. So our EBV mRNA-1189 phase 1 is designed in two parts. Part A is in adults 18 to 30 years of age, and part B is in adolescents from 12 to 17 years of age. Today I will talk mainly about part A. So here this is designed as a randomized equally across four different arms, with three different dose levels of mRNA-1189, and a placebo group. We have about 270 participants enrolled across part A, and the vaccination schedule is three vaccine doses at 0, 2, and 6 months. The duration of the study is a total of 18 months, 6 months of dosing and 12 months of followup, this study is being conducted in the US.

So first, looking at the reactogenicity data, we've observed that mRNA-1189 across the three different dose levels is generally well tolerated. So this is systemic reactogenicity that is being shown here on this slide, with EBV seronegatives at the top and EBV seropositives in the bottom. And we observed that the frequency and severity of the systemic SARs tend to increase after each dose regardless of the EBV serostatus, but they're predominantly grade 1 and grade 2. We also observed that the low-dose group is generally better tolerated than the medium and the high-dose levels as far as systemic reactogenicity is concerned. While not presented here, we observed that the local reactogenicity was very comparable to our other mRNA vaccines with pain at the injection site being the most common reaction.

So now going into the immunogenicity data. So this is our gHgL binding antibody titers that we observe in our trial. So on the left is the graph in EBV seronegatives. So these people basically start with no memory response to start with, and on the right is the EBV seropositives enrolled in this trial. The dotted line in the middle of the graph throughout all of the subsequent slides as well refers to the EBV seropositive benchmark, which is the level that is observed in EBV seropositives at the start of the trial. So that's the baseline. So what we observe is that the binding antibodies to gHgL increased after each injection in both seronegatives and seropositives, though the effect was more dramatic in seronegatives as expected. At the end of three doses, there was really no obvious dose response across the low, medium, and high doses regardless of serostatus. And after three injections, we were thrilled to note that even in seronegatives, starting from way below baseline, we are able to boost those titers well above the EBV seropositive benchmark. This is the gp42 binding antibody titers. The trends were very similar to what we saw with gHgL, in that the titers increased with each injection in both seropositives and seronegatives, much more dramatic in the seronegatives compared to baseline. But in both cases they again boosted well above the natural infection benchmark, that's the dotted line. And again, we did not observe a very strong dose response across the three dose levels. This is gp220 binding antibody titers. This is the last antigen in our composition. And here the trend was slightly different from gHgL and gp42, in that the titers increased after each injection in the seronegatives, but in the seropositives they seemed to peak right after a single injection already. In addition, there was again not much of a dose response between the three dose levels that we saw, and at the end of three injections, again, the levels in seronegatives had crossed the EBV seropositive benchmark at the start.

Then we looked at functional antibody response in terms of B cell neutralizing antibodies. So because EBV infects and goes latent in B cells, this is an important measure to know how our vaccine is doing, and here again, this was an interesting assay as we looked at the results. So while the levels of B cell neutralizing antibodies were below detection in seronegatives, as we would expect, they were actually below detection in most of the seropositives as well. So this tells us that natural infection leads to a pretty low neutralizing response against EBV given its immunivation capabilities. Now what we see is that this B cell neutralizing antibody response is boosted above detection levels in both seronegatives and seropositives following mRNA-1189 administration. And while the titers were quite similar, there was a slight dose response where the highest dose level did have numerically higher titers. And this was true in both seronegatives and seropositives.

As far as the three injections go, there was a larger impact of the second and third injections boosting the levels in seronegatives compared to seropositives. But overall, again, at the end of three injections, we could see titers that were well above the benchmark at the start. Now some exciting additional data that we would like to share, and this is in the impact of mRNA-1189 on EBV shedding in the seropositive cohort. Because our seropositive cohort sample size was small, in this analysis we pooled all the three dose levels together and presented this as mRNA-1189 in the blue, and the placebo is shown as gray. So these assays are measuring the viral DNA in saliva collected on a monthly basis in seropositives as soon as they receive the doses of mRNA-1189.

And what we see is that the pooled mRNA results show us that there is a measurable decrease in the EBV that is being shed in saliva in the seropositives that have received mRNA-1189 compared to placebo. The graph at the bottom, you can think of it as a yes- no graph. So it is the percentage of participants that have detectable virus in their saliva versus not, and we can see again that with the impact of the vaccination over time, that the number of participants with detectable virus tends to go down in the mRNA-1189 group compared to placebo. And what is also exciting is that we see this impact last through up to day 505, which is month 18, or one year after the last dose of vaccination.

So now I'll switch gears to talk a little bit about mRNA-1195, which is our EBV therapeutic vaccine. So mRNA-1195 is currently in phase 1, so it is again designed as two part trial, part A and part B. Part B is in

EBV seropositive participants, 18 to 55 years of age. We are testing two different compositions of mRNA-1195 across four dose levels, with an additional arm of mRNA-1189 for comparison, and a placebo group. So there are 10 arms in this study. A total of 350 healthy EBV seropositive participants have been enrolled, and the vaccination schedule is similar to 1189, three doses at zero, two, and six months, and we've completed enrollment in this study. And this study is also being conducted in the US.

So to summarize the EBV section, we know that EBV infects the vast majority of the world population and it can cause serious health effects in the short and the long term, including IM, cancers, and MS. As far our phase 1 results go, we observed that mRNA-1189 is well tolerated in adults 18 to 30 years. We are able to demonstrate a good immune response against the constituent antigens, gHgL, gp42, and gp220. Regardless of serostatus. In all of these groups, the titers were above the natural infection benchmark and there was minimal dose response across the three different dose levels. This also extends to the B cell neutralizing titers, and we were also able to see a measurable reduction in the viral shedding in EBV seropositives following mRNA-1189. mRNA-1189 continues to progress towards later stage development with the ongoing adolescent trial, and we have mRNA-1195 in our ongoing phase 1.

So now I'll switch over to give a brief update on our HSV program. Herpes simplex virus, HSV-II, infects nearly 13% of adults worldwide, and it is the primary cause of genital herpes disease, or GHD. There's an estimated 4 billion people living with HSV, but the vast majority are HSV-I, while about half a billion of them are infected with HSV-II. There is a significant unmet medical need because there's almost 18 million people in the US living with HSV-II disease, and there is not only a physical impact, but there is a social and emotional impact to this infection that is pretty significant. And there are disease disparities as well. This disease disproportionately infects two-to-one women versus men, and it also has a higher incidence in racial and sexual minority populations with non-Hispanic black persons being the most affected.

So we have a candidate in phase 1/2 trials right now, mRNA-1608, which is designed as a therapeutic vaccine to help reduce the recurrence of recurrent genital herpes disease in people living with the disease. So this trial is now fully enrolled. It is a randomized four arm trial with three arms of three dose levels of mRNA-1608, low, medium, and high, and we have a control group that receives BEXSERO at a schedule of zero and two months. We have about 300 people enrolled so far, and about 35% are men, so we would like to understand how the vaccine works in both genders. And the duration of the study is about 15 months, so dosing, and then 12 months of follow-up, and this is also being conducted in the US. And with that, I will hand it back to Jackie to walk us through our varicella zoster program. Thank you.

Jacqueline Miller, M.D.:

Thank you, Sumana. So we'll talk about one final latent virus program today, the varicella zoster program. So herpes zoster, as I mentioned earlier, is caused by reactivation of the virus that caused chickenpox. And really we understand that this is due to declining immunity as one gets older. So the reason why the rate increases so drastically between 50 years of age and 80 years of age to the point where one in three of us at age 80 will have experienced herpes zoster is because we have a declining ability to respond to reactivating infections. And it's particularly actually our ability to activate T cell, so reductions in T cell immunity.

We investigated a candidate vaccine targeting the glycoprotein E antigen. And this was a phase 1/2 study. It was actually relatively large, designed to again enable us to move into phase 3. We included three different dose levels, and then at the highest dose level we investigated what a single dose could look like. And instead of placebo, we actually compared this time to Shingrix. We insisted that at least 35% of subjects be above 70 years of age, and again, that's because we know that in older adults the

rate really starts to rapidly increase. So subjects either got two doses or one dose, and they are followed for 12 months after vaccination. So what I'm sharing with you are the T cell data today, and these to start with are the CD4 cell data. So these are CD4 cells that specifically recognize that glycoprotein E antigen. And by the way, it's the same antigen that's in Shingrix, so we can actually compare against a licensed vaccine.

We have approximately 25 subjects per arm on this graph, with the Shingrix group in gray and the mRNA-1468 dose levels in various shades of blue. And what you can see from the CD4 perspective is that all of the vaccines... A little bit after the first injection we already start to see some increases, but particularly after that second injection, we see increases that are at or above the level of Shingrix. And I should explain what you're looking at on this slide is a box plot. The line in the middle is the median, and then box itself represents the interquartile range, so between the first and third quartile. And if you look at those medians, it's what really gives us confidence that this platform can induce the right kind of immunity to hopefully prevent reactivation of herpes zoster.

And now what's really exciting to us are our CD8 cell data. So Shingrix is known to be a very good inducer of CD4 cells. It has not actually been shown to demonstrate CD8 cell induction, and we observed the same in our assay. However, we did see induction of CD8 cells in all three dose levels of mRNA-1468. So again, adding additional T cell immunity to the observation. From a safety perspective, we saw relative comparability in both local reactogenicity and systemic reactogenicity between mRNA-1468 and Shingrix. In all three groups, the majority of reactions are grade 1 to two, and the reactogenicity profile was very comparable to what we've seen with other vaccines in the platform. So in summary, we elicited comparable or higher CD4 and CD8 T cell responses as compared to Shingrix. 1468 was also generally well tolerated across all the dose levels we've tested. So these were our first results. We're expecting additional results later this year, in particular looking at the durability of both antibodies and T cells, and we are advancing this program also to towards phase 3.

Okay, now for something completely different. Norovirus is our first enteric virus program, and norovirus actually shares a little bit more with the respiratory portfolio in the sense that we are injecting a vaccine intramuscularly, and what we're really hoping to do is deliver a functional antibody to an epithelial surface, so not the respiratory epithelium, but the GI epithelium to prevent spread of infection at the cellular level. So among enteric viruses, norovirus is a leading cause of diarrheal disease, and it's associated actually with 18% of acute gastroenteritis worldwide. So it's a really big player overall when you consider how many enteric viruses there are. The highest incidence is in children, and the morbidity and mortality is greatest in low-income countries. But in high-income countries, older adults and the immunocompromised population actually have more severe disease, including death.

And this really explains our strategy, which is as we have done before, really investigating the vaccine in older adults, but then moving quickly down to the pediatric population. So the burden of norovirus in older adults is expected to increase with societal aging, and also the increased need for institutionalized care. So norovirus is one of those viruses that can absolutely rip through a nursing home facility. So we think that globally we have the opportunity to prevent 685 million infections and approximately 200,000 deaths. And globally, this is associated with $60 billion in healthcare costs. So we've conducted a phase 1/2 study, and we have two candidate vaccines that we call 1403 and 1405. It's a randomized observer, blind, and controlled study with two age groups, so 18 to 49 year olds, but also older adults, 60 to 80 year olds. And individuals received either one or two doses. Again, we're looking to see if we can, especially with these vaccines where we're boosting, utilize a single dose schedule. And then participants again will be followed up for one year after their injection. And the study's been conducted in the US. So in terms of norovirus, there is a lot of diversity of genogroups and genotypes, but there are two main groups, GI and GII, that cause disease in humans. And there are 10 genogroups overall, 49

genotypes. So again, this is a pathogen that has a lot of diversity, so we'll be hoping to look for cross protection as we investigate our product.

