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EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc Vaccines Day

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PRESENTATION

Stephane Bancel - Moderna, Inc. - CEO & Director

Good morning or good afternoon. Welcome to Moderna Fourth Vaccine Day, a welcome back. For those of you that are here in town, you have the bonus of having a beautiful spring day. So on behalf of the team, welcome. Before we start, let me just remind you that we'll be making today forward-looking statements that investing in Moderna involves risk. You can find those statements or various factors on our website or SEC filings. So I think you will agree with me that if you think about the last 100 or 150 years, the impact that vaccine had on humanity has been already profound.

The health impact, obviously, reduction of disease, eradication of some diseases, some prevention of cancer, huge long-term benefit to people. The social impact and also, of course, the economic impact. If you look at this interesting data on Slide 4, the CDC has estimated that children born in the U.S. between '94 and 2013 has seen a prevention of more than 700,000 deaths in the U.S. And if you globally, most probably vaccine is the best return on investment for health care dollars.

Despite those great progress and this great impact, we believe there are still challenges and there's more to be done. First, there are still viral infections that drive diseases that do not have vaccines. We have an aging population around the world, and older people are more susceptible to severe disease with infection. We still have a lot of latent viruses driving cancer that don't have vaccines available and climate change is also impacting human pathogenic diseases.

So let me start with the first one. If you look at the 4 major viral diseases; RSV, flu, norovirus and HIV that does not include COVID. There's an estimated 1.7 million deaths globally. That's deaths every year, that we believe can be prevented. There are around 220 viruses known to scientists around the world that hurts human, but there are vaccine available only against 18 of these. And if you look at one of the impacts of the pandemic, actually, the fight against infectious disease outside of COVID has actually taken a back step versus what it was in terms of trajectory pre-pandemic.

Aging comes with issues. Look at the T-cell, native cell productions based with age on the left panel. After 40s, it can go downhill, just on 50 last summer. So I know which part of the graph I stand in. And then if you look at what's happening in the world, there's aging population, as we all know, not only in OECD countries, but around the world. So if you think about it from a health care standpoint, you have older and older people on the planet and more and more of them and look at the -- what happens to naive T-cell production with aging.

So we need new solutions. And then there's still a lot of latent viruses that have massive long-term health care implications. You're highly aware of HPV and what it has done in terms of cancer prevention. But CMV infections drive birth defects, is a big issue with transplants, EBV, multiple sclerosis, lymphomas. So there's still a lot of work to be done here to all people. And last but not least, with climate change, we are seeing a shift in species of animals.

We're seeing animal moving closer to humans with deforestations and enhance risk of outbreaks and god forbid pandemics. So the good news here is we believe that Moderna's mRNA vaccine platform can address those challenges in multiple ways. The first thing that we have been very excited about this platform since starting the company is the ability to do high biological fidelity. We can do complex antigen, like we've shown with CMV with pentamer, 5 protein made in (inaudible) like when you have a virus infection, coming together to form a very complex antigen.

The ability to do combinations, the ability to have high efficacy as we've shown. Speed, we talked a lot about for our first 9 years of a company. I think now everybody got a good sense of a speed of mRNA technology and the speed of Moderna's platform because our investment in manufacturing, in robotics and in digital. And then the flexibility of manufacturing. In traditional vaccine, you need to dedicate a plant for every products. With mRNA, it's really amazing. We use the same reactors in the same room, with the same people to make all our vaccines.

And it's all the same raw materials, but one component that's different by product. So we have already interesting capital efficiency. As you know, since we first went into the clinic in December 2015, we have been working on vaccine against viruses. Today, I'm very excited to share with you that the team has been working really hard to expand that field of application of our vaccines to bacterial infection.

And so the team will work you through one of our candidates, which is against Lyme disease that is our first step into a vaccine against bacterial target. I won't go through the slide in detail, obviously, it's for your reference, but you can see how just in the last 2 years, there's been not only an acceleration in our pipeline, we had 3 Phase II in 2021. We have now 9 Phase II ongoing in vaccines. We've now 5 Phase IIIs, but not only an acceleration toward approval of those products, but an expansion in the pipeline is breath at the same time.

I have to really give a big kudos to our teams in the labs, in clinical development and in manufacturing because this is a lot to make happen every day. So with this quick intro, I'm going to start by turning it over to Stephen to talk to you about development strategy. And then Jackie is going to talk to you first about respiratory viruses, and there's quite a lot there with our team. We'll take a coffee break. We'll come back to talk about latent viruses. Then Jackie will talk to you about our new kids on the block, the enteric virus for norovirus candidate, which is announced today and the Lyme disease I just spoke to you about.

Then Raffael will give you a bit of an update on our thinking in terms of commercial. Jamey will share some financial framework including what we've put in the press release this morning, the 2027 financial framework about the respiratory franchise, and I will come to close with just 2 slides before the team and I take questions. So with this, Stephen.

Stephen Hoge - Moderna, Inc. - President

Good morning, good afternoon, everyone. Thank you for being here. So in providing a little bit of an overview of R&D strategy, I'd first like to frame up where we are with the platform. So today, our platform really has 2 major vaccines franchises, franchise where we have multiple products in development. The first is respiratory, we'll spend a good amount of time talking about that today.

And the second is latent, which we'll talk about as well. Everybody understands we've talked about before that respiratory viruses really drive an incredibly high burden of disease, particularly in the very young and the very old. And that drives seasonal disease and is one of the major causes of hospitalization and death globally. There are also high-risk populations that also benefit from protection against those respiratory infections. Latent is a little different. In latent, the immediate impact of infection does exist and creates burden of disease, but in many cases, it is the long-term sequela of those disease from those latent infections that drives the largest burden of disease.

We've got vaccines against both that we've been developing. But today, in addition to those 2 larger franchises, we've been expanding our list of emerging programs. We've already had substantial efforts in global health. We'll talk through some of that again today. But we've added to that, the 2 vaccines that Stephane referenced, a vaccine against norovirus, our first enteric virus program, which is a leading cause of diarrheal deaths globally. And our vaccine against Lyme disease, which is our first expansion into bacterial pathogens, and we're very excited about that.

So we'll provide a number of updates across that pipeline, obviously, starting and relying heavily on our work in our respiratory franchise. We'll be printing our next-generation COVID-19 vaccine, which as we announced today, has actually already moved out of Phase II and into Phase III with the initiation of that pivotal study. But Jackie will present some of that Phase II data. We'll talk about our flu vaccine program. Actually 1010, our first of 5 flu vaccine programs and some really encouraging data that we've seen today that we think this keeps us on path for potential approval as early as next year.

That data while we didn't yet accrue enough cases in the efficacy study, the P302 efficacy study to demonstrate efficacy, we would have had to have been substantially superior to the license comparator in order to do that in this first term analysis. But at the same time, as we announced today, we've now seen immunogenicity data from that study, which as Raffael will walk you through, gives us a high degree of confidence in the performance of that flu vaccine and the potential again for an accelerated approval next year.

We'll also talk about some exciting next-generation flu vaccine data as we continue to advance multiple rounds of improvement and I'll talk through that in a second. Raffael will cover that. And then it's a real honor to have Dr. Schief here today to talk us through the incredible progress and work that he's been leading in HIV vaccines and particularly our first mRNA vaccine HIV, mRNA-1644. We'll provide quick updates on some of the new development programs, as I mentioned, norovirus, Lyme disease and our next-generation COVID-flu combo.

So let me just provide a little bit more framing on the role of the platform in developing our vaccines portfolio. As Stephane referenced, there are 3 key features to that platform that we think are really advantageous. The first is the high biological fidelity of how we make our vaccines work, just like a virus infecting you. We use mRNA to make the protein in situ, in the body. And we think that allows us to do a number of things including complex antigens, the ability to combine multiple different vaccines and creates the potential for high efficacy because the vaccine might look more like the virus that is trying to protect against.

We've all seen Stephane reference, I'll talk through some examples, speed of the platform, not just in COVID, but beyond. And then as others will speak to later, we'll talk about the flexibility and substantial capital efficiency of our platform, particularly on the manufacturing side. So first, just a couple of examples. You're all familiar with the potential benefits of mRNA vaccine in terms of efficacy. Our COVID-19 vaccine mRNA-1273, a first generation of that COVID vaccine so 93.2% efficacy in this Phase III study. And now we were announced late last year or early this year, I should say, that our RSV vaccine met its primary endpoint, saw very strong efficacy of 83.7% in its Phase III trial, and we'll provide some updates on that today.

We've also demonstrated speed. Now if you look at COVID in all 3 cases with mRNA-1273 as well as both of the bivalence, we were able to move forward from Phase I to Phase III data in less than a year, which is pretty remarkable, but you might say that's COVID. Well, we'd say that there are other examples out there that show the potential speed of our platform. For instance, a flu vaccine, went in from its Phase I trial less than a year ago or less than 2 years ago when we filed the IND to Phase III data now in multiple studies and ongoing studies at that.

And RSV was able to accomplish that in about 2 years and 4 months from Phase I to the Phase III pivotal data readout that we now intend to file for approval this coming -- this quarter. That pace compares, we think, quite favorably with a more standard industry time lines of 6 to 8 years from sort of Phase I to Phase III data and really underscores the potential power of this platform to move incredibly quickly. We also benefit from using the same manufacturing across. In fact, that's 1 of the reasons we can move so quickly. That manufacturing platform, which we first built in Norwood

starting in 2016, and we leverage throughout the pandemic to address a global public health threat, is a manufacturing platform that makes our -- both of our bivalent boosters.

It makes all of the vaccine candidates in our clinical pipeline, which are quite substantial and varied in presentation and form and then, of course, it also supports our discovery work in the preclinical side, which allows us to move that forward. The fact that we use that one platform across all things is why we are able to move so quickly across so many diverse sets of vaccine candidates. Now the last thing that I want to emphasize before turning it over to Jackie is that those features of the platform, the biological fidelity, the speed and the agility of that manufacturing capability also allows us to have one more advantage, which is we can think differently about how we drive (inaudible) innovation in our clinical pipeline.

Traditionally, you might think of these as long serial investments, but life cycle management really driving over perhaps decades how you drive improvements in your product. mRNA doesn't require that. mRNA allows us to think in parallel about as soon as we have opportunities to improve, how do we drive those improvements in the product? And, let me give you a few quick examples of what that looks like. In COVID, we've actually already seen this. So we went through rapid updates to meet the evolving threat of the virus but that we also -- to meet the needs of the endemic market.

That started with our Spikevax vaccine, mRNA-1273. Moved quickly within almost less than a year to bivalents, 2 different bivalents; mRNA-1273.214 and 222 launched last year. And then as we announced today, the start of a Phase III of a next-generation bivalent that is refrigerator stable. All of that in just 2.5 years. Again, not the exception or the rule, look at what we're doing in influenza. In influenza, we've been able to drive rapid expansion of antigens to improve the potential for matching against the influenza strains that circulate every year. And again, mismatch or the incorrect matching of vaccines is something we've all lived through and seen regularly with these vaccines.

Starting with a quadrivalent vaccine. We've now read out a couple of Phase IIIs there, and we still got importantly our efficacy study cooking. We're moving on to pentavalent and even hexavalent products with mRNA-1011, 1012 and moving on to neuraminidase products, and Raffael, as I said, will present some of the data from the 1020 program and why we are so excited about how those additional antigens might improve the performance of influenza vaccines long term. And then, of course, RSV, let's not leave that out. We've demonstrated quite quickly the progress of the 1345 program, but actually have already moved it into multiple combination products.

Combination products targeting different populations in that respiratory viral illness. Spectrum from pediatric combinations to 2 different adult combinations, mRNA-1230 and 1045. All of these have been happening in parallel over the course of just 2 to 3 years. That kind of rapid cycle of innovation is what gets us most excited about the potential of mRNA to really have an incredible impact on the burden of respiratory disease going forward. Okay. With that, I'd like to invite Jackie Miller, our Head of Development for Infectious Disease to come up and frame some of the next few slides.

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

So good morning. Thank you so much for the opportunity to be with you today to talk about our respiratory portfolio, our latent portfolio, also known as herpes viruses and HIV and then our emerging portfolios. So first, I'd like to talk about the respiratory platform. And as Stephen was mentioning, we've made quite a bit of progress over the last few years. So what you see on the left side are approved in Phase III programs. And we refer to these internally as our big 3. Why? Not just because they're first, but because they're foundational for the rest of the portfolio, as Stephen was just explaining. So first, there are our COVID-19 vaccines, our influenza vaccine for which Raffael is going to share some additional data. And then RSV will give a very brief update from one of my team members, Christy Shaw, who will talk to you about some of the emerging data. And if you're interested to hear more, we'll be presenting more data next week at the ECCMID conference in Copenhagen.

Then as we think about iterating on those programs, the next-generation platform in the middle column really talks about improvements upon the initial formulations and sequences of those vaccines. So you've already seen this with the COVID-19 bivalent vaccines where we've worked quickly to update our vaccine to try to keep pace with the evolution of the virus. For influenza, as Stephen mentioned, we're looking at expanding on current quadrivalent formulations to be able to cover an additional spectrum of strains and then finally, we're actually looking to improve the breadth of immunogenicity by including other antigens, neuraminidase that we know can be quite effective and important in protection against disease.

And then finally, we're taking all of these products and combining them. And because we are able to iterate, manufacture clinical supply relatively quickly, we're able to make combinations of these products at various stages of their improvement. So you'll see that we have a couple of COVID flu combos in development, capitalizing on improvements that we're making to the COVID vaccine and then we'll talk a little bit about some of the other RSV containing combinations as well.

So today, the new data that you're about to see come from our COVID-19 program. We actually have an improvement on the formulation of COVID-19 that will really assist in making presentations that are more feasible for public health implementation, so improving refrigerator shelf life and introducing the potential to utilize prefilled syringes. This is really important for people on the front lines of vaccinating because it will increase their ease of use. And then we have some updates to provide you about influenza. So some emerging data from our seasonal influenza program, mRNA-1010 from the pivotal Phase III efficacy and safety trial. We have immunogenicity data today and then also some data from the neuraminidase containing next-generation influenza vaccine formulations.

So let's start with COVID-19 because COVID-19, it feels like, at least for the last few years, everything starts and ends there. Although I hope now we're in the period where we're moving beyond that. So what's happened recently with COVID-19? Well, we just got back from another VRBPAC meeting where there was a discussion around what do we do to simplify implementation of the vaccine. So you may be aware that if you were getting boosted this fall, you were able to get a bivalent vaccine. Hopefully, you all did. If you were getting a primary series, however, regardless of your age, you were still getting the original formulation of 1273.

And the discussion at the VRBPAC really centered around, does that continue to make sense? Or should everyone get the same formulation of vaccine. If we decide that these strains are prevalent, these strains are important for protection. Should everyone have the opportunity to receive that formulation? And based on data that the Moderna team developed, pediatric population, which primarily is getting primary series, of course, we showed some human clinical data to the VRBPAC and there was general consensus even if there's not consensus about what that new formulation should look like, there's consensus that we shouldn't be doing different things for primary series or booster doses.

This not only gives everyone access to the same vaccine, but again, reduces errors because there aren't so many vials to choose between. So that kind of sets us up for moving in the fall to manufacture the vaccine that will ultimately be recommended. We're anticipating a VRBPAC meeting later this quarter to confirm what product will we be making for the U.S. market come the fall. And we have also, in the meantime, been investigating both the immunogenicity and efficacy of the bivalent vaccine as compared to the original monovalent formulation in order to demonstrate that we actually are providing an incremental benefit.

So I'm looking forward to sharing those data with you today. And then finally, as I mentioned, we'll talk about next generation, what's coming next in the COVID portfolio. So in addition to harmonizing the primary and booster schedule, the VRBPAC also had debates around evolving our COVID vaccination program to something that looks a little bit more like flu where we take the temperature, so to speak, every year from an epidemiologic perspective and try to predict better matched strains for the fall.

There was also a general agreement that there may be some populations for whom we want to give more than just an annual fall booster. And that's because severe COVID disease continues to occur more frequently in older adults and those with compromised immune systems. As I mentioned, we're now in the process. I feel like VRBPAC has become a bit of a [cottage] industry for the COVID team. We're preparing for another VRBPAC where we will share some of the work that we're doing to make some selections about how we pre-prepare to manufacture for the fall, and I'll tell you a little bit more about that in the coming slides.