The development has really been challenging to date, and it's the shifting of the genotypes, but it's also, this is a virus that if you're using traditional vaccine methods, it doesn't really like to be cultured. So unlike rotavirus where there are versions of either live attenuated virus or a live attenuated reassorted virus, that strategy actually hasn't been successful with norovirus. So to protect against 70 to 80% of disease, you actually need a multivalent vaccine. So what I want to show you are the results from our 1403 product. It contains three genotypes, and you see that here there are both genotype II and genotype I. Genotype II right now is the most prevalent worldwide, but we include genotype I because of course that can change over time.

And what you see on this slide is the serum histoblood group antigen antibody titers, and that's important because it's a functional assay. So really looking at the biology of how norovirus causes its mischief, versus just a binding antibody. And that's why we think this really gives us a reason to believe to progress towards phase 3. What we see at all dose levels was a really robust increase in antibody titers, especially relative to the placebo group, and we actually see similar titers between the younger and the older age groups, so that gives us hope that we'll be able to select a single dose across age groups.

In terms of the reactogenicity on this slide, again, you see placebo versus the active vaccine. With respect to younger and older adults, we see a similar pattern that we've seen with other vaccines in the mRNA platform, which is that we see more reactogenicity in younger adults versus older adults. But overall the patterns are relatively similar. To some degree. There's a dose response in younger adults. In older adults, the reactogenicity was a bit more comparable between dose levels. But in all cases, grade three events were relatively rare.

So this is the leading cause of diarrheal disease globally and results in a substantial health care burden. The HGBA-blocking antibody titers that were observed were induced across all dose levels, and for both genogroup I and genogroup II. We did not see any safety concerns related to the vaccine, and the single dose was well tolerated and showed a favorable reactogenicity profile. So we're advancing this program as well towards phase 3. Okay, so I believe we have a break now where we're going to get a little bit of coffee and you get a rest from the sound of my voice. When we come back, we'll talk a little bit about the respiratory vaccine portfolio. So thank you so much. And Levina, when do we want everybody back? 15 minutes please. Thank you.

Okay, round two respiratory portfolio. So to go through these vaccines, I'm going to speak first on COVID, then you'll hear from Christy Shaw, she's our portfolio leader for respiratory vaccines. And then Raffael Nachbagauer is our program leader for influenza, and he'll go through flu and combos. So respiratory viruses. I know you've seen this slide before, but I think it always bears repeating that these are viruses that actually infect us lifelong. Most of them you get multiple times over the course of your life. The biggest impact is actually in the very young and in older adults, and that's why we've prioritized our program first to look at older adults and now moving down into the pediatric programs as you'll hear about, particularly from Christy. So for COVID-19, we continue to monitor the evolution of the strains to be prepared

For the next strain selection meeting this year that's going to occur on May 16th. For the selection for the 24/25 season, we actually do our own epidemiologic monitoring and we do testing of various strains and actually begin to manufacture a few different kinds of strains through the course of the year to make sure that we are ready for what will be ultimately selected. We assess these strains in animals and we are going to conduct a clinical study. This year, we're going to do that at the beginning of the year when that new vaccine is actually launched. So we think we are really well-positioned for this season's

campaign. We've now had a couple of years where we've swapped out the strain and been able to deliver in time for the initial season. And then we're going to continue to monitor both the epidemiology, but that clinical trial is going to generate serum samples with this year's strain. And those serum samples are incredibly precious to us, because they enable us to test the neutralizing ability of people vaccinated with this year's vaccine to neutralize the new variants as they emerge.

So now I want to talk about the next generation of COVID vaccines. So we've been talking about the 1283 program for a while and we believe this is really going to facilitate a lot of additional benefit in our respiratory portfolio. So this version of a COVID-19 vaccine contains the two parts of the spike protein that lead to the best antibodies. So antibodies can be generated across the spike protein, but the most and the most effective antibodies are generated against the receptor binding domain and the N-terminal domain. So this construct actually includes both of those domains together and takes out the parts of the protein that don't induce as much immunity. We believe this is really going to help enable combination vaccines, because we found that with an adapted antigen we're able to reduce interference. And we also think that this will allow us to offer a more competitive COVID-19 vaccine.

It's designed to be refrigerator-stable and will improve upon the storage conditions with the current vaccine. So we had a pivotal Phase 3 study and it enrolled about 11,500 subjects and they were randomized one to one. They got the BA.4/5 version of either 1283 or 1273. And the comparisons are going to be in terms of safety immunogenicity, but also relative vaccine efficacy. So we're going to be investigating whether this vaccine is able to protect as well as 1273. We are following these participants for up to 12 months after study injection and the study is enrolled and is being followed in the us, UK, and Canada.

So what we saw from our interim analysis, and you read this in the press release earlier this week, was that we met our primary endpoints with respect to non-inferior immunogenicity, and that was against both the BA.4/5 antigen, as well as the original Wuhan strain. And in addition, we noted that the lower bound of that geometric mean ratio actually exceeds one. So at least day 29, antibody titers are actually higher with this new construct. We met the non-inferiority hypothesis, which said that the lower bound would be greater than 0.66, so we well exceeded that rate. And the zero response rate also demonstrated non-inferiority.

Okay, and then in terms of are we providing the same level of immunity across age groups because that really we think is one of the biggest benefits of mRNA 1273 and don't want to lose that benefit with a next generation vaccine. The answer is actually we do see excellent immunity across age groups. Non-inferiority would be met even in the age subgroups, but we actually saw the highest titers in the oldest subjects. So at a very least, we know that the vaccine performs very well in older adults. I think the study wasn't designed to demonstrate differences in age groups, but I'll say we feel encouraged by bringing this product forward.

And then in terms of reactogenicity, we see that it's very comparable to 1273. So here on the slide, it's a little bit difficult to read, but the left-hand bar is always 1283. The right-hand bar is 1273. And for both local and systemic reactogenicity, we see comparable levels at both grade three events, now that these are subsequent booster doses, really relatively rare and the vast majority of events grade one and two. So we've demonstrated that we elicit titers that meet non-inferiority criteria and are in fact statistically significantly higher than with 1273, with a similar tolerability profile.

So our next steps we are going to conduct for 1273 as I mentioned, this year's clinical trial once the new variant is selected. And then for 1283, we're in the process of discussing with what next steps could be towards a data package for regulatory submission. Okay, so now I'm going to hand over to Christy Shaw, who's going to talk about RSV.

Christy Shaw, Ph.D.:

All right, good morning everyone. Yes, I'm going to be talking about respiratory syncytial virus, or RSV and I'm the portfolio head for our respiratory vaccines. So this vaccine is called mRNA 1345. And first, I want to show this visual of our development program in adults 50 years and above. Each kind of column is a different study or a part of a study and a key one is the study to the very left of the slide, which is our phase III pivotal efficacy and safety study in adult 60 and above. The 301 study. This is a study we've previously shared with you that it has met success criteria we've filed for licensure and are waiting to hear back from the regulatory agencies. I'm going to give a little bit of update from the stat study first. The slide also shows studies that are ongoing to assess revaccination, as well as co-administration of 1345 vaccine with other licensed vaccines.

So looking at the slide, if you look at the second group, we have a 24-month revaccination study. It's a subset of the individuals that are in the pivotal efficacy study, get a two-year booster. We also on the right of the slide have a separate study, looking at a one year 12 month revaccination. That is in the 302 Part C study in adults 50 years and above. The other studies on this slide are our co-administration studies. In the middle, there's the 302 phase III study in 50 years and above. It has two parts that look at co-administration of our RSV vaccine with a quadrivalent influenza vaccine. That's part A. I'm going to share data from that today. And then part B next to it is co-administration of the RSV vaccine with our spike vaccine mRNA vaccine. Also show data with that.

On the very right of the slide is the last one, and that's a co-administration study of our RSV vaccine with a high dose influenza vaccine. That study's fully enrolled and the data should be coming soon. But first focusing in on the pivotal study and a summary of the data we've shared and a little bit of update as the study on goes and the data that are accumulating. So this is an overview of that pivotal study. As you likely know, it enrolled around 37,000 people across 22 countries, and was randomized one-to-one for individuals to receive the vaccine or placebo, and the individuals are followed for two years.

It's a case-driven study with a primary endpoint to prevent RSV lower respiratory tract disease. Approximately a year after the study initiated, we had accumulated enough cases to evaluate efficacy, and the results as is reported previously are summarized here. At the time of this primary analysis, we had a median follow-up of 3.7 months and a maximum of 12.6 months. We have two primary endpoints in the first two lines of this visual on the left. Prevention of RSV lower respiratory tract disease with two or more symptoms is the first one, and with three or more symptoms is the second. And the efficacy values reported are 83.7 and 82.4 respectively against those two.

In both cases we met the predefined study success criteria as a lower bound of the 95% confidence interval was above 20%. We also had a key secondary endpoint that we reported against RSV acute respiratory disease that just required one symptom, and here it was 68.4% efficacious. In all cases, again, the lower bound of the conference rule was above 20%. These results were recently published in the New England Journal of Medicine.

We've also in the same efficacy study, been evaluating the antibody response. Here is showing the RSV A and B, These are two subtypes of RSV, the neutralizing antibody responses against these two different strains. We've seen that a single injection of RNA 1345 induces a boost in RSV A antibodies approximately eightfold and RSV B, approximately fivefold. And shown on the visual here are the baseline and the day 29 after vaccination titers, both the geometric mean titers and the fold rise in the red numbers, across different decades of life. So the sixty-year-olds the seventy-year-olds and the eighty-year-olds both for A and B virus. And you can see that the results are quite consistent across the age groups, and we are particularly pleased to see this held true even in those above 80 years old, as you know that the risk of more severe disease increases with age and we are able to maintain antibodies throughout these age groups.

So I want to take a quick step back away from the data for a moment and talk about how our study over time when different events in the study were happening, the enrollment, the analyses, and overlay it with the RSV epidemiology at the time. And this is the EPI, particularly in the United States as we enrolled at least half of the individuals in our study in the U.S. So RSV, as you know, is a quite seasonal disease and before the pandemic, we had very usual peaks of RSV disease from November to May. You can see that in the gray shading on this graph, which is averaging out over a couple of years before the pandemic. Coming out of the pandemic, RSV was not normal. You can see that in the tracing in the orange on this slide for two different seasons that overlap where our study was conducted both the 21/22 and 22/23 RSV seasons were earlier than normal, shifted to the left, and notably the 22/23 season was quite high in terms of the number of hospitalizations in 65 years and above, which is the Y-axis. Sorry, I forgot to mention that.

This is based on data from the CDC and RSV.net. We had a very high abnormal and early peak of RSV in 22/23 season. So that's the EPI. Now the lines on the top are some milestones for our study. You can see the vaccination period started in 2021 at the end went for about a year. And the primary analysis we just reviewed the data for was triggered in November 2022, when we had accrued enough cases, and this was our primary analysis. That primary analysis you can see encompasses in the U.S., At least kind of the back half of the season in 21/22 in the front tail of the season in the following year, 22/23.

So the study continues though, as I said, it's a two-year follow-up study. So after more time had passed and most of the participants had a safety follow-up of approximately six months, we decided to conduct another analysis. We call it the additional analysis. And we did this in agreement with FDA. This happened in the May 2023 timeframe. And you can see it happened to coincide with the end essentially of the Northern Hemisphere 22/23 season in May. So showing data from that second that additional analysis, we are pleased to see that the efficacy remained high. So we were able to show the vaccine continued to protect against RSV for this longer period and notably through the very high transmission 22/23 season. You can see the efficacy values here on a table similar to the one I just shared with the two primary endpoints, seen efficacy of 63% and the secondary endpoint of ARD of 53.9% in all cases.

Again, the lower bound of the confidence interval was above 20%, which had been our predefined success criteria. We also did an analysis looking at RSV-RTD-associated shortness of breath. This is a key marker. It's been published as such to be linked with severe disease. And here you can see the efficacy was actually 74.6% and this was a post-hoc analysis. On the right you can see one of the endpoints, the RSV LRTD with two or more symptoms. This is one of the primary endpoints, illustrative of the cumulative incidence curve for the R endpoints. And you can see a very early separation between the curve for the vaccine group compared to the placebo.