And then finally, what we were able to demonstrate last year where we prepared an Omicron BA.1 containing vaccine was that when there is a need to pivot, we can do so with this platform. In the U.S., in the fall, we received a BA. 45 containing vaccine, and that was a process that we initiated upon a VRBPAC meeting on June 28, 2022. Okay. So now I'd like to talk to you about that data I mentioned that we've been generating to try to really get our arms around what is the incremental benefit of giving a bivalent vaccine.

So last fall, in the United Kingdom, 2022 fall, in the United -- 2021 fall, sorry, in the United Kingdom, we investigated BA. 1 containing bivalent vaccine. So half 1273, half BA. 1. And we randomized and compared it to the original 1273. So this is -- in the same study, randomized 1:1 to receive same subjects in the same country being exposed to the same circulating streams. And what we were able to show was about a 10% incremental

benefit. So this was not statistically significant. We did not capture enough cases, which maybe isn't surprising in a highly vaccinated population. All of these subjects, we're getting a second booster dose. But we decided, as we saw a trend towards improvement with the BA. 1 containing vaccine, to look and see what does that mean actually at the circulating strain level.

And so this slide is a bit complicated. I'll take you through it slowly. When you look at the BA. 1 strain, so disease caused by BA. 1 strain match to what was put in the vaccine, we see that the randomized cumulative distribution curves separate. We also saw a clear separation of the curves when we looked at a BA. 4 containing strain. And so that really indicates that by including this variant, we're able to improve upon 1273 even for a strain that's not matched in the vaccine. And when you combine them, we combine these 2 together to have sufficient cases for a statistical analysis.

We saw a relative vaccine efficacy of over 37%, and that was statistically significant with a lower bound of 6.9. Now when we compare that to BA. 5, a strain that actually was known to be more virulent and more transmissible than BA. 4, we didn't see the same level of incremental benefit. So it does suggest actually that strain matching is important, and that's really the importance of this VRBPAC discussion. We'll finalize our selection closer to the fall booster campaigns and closer than we've been able to accomplish with influenza vaccines, again, because an mRNA platform is relatively easier anyway to pivot.

Okay. So what about the BA. 45 containing vaccine that all of us received? Well, in addition to the randomized controlled trial, we also partnered with some larger organizations to deliver some real-world evidence. We've had an ongoing collaboration with Kaiser Southern California. And they have evaluated vaccine effectiveness now since the vaccines were originally launched for emergency use authorization. On this slide, in the far right column, they looked at absolute vaccine efficacy for individuals who received a 3-dose schedule.

So they had 2 doses and a bivalent containing booster versus people that were unvaccinated and the vaccine continues to be highly efficacious. So against hospitalization, vaccine efficacy was 83%. Against visits to the emergency department or urgent care centers, vaccine effectiveness was 57%. And now what about with individuals who did not receive an updated booster? So these -- this column in the middle compares. Those subjects who received at least one bivalent containing booster compared to subjects who had at least the full primary series and sometimes even a booster with 1273, the original vaccine.

And we still see improved vaccine effectiveness. So the relative vaccine effectiveness was 73% against hospitalization and 56% against emergency department care. So put it another way, against unvaccinated adults across age stratum, we saw improvement in vaccine effectiveness of 12.8 to 20.0x higher. And then those who did not receive the updated booster lower because original vaccination is still quite effective, but still demonstrating the improvement getting that bivalent booster.

So in summary, we have generated data to show that updating the vaccine actually does result in a clinically meaningful improvement in protection. And we have actually shown that both for the BA. 1 containing nonmatched vaccine as well as the BA. 45 containing vaccine across a number of different countries and also different health care systems. And then we believe that this evidence really emphasizes the need to remain vigilant about COVID-19 disease.

And so looking forward to the work we will do for the fall. And I mentioned this briefly, but just to show you on a time line what happened last year with respect to manufacturing readiness and then execution of delivery of the vaccines. So starting in the spring time, we begin to ramp up the production of the strains that we think will need to be in the vaccines. Last year, that was BA. 1. We also do preclinical evaluations in mice in parallel. This is to show continued confidence in the ability of these vaccines to generate the desired neutralizing antibody responses.

We then move to large-scale manufacturing once the final VRBPAC selection has been made. And as I mentioned last year, that was June 28. So we pivoted from the BA. 1 manufacturer to BA. 45 manufacturer and then delivered the bivalent vaccine for the fall booster campaign, which occurred last year immediately after Labor Day. And so how do we get prepared for what we're going to have to do in the fall? Well, we've been compiling strain library. So you see some of the selected variants of concern on the slide for which we do continuous epidemiologic monitoring.

We also, in some of these cases, produce research-grade lots in order to do initial preclinical evaluations to really be prepared if this is the strain that's going to take off. And we will continue to expand that library, which is how we think we can be better prepared for future epidemic strains

of SARS-CoV-2. So now I'd like to shift gears and speak about that next-generation COVID-19 program I mentioned earlier. A picture is worth a thousand words. So let's look at the right side of the slide first.

The picture that you see of mRNA-1273 represents the confirmation of the spike protein that's currently translated by the mRNA sequence delivered in our vaccine. What you see in green is the end terminal domain containing many of the T cell epitopes against this virus. And in red, the receptor binding domain, where all the action happens to get the virus into the cell. But you'll notice there's quite a lot of gray part of that protein. And while there are still potentially epitopes on that protein, those are not the ones that have been found to be most important in protecting humans against disease.

So we created the construct of that end terminal domain, receptor binding domain connected by a linker molecule. What does that do for us? Well, rather than a trimeric confirmation, this results in a monomeric confirmation, meaning one protein chain, better accessibility of all of those very immunologically rich epitopes. And we believe will result in a more refrigerator stable product enabling us to provide some of those improvements in terms of mRNA vaccine delivery. So let me talk a little bit about the study that we conducted as a booster dose with this product and the data I'm going to share today.

So in our Phase II study, we actually looked at this new construct as a booster dose both as a monovalent vaccine. So those are the 3 groups in gray, where we looked at a single dose level as well as a beta containing bivalent vaccine. And there were 2 dose levels, 50% of the original Wuhan sequence, 50% of the beta sequence, 2 dose levels in green. The comparator vaccine was mRNA-1273 in yellow. And then as there have been some discussions, regulatory agencies about bivalent vaccine versus monovalent vaccine, which could be better, we also thought it prudent to look at a monovalent beta containing vaccines.

So 2 dose levels in pink. That was a cohort evaluated later, and it's not the data I'm going to share today. I'll share the data from Part A. So this vaccine was given as an initial booster dose. So everybody had mRNA-1273 as a primary series. And we ultimately looked as a forced dose or second booster dose with that data containing vaccine in pink. And we followed now those subjects for about a year. And what I'm going to show you are the data for safety and immunogenicity, immediately after the vaccine was given and then 91 days later to look at antibody persistence. So these are the reactogenicity data and these are our standard local events that we follow pain, erythema, swelling, and tenderness in the axillary lymph nodes.

It's a little bit hard to read the different numbers, but let me tell you that in each panel, the mRNA-1273 is the data that are on the right-hand side of the panel. And what we observed was despite being able to utilize lower doses of the 1283 formulation, we see relatively comparable rates of adverse reactions across the board. And the same was true for the solicited systemic symptoms. Again, the last bar graph in each of the panels is the mRNA-1273 so across dose levels, we saw comparable results.

And then here are the immunogenicity data. So despite comparable results and lower dose levels, in all cases, regardless of whether it was a 1273 like Wuhan, like sequence or a bivalent beta containing sequence, we see higher postvaccination antibody titers immediately after vaccination on day 29. And that improvement in vaccine titers is -- it persists until 3 months after vaccination. That was the Wuhan responses. These are the beta containing results and once again also for the beta containing variant. In all cases, 1283 and 1283 bivalent, we see higher numerically antibody titers than with 1273. This really gave us confidence to be able to move forward into a Phase III study. So in summary, what I've shown you is that the safety and immunogenicity of a much shorter transcript was comparable with this 1283 product compared to 1273. And based on these results, we were able to launch our Phase III study late last week.

So let me talk to you a little bit about the design of that Phase III study. We've designed that study to demonstrate noninferiority of immunogenicity. And we also will be comparing the safety profile to the original 1273. And in addition, because we are vaccinating now and leading into the fall season, we know that cases of COVID at least are still being reported, we're going to do our very best in advance of the fall season when a new variant containing vaccine will be launched to capture enough cases to demonstrate efficacy.

That's why efficacy is a secondary endpoint. We're investigating this vaccine in those initially ages 12 years and up. And then eventually, we'll be moving down into the pediatric populations. The goal is, we move forward and the results are favorable in Phase III with 1283 will replace that vaccine in all populations. So to summarize what we've just reviewed with COVID, our clinical data and real-world evidence with the bivalent

vaccines have demonstrated an incremental benefit and effectiveness. And we have built a system within the company to be able to respond to the strain selection and implement that in the fall.

Those activities include epidemiologic surveillance, proactive preparation for manufacture by our colleagues in CMC and preclinical evaluation of our vaccine candidates. And then we have initiated enrollment in our next-generation Phase III clinical study. Okay. So now I would like to introduce Dr. Raffael Nachbagauer. He is the program leader for our team for our influenza vaccine portfolio.

Raffael Nachbagauer

Thank you so much, Jackie. Good morning, everyone, and I'm really excited to give an update on our influenza programs today. And I actually want to start by going back to our Phase II data that we disclosed last year to remind everyone what we had seen back then and the data that actually made us go forward into our Phase III studies. So the study was conducted in the 2021, '22 Northern Hemisphere season in the United States. And we saw immunogenicity data in that population that was in line with the potential for superiority for both influenza A strains, H1N1 and H3N2 which are the major drivers of severe disease in older adults. And the data was also consistent with non-inferiority for influence of these strains in the study. Encouragingly, the geometric mean titer ratios were also consistent across age groups, which meant that we also expected to see good immune responses in the older adult population.

So based off of those data, we then initiated Phase III studies subsequently. And we had 2 Phase III studies that were initiated last year simultaneously. First, P301, which is an immunogenicity and safety study that we conducted in the Southern Hemisphere. In adults, 18 years and older, we enrolled about 6,100 participants in that study. And we recently disclosed some updated information on this study where we did see a good safety and tolerability profile in P301.

The trial met all its endpoints for Influenza A, including superiority for H3N2. The trial did not meet noninferiority for its influenza B endpoints, unfortunately. We also started a P302 efficacy trial in the fall of last year. This study was ongoing simultaneously. And we initiated it because as part of the accelerated approval that we were going to file for -- with P301, we needed to conduct a confirmatory efficacy trial. We thought we wanted to start early because as everybody knows, Influenza made its come back last season. And so we enrolled about 22,500 participants in the Northern Hemisphere with heavy enrollment coming from the U.S. and Europe. And the primary endpoint in this study was relative vaccine efficacy to a license comparator vaccine.

We did, however, also have a secondary endpoint to measure immune responses in a subset of this population. As Stephen mentioned earlier, we have not accrued enough cases to date at the interim analysis to declare early success. However, we are continuing to follow up for the study until the end of the influenza season. And importantly, again, the DSMB did not identify any safety concerns at the time of the interim study. Looking at the safety holistically, we have now dosed over 14,000 participants in total with mRNA-1010 and what we've really seen is a consistent safety and tolerability profile across all the studies, starting from Phase I all the way through Phase III, where the DSMBs have consistently not voiced any safety concerns.

And the reactogenicity profile is similar to what we have previously seen with our COVID vaccines. Now the P301 results, I think you've seen the high-level summaries, but if we look at the data in detail, what we saw there was that we still made the noninferiority endpoints for both of the influenza A strains and the superiority for H3N2 was actually maintained, which we had previously seen in Phase II. However, we did not make noninferiority for the influenza B streams in this study. This was a bit of a surprise given that we had seen strong data coming out of Phase II. And since we wanted to find out what was really going on, we decided to dig a little bit deeper what the reasons for those differences could be.

And we really ended up honing in on the study location and study populations being the main driver of the differences between those 2 studies. Because Phase II, as I mentioned, was completely conducted in the United States, a population that is heavily immunized based on the broad recommendations that everybody knows here. In comparison, the enrollment in P301 was heavily coming from countries such as Argentina, Philippines and Colombia, where the recommendations are not as broad and we think this is reflected also in our enrollment data, where we saw that 97% of participants actually had not received an influenza vaccine in the prior season.

We don't know the immune history prior to that. But there -- if you didn't get a vaccine in the prior year, there's a likelihood that you might not regularly receive influenza vaccines. And the reason we think that those differences in immune histories could play a role is that there's actually a wealth of data out there that indicates that traditional -- the traditional vaccines that are currently licensed actually struggle to elicit potent and consistent immune responses in heavily immunized populations where they do quite well in people who have not recently received influenza vaccines.

And we're actually quite encouraged that is this heavily immunized population where we might actually see an indication that mRNA-1010 gives consistent performance and actually outperforms on the influenza A streams? And we decided to dig a little bit deeper by looking at a sub cohort of our P301 study. We had only 200 participants enrolled in Australia but the reason we looked at this country is that Australia has a similar broad recommendation for influenza vaccines as the United States. And when we looked at those data, we actually saw something that reflected more of what we had seen in Phase II than it did for the rest of P301.

And so we were quite encouraged by those results. And then looking at the P302 immunogenicity data, which, as we mentioned, we conducted in a subset of about 900 participants, we saw titers that were actually more in line with what we had previously seen in Phase II. Importantly, P302 is primarily an efficacy trial. So we did not prespecify the immunogenicity endpoints. That said, we saw geometric mean titer ratios that were in line with superiority for both of the influenza A strains and noninferiority for the influenza B strains just like we did in Phase II. And again, this is consistent with more heavily immunized population seemingly giving similar performance of mRNA-1010.

These data are really encouraging to us. And we're going to base P303, our upcoming immunogenicity trial off of those data. We are actually planning to utilize the safety data that we have collected to date and generate additional immunogenicity data with an updated formulation of mRNA-1010 that we actually expect to improve the influenza B responses overall. The goal is to seek accelerated approval based on P303. And still wait for P302 in case we are able to demonstrate efficacy in this study and otherwise conduct a confirmatory efficacy trial subsequently.

And this study is about to start later this month. So to summarize our observations and learnings in mRNA-1010 to date, we saw an acceptable safety and tolerability profile that was very consistent ranging from Phase I to Phase III. In our Phase I/II studies, we saw strong immune responses for influenza A that were consistent with the potential for superiority. Those strains are the main driver of the season in older adults. In particular, we saw titers in line that with noninferiority for influenza B. In P301, in a very different study population, we did not see noninferiority for influenza B strains. However, looking into subsets of populations that were more heavily immunized as well as P302 immunogenicity data coming out of the U.S., we yet again were able to confirm the results from Phase II as we previously had.

As I mentioned, Phase III efficacy is still ongoing. We're still following the participants until the end of the season. And unfortunately, we did not prespecify the immunogenicity results, but P303, our upcoming immunogenicity trial is intended to allow us to file for accelerated approval. As you all know, mRNA-1010 is just a start for us for our influenza programs. We're actually planning to build upon mRNA-1010 with vaccine candidates such as mRNA-1020, 1030 that will include an additional antigen, the neuraminidase. And another improvement that we are also working on are our mRNA-1011, 1012 candidates. Those vaccines are supposed to broaden our immune responses against influenza A strains, where currently, we have to pick 1 H3N2 or 1 H1N1 strain out there. When we know there's a lot of difference, it's co-circulating. So providing public health authorities with the ability to choose more strains gives us a higher likelihood of actually matching the right strains that occur in the circulating.

And as Stephen alluded to, we actually generated some immunogenicity data in our mRNA-1020, 1030 program last year. And I'm really excited to show an initial sneak peek of those data today. We had Flublok, an enhanced influenza vaccine, as a comparator in the study. It is a very efficacious vaccine. And it actually does not contain any neuraminidase at all because it's a recombinant vaccine that only contains HAI. One reason why vaccines don't contain a standardized amount of neuraminidase to date is that it's really hard to quantify and standardize in the vaccines. And in the context of a recombinant vaccine, it's just really hard to make.

And it's important that this limitation does not translate to mRNA vaccines where you can actually encode for NAI with our mRNAs quite well. Why NAI is a net attractive target is also related to data that shows that NAI is independently correlated with protection from HAI titers. So in addition to the protection that you're getting through the hemagglutination inhibition titers, you get also protection through NAI. And what we saw in the study was that we actually got similar HAI titers to Flublok with our lead candidate from our mRNA-1020, 1030 Phase I/II study. And if you look at

the bottom, you see that for neuraminidase inhibition, of course, only mRNA-1020, 1030 lead was able to elicit NAI full rises that actually were in the 2 to 4x range, which makes us really excited.