The bottom axis is time from vaccination, and they separate early and the separation is maintained throughout the observation of the study. All right, moving on to the safety from the study or the reactogenicity data on the left are the local solicited adverse reactions and on the right are the systemic. You can see that the RNA vaccine, the most common local reactions were pain mostly grade one. And in the solicited systemic reactions it was mostly headache fatigue, arthralgia and myalgia. And in those cases it was only slightly above really what we saw in the placebo group with mostly grade one and grade two.

So summarizing the data we have from the study so far, in these adults 60 years and above, we were able to demonstrate efficacy of at least 82% against our primary endpoints in the primary analysis. We're also seeing a high antibody responses that are very consistent across age groups in the study. The vaccine is well-tolerated and it continues to be quite safe as well. I didn't get into a lot of the safety data, but we've continued to see no concerns or no safety concerns identified.

As I mentioned, we have submitted our application for licensure in a number of countries around the world, and are waiting for regulatory approvals currently. We do hope to launch this vaccine in the United States this year after recommendations from ACIP. So we are, as I mentioned, doing a number of other studies in the adult age group, and I want to focus next on the two studies or it's one study in the middle here with two parts, which is co-administration, which really helps to use this vaccine. Individuals can go pre-season and get their RSV vaccine together with a flu vaccine or together with a COVID-19 vaccine. So the study was conducted in individuals 50 years and above for part A and B of the study.

I will share the part A data first. In this part of the study, individuals received either two shots together, different arms, at the same day, one with the RSV vaccine and then the other arm, they got a quadrivalent influenza vaccine. And this was a standard dose vaccine. Control or individuals in the study got just one of those vaccines and a placebo in the other arm. These individuals are followed for six months and we measured the antibody responses at baseline, and then day 29. And here are the antibody results on this slide showing the day 29 geometric mean titer ratios of the concomitant vaccine divided by either the respective individual vaccine.

So you can see in the COAD group that you are having antibody responses to both the RSV strains, subtypes A and B, as well as all four influenza strains contained in the flu vaccine. What's shown here is the geometric mean titer ratio, as I mentioned. And all of six of these assays did meet the non-inferiority criteria. Specifically the lower bound of the confidence intervals were above 0.667. So this study was successful to meet its immunogenicity endpoints.

Going to the solicited reactions for this COAD study, in the panels that will come for this study and also the second part of the study, you can see in every type of category of reaction there's three bars. The first bar will be the co-administration group, in this case flu plus RSV, and then it follows by the RSV vaccine alone and then the flu vaccine alone. So here as usual for our vaccines, the most common local reaction is pain grade one. And we are quite pleased to see that the local reactions for the COAD group look very similar to the RSV alone group. This trend maintained in this systemic reactions for this co-administration study shown here. Again, very well tolerated grade one, grade two, and importantly the COAD group, the first bar in each panel looked quite similar to the RSV alone group, which is the second panel.

Okay, transitioning to the second part of this COAD study, which was co-administration of the RSV vaccine with our own mRNA COVID-19 spike vaccine. Again, this is two RNA vaccines. I think this is the first COAD study that's been done with two RNA vaccines. This was a phase III study in adults 50 years and above. People got the COAD or the individual vaccines separately.

Same kind of format for the data. First, the antibody data showing the titer ratios of the concomitant group divided by the non-concomitant administration of the standalone single vaccines. RSV antibodies in this case now we're looking at the two different COVID-19, SARS-CoV-2 strains. This was the bivalent vaccine at the time. And like the previous study I just shared here, again, all of the endpoints met the predefined success criteria. Non-inferiority was demonstrated. The lower bound of each one of these is above the 0.667 predefined criteria. So another successful readout from this study.

And really exciting I think is the solicited adverse reactions. Again, two different RNA vaccines given at the same time in two different arms. Here, the COAD group is the first bar on every panel. The RSV vaccine is the second and the COVID-19 mRNA vaccine is the third. Here, quite-well tolerated. The two COADs, two RNA vaccines, the first panel, mostly grade one pain. And then following lastly, the systemic reactions. Again, two RNA vaccines, I'm saying the same thing a couple of times, but it's really cool data set that we're seeing quite well tolerated to see that co-administration with the rates and severity looking not that much different from the COVID-19 vaccine alone.

Summarizing the safety data for this COAD study, compiling the data from the two parts of the study together. So COAD with either flu or with COVID-19 vaccines was very promising and we saw no reports of no deaths, no serious adverse events or adverse events of special interest assessed by the investigator. Specifically this means we saw no anaphylaxis, no Guillain-Barre syndrome, no ADEM, no Bell's palsy facial paralysis, no acute myo or pericarditis in this COAD study. So summarizing totality of the data from this COAD study, the two parts we did meet the immunogenicity predefined success criteria for both COAD of the RNA vaccine, the RSV vaccine with a quadrivalent standard dose flu vaccine, as well as the RSV vaccine with Spikevax COVID-19 vaccine. This included success on immunogenicity, but also we saw a very safe profile with tolerated reactogenicity as well. Okay, so the last thing I wanted to share with you today is a brief look into the future. And as you know, RSV is not something that just affects older adults. There's a large burden of disease across the age spectrum. There's a high incidence in young kids and in toddlers and older adults, but even in the middle, older kids and younger adults who have underlying conditions that put them at risk for more severe disease, there's quite a lot of burden there as well.

So as soon as we saw a success of our vaccine in the older adult population, we went about starting studies in all of these age groups, because we really think that this vaccine has the potential to protect all of these vulnerable populations from RSV disease. The most advanced of these studies is on the left, which is a phase III study in high-risk adults 18 years and above.

And that study is ongoing. In the middle of the slide, we have two different studies ongoing that are phase II studies. The first one is in pregnant women as well as their children. The women get vaccinated, but we follow the children as well. The infants that are born to those mothers. So that study is ongoing as well. The third study is a phase II study in children, both two to five-year-olds and five to eighteen-year-olds who have underlying at at-risk conditions. And that study is ongoing.

Lastly, on the right of the slide, we actually have two phase I studies going on that include children below the age of two. We have already enrolled fully and have reported data at conferences for the study in 12 to 16 months. These are RSV seropositive children, but we also now have a study ongoing in five to 24-month-old children as well. Data from all these studies have the potential to have data released this year, interim data. So stay tuned and we have a lot more to come from this program. So now I'm passing off to Raffael for combos per flu, and then combos.

Raffael Nachbagauer, M.D., Ph.D.:

Good morning. I'm Raffael Nachbagauer, and I'm leading the influenza portfolio here at Moderna. And I'm delighted to give an update on the current status of our first flu and then flu-COVID combination programs. Today. As we previously shared, we conducted mRNA-1010 P-III for our flu program. This study was designed to test the immunogenicity and safety of our improved mRNA-1010 vaccine. This study enrolled last year a one-to-one randomized 18 years and older in mRNA-1010 or a standard dose licensed comparator Fluorex. And we had previously shared those data, but showing it here again that we met all eight co-primary endpoints for mRNA-1010 in this study, which includes the GMAT mean TATA ratios as well as the seroconversion rates. We furthermore, as you can see on the right saw higher GMAT mean TATA ratios against the standard dose comparator for all four strains. And while not shown here, we saw the similar trends for seroconversion rates.

And importantly, we saw that those trends of strong performance of mRNA-1010 compared to that vaccine were maintained in all age groups and also in the older adult population. In terms of the safety profile, it was in line with the prior clinical studies that we conducted for mRNA-1010. The mRNA-1010 showed an acceptable reactogenicity profile with the majority of reported events being grade one and grade two in nature. The reactogenicity was higher for mRNA-1010 than the standard dose license

comparator. But we did see a trend of direct degeneracy overall being lower in the older adult group compared to the younger adult group.

Last year, we also showed some initial phase II data of mRNA-1010 compared to Fluzone high dose, which is an enhanced vaccine for older adults. And it was quite encouraging and we mentioned then that we intend to test this more formally. And so we did just that. We started an extension to our P3 study that enrolled last year. Older adults, one-to-one randomized, to receive either mRNA-1010, or Fluzone high dose. The study is fully enrolled and we're expecting to get results from this study this year. To briefly summarize, mRNA-1010, we met all our co- primary endpoints in the P-303 study. We saw an acceptable reactogenicity profile and we're currently in discussions with regulators and intend to file this year.

Now shifting gears to the flu and COVID combination vaccines, and I just gave you that update on mRNA-1010. You heard earlier the exciting updates on mRNA-1283. And that's really important because both of them are our components that go into our combination vaccine mRNA-1083. So that vaccine encodes the mRNAs for the flu components as well as for COVID. And we previously shared that we had some really encouraging data in our phase II study that showed strong immune responses for both the flu and the COVID components. And based off those data, we went into phase III study.

In these phase III study enrolls is intended to test the immunogenicity and safety of mRNA-1083. It enrolls adults 50 years and older in two age groups, 50 to 64 and 65 and older. In this study we're comparing mRNA-1083 to licensed influenza and COVID vaccine comparators. And the study is also fully enrolled and we're expecting to get data from this program later this year.

To summarize mRNA-1083, it is our influenza and COVID combination vaccine that showed strong immunogenicity against influenza and COVID in our phase II study. We believe that this combination vaccine can really address the burden of those two respiratory viruses as a combination vaccine quite well. Importantly, it leverages the data from our standalone programs mRNA-1010 and 1283, and can really combine those features quite well in a single vaccine. We're expecting data later this year with our phase III study that we have fully enrolled. And with that, I'm handing it over to Stéphane.

Stéphane Bancel:

[inaudible 01:29:35].

Good morning, everybody, and thank you for joining us today. Before we talk about times and sales, I just want to reflect a second on the importance of the advancements of our pipeline for patients. If you think about it, with an aging population and with countries that have more and more healthcare budget problems,

What we're dealing with in the world is actually sick care. We call it healthcare, but what we do collectively is actually sick care. And if you look at this slide and what the products that the team described this morning are doing, is they're preventing disease. And there's no better tool in life and in healthcare than preventing healthy people from getting sick. And if you look at the breadth of what we're doing with respiratory viruses, helping the elderly, helping people at high medical risk because of comorbidity, helping the very young infants, that's what is really exciting to us. And if you've got a latent virus, which I think today is an important inflection point for a latent virus portfolio, many of you have followed CMV for a few years even before COVID, but if you look at the data today of EBV, VZV, Norovirus, I think there's no doubt that Moderna has a very strong platform to be able to address latent viruses as well.

And I'm going to talk of course, what is the commercial impact of those two opportunities? So let's start with respiratory. If you look at it, and I'm going to walk you through the numbers. We believe the total

addressable market for respiratory portfolio is around $27 billion per year. Let's start with COVID. We believe COVID is around the 10 billion market across the planet. We should not forget that. Of course the pandemic is behind us thankfully, but COVID is going to stay with us forever. The SARS-CoV-2 virus. And if you look at the clinical data and [inaudible 01:31:33] just in the season, October to March 2023/2024, if you look at the numbers on this slide, there is a very large number of hospitalization due to COVID that happened just in this country. So if you project that across the planet, a lot of people got impacted by COVID, and some of them could have been prevented thanks to vaccination.

Look at the difference, 482,000 hospitalization through the season to date compared to 200,000 for flu and around 160,000 for RSV. The other piece that we really want Moderna to take a leadership role on is, better education and better partnership with healthcare professionals, and public health leaders, in term of Long COVID. Long COVID is a really, really big issue, as many of you know. I'm sure most of you have people that you know in your group of friends or coworkers that have been affected by Long COVID. I personally have a couple of people in my life that have been affected by Long COVID, and I can tell you when you hear their stories, it is just terrible. It is terrible, and it's affecting young people. So we really want Moderna to take an active effort in terms of the leadership we want to drive in the [inaudible 01:32:54]. I do not think we did our best work last year, and you can count on us to really double down on what we're going to be doing in term of Long COVID.