What's really important to highlight also is that nobody today, to my knowledge, has been able to deliver 8 mRNAs for influenza vaccines encoding for both the HAI and NAI. So this is really exciting clinical proof-of-concept data for us. And this build slide only shows that if you plot mRNA-1010 in this graph as well in the bottom, you see similar to Flublok, it does not elicit NAI titers as we expect since it doesn't encode for neuraminidase.

But on the top, you actually see that even mRNA-1010 elicit similar titers to this highly efficacious recombinant vaccine. And with that, I want to bring you back to our overall view of our influenza portfolio. I told you quite a bit about mRNA-1010, which we consider really the foundation first stepped out towards our influenza portfolio that we think is going to consistently improve over time. Building on top of mRNA-1010, our mRNA-1011, 1012, which are candidates that encode for additional HAI antigens that really broaden the coverage against circulating strains. And then building on top of that mRNA-1020 and 1030 will essentially include the NAI antigens. And if you look all the way to the right, we actually think that subsequently, we could include all the features of those different candidates into single vaccine, which we think could really improve efficacy of influenza vaccines quite substantially.

And with that, I'm going to hand it over to Christi who's going to talk about RSV.

Christine Shaw

Hi, everybody. Christi Shaw, I'm the leading Infectious Disease portfolio for respiratory. All right. First, I'm going to be talking about our RSV vaccine and sharing some of the data that we've presented at a recent medical conference. And as Jackie mentioned, we do have another conference coming up very soon, where some additional data will be presented. So starting with the epidemiology, RSV is a very common respiratory pathogen, where the burden is most relevant or evident is in both young children and older adults as articulated on this slide. And in the U.S., there's actually millions of medical visits that are associated with RSV every year, and it leads to high health care costs associated.

And most kids have had RSV or have been infected with it by the time they are 2. And kids and adults continue to get RSV throughout their life. It's usually not such a big problem in a healthy adult but becomes more of a disease risk in older individuals as shown on the right on this slide here. And recent publications have shown that in high-income countries, there's up to 0.5 million hospitalizations yearly due to RSV but that number is actually probably an underestimate, considering that testing is not routine for RSV, particularly in older adults.

So our RSV pipeline is actually addressing both of these areas where there is a high burden in both of these populations. You've heard a lot recently, and I'll tell you more today about our older adult program where we have successfully demonstrated efficacy in a pivotal study. We have a very competitive, we feel, portfolio compared to the other vaccines out there. And we do hope to file, as mentioned already, for BLA in the U.S. this quarter with -- in our best case scenario, getting a regulatory action towards the end of this year or maybe into early next year.

But we also do have a very active pediatric program, not getting into too much detail of that today, but some specifics are on this slide here. We actually just recently initiated a pediatric study in children 5 to 24 months of age. This study not only evaluates our RSV vaccine in those kids but also a new combination vaccine for pediatrics that also includes human metapneumovirus, which is another common respiratory pathogen in kids. So that study is ongoing. So hopefully, data to come soon from that study.

We also, in our Phase I study, did evaluate our RSV vaccine in women of childbearing potential. This sets up the stage, should we pursue a maternal vaccine program for RSV and the mechanism of protection there would be passive transfer of antibodies to protect infants from disease. So we're really covering the spectrum of age here. And also, interested in pulling RSV into our combination respiratory vaccines. I'll speak a bit more to those, but you can see here that we have adult combination vaccines with flu and also with flu and COVID that are in clinical development now.

And I think one of the really neat things about this platform is that you see on the bottom, RNA right now, to our knowledge, is the only technology that is addressing all of these populations with a single vaccine, a single platform. This is not true for some of the subunit vaccines or live attenuated vaccines, for example, which only addresses certain niche of the burden. All right. So digging into the older adult program. So this is the update

we have on our Phase III pivotal efficacy and safety study. This is a big study. We've enrolled more than 35,000 participants across the globe in 22 countries, Northern and Southern Hemisphere to capture RSV wherever it happens to be circulating.

Individuals were randomized to either receive a single dose of vaccine or placebo and everyone's followed through 2 years of the study. So the endpoint here is prevention of lower respiratory tract disease. And it is a case-driven study. So we're continuing to accrue cases through the studies from when it started, and we still are. But about a year after we started the study in November, this past year, we had accrued sufficient cases to trigger our first analysis of efficacy.

And those are the data that we have presented on, and I'll share more today. Now the primary endpoint of lower respiratory tract disease actually has two symptom definitions. So we have 2 co-primary endpoints. They both require PCR-confirmed RSV infection. They differ only in the number of symptoms that trigger or that encompass that case definition. So you can have 2 or more symptoms shown on the right of the slide to meet the first definition of LRTD with 2 or more symptoms. And a subset of those individuals have 3 or more symptoms and those same set of symptoms, again, shown on the right.

These have to occur starting -- the definition is from 14 days after vaccination through a year for our primary endpoint. Although as I mentioned, we are continuing to look at data through the second year after vaccination. Okay. So getting into the data from the study. This is the demographic or baseline characteristics in the study. There are 35-plus individuals, 35,000 plus, as mentioned and first, you can see the quite balanced across the 2 groups vaccine and placebo in terms of characteristics.

And I want to point out a couple of key features that we have been able to recruit a high number of individuals that we think or that we know will be more susceptible to severe RSV disease, of course, this is the population we're even most interested to treat with this vaccine. Specifically, if you look at the age, we have more than 30% of individuals that are above 70 years of age and also more than 5% that are above 80 years of age. Also interested in those individuals with underlying conditions that put them at risk for more severe RSV disease.

Those are we call comorbidities of interest and the specifics are at the bottom, COPD, asthma, chronic respiratory disease, diabetes, CHF, and advanced renal or kidney disease and in that population, we have about 29% of those as well. We're also pleased to say that we have more than 1/3 of the participants that are nonwhite. And similar number that are Hispanic or of Latino ethnicity. Okay. First is safety and then we'll move to efficacy. So for safety, this is the solicited local adverse reactions that occurred within the first week after vaccination. And it's a pretty favorable profile.

So this local reactions are driven primarily by pain in this case. They are more than placebo, but the rates are really -- the severity is really grade one, which is quite mild in severity, with very few of the higher grading. When we move to the systemic solicited adverse reactions. While there are slightly more reactions of arthralgia, fatigue, headache and myalgia in the vaccine group, again, they are more mild and some moderate reported events. So overall, a quite well-tolerated vaccine. And then moving to the efficacy results. So this is the top line primary endpoint efficacy.

Again, we had 2 case definitions and 2 co-primary endpoints associated, RSV-LRTD with 2 or more or 3 or more symptoms. On the top are the 2 or more symptom data and at the time of our analysis, we had accrued 9 cases in the vaccine group and 55 in the placebo group, which equates to an efficacy of 83.7%. We saw a very similar level of efficacy in the 3-plus case definition, 82.4%. And as expected, there were fewer cases there as this is a subset of the individuals that had 2 or more symptoms.

But the case split was very favorable as was the efficacy and both of these actually did meet the predefined success criteria for the lower bound of the (inaudible) interval higher than the level that we had predefined for success. Okay. So once we had to achieve success and efficacy and have a safe vaccine, we're starting to look more into other more nuanced or detailed analysis of efficacy. And here and on the next slide, I'm just going to show 2 of them that we have shared so far. And this is subgroups by age here and comorbidities on the next slide. So by age, again, older individuals are at more risk for disease. So we looked at it by decade here, 60 to 69, 70 to 79 and you can see that the efficacy is maintained as individuals' age, which is very good to see. As with all of these graphs, the confidence intervals are wider, for the 3-plus LRTD case definition just because there are fewer individuals that met that criteria at the time of the analysis so far.

You might see that there are no data on here for the 80-plus individuals, although we did recruit more than 2,000 or about 2,000 individuals. That's only because at the time of the analysis, there just had not been any cases in that 80-plus group, but there may be as the study continues. And then the second analysis by subgroup that I'm sharing is that with those underlying comorbidities and here, it splits into at least one or more comorbidity of interest. It's that same list of symptoms or conditions I mentioned earlier, shown on the bottom of the slide.

Both for 2 plus or 3 plus LRTD symptoms definitions. And again, very good maintenance of that efficacy level in both populations, those quite healthy and those with the underlying conditions. So there's no drop off of efficacy as with these conditions. And these, again, are those that put individuals at risk for severe disease. So we think the vaccine is holding up quite well in the population that matters the most.

Okay. So some kind of key highlights, some summary, a couple of new points for the data I shared so far. First, we have a very well-tolerated vaccine, mild and some moderate events. One new piece of information that we shared at a conference recently was we have no cases of Guillain-Barre syndrome reported in our study so far in either vaccine or the placebo group. On the efficacy side, we have high VE, as described. And the number of cases that support this are a total of 64 which is a lot is just a higher number of cases than some of our competitors or both of our competitors have reported for their endpoints.

So it's a very robust data set in that regard. And we have great maintenance of efficacy in the populations that matter most they get severe disease. All right. Summarizing again, kind of similar to the last slide, efficacy that's maintained in the subgroups that matter, great -- tolerated vaccine and no other safety concerns have been identified. As I said, no GBS. We do expect to submit -- we're on track to submit our BLA file in the U.S. this quarter. And we do have an option for a priority review as we've disclosed previously.

Okay. So that's RSV. Moving on to combination vaccines and many of these do include RSV. So these are the adult combination vaccines I'm focusing on. As I mentioned earlier, we do have a pediatric combination vaccine with RSV. But in general, our kind of philosophy for combination vaccines is building on that, that Stephane and Jackie and Raffael already alluded to. We're going to keep iterating these things until we get it right. And even then, we're going to keep going until we get it even better.

So we have all of these first-generation single virus vaccines. We've already shown efficacy for RSV, for COVID. Flu has got some great data. We're going to keep moving on those. But at the same time, we're improving those single virus vaccines. Jackie described some ways we're doing that with COVID, Raffael described how we're doing with that flu. So we're going to keep iterating on that. In parallel, we're also putting these things together into combinations. We see a lot of benefits for individuals and health care systems to do combination vaccines.

But we're not stopping at a first generation. We're going to -- as we improve the components we're going to keep putting them together and keep making this vaccine updated more and more and better vaccines. They may be better for different reasons. It could be stability, efficacy, safety, other things, shelf life, and these kinds of things, lots of ways we can improve, and we will improve. So here is a visual of where we are with our adult combination vaccines for respiratory. First, we are really pursuing those vaccines where we see the most benefit to our health care and to individuals. In terms of what are those concrete benefits, they're shown on the right, better compliance and uptake and benefit to health care and also to an individual for consumer, rather get 1 shot instead of 2 or 3.

The specific vaccines that we have developed or are developing so far are shown on the left. Again, these are the adult combination vaccines and with the status update where we are in their development. So we have maybe our first or most advanced vaccine as a COVID, flu combination. This one is called 1073. We had completed enrollment on this study, and it was a combination of our Spikevax 1273 vaccine as well as our first-gen 1010 vaccine. We also recently completed enrollment in a study that evaluated 2 other combination vaccines, the 1045 and 1230 vaccines. These include RSV also so we have an RSV flu, which is 1045. This makes sense because those pathogens are well known to circulate at the same time.

They cause very similar disease so we see some advantages there. We also -- if there's any unusual timing of COVID update sequences and so on, that would not be a problem for the flu, RSV combo. So we're keeping that as an option that's moving along. And then we think the ultimate -- one of the ultimate vaccines would put all 3 of these together into a triple combo. That vaccine is also in this Phase I study. Enrollment is complete. Data will be forthcoming. That also the triple combo included our first generation programs for that components.

Then lastly, as we announced earlier, we have a new vaccine. This is, I think, our first example of our second-generation combo vaccines. So we're already pulling in the improved components that we have for the stand-alone single virus vaccines. As shown here, you can see this combo will include the 1283 that Jackie described today, which has the shorter mRNA, better ability to have long-term storage and potentially refrigerator or potentially a prefilled syringe.

That vaccine also, the 1010, also includes some updates in the flu component as well. So overall, we think this could even be a better for a number of reasons, including storage and even potentially efficacy and safety. News on that vaccine is so we have submitted the IND. And so it's with FDA currently under review. So next steps for combos. We are really continuing to build on the data that we have for the individual programs to put them together into the best and next combination vaccines. And we are continuing to focus on the diseases that we think matter the most and will have the most impact on health care around the world.

And we do -- for this new combination vaccine, the second-gen flu, COVID. As I said, IND is under review. And if that goes well, we do hope to start enrollment in that study soon, definitely in this quarter. I think that's it for me, and we're at a break.

(Break)

Unidentified Company Representative

Okay. I've been requested to tell you that we'd like to get started again. Okay. So I know that was a brief break. Hopefully, you got a chance to get up and stretch your legs because we have now the second half of the presentation. And unfortunately, the clicker is not working for me. So -- yes, can we go back one, please? It advanced to 2 actually.

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

Excellent. Thank you. Okay. So now we're going to shift gears a bit and talk about some of the platforms that are earlier in development. As Stephen mentioned, these viruses, the herpes viruses and HIV, I think are incredibly impactful. It's a very exciting part of our portfolio because these not only cause near-term disease, but can cause long-term impact for people as well. We're going to focus today on cytomegalovirus, which is currently in Phase III of development. We also have age de-escalated down to adolescents. Why? Because there's an existing adolescent vaccination platform and the important thing with these latent viruses is to actually vaccinate people before they become seropositive because when they have the long-term complications are because people have already been infected and those viruses reactivate.

And then finally, as Stephane mentioned, CMV is actually a real problem in the transplant population. There was a famous paper actually written in the 1980s called the troll of transplantation so that's how I think of CMV, the troll of transplantation. And I'm so excited to talk about the Phase II study that we've initiated. And then I'm going to welcome our very special guest, Dr. Bill Schief, and he's going to talk about the ongoing Phase I work we have in the HIV space. So first, a bit about cytomegalovirus. We are targeting multiple impacts of cytomegalovirus. So the first thing that we are evaluating is an indication to prevent primary CMV infection in seronegative women. The reason for that is when women become seropositive during pregnancy, they can pass that virus through the placenta to their unborn baby and -- like rubella, like varicella, there can be a congenital syndrome that comes with infection called congenital cytomegalovirus disease.

It actually is the most common infectious cause of congenital sensorineural deafness worldwide. We also are potentially interested in investigating the vaccine in women of childbearing age. Again, maternal vaccination is becoming more of a platform. And as I mentioned, the people who really need this vaccine the most are those who are in the transplant and immunocompromised space. And then we're also looking at what age groups could you really target to address cytomegalovirus before someone ever becomes infected because if you don't become infected, you can't reactivate it and suffer the longer-term health consequences.

So I mentioned the congenital CMV syndrome. This syndrome in newborn babies can lead to \$1 billion in annual health care costs. So it's not actually, as rare as people think, one in 200 babies are born with congenital CMV infection. And of those 1 in 200, 1 in 5 of them will have severe

and life-altering complications from their congenital CMV infection. So at birth, this syndrome comprises symptoms such as microcephaly, chorioretinitis. There can be a seizure disorder that accompanies the neurologic complications along with sensorineural deafness.

And then in the longer term, so it's not always obvious the problems that an infant will have when born. There can be cognitive impairments, the development of cerebral palsy, and the seizure disorders and sensorineural deafness obviously are not conditions that get better over time. So we have a Phase III trial ongoing, and I'm so pleased to report that it's now over 50% enrolled. And it will be evaluating the efficacy, the safety and immunogenicity of our CMV vaccine, which is mRNA-1647. We have 150 sites in the U.S. and globally where we're conducting this study. And we've specifically targeted women at higher risk for contracting CMV.

Why? We're trying to enrich for the capture of those cases. So we're following cases after dose 3 of vaccine. As with our other clinical development programs, diversity and inclusion continues to be an important goal for us. And we have published our targets for enrollment to ensure the generalizability of our results. And as I mentioned, primary infection is the key indication we're targeting. So we are monitoring these women carefully for seroconversion to CMV.

So the reason, as I mentioned, that we de-escalate to adolescents is, again, to increase the likelihood that we are able to vaccinate before someone has naturally seroconverted. And we believe that the majority of cases could actually be prevented if we added a CMV vaccination at the same time we're vaccinating teenage girls with other vaccines, such as the human papillomavirus vaccine. This would ease implementation to the vaccination schedule, so wouldn't require additional visits for the use of the vaccine. So now let me talk a little bit about that adolescent study.