Video:

Before the Long COVID, I was active. I enjoyed life. Long COVID has taken away my job, my health and quality time with my family. Most days I wake up dizzy, nauseous, and in pain. In a lot of ways, my kids have to take care of me and I'm the one that should be taking care of them. Long COVID is real, and we're still fighting. The only way to prevent Long COVID is to not get COVID.

Stéphane Bancel:

So you're going to see us doing much more in the coming season in term of Long COVID, we're actually also partnering with a lot of large corporations to help them through what they're doing with their employees in term of benefits, to make sure that COVID vaccination is available in a lot of workplace across the country. Because we have to do better on COVID, collectively. If you look at the vaccination rate of COVID versus flu, it is very bad for COVID in terms of what we do to protect people. If you look at the elderly, a group that we all know is at high risk. The vaccination rate against COVID last season in the US for older adults is roughly half the UK. Half of the UK. Think about the number of people in this country that end up being hospitalized because we have not done a good enough job collectively. Public health leaders, healthcare professionals and health industry, to really make sure people get the facts. We have of course to deal with a lot of misinformation, but it's our job to get the facts out so people can get protected.

Another piece that we think should help get more people protected is working with public health leaders to ensuring that the vaccines for COVID are available sooner. If you look at this season that is just finishing as we speak, as you know, the flu vaccines were available in August, early August, like they do every year. But unfortunately for a lot of people, the COVID shots were only available mid-September. And if you look at the data in the US, there's around 3 million shots of flu that were given before the COVID vaccines got approved. Well, we think in the fall of 2024 there's a great opportunity and we're very, very pleased [inaudible 01:35:22] the VRBPAC meeting for strain selection, we'll be meeting mid May, allowing if you look at the timelines, to have vaccines available in pharmacies in August. And our goal is to get working with the FDA and of course the CDC and public health leaders to

get the vaccines available at the same time as flu, so that co administrations can start early on in the season, which we think will lead to a higher vaccination rate.

As we shared on our last call, our focus on COVID is really of course the US, and in the US is how do you drive up vaccination rate in the elderly? And we think an earlier product availability will help better education. How do we do and do partnership with pharmacies, and doctors, to help people that have high comorbidity factor? For example, if you are going to get your COPD drug at the pharmacy, how do you get the right messages of what is your increased risk of getting disease and hospitalized by COVID, if you have COPD? It's actually around 50 times higher than somebody of the same age as you that does not have COPD. So there's a lot of data in fact that we can bring to consumers by partnering with the pharmacy partners as well as healthcare professionals. So we're going to do a much better job in the season to come to help get the message out. And I just spoke about Long COVID.

As we shared in the EU, a market for which we have been excluded last year because of a tender that was set up during the pandemic with the other mRNA player. We are very pleased that in January, a new tender has been put out for up to four years, for up to 36 million doses in which of course, we are participating. And outside the US, we're really working with our teams to help our game and make sure we're very focused in our ability to get vaccines available. And in some markets I'm very pleased that we have done very, very well. In countries like Taiwan, Israel, we are now the only vaccine provider, which is great. Let's not switch gear a little bit to RSV. So we believe the RSV total addressable market over time as the market is being developed is around $10 billion. We believe there's a big portion of that for the older adults, but we believe the pediatric market is actually a great opportunity. If you look at the antibody treatment that are available at a much higher cost today, there's actually a very good uptake.

As you know with COVID, we have been able to get the regulators approving our COVID vaccine into the infant setting, six months and above. So we want to do the same thing with RSV, and bring RSV available to young infants to protect them through vaccination in those critical few early years of life. I think a lot of people were surprised that the total market already in the first year, only in the few countries because a few countries got approval, only for flu season was already $2.5 billion. So we are quite comfortable that the time for RSV is pretty large. As you know, we believe we have a very strong profile with our RSV vaccine with very strong efficacy, and the team just walked you through the data a few minutes ago, very strong safety profile, including the fact that we had no Guillain-Barré syndrome, which as you know is really important in our phase three study, and the ease of administration.

As you know, we will be, if a product gets approved by the FDA, the only product available on the market in a prefilled syringe. So why is that important? I think for at least two reasons. First, as you know, and you have a few media title of what happened last season, the fall season is a very complicated season for pharmacists, because they have a lot of demand on their time. If you think about it, they have to provide the cholesterol drugs, and now the GLP-1 drugs and all the drugs that people usually go to the pharmacies. But they have also in that very short window of a few months to provide a lot of vaccination. It used to be pre COVID only flu, and the flu market in the pharmacy is a prefilled syringe market. That's what people are used to do, and used to use. Why? Because it's very, very quick, very easy, reduce medical errors.

Of course, COVID that we offer now also in prefilled syringe was very well received by pharmacists. If you look at the two products that are available today, one of those requires nine steps of preparation in the back of a pharmacy for every consumer walking into a pharmacy. Nine steps. The other products available is four steps. It not only takes a lot of time from a pharmacist in a very busy season, but also it increase the risk of medical errors.

So we really believe our product being the only PFS product could be a game changer to the pharmacist. And we're running a study for which we're sharing today some preliminary results. The full study will be

shared when it's done, but we thought given with the vaccine day, it was quite interesting to share it with you. It's a motion study, basically. We have pharmacists being followed very thoughtfully through a study looking at the time it takes them to prepare a PFS product, versus a traditional single dose product. And as you can see the difference of time, what I care the most about is a column on the right. In one hour of a technician in a pharmacy, you can prepare 85 PFS product, whereas you can prepare 22 product that has to be reconstituted. So if you think about it, it's a 4x productivity improvement, this is not 4% or 40%, it's 4x. So think which one the pharmacies prefer.

So we think that with a very strong safety profile, with very strong efficacy profile, that differentiation is going to be key. And we really look forward to regulators around the world starting to approve the vaccine this year to be able to provide this solution to pharmacists, to protect as many people as we can. Let me now pivot to flu, which as you know is around a $7 billion market. What's interesting about flu is that, flu for a Long time has not really been growing as a market. The number of vaccines were not really growing, and the price were not really increasing, until recently. With the advancement of enhanced vaccine that I use mostly for the elderly because we are at higher risk. And you can see on the graph that there is really no growth in the standard dose flu product, but there is very, very nice growth and very good average selling price for enhanced product.

And as the team showed you, we kind of lack a lot the performance of our 10/10 products. And as you remember from previous vaccine days, 10/10 is only our first step at making flu vaccines. We have many more vaccines in the pipeline where we believe over time, we're going to improve the efficacy of our products versus standard products. So that will allow us to play in that market and the successful data that Rafael shared with you, we look forward to filing the products to the regulators, and to start with those products available to patient. The last chapter in respiratory vaccine is of course combination. I don't know about you, but having a COVID shot and a flu shot, two needles is not fun. I will prefer to have one needle and I will look forward to the team being able to bring that to consumers and also to help the healthcare professionals with combination products.

If you look just in the US, 150 million shot of flu, 42 million shot of COVID, what if we had a flu plus COVID product combined that provide an enhanced flu performance, and the most efficacious flu COVID vaccine available in one shot? We believe that will change a lot of things for consumers, and for healthcare professionals and for payers. And we really are working hard to bring this to market. And I think what has happened in the last few months before the 10/10 positive phase three data that we shared at R&D day in September, and the positive phase three that we shared yesterday, are the two components that will bring this solution to market, that could be available as early as 2025 in some markets for the season. So as for respiratory viruses, north of $25 billion of total addressable market.

Let's now move to latent. So we believe a latent virus is also around the 25 billion total addressable market annual sales opportunity. So let me go through the key of them. The team described CMV in detail this morning, so I won't go back in details to the burden of disease. I just want to remind everybody that there is no vaccine available on the market. Which will mean that if we have positive phase three this year, we should be able to have quick review by regulators, and we should be able to have a product available. We think HPV is an interesting model of what the CMV market could look like over time. So we believe the CMV market should be able to be two to 5 billion in sales, and we believe that we'll be the only player in the market for a while.

Then you look at EBV that again, the team described in detail this morning, the short term sequel of disease around infectious mononucleosis, which we think is around a billion to a billion and a half opportunity. And then if you look at MS, MS has an economic burden of around $85 billion per year, between the direct cost and indirect cost of MS. So we believe when you look at MS, this is potentially a

$ 10 billion opportunity for all EBV vaccine. And there's no vaccine available on the market. So quite a different competitive dynamics versus what we're seeing in the respiratory market.

Let's keep going. VZV. So VZV, while there's a product on the market, you saw the data that Jackie presented this morning, we're very, very pleased by the CD4 and CD8 data. To be honest, they surprised some of us, including me, that they were as differentiated from Shingrix, which has been helping a lot of people. And if you look at the size of market already, it's already north of $5 billion. So what if we could be participating in that market as a second player? What if we would get 20, 30% market share? Let's not dream too big. The interesting thing about our technology, and Jerh, is going to talk about that in a minute, is we use the same manufacturing infrastructure for all of our products.

COVID and flu need seasonal updates, which is why as Jerh will tell you, in the spring and the summer, our team is really, really busy because the window is very tight to supply the product on time. But in Q1, right now our facilities are not very busy. So what if you could make VZV product in Q1? And what if you could be a billion plus dollar per year. Your incremental gross margin will be north of 90%. So you don't need the finance team to do the analysis or what's the NPV of such an opportunity. So we can help people, and we can create value at the same time. And this is really exciting to us. Norovirus. I know a lot of people, including people in this room, wish there was a neurovirus vaccine. And we think it's a big opportunity not only for adults, and other adults, because getting Norovirus is never fun. But also for the pediatric setting. And you also get a sense for a pediatric setting, the rotavirus market is around 1.6 billion per year.

So if you look at the pediatric setting, and the elderly setting, we believe this is a 3 to 6 billion market opportunity. And again, as the team explained this morning, there's no vaccine currently available on the market. So again, we can do good for the world, and we can create a lot of value at the same time. So if you look at the two infectious disease opportunity we're going after, there's around 27 billion of total addressable market in respiratory and growing with an aging population, growing with people in middle and low income country having access more and more to vaccines. And the latent vaccines where we think there are very few players available because of the complexity of a biology that Jackie described this morning, and the unique ability of mRNA to do multiple antigen at the same time made in human cells like, when you get a natural infection.

So we think this is very large addressable market for Moderna and we want to make sure we maximize the use of those vaccine to protect as many people as we can. So with this, I'm going to turn over to Jerh to talk to you about why we think this is a great manufacturing platform.

Jerh Collins:

Hey, thank you so much Stéphane. Good morning everybody. It's really good to see you all and it's a real pleasure to be here. Yes, Stéphane, the team are very busy today. I can attest to that. I want to cover a few things. I wanted to give you an insight to what our manufacturing platform is, and as to Stéphane says, how we are able to actually scale substantially and sustainably, and also why we have a very strong cost model behind that. But also maybe give you an insight into the type of innovation that we're deploying as well too. I think one of the elements to understand about our manufacturing, is we can really amplify the platform that we have. So let me take you through what I mean by that. So basically in a very simple way we're able to sequence, we're able to sequence the mRNA, then we go about making the DNA, and then we amplify that which then allows us to manufacture the mRNA.

Then we build the lipids and we build what we call, lipid nanoparticles, which gives us our drug substance. And then we fill, which we call fill finish. This is our drug product. So this basically is our process that we make, and that we use for our commercial product for COVID-19 vaccine at the moment. But the beautiful thing about this process is, it scales exactly for all of the other latent vaccines

that we talked about and all of the other respiratory vaccines. And there's a few things unique about it. I think one is, the fact that the processes are very, very similar. Our quality systems are exactly the same. So we're able to introduce a quality system right across our organization from actually research to development to manufacturing to commercial, one common quality management system. Which is very unique. And that's because we're operating on one singular platform.