We actually are currently conducting a dose-ranging study to select that final dose including the dose that we're currently investigating in the efficacy trial in adult women. This study includes 770 participants across about 70 sites globally, and the patient population will be 9 to 15 years of age. Again, meant to target the age range for the adolescent vaccination platform. And as we did in our adult dose-ranging studies, we'll be looking at neutralizing antibody titers to both epithelial cells and fibroblasts. Okay. So shifting gears a bit to the transplant population. Why is CMV the troll of transplantation?

Well, it plays an important role, actually, in graft rejection and you can imagine, if you've been waiting for your organ transplant and then you develop an infection that eventually causes you to lose that graft. This is a really devastating consequence for these patients. Their immunosuppression puts them at higher risk, not only for capturing or being infected with new strains of CMV, but actually reactivating previous strains.

And you don't have to have been a seropositive person at the time of transplant. CMV infects epithelial cells. And as such, when you transplant an organ, you can actually transplant your donor CMV infection into the recipient. So they have a lot of reasons to be at increased risk, and they have a lot at stake to prevent their infection. So there are currently no approved CMV vaccines, not only for post-transplant but overall, and there really is a high cost and some toxicity associated with the existing prophylactic mechanism.

So currently, all patients, standard of care are getting CMV prophylaxis at least for some time after transplant. And those medicines though, over time, just like with antibiotic resistance can lead to resistant strains of CMV. So there's a lot at stake and a lot of good reasons to develop a safe and effective vaccine. There are about 62,000 organ transplants each year in the U.S., 40,000 of which are renal transplants. And we're going to talk a little bit more about hematopoietic stem cell transplant or bone marrow transplant patients, but they are about 22,000 of them.

So enrollment has begun in the study we call P205. It's a Phase II study, and it's really meant to be a proof of concept that this vaccine can impact CMV infection and reactivation post-transplant. So right now, to start, where we're curing seropositive individuals who have gone high-risk, allogeneic stem cell transplants. And the primary outcome measure is the time to first reactivation once their initial prophylaxis is over.

So we are going to give the normal prophylaxis that these patients would receive while they are waiting for their bone marrow transplant to take, the way bone marrow transplant works, you ablate the bone marrow of the patient and then you replace it with the transplant. And it takes a while for that bone marrow to begin producing white blood cells again. So obviously, initially, while they have no white blood cells, we want them to have their prophylaxis. But once their immune system reconstitutes after about 100 days, we're going to give an accelerated schedule of the CMV vaccine. So 25 days apart. Why? In these patients, we really need protection to be induced quickly. And we will be following them very closely. They actually get quite close follow-up as standard of care.

And if we see signs of increasing either viremia or symptoms of CMV disease, we will then obviously start antiviral therapy. Okay. So with that overview, I'd now like to turn this over to Dr. Bill Schief. He's a Professor of Immunology and Microbiology at The Scripps Institute and he's also the Director of -- Executive Director of vaccine design at IAVI. He designed our 1644 mRNA vaccine program. So excited that he's going to share the results with you today. So please welcome Dr. Schief.

William Schief

Thank you. It's great to be here. I've presented at Vaccines Day before virtually, but I never knew what it was like in person. So it's great to see you guys. Let's see how I do this? Okay. Yes. So I'd like to give you an update on the clinical trial we call IAVI G002, which we're thinking of as a first step toward making an mRNA HIV vaccine. And this is actually the first public presentation of data from this trial. Fresh trial is not completed yet, still in the middle of the analysis. So it's really exciting to share you guys -- share with you the data.

And so we've heard a lot of great presentations about COVID and flu and RSV and other viruses that are similar in HIV in the way that they infect human target cells, their type 1 fusion spikes and the spike of HIV has shown in this light gray with antibodies bound to it. And probably the major challenge in making an HIV vaccine and why Moderna hasn't already made 1 and showing you amazing results like we're showing for flu and RSV is that the spike -- the surface of the spike and the amino acids that cover the spike change much more dramatically between one isolate and another for HIV than they do for influenza or RSV.

And so it's really difficult. They were talking about -- all the speakers have talked about making cocktails of different antigens to -- and updating the cocktails every year to do strain matching. And that works for influenza, as we all know, works extremely well, and you saw great data and it works for COVID, as Jackie showed, but it wouldn't work for HIV. It's far too diverse. And so what do we do? Well, the field has been thinking about this for a very long time and doing a lot of research. And if you look at people infected with HIV, a very small percentage of them make what are called broadly neutralizing antibodies.

And those antibodies bind to patches on the spike that don't change as much. And it's not so easy for the human immune system to figure out how to do that. It requires very specific sets of human antibody genes and usually a lot of mutation for the antibody to evolve the ability to just grab on to exactly the right spot. But by studying lots and lots of individuals, the field has isolated and this slide is showing examples of different broadly neutralizing antibodies called bNAbs that bind to different sites on the spike. And the idea here is we know that the human immune system can produce these very infrequently in response to natural infection, but can we design a vaccine that intentionally and reproducibly induces broadly neutralizing antibodies so that when someone is exposed to HIV, they've already got bNAbs in their blood and they don't get infected, no matter what isolate is challenging them.

And so we have -- the bullets here are showing that we have broadly utilizing antibodies that neutralize diverse isolates, some up to 99% of all isolates. Lots of work has shown that if you give a bNAb to a nonhuman primate and then you challenge it with a shift kind of like an HIV that could infect the primate. If the bNAb is present in sufficient high concentration, there is no infection. You get sterilizing immunity. And a recent set of human and clinical trials showed that bNAbs can also protect humans.

And so the idea is if a vaccine could elicit bNAbs, it could prevent HIV infection. And to really do that of the style of Moderna, 90% infection plus, the responses need to be broad, potent and durable and that's what we're going for. And I just want to say that presentations were so beautiful and the technology is so beautiful. The examples for COVID and flu that you've seen already but -- and there are analogies here. So while HIV is so much more diverse than influenza or coronavirus -- SARS-CoV-2, broadly-neutralizing antibodies have been isolated for those viruses as well.

And you could imagine if the strategies I'm talking about are effective for HIV, you could imagine deploying them also for less diverse viruses and that could help make the vaccine -- lower the requirement for strain matching and updating the vaccine every year, maybe you could make a vaccine that induces bNAbs and you'd only have to update it every 5 or 10 years or even if you did update it, you might just get even higher effectiveness. So it's sort of an exciting new technology.

But back to HIV. So today we're just going to talk about one class of HIV bNAb, VRC01 class bNAbs that bind to the CD4 binding site. So what is required to induce protective bNAbs? I mentioned that these antibodies have very specific sets of human antibody genes, and they gain lots of

mutation that allows them to bind to the specific patches, epitopes they bind to, they don't change much on the spike. And so in order for a vaccine to induce these, we need to start -- the vaccine needs to trigger naive B cells that have the right naive B cells that have antibodies on their surface and antibodies have -- each B-cell has one set of antibody genes.

And so we need to trigger the B cells that have the right set of antibody genes that gives them the potential to develop into a bNAb and then the vaccine needs to elicit -- that needs to take those B cells through a set of immune reactions to gain somatic hypermutation, finalize the process of becoming a bNAb, convert the cells and the plasma cells that secrete bNAbs in the blood and from the bone marrow. Sounds easy. And so the strategy that we're pursuing to do this, to achieve this is called germline targeting and it really keys off the first shot of the vaccine.

The job of the first vaccine component, the prime, the vaccine prime, is to find and trigger those naive B cells that have exactly the right genes and expand them and get them to mutate a little bit in the right direction. And then if that works, then we deliver a series of shepherding or polishing immunogens that are intended to engage the red cells that were generated by the previous vaccination, expand them further, get them to make more somatic hypermutation in the right direction toward bNAb development. And finally, in the last polishing stage, we need to make sure that we have a very high level of plasma cells with the right bNAb sequences on board that secrete bNAbs into the blood.

And it's more complicated than a normal vaccine strategy, but it's not terribly more complicated. You see you added multiple shots. Many vaccines you give multiple shots. Here, we just have to use a different component for each shot of the vaccine. And one of the huge assets of this strategy is we know what we're looking for. If we're trying to induce a specific class of broadly neutralizing antibody, we know what genes that antibody has. So we can -- while we're doing a human clinical trial of the kinds that Jackie talked about, you can interrogate the B cells halfway through and ask, are we getting the sequences we want? Is this working or is it not? And if it's not working, you could stop and you'd know why we need to redesign the components before.