So that element of similar processes not only allows us scale, but allows us to do things very fast. We can implement continuous improvement, we can implement innovation, we're able to do it on a platform basis and that allows us speed. So first quality, second speed. Now, one of the challenges that I love about this, is this amazing platform that our team and Stéphane showed this morning. I'm excited by that. Because I don't have to look at how do I set up 15 different types of manufacturing sites, 15 different types of manufacturing processes. It's one common process. I focus a lot on the chemistry that is individual for each mRNA sequence. But other than that, I'm using similar processes, and that allows scale. So we're able to scale very fast. We're able to operate at a development scale, and at a manufacturing scale within the same equipment.

And this is one of the unique benefits that Moderna has. The ability to speed, or to drive speed from development into commercial manufacturing. And we've proven that at large scale already. And then I think, and I'll touch on this towards the end, and Jamie will double down on it, but this allows us to, I would not only say lower our capital investment, but actually have optimal capital investment. We're able to implement technology that can operate across very different scales with the same technology. And that drives a cost efficiency model. You've seen some of that come true as we communicated already, and how we're driving our COGS down. But I'm actually very confident that we have a strong framework to continue to drive our COGS down. And that with this manufacturing system, we have a very strong framework as well to be able to scale substantially.

So I think many of you heard about Norwood, and anybody who hasn't visited, I offer an open invite to come to Norwood. You can just let me know afterwards and we can put something together. Norwood is pretty unique in manufacturing, because it has everything end to end. From a point of view, it has research, development, manufacturing for clinical, manufacturing for commercial, quality fill finish, all in one facility. This is pretty unique. It offers a number of advantages. I think you've seen them in relation to how we were able to deal in the pandemic, you've seen them and how we were able to move very fast from pandemic to endemic. I think the other advantage that it has is that it allows us to operate in parallel, many different products. All of the products that you've seen already this morning at this moment in time, we're either manufacturing for phase one, phase two, phase three or commercial, all in the one facility.

So Moderna is pretty unique in that. And on top of that, now we're starting to build out new facilities. So let me give you an indication of where we are. We're starting to build out in Canada, in Lavelle. Actually the facility has just finished construction completion. We've just finished engineering runs, and we're starting to go in now to operational qualification and subsequently process qualification at amazing speed. I remember our head of engineering only showing me pictures 13 and a half months ago when the ground was bare, and covered in snow. And we're now already starting to go into engineering runs. This is amazing speed that Moderna operates at. We're doing exactly the same in United Kingdom in Harwell, and also the same in Melbourne in Australia. Also where...

I see Tracy in the audience with us today. I'm really proud that the new site head of our Melbourne facility was previously our head of quality for drug product. So we now have the engine inside as well. Not only from a point of view of technological engine, but we have a talent engine to fuel the scale that's coming. So I'm pretty excited about this, because these facilities will not only allow us supply for these individual countries, they allow us operate at scale, they allow us to global supply chain, and on

top of that allow us to be prepared for any potential pandemics come forward. So this gives us a full capability in relation to our drug substance manufacturing at scale for all of the products that you've seen this morning. And then on top of that, we have resized or external manufacturing organization. We work with CMOs to supply the drug product and we do that. Actually you can see on the map, we do that globally. We're in Asia, we're in Europe, and we're in Australia.

Sorry, in Australia, we have the drug product facility as well in our site. And then we're in the United States. This allows us from a regulatory point of view, as well get speed and access to those markets. And this is really, really important. I think Stéphane had mentioned our prefilled syringes, which was one of our key success factors. Last year was our first year with prefilled syringes. And it allowed us to do some amazing things, and we've seen that in the United States. But we're continually doubling down in this technology for all of the combination products we have, and for all of the other products that Stéphane mentioned earlier and the team this morning. So this is a little bit what our footprint looks like going forward, but we don't stop there. I am obsessed about continuous improvement, operational excellence [inaudible 01:55:56]. Unfortunately, it's in my blood now and I can't get it out. But I'm very excited by the new technologies that we're coming with as well and how we're applying robotics and AI. I think the ability to get translational learning from many of the other industries and bring them in at speed to Moderna is something that differentiates us as well. So we're already advanced in robotics. We're using robotics as we speak in our quality control laboratories in Norwood. It's pretty unique at that stage. This will allow us speed up our quality control, speed up our assurance, at the same time drive efficiency. As we scale up and scale out our manufacturing, we won't necessarily have to increase our headcount at the same space by delving into the whole area of robotics and automation. And just to give you some numbers, we've basically increased the efficiency of our release time by 45% in one year already. And we have plans to continue at that pace.

Network efficiency is really important. We've got a great relationship now with our CDMO partners. We have removed some sites from our network. A lot of the reasons behind that was looking at their capability to drive efficiencies with us, and their quality and capability, and we've doubled down on other sites basically also in relation to that. We've got a full integrated manufacturing capability with our CMOs, where we operate holistically together, with our head of drug product leadership on doTERRA. So that's a little bit about the efficiencies there. And then AI, we're starting to drive AI very significant in several areas in supply chain, where we're looking at how do we optimize our supply chain. We're doing that as we speak. We're also doing it in our INT, and how we're driving a very complex supply chain and we've got already significant improvements in that area. And the other area we're starting to drive artificial intelligence is basically in our data in relation to quality assurance, and in our release processes.

So we will continue to invest in that with our head of technology, Brad Miller. So that's a little bit about what we're doing in relation to driving our network efficiency using robotics, and then using artificial intelligence. We did announce last year, January of 2023 that we purchased an enzymatic facility, a company in Japan called, Oriciro. I'm very happy to tell you now, just a little over 12 months later that this technology is alive and well, and we're using it fully in our organization. In essence, what it is an end-to-end precise control through chemistry. So there's no biological process in this manufacturing. It is now end-to-end chemistry, using a cocktail of up to 13 enzymes. And we're unique in the industry, actually. We're unique in the globe, and the ability to do this end-to-end. Some others are still using some of the biological elements in it.

And it's now no Longer in research. We're actually starting to use it in the current sequences of our COVID-19 of this year, we've applied this technology and it actually has reduced in the earlier sequence step, it reduced by 50% the throughput time. So this is where we're using it. We're already using it in our research, where we're actually developing our high throughput operational sequencing. 20% of our research sequences are now being used by this technology. And we're already developing it in our

individual neoantigen therapy to basically take this live already in the second half of this year, which will be significantly a differentiator to us, in our ability to scale out, which is what's really key in that area. So this is something that not only we're very excited about, but it's already in use. So these give me the confidence that we have a very strong framework, that we're able to scale without necessarily increasing our costs in the same manner.

So if we look at the cost of good sales in relation to a 4 billion, we'll be at around 35%. And we've then done a number of analysis

... Analysis on the future pipeline that Stéphane and the team have earlier produced. And you see, when we get to $6 billion sales, our cost will be approximately 30% and so forth, down to 25 and down to 20%. And so I would say probably a few messages to leave you with. I got a great team, it's not me, it's an amazing team, we've hired some fantastic people. We're delivering and we will continue to deliver. I think the second element is we've got the ability to scale substantially and sustainably, with a very, very effective cost system behind it. And then the third element is actually what you've seen us already deliver in a short period of time in COGS, this framework is very strongly in place, and we will continue to deliver this with the team. And I think that's a nice segue to you, Jamey.

Jamey Mock:

Thank you, sir.

Jerh Collins:

Thank you.

Jamey Mock:

Thanks Jerh. Well, good morning. Let me say thank you again for joining us in person or via webcast. I have a very fortunate job and the luxury of having a fun and challenging job to understand how we're going to invest behind this terrific pipeline and platform. And not only that, but in learning how to, and understanding how to navigate the next few years to be able to fund it as well, which I'll get into today. So first I think the title says it all. And hopefully you heard from all the speakers today that our platform is working, and that's hopefully the takeaway. We announced a handful of news on the left-hand side of this page. And what does that mean? That means that we need to continue to invest behind this platform and pipeline. And that is a good thing, because we expect to grow over time.

And the success rate that we're seeing is depicted on the right-hand side of this page. So some of you have seen this before and it's updated with our latest data, but it tries to show our success rate by phase, versus the industry averages. And albeit a relatively small population size, I'll walk you through it. In phase one we are 2x the industry average at 70% versus an industry average of 35%. That's on 20 candidates. Phase two, we are almost 3x at 78% success rate on nine candidates. And through phase three, we have an 80% success rate versus the industry average of 69% on five candidates. So still a relatively small population size, but overall very encouraging, and why we are confident in investing behind this pipeline and platform.

So I talked to you a little bit about capital allocation. Many of you know what our three priorities have been over the last few years. One is to reinvest behind the business. We largely do that through R&D, which is what the subject of this whole conversation is, and I'll get back to that. Reinvesting in the business. We also talk about capital expenditures. Jerh just talked to you about the sites we're putting in across the globe. And once we're complete with that, we feel like we have the scale as he just mentioned, to really be able to increase our overall growth of the company for many years to come. As well as SG&A. Our second priority was to invest in external attractive investments, either in licenses or

acquisitions. Jerh just mentioned the OriCiro acquisition, which has been our only acquisition, but it has advanced our overall technology.

And then the third is to return capital to shareholders. We largely have done that through share buybacks. And as a reminder, we have paused that because we want to invest behind this terrific organic growth engine that we have. And as I mentioned, we have a lot of opportunity to do. So this kind of lays out the next few years. We first showed this at our R&D day in September. Kind of what are the spend priorities over each of the next few years. You can see respiratory for the next few years is our number one spend driver. Thereafter is late in another. And based upon everything you heard today, you can see why that actually eclipses respiratory come 2026 from an overall dollars perspective. So in respiratory we have a lot to do in terms of the RSV, other indications, flu combinations, life cycle management. And then late in another, you can see we have a pretty broad portfolio as well that we are excited about. But we're still investing behind oncology, still investing behind rare disease, and our overall platform, as we advance our manufacturing sciences, our delivery sciences, etc.

So last year I talked about what does it look like, what do we look for in a vaccine candidate? And we look for three things. One is an efficacy improvement versus the nearest competitor. The second is an overall large TAM, which Stefan talked you through. We have a 52 billion TAM in infectious disease. And the third is recurring durable revenue. So that was an individual vaccine or candidate. This page tries to talk about how do we prioritize across the entire platform. And when we have many different vaccines, or 28 vaccines, as Stephen walked you through earlier today, we have to pick and choose which ones we're going to fund, and why. So we really look at three things. First is to advance the pipeline. So we don't want to be just a COVID company, and soon if everything goes well, we will not just be a COVID company, in the not too distant future. But we want to basically bring forward additional products into our pipeline as fast as possible and start selling those.

The second is to diversify our revenue streams. So that's not just within respiratory. So within respiratory, we'll hopefully come out with RSV this year, and flu and combinations over the next couple of years. But that's also late in another, and we want to diversify our revenue stream there. That's also in ecology as soon as possible and rare. And after that, hopefully in many different therapeutic areas. And the third is to reduce risk, which we've done since day one in the company. Whether it's biology risk, technology risk, execution risk, financing risk. Everything we do looks at reducing risks overall to help drive as much value creation as possible for all of our stakeholders, most importantly our patients. So then the challenge here is how to fund this. And that's a good challenge and that's a fun challenge, because we have an abundance of investment opportunities. And there's really three that we look at.

One is self-funding. So that's taking the cash on our balance sheet, which at the end of last year was $ 13 billion, in addition to the operating cash flow that we will generate over the next few years, and looking at that and saying, "How much can we self-fund on our own?" So that's number one. Project financing, which I'll talk to you about on the next page, because we announced a deal this morning, and I'll walk you through that. And then partnerships, strategic partnerships. Not just for money, but like Merck as an example, can they bring development expertise, can they bring commercial expertise? Whatever it might be to help advance our pipeline. So those are the funding options. So as I mentioned, we announced a terrific and exciting new program this morning. A development and commercialization funding agreement for our flu program so that we can strengthen the product label and fulfill all of our remaining regulatory obligations. It's for as much as up to $750 million over the coming years, should we need it. So we'll see how much we need over the coming years. And then it's pretty straightforward. It's based upon the commercial success of the flu program. And that comes in the form of cumulative commercial milestones as well as a low single digit royalty that we will pay on the flu program. Overall, we keep all the rights and control of this program, so we're pretty excited about it. As it pertains to our

R&D framework, this will offset the R&D line. So as we spend the money, this will be a credit to R&D. And so you'll see no net impact on the P&L from an R&D standpoint.