And if it is working, you say, how we can keep going. And it lends itself very well to optimization. It's a very sort of engineering-oriented approach. So we think that even though the problem is very difficult, because it lends itself to this optimization and engineering approach, we think we can solve this problem. So in December, we and our colleagues, and you see there's many authors in this paper, we published a paper in science that showed clinical proof of principle for that first step.

It showed -- for one example it showed that we can trigger the B cells that we want that have the right genes that are precursors to one particular class of bNAbs. And in this clinical trial, IAVI G001, the ImmunoGen triggered bNAbs precursors in 97% of the participants. And in the middle panel here, you'll see this little blue nanoparticle. The vaccine was called eOD-GT8 60mer. It's a self-assembling nanoparticle, 60 copies of a little domain that we engineered specifically to have affinity for the bNAb precursor B cells we were looking for. And on the right, you can see in the low dose, we induced bNAb precursors in 18 out of 18 participants and in the high dose, 100 micrograms, we induced precursors in 17 out of 18. So it worked extremely well and the responses were very strong.

So this gave us -- showed that the concept works in humans. And that opens the door really to our thinking about, okay, how we -- are we really going to make a vaccine? What are -- how are we going to get there? And so we -- with that data and with lots of other preclinical data that I don't have time to describe to you, we have 2 major goals in mind. First of all, we've shown, like I just showed you on the previous slide that we can get that first step to work in humans, but in order to induce bNAbs, we have to go through the whole pathway and actually induce bNAbs. So the first goal is to prove that we can do that in humans for at least 1 class of broadly-neutralizing antibody and then the second goal is much more -- is more practical, is thinking about, all right, let's really make a vaccine.

We believe in order to make a highly protective HIV vaccine in Moderna style, highly protective vaccine, we need to induce multiple classes of bNAbs, probably 2 or 3 in parallel to get enough coverage across the -- against the huge diversity of global isolates. And so we've got to go through that sequence of vaccines -- of vaccine immunogens for multiple different classes of bNAbs and then combine them. So we've heard discussions of combination vaccines of RSV and flu and COVID, well, this would be a combination vaccines for different HIV bNAbs. So Moderna knows how to do that kind of thing already in the technology lenses stuff fairly well to that. And I have to say that formulating those goals would be impossible without a partnership with Moderna.

You can't plan -- in that previous slide, we're thinking about multiple, many Phase I clinical studies to evaluate and optimize the vaccine components, and you can't really think about that without partnering with Moderna and using mRNA technology. And it's been a fantastic partnership to accelerate HIV vaccine development and clinical testing and to enable delivery of membrane-bound trimers, which is another sort of a technical thing, the way the Spikevax works, is with the spike delivered on the membrane-bound trimer and that's very helpful. In our field, we believe that, that's really in HIV, we believe that's very helpful, too. And it's much more difficult with protein vaccination to try to do that kind of thing. So there's a little technical enablement there as well. And so we do envision connecting multiple Phase I studies over the next 5 to 7 years until we converge on potentially protective vaccine that merits advancement to Phase II.

So to start, we're with Moderna -- in partnership with Moderna, we're conducting 3 Phase I trials testing Moderna mRNA for HIV vaccine development. And the first trial is IAVI G002. It's falling on to the trial I just talked about. And this is the 1 I'll talk -- I'll show you data for today. And that is testing this GT8 prime, which is the nanoparticle at the bottom on the left, the same molecule that we tested in IAVI G001 as a protein, now we're delivering it with Moderna mRNA. And we're testing it. We want to know will it do the same thing or better at U.S. sites. We're also following that with a heterologous boost to ask, okay, if the prime works as we hope it will, can we test the next step in our strategy? Can we advance the maturation of the B cells further, like we say we are intending to do.

And so that's happening now. IAVI G003 is testing the prime, the GT8 prime in Rwanda and South Africa, where a vaccine is most needed. And then HVTN 302 is testing an entirely different set of molecules, native like trimers, sort of very analogous to Spikevax. And in that case, we're testing different ways to deliver HIV spikes not to induce bNAbs right now, but just understand when we need to deploy those in our sequences for our vaccine, what's the best way to do it, soluble or membrane bound or with the modification that we think might help immunogenicity. So I'm going to focus on G002 today. So here's the study design. It has 4 groups.

The first group is basically a repeat of IAVI G001, but now it's with RNA. We get 2 shots, 1 at week 0 and 1 at week 8. The second group is now looking at, can we give a heterologous prime boost? So in group 2, you get 1 shot of the prime and then the second shot is this heterologous boost, this core nanoparticle. The third group is you get 2 shots of the prime, followed by 1 shot of the heterologous boost. And that's really motivated because in our prior clinical study, we made -- we induced VRC01 class bNAb responses and we made lots of antibodies that were VRC on class at different time points, and we saw more mutation and higher affinities in the antibodies induced by 2 shots of the prime compared by 1 and so we -- it could be that we need to give 2 shots of the prime in order to get the most -- to prime a set of B cells most effectively in order for the heterologous boost to work.

So comparing 2 and 3, we're really excited about that. And then group 4 is basically a control. If the booster immunogen itself can induce VRC01 class antibodies, it would be better off. It doesn't in preclinical model, so we don't think it will hear, but it will help us interpret the results. So the aims of the trial are to evaluate the safety and reactogenicity of the vaccines. To test the GT8 60mer priming immunogen, will mRNA generate VRC01-class responses as in G001. And when I say VRC01 class, that's this 1 class of broadly-utilizing anybody that we're going for in this trial. And then the third point is, will the heterologous boost, the core boost, will it generate increased maturation toward bNAbs and I don't have data on that today.

So just for the enrollment and safety update, we -- it's fully enrolled. We have slightly over enrolled. All study vaccinations are completed. For local and systemic reactogenicity, we see them in almost all the participants, mainly mild and moderate, as you would expect for an immunogenic human vaccine. There have been no serious adverse events, no adverse events of special interest. No study discontinuations and no pause criteria triggered. So all good. We do see adverse events of the skin reactions, pruritus, urticaria and/or angioedema in 11 of the participants, 18% of the participants following 1 or 2 doses of the prime or 1 dose of the boost. The rash is delayed and generalized in distribution. It's not the injection site. It's persistent in several cases, but predominantly managed with oral antihistamines.

It's mostly mild or moderate in severity. No anaphylaxis reported. 4 participants discontinued vaccinations due to the adverse event but continuous safety follow-up. And we're conducting an ongoing evaluation of these adverse events, including consultation with external Allergy and Immunology experts and we're planning additional investigations to understand potential mechanisms. So for the -- I've just got a couple of data slides on the immune responses that we think are quite exciting. So first, just serum antibody binding responses. I've given you another image of what the vaccine looks like there on the left. It's a self-assembling nanoparticle. And it's the same nanoparticle that we delivered as a protein in IAVI G001.

And this assay is a validated assay. So we've plotted serum antibody data from both clinical trials on the same graph, which is allowed by the statisticians. And you can see the data in blue -- and what I'm showing you are serum antibody binding to the monomer, the GT8 monomer.

So it's 1 monomer out of the 60 copies that are present on the nanoparticle and you can see the data in blue are from G001, we've combined data from high and low dose because they sort of cluster all together. And you can see the data from G002 are consistently higher in terms of serum antibody binding responses at week 2, 4 or 8 after just 1 shot of this vaccine. And so very encouraging. This is, I think, the first human data from a self-assemble nanoparticle delivered by RNA. It was -- I think Stephane said the RNA technology allows delivery of these complex antigens. So this would be another example. It's pretty nontrivial though from the antigen standpoint, in the human clinical -- in the first clinical trial we made protein.

We went through a laborious process to purify the nanoparticles and make sure they were -- what we actually injected as a vaccine, we're very well -- well-assembled complete 60mer nanoparticles. And with RNA, you don't purify, you give the RNA and you rely on the amino acid sequence, the mRNA to translate into amino acid sequence that will self-assemble on its own. And this works in preclinical models, but it's very comforting to see up in humans, you get these stronger responses, which it doesn't prove that it's self-assembling like a 60mer, but it's strongly indicative that we didn't need purification, the RNA just generates the nanoparticles