And we are keeping our 2024 R&D guidance or framework of approximately four and a half billion dollars. And so we're excited about this because it checks all those boxes on the prior page. It allows us to accelerate into new programs, it allows us to diversify our revenue stream, and it reduces the risk, frankly, of the flu program as well. So I think overall is what I hope you take away from this portion of the presentation is that everything's working very well. There's a large pipeline ahead of us to invest in. The early results are very encouraging from a success rate perspective and all the news you heard today. And we're excited to fund it as much as possible over the coming years. So with that, I'll turn it back to Stefan.

Stéphane Bancel:

Thank you, Jamey. So I could not be more happy today. As you know, we set this company a long time ago now, because we believed MR&A as an information molecule could be built into a platform, which had never really happened in this industry. And through this platform could help a lot of people over time. Well, if you look at all the pieces my colleagues presented today, that's exactly where we are. Most biotech company, if you get one drug approved, they're scratching their head with number two. If you look at large pharmaceutical companies, that has been massively documented, there's a massive patent pipeline, a patent cliff coming for most of them in the coming few years, because of a lack of innovation.

And if you look at where we stand today as Moderna, it is quite remarkable. The platform is working. The platform has not only helped already hundreds of millions of people around the world, because of people got a vaccine during COVID, but this is just the beginning. We have this opportunity to have an impact on so many people around respiratory vaccines, and prevent so many people from being hospitalized and from dying. Both the elderly people, with comorbidity factors, and the infants.

We should have a world where nobody gets hospitalized because of a respiratory virus. Actually I think we have the tools to eradicate through combinations. And then look at the damage that latent viruses due to people. Can you imagine a world where in a few years from now we'll have vaccines helping people that have EBV infection already in their body, so we don't have sequelaes of that virus hurting their body all their lives? Or teenagers being able to get, like they get HPV vaccines today, being able to be protected all of their life. Just think about number of lives that could be impacted around the world. And that's where Moderna is today.

So the platform, is working. The number of products and the quality of the product is amazing. We're announced just today, three more products are moving to phase three. Three products. Think about the number of launches we're going to have in vaccines in '25 and '26 and '27. And of course, we're expecting and hoping that RSV is going to be approved soon in '24. But think about what the next few years in vaccine are going to look like. And as Jerh showed you, that's one of the beauty of this platform, which I fell in love for the very first day I heard about the mRNA as a drug. It's all done in the same manufacturing process. And most of the process for most of our life, was chemistry-based, enzymatic. No cells, and the first steps we're still using cells to make the plasmid. And through the OriCiro acquisition, we remove that. So we can go 100% synthetic.

And the ability we have to scale that and not have manufacturing issues. If you look at most of our pharmaceutical products, because you have a dedicated manufacturing plant, the issue people have is that they don't have enough capacity and they're shorting the market, or they have too much capacity, or they have to write off a plant because a product failed in phase three. That is not the case for Moderna. Look at the probability of success that Jamey shared with you. Of course, the end is still small,

but you start to get a sense, which is this platform really behaves like a platform. If we design the biology right, it works, which is kind of science fiction in this industry.

Because in this industry, most things that go in the clinic never help a patient. So that's where we stand today. It's a really exciting time for the company. And what is even more exciting is what I think this company can do in the next few years and the next decade for patients around the world. But that's only vaccines for infectious disease. Look at everything else that's happening at the same time. We could not be more excited about the progress that we're seeing in our individualized neonatogen therapy or INT products. As we shared, the three-year data are actually stronger than the two-year data. That is rare in oncology. And I'll bet you that the five-year data will be better than the three-year data.

We're working really hard to enroll in many studies in our patients. We're going to continue to add with our partner Merck, more study to help more people that have cancer. And we're working really hard in manufacturing. That's another thing that Jerh and his team and Stephen are doing with a new plant in Marlboro, is to get that plant ready so that we can at the right time in the enrollment of our phase three in melanoma, file with [inaudible 02:13:15] we believe for accelerated approval, to try to get that drug earlier to patient to help a lot of people. One in two people have shown that three-year mark can be helped by preventing recurrence of disease or death. This is the best drug available today. That's the type impact we can have. And then of course, rare disease. Any of us who have a child, remember how scared you get when your child has just a fever.

Think about what it must be for so many families to have a child with a rare disease. What he means for the siblings, what it means for the parents, what it means for the grandparents. Well, our P and MMA programs are progressing really nicely, and we're exploring with our partner at Vertex, the ability, as you know, to inhale mRNA for a cystic fibrosis program that we're doing together, dosing in the clinic as we speak, that we hope to have clinical data soon. So more than that, let's keep on expanding What we can do. While we're very excited about our infectious disease vaccines and what they can do to protect people, we are as excited about what this company can do in oncology and in rare disease, and many therapeutic areas moving forward. So thank you again for joining us today. And now would like to get our team up on the stage so that we can take question and answers.

Q&A Host:

As well as online. Starting with Tyler Van Buren. Please introduce yourself and your affiliation.

Stephen Hoge, M.D.:

I always feel weird [inaudible 02:15:01].

Tyler Van Buren:

Tyler Van Buren from TD Cowen, thank you very much for the presentations this morning. So I have a couple high level ones. Stéphane, it was pretty unique to see you take on the responsibility of chief commercial officer, so I'd love to hear you just reiterate why you did that, and more importantly, what you've learned since you've taken a closer look under the hood of the commercial organization. And the second question is for Jamey. The Blackstone deal is obviously a creative one, and you touched on project financing briefly in your prepared remarks. But do you plan on doing more of these types of deals potentially to lower that four and a half billion R&D spend and OPEX load? And/or do you have more of those types of deals accessible to you?

Stéphane Bancel:

Great. So if you think about what we've done at Moderna since what, 12 plus years now, 13 years 14 years, I forgot, is we try to take what we learned from traditional pharmaceutical industry making products, making great medicines, and try to figure out what is unique to mRNA. We've done that with Stephen in research, and I think we reorganized and reinvented research a few times. And then we started doing that in development. And same thing, we reinvented and we structured and we organized research as a development a few times. Same thing with manufacturing. And I think we came to the realization late last year that to really build a commercial organization that looks like Moderna, not like you find in another company, because of the uniqueness of our science, the uniqueness of our culture, that we needed to do something differently. And after a lot of discussions with Tracy and Stephen and the board, we like, "Well, maybe we might need to do it ourselves."

And so Stephen and I basically divided the commercial world, but Stephen is basically leading medical affairs, and all the products that are in pipeline. So INT, rare disease, and so on. And then I'm really focused on the geographic regions. So the countries where we have commercial teams. We three direct reports. US, Europe, and basically the rest of the world. And also end of marketing for the products that we call inline. So products that are available in the market. So what did I learn? How long do you have? Because in the last 90 days, I learned a lot. And as you know, I'm familiar with commercial world, because I spent several jobs of my life in the commercial world. But first, the world has changed a lot compared to what it was 10 plus years ago when I was running Lilly Belgium, for example, earlier as sales rep.

And I think that the punchline is our commercial organization, well has done a lot of great work. I'm very proud of what we've done last year, for example, market share in the US. I mentioned Taiwan, where we got a 100% market share in mRNA. Or Israel, as you remember, in the pandemics, Israel used the other mRNA vaccine. And if you go what happened last fall, they use the mRNA vaccine that has the best real-world evidence data. I don't think we're performing like Moderna yet in term of the customer intimacy. What we're spending a lot of time on with a key pharmacy chain, is really sweating it with them in the pharmacies in the warehouse. So, "Okay, how do we delight you? How do we become the best vaccine company to supply you by sweating the details of a product, physical flow of the IT integrations with them?" There's a cool thing I cannot talk about yet that the team has come up. The team is filing some patents on it, obviously why I cannot talk about it, that I think will really help a lot pharmacists in the pharmacy in the season just coming, in a few months. So a lot of things. Something on the medical side of the house is how do we strengthen the partnership with health networks, hospital networks, to really make sure we think kind of top-down with them, working with the chief medical officers, to not go to doctors one by one like the older way, with MSLs going doctor by doctor. But how do you use the amazing amount of data we have, the real-world evidence data we have, the clinical data we have, to help the doctors do their job better, because they have access to data at scale.

Then we're doing a lot investment in digital information. We're playing with a few cool things in AI as well to see how can we accelerate basically global rollout of a campaign, a marketing campaign. In the olden days, you will pay agencies to translate. Well, now we launch an mTranslate system, which basically you can upload a Word document for your marketing campaign, let's say for launch of RSV for example. And it's translated in German right away. All in house, so you save time, you save money. And then you can use the same thing with photos, because in some countries you have regulation that the photos have to be in a specific way if you use photos of patients. But in some countries they cannot smile. Sometime you do passport photos, you're not allowed to smile. Where in some countries patients cannot smile on an ad. It's forbidden by law.

It's the regulation. So you can put that into the AI system and then you can literally do campaign. And the time from campaign creation to campaign rollout in a country is much faster and much cheaper. So again, if you want, we can speak hours about all the things that we're doing, but I'm really excited, because we have a great team. I think the customer obsession and customer intimacy, people are getting very excited about it, because I get a lot of text when people learning something new and spreading it across the team. So I'm already excited about what's coming down.

Jamey Mock:

Thanks for the question, Tyler. As it pertains to project financing, maybe just to restate it, do we plan to use it more often? So maybe I'd go back to what we said at R&D day first last year in September, that we were going to spend $25 billion over the next five years. And as you heard today, everything is still working. So we're still expecting a need for that amount of investment. But we will look at all those priorities. Self-funding is number one by far in a way. We'd obviously like to self-fund as much of this as possible, but we've also made commitments.

We've talked about, we want to break even in 2026, and we've said where we're willing to take kind of our cash balance levels down to. So we're obviously looking at that. Do I foresee project financing? There's certainly discussions, and that could continue to happen. So yes, I think that is a tool in our toolkit that we would probably look to again if need be. But we're trying to be proactive about it and thoughtful about it over the coming years on how to fund as much investment as possible.

Michael Yee:

Hi, it's Michael Yee from Jefferies. On RSV, I know you have an upcoming approval, and now Stéphane, your chief commercial officer. And people are trying to understand the value proposition of the pre-filled syringe. But as I understand it, most importantly, these are direct discussions and direct contracting, which will play a key role. So do you have confidence that the relationships and the intimacy of the relationship of contracting will be there to drive significant sales? If you look at GSK and Pfizer, where those numbers are, that you're going to be very competitive there this year. So that's the first question on RSV. Talk about that. And then on CMV, I know there was data previously showing 50% plus efficacy. You have an analysis coming up or a full analysis. Is there a level of efficacy that matters or is relevant commercially, clinically, etc. Just because if you hit it, but you've got to be relevant, you can talk to that a bit. Thank you.

Stéphane Bancel:

So we start with RSV. The vaccine not being approved, we are not negotiating contracts because we can't. But our medical teams of course are engaging with customers. And as you could see from a few media clip I put on my slide, and you're highly aware, the season and the peak in season is a huge problem for pharmacy in term of capacity of pharmacists. Because they have to do all the regular drugs that they have to supply. And then you have this big peak with flu, COVID, and now RSV, that takes a lot of time from the technician. And management is highly aware of it.

So when you talk to the CEO of a big retail pharmacy or members of a board, I mean they know this is a big problem. Because unlike for example, Amazon, we can scale very quickly in Christmas season, because the training requirements and the qualification skills is very different. In a pharmacy, you need to have a pharmacist or technician, and you need to train them. And so you cannot very quickly scale up the capacity in season. And so any solutions like the pre-filled syringe, which by the way is people are used to, as I said, flu is pre-filled. Now with our launch of COVID in pre-filled last year is also PFS. So people don't like reconstitution. And so we believe it's going to be an important argument in the season.

Stephen Hoge, M.D.:

And on the CMV question. So our minimum TPP, which is based on our market research and what we think will get a strong recommendation, is the powering for that final analysis. It's about 50%. And we hope to do better than that, but we do think that a minimum of 50% is necessary for the vaccine to have the kind of uptake that we would want to see commercially for success.

Max Gore:

Great, thank you. Max Gore, Morgan Stanley, on for Terence Flynn. Can you provide any additional updates regarding timing and ongoing conversations with regulators for seasonal flu? Specifically any feedback following the P303 update? And lastly, does the Blackstone deal include royalties on the COVID, flu, combo? Thank you.

Stephen Hoge, M.D.:

So first off, on the phase three P303 conversations with regulators on flu, those are active and ongoing. And so we don't have anything shared today. As we conclude those discussions with regulators and move forward to the next step, which is we hope filing, this year is our plan, we'll of course update them. But not before.

Jamey Mock:

And on the second part of your question related to royalties on combination, the answer is yes, but on an apportioned basis. So if the flu program is successful and utilized in a combination vaccine, based upon the relative fair value of flu and that pricing in that component, then there would be a royalty on a combination vaccine.

Q&A Host:

We'll shift to questions coming in online. I think this one is for Jacqui or Stephen. On the shingles or Zoster vaccine candidate, wondering if you can give us more color on how you're thinking about the phase three design. Will this be a head to head against Shingrix? And if so, will you have to show superiority in order to gain approval?

Jacqueline Miller, M.D.:

So excellent questions and things that we are actively discussing both internally, and then also need to discuss with regulators. So I need to sort of preface it with, I don't think all of those plans are set. But from a viewpoint of what we think it will take to be licensed, we do believe that we will need a vaccine efficacy trial. Whether that needs to be relative vaccine efficacy, I think remains to be seen, because it'd be quite difficult to show relative vaccine efficacy. Shingrix has quite high efficacy to be begin with. So we think that there's a path forward, since that vaccine isn't universally available, to potentially look at placebo controlled. However, we recognize that additional work against Shingrix is going to be important, because that really is the benchmark. And so we're including that in our plans as well.

Evan Wayne:

Hi, Evan Wayne from Guggenheim. I just have some questions on flu. So you've highlighted a multi-generational product development with flu. So just firstly with 1010, can you talk about some of the additional work you're thinking about, as to strengthen the label and to get some of the preferential recommendation? You've highlighted the head-to-head immunogenesis study against flu zone high

dose. So how would that add to the label? Or I guess what is the thinking to getting to preferential at this point? And then with some of the next-gen programs like the 1112s, 2030s, I guess, where are we with developing these next-gen programs into later stage trials? And how are you thinking about timing and [inaudible 02:27:32]? Thanks.

Stephen Hoge, M.D.:

Great. Maybe I'll take a first pass and then ask Jackie to fill in anything I missed. On the flu program in general. So we're currently pursuing a strategy towards conditional or accelerated approval based on the immunogenicity endpoints. And we're quite pleased with that. As you saw, we see GMRs above one, we think we're demonstrating what looks like an enhanced profile already with a P3O03 product, our second-generation flu vaccine. But that strategy will require us to eventually demonstrate effectiveness or efficacy in a subsequent trial. It's a part of the regulation expectations, and that really becomes important, because there's an initially, even if you get approval on immunogenicity, and even a recommendation towards enhanced on immune use immunogenicity, we have an obligation to demonstrate that relative efficacy advantage over standard dose vaccines, or appropriate. And that's the work that we will do on our first-generation product, particularly if we go forward from an accelerated approval perspective. It'll be our obligation. Following behind that, we have work that we're doing across a range of second-generation products. You talked about it. We see an exciting, frankly, a substantial need, on a multi H3 vaccine. So a polyvalent vaccine. If we go from quadrivalent to trivalent, we want to go back to quadrant, but add two H3s. Because the truth of the matter is there's that kind of diversity in circulating strains of influenza. We think it'll be a more effective vaccine. We haven't made the final decision on when we're going forward in phase three in that at this time. We're really focusing our conversation with regulators right now on the work that we're doing with our second-generation 1010 product that we referenced. And then there's the neuraminidase improvements, which we think will also enhance efficacy. And I think one of the biggest challenges Jacqui and her team have, is with all of these great opportunities to improve upon current flu vaccines, over and above what we hope is already an enhanced profile, do we combine them, or do we run them in sequence? And I think we're still working on that.

Jacqueline Miller, M.D.:

Yeah, absolutely. I think the only thing I would add is we're really laser-focused on understanding the pathway to licensure in our data submission package for 1010. Because like with pandemic flu products in the past, that's really the foundation for every improvement we'll make on top of it. And so really securing that is actually the next most critical step. And then in the meantime, we're still discussing options

... options for how we prioritize these other options.

Stephen Hoge, M.D.:

[inaudible 02:30:04].

Ellie Merle:

Hey guys. Ellie Merle from UBS. Two questions, first on CMV, second on EBV. Just in thinking about the timing for CMV, just given you're already at 50 cases and that you need the 12 months median of safety, how should we think about the timing between the interim and the final analysis? Is there a scenario that by the time you have the 12 median months of safety that you would also have enough events for the final analysis? And if this were to occur, what would this mean from a powering perspective?

And then just second on EBV, I mean I think you mentioned like 10 billion for this MS prevention opportunity, just how would you measure efficacy in this population and just any types of development precedents we can look at in thinking about how clinically this could be measured. Thanks.

Jacqueline Miller, M.D.:

So CMV, I guess first. So CMV is not going to be what you're used to seeing with respect to COVID and RSV. So COVID, there was a pandemic and cases were just accumulating, accumulating. So even the day we cut the database, having the DSMV a week later, we had already far exceeded the next jump in our analysis. RSV was the same. We actually had our data cut during the tripledemic and actually Christie showed you the slide with the huge peak in RSV that was a bit unprecedented. It was a post-pandemic, we're all back interacting with each other.

So I expect actually that the cases are going to accumulate more slowly and regularly with CMV. And I think if we do need to move to that final analysis because we aren't successful in the first go around, there probably will be some months in between. And I think we'll just have a better sense towards the end of the year when we see how the cases accrue. And then... Oh, go ahead.

Stephen Hoge, M.D.:

If I just add to that. So I think with the 12-month median follow-up, there is a chance that it's higher than the 81, but I think to Jackie's point, we don't think it gets all the way to the final. I mean we don't know, we don't control this, but it could end up somewhere in between, we will see. But, we do think it'll be more steady. And then...

Jacqueline Miller, M.D.:

And then... sorry, threw off my track. EDV, we were talking about powering for efficacy for the infectious mononucleosis. So that actually is the case that we intend to make our primary endpoints, infectious mononucleosis and susceptible adolescents. And there actually is a bit of a roadmap at least for a proof of concept study for how to do this. So other manufacturers have looked in the past. There was a product that actually also was about, I want to say it was 50%, 60% effective as well. So we would do a placebo control. We'll probably be looking and targeting that really seronegative adolescent population going right into their high-risk period. So that's individuals who are about 10 and over. And yeah, that's our thinking right now.

Stephen Hoge, M.D.:

And on the question of multiple sclerosis, obviously, we're quite passionate about that prevention as well. A lot will depend upon the IM results that Jackie just referred to. So for sure if we prevent infection mononucleosis, we expect to do with that. There's one path, it's a perhaps slightly different path and perception of what you do if we prevent infection, which given the viral shedding data that we're seeing, it's not implausible even if right now we don't know the probability of that. So we'll be informed by that first Phase 3 in infection mononucleosis and be able to answer more clearly the questions of what we're going to do on the MS endpoints and outcomes, that will take a little bit longer, but obviously are much more valuable from a public health perspective.

Ellie Merle:

Thank you.

Courtney Breen:

Hi there, Courtney Breen from Bernstein. You spoke a little bit about the probability of success from Phase 1, Phase 2, and Phase 3 and kind of outperformance relative to the rest of the industry. This is obviously on a small end as I think you all mentioned. As you think about the future of Moderna and continuing to expand this portfolio, what are you doing and how are you thinking about the expansion to continue to maintain that high PTRS kind of success rate and where do you think that may begin to drop or move towards the industry average over time?

Stephen Hoge, M.D.:

Well, leading R&D, I'm going to say I hope it never drops. Certainly, there are instances where we might go after higher-risk opportunities that could hypothetically have lower POS' and I don't think we will ever be shy of that. But if you look at the way we've conducted ourselves as an enterprise, whether it's the work we did in cancer with melanoma and INT or the three latent viruses that were presented today, EBV, CMV, and VZV as well as the work we're doing in norovirus, we've actually been quite willing to go at things that are extremely novel.

And I think our success in the early stages development increasingly late-stage development speaks to the fact that our approach technologically may have led to a secular shift in what's possible. Let me just pull that apart for a second. We provide instructions to your body on what the virus looks like. We don't have to make the virus, we don't have to grow it up in a vat or inactivate a living virus or try and make a protein in steel that looks like it. We actually give your body the opportunity to learn what it looks like in real life. And what your body then does with its immune system is it figures then how to protect you against that virus.

The instructions that we're providing look exactly like the instructions the virus uses when it infects you. And that's the core of the mRNA thesis in infectious disease. And similarly to some extent what we're doing in cancer relates. I think that advantage is technological and so we certainly hope it continues to show up as when we go replicate the appearance of an infection without infecting you in early stages or late stages of development, the rest of it is your immune system and biology working and it's a feature of messenger RNA that allows us to do that.

Now, there are things that we are not doing. To be fair, we are still not in substantial ways in bacterial vaccines. You don't see us doing polysaccharide vaccines. Because those are outside of that technological capability. Right now, we're going to try and move into bacterial but obviously not polysaccharide. And so what we're trying to do is stick to what we know and make sure that where we have a technological advantage, we do a lot of it. And over time I hope that that continues to be a higher POS across the stages of development.

Q&A Host:

Take one more for online. In terms of the timing for availability in the '24, '25 season for both flu and COVID, are you expecting the availability of those vaccines at a similar time for this upcoming season? And what about RSV?

Stéphane Bancel:

Sure. So let me take this one. So the current dialogue with the regulators and public health, which is led by CDC obviously in the US is to have a similar date. I mean, again, they're deciding, not Moderna. But, what I think they really want to do is what I described on my slide, which is how do you make sure the vaccines are available around the same day to be able to fill the channels into the pharmacies. So viable

if somebody wants to come for a flu shot that they can be told, Hey, you can also have your COVID shot, just show me your arm.

And that's the current path that we are on, which is why the VRBPAC data has been moved earlier into the season on May 16th to be able to provide that. So Moderna will be ready to execute on that plan, again, is done at the end for regulators to make sure all the pieces that they control happens. But we are cautiously optimistic. RSV being not strength dependent. RSV once approved is approved, there is no need for updating RSV.

Nassan:

Hi, this is Nassan from JP Morgan here for Jessica Fye. I have a two-part question. We know that the data for 1010 in HD flu is coming. Is approval contingent on that data being positive? And then second, is the approval for combination COVID flu contingent on 1010 being approved.

Stephen Hoge, M.D.:

I'll take a stab at both of them. First, on the flu point, we're in active dialogue at this point. We think the package we have based on P303 already meets the guidance. And so I think the fair answer is we don't believe it's contingent and we're continuing with that. We do think that demonstrating performance versus Fluzone HD really matters ultimately commercially and in the market. And so that's why we're running that study. But again, the discussions are ongoing with regulators and it's ultimately up to them and so we'll update you when we have more. It's not our expectation at this time.

On the question of 1083, I think our perspective there as well is that that's pretty much a standalone vaccine in the same way that you develop vaccines that are polyvalent against many different strains of many different viruses. Our approach to development in 1083 has been to treat it as a standalone, but it has certainly helped by the experience that we see with 1283 today. And by all of the experience, we will bring forward on 1010.

So while we wouldn't expect that those things would be directly linked and certainly not a requirement, I think it's an advantage that we've conducted the independent development of those vaccines. And at the end of the day in our conversations with regulators, they'll tell us what they think and that's probably what matters most. We don't have that today.

Myles Minter:

Myles Minter meant from William Blair, it's pretty clear that the ACIP is worried about Gullain-Barre Syndrome in RSV and they just brought that up at the recent meeting that they're investigating it. Can you give us an update as to GBS incidents across the entirety of your mRNA vaccine platform? And I'm coming from the perspective like I want to know whether they're thinking about it from a product basis because your data's really good in RSV or they're thinking from it more from an mRNA vaccine platform basis when they're going to make their recommendation in June if you get approval?

Jacqueline Miller, M.D.:

I can speak to that, although I'm not going to be able to give you exactly what you're asking for today because I didn't come prepared with that number. But what I would say is, so because we are a platform company, we're always looking at data across the platform. That said, where we are right now as a company, the data we have available are really far outweighed in three programs, it's COVID, flu, and RSV. The one thing I will say about GBS is that I wouldn't say it's necessarily an mRNA concern. So first thing is both of the licensed RSV vaccines have seen reported cases and one of them is not an mRNA vaccine. There are other vaccines-

Stephen Hoge, M.D.:

Both of them.

Jacqueline Miller, M.D.:

I'm sorry, both of them have seen... Yes, you're right, I'm sorry.

Stephen Hoge, M.D.:

Neither is an mRNA.

Jacqueline Miller, M.D.:

Neither is an mRNA vaccine. I really talked myself in the corner there, sorry. But the second thing I wanted to say is, there are other vaccines that are not even protein-based where there is an association potentially with GBS. So GBS is actually something in the vaccine world that we always do long-term following for. And I expect that we are going to be following all of our products whether we see it in the clinical trial or not longer term just like the competitors do.

Stephen Hoge, M.D.:

Mm-hmm, yeah.

Myles Minter:

Second question is just on 1283. Do you expect that the superior immunogenicity that you saw in some of the age groups, particularly the elderly, is that going to translate into enhanced durability as well? And I guess when will we be expecting sort of 6, 9-month, 12-month data from that, if anything? Thanks.

Jacqueline Miller, M.D.:

Yeah, I can take that one, too. So we certainly are continuing to follow and we have antibody persistence data that we're planning to generate for COVID-19. But I'll say COVID, at least at the present time, presents a really big challenge where following beyond a year doesn't really make so much sense because we do annual strain updates. So it's a little bit more like the flu situation... Drops off there. Good to know. Important safety tip. So much like with flu, what we're really focused on is demonstrating durability through the season. And I think where you really see the effectiveness data, first of all, will be in the relative vaccine efficacy data that we're hopefully going to be unblinded to later this year. But then also once we launch looking in the longer term effectiveness studies, real-world evidence studies like we've been doing for now, that's really I think where a lot of the durability data will come from.

Stephen Hoge, M.D.:

But from a commercial strategy perspective, it's not a part of our thesis on launching the product. In part because we really just believe at the end of the day, the durability of last year's flu vaccine against this year's flu, it's kind of not relevant. And I think the challenge we have with SARS-CoV-2 is every six months it is evolving at a pace that requires an update to vaccines. So it's hard to imagine a world where any vaccine using last year's strains going to be able to protect this year. It's evolution.

And so it's not a part of the thesis for launching the product commercially. We're really much more focused on, first and foremost, the ease of use of a prefilled syringe, refrigerated stability, and hopefully a long-term refrigerated stability. And then obviously the combination of vaccine with 1283 and 1010.

Alex Hammond:

Hi. Alex Hammond at B of A for Jeff Mitchum. Thanks for hosting. So just two questions for us. So on the ACIP meeting later this year for the RSV vaccine, can you walk us through the potential recommendation outcomes and how might this impact the commercial opportunity? And then second, can you talk about how you think about profitability and how pipeline prioritization has changed post-pandemic? Thank you.

Stephen Hoge, M.D.:

So from a medical perspective, and Jackie can chime in from a development perspective, it should not be our place to project what the ACIP will decide. It's ultimately up for them. The outcome that we believe is supported by the data will be a recommendation for mRNA 1345 RSV vaccine right alongside the other RSV vaccines and the 60-plus population. That would be also the population that we're seeking approval in.

A big question will be also then, what do we do in terms of re-dosing or re-boosting, and is that now every other year or every year or something less? I think there is data from ourselves and the other manufacturers in the real world data that will dictate that decision. I wouldn't even begin to pretend it's our place to have conjecture on it. So our focus is on making sure that we get the product approved, that we get a recommendation for vaccination. We do think our profile is very competitive in that space and that'll be the number one thing that we're focused on we're quite optimistic about.

Jamey Mock:

And maybe just to make sure I understand the second part of your question, long-term profitability, is that what you're asking about and prioritization of the pipeline? Sure. So yeah, thanks for the question. So nothing's really changed in terms of our outlook for profitability. So we've said in 2026 we plan to break even. And as it pertains to the pipeline prioritization, that's really everything that we tried to discuss today, which is, look, the pipeline's working. We still think, and we had set out that we might need $25 billion. We'll see what our operating cash cashflow and profitability generates over the next three years.

You might have noticed on that page, we only put it through 2026 now, so that's kind of our next three years that we're looking at. We'll see what comes in 2027 and 2028. But as I mentioned before, we believe everything's still working and so there's still probably a need for 25 billion. We'll see how we get there, but the profitability objective remains intact and we'll be financially disciplined along the way.

Q&A Host:

Okay. We'll take some questions from online, all lumping together for the respiratory portfolio. A clarifying question on RSV. Will 1345 require a VRBPAC meeting similar to Glaxo and Pfizer last year? And if so, when do you believe one might be scheduled? A second question on the respiratory portfolio as well. For co-administration studies, are there plans to do RSV, flu, and COVID in a co-administration study following the approval? And then finally on COVID in EU, the tender is quite large in that it is up to 36 million doses per year for up to four years. Is there an estimate for the minimal number of doses for each year?

Stephen Hoge, M.D.:

So first on the specific question on the VRBPAC, at this point, we do not expect that. That's been our dialogue with the FDA. Of course, they're always able to change that, but at this point, it's not our

expectation that there'll be a VRBPAC subject to the FDA's judgment. Jackie, do you want to take the co-ed?

Jacqueline Miller, M.D.:

Sure, sure. So talking about the co-administration, will we do a study of RSV, flu, and COVID? What I would say there is a lot depends on additional data that are coming through this year. So if our COVID flu program in Phase 3 actually reads out positively, I would actually argue the study I really want to do is the COVID, flu combo vaccine 1083 combined with RSV preferentially. Again, kind of using Stephane's math, two needles is preferable to 3. And we actually think that will play out also in the study conduct. But we're really encouraged by the co-ed data we already have.

Stéphane Bancel:

And on the European tender, given we're in the middle of working with the EU on the tenders, I cannot comment on any specifics of the discussions for that tender. What I can say is the reason that EU put in place this tender is that there's quite a number of doctors, healthcare professionals, and public health leaders that across EU have voiced a lot of frustration not to have access to Spikevax because they know that through the real-world evidence data that Spikevax provide less hospitalization than the other mRNA vaccine. And so they really wanted to have that tool, especially for older patients, for immunocompromised patients. And so the tender is going on because there's a lot of demand at the country level to have access to that tool as well.

Q&A Host:

Staying on respiratory vaccines, one additional question just came in. Is mRNA 1083 still on track to launch in 2025 and will the switch to trivalent require further trials for mRNA 1083 before approval?

Stephen Hoge, M.D.:

So as we said last year, we're expecting to launch, that's our target. However, the first step is we've got to get through the Phase 3 data, and then of course we'll meet with regulators, share that data, and submit, and then they'll have to approve and then we'll be able to launch. At this point, we are excitedly waiting that Phase 3 data result, and then we'll provide more clarity thereafter. But at this point, it continues to be our hope and expectation that we'll be in a position to launch 1083 by 2025. On the second part of that-

Q&A Host:

Trivalent.

Stephen Hoge, M.D.:

Trivalent. Oh, yeah. Quickly on that, we've obviously been engaging with regulars. It's one of the subjects of ongoing discussion around 1010 and flu is how we pivot from a quadrivalent package into a trivalent package. At this point, again, our expectation is that we do not need to do any additional work, just like other manufacturers are making that shift. It's quite a different thing when you're removing a B strain that's now extinct and you can probably rely on the data you already have for the other strains that are in there. So again, subject to those ongoing regulatory conversations and people are allowed to change their mind, but we would not expect there to be a need for additional work at this time.

Q&A Host:

Okay. We will go to the next question online. Please provide additional color on your framework when deciding which pipeline assets to prioritize.

Stephen Hoge, M.D.:

Sure. It's a problem. So look, we have a happy problem, which is we have more investment opportunities than most and in many ways more than even we can sometimes prosecute. And so we do have to do a high degree of prioritization across. As you can see from the portfolio we brought forward, there's a heavy focus right now on those places where we can have the most impact on unmet medical need.

And so first and foremost, you look in the respiratory disease space, continues to be a leading cause of hospitalization and death. It's a scourge in many populations and what you saw Jackie and her team present across RSV, COVID, flu, the combinations, and moving into younger pediatric populations is a recognition we think that's an impact we can have quite quickly. So going after unmet need and having a fast impact there.

We also prioritize things that we see as huge unmet needs that maybe take a little bit longer, but the overall scale of that impact from a public health perspective is maybe even larger. And so what you see us doing, the latent virus vaccine portfolio with vaccines like CMV with, vaccines like EBV, norovirus, others, we are trying to very systematically go after a place where there's high unmet need, no current approach, and make sure that we address those concerns with our platform, with the technology that we think is uniquely capable of doing that.

Again, we feel an obligation, but it also has the advantage of being, there's obviously no current competitor in that space, and so also thinks we help address an unmet need, but also help ourselves from a commercial perspective. And then there are things like INT and cancer in partnership with Merck, a place of high unmet need, first in melanoma, non-small cell lung cancer, many other cancers to go. Obviously, you can see why we start to run into a challenge with prioritization. And then we're committed to things like rare disease because we again, feel a unique obligation given what our platform can do to address those unmet needs.

In many of those cases, we're the only program in development and we have to do it. The challenge then is what are all the other things that you don't bring forward? Obviously, we don't bring them forward, we don't talk about them, but there are programs that maybe we don't perceive right now that our technology is uniquely able to answer that unmet need. And so therefore we defer development or in some cases discontinue development.

We work closely with the whole EC and thank you, Jamey, for the Blackstone help deal. But we work to make sure that we're balancing our balance sheet, our operating cash flows, and potential for other sources of financing against that. And we go through a process every six months to try and make sure that we've maximized the value we can bring to patients. Ultimately, that is also something that we think will maximize the value created for Moderna and shareholders.

Q&A Host:

So we've exhausted all the questions in the room and online. Thank you very much to all of our presenters. We will be serving lunch and you will have the opportunity to speak with the presenters today during that lunch period. Stephane, do you want to make any concluding remarks?

Stéphane Bancel:

Just to thank everybody who joined us in person and who can join us for lunch, and to those of you that joined us online. Thank you to the team. As I said in my close, it's a super exciting time. I cannot believe we're just almost three more Phase 3 that are going to happen. So a very exciting time. Thank you very much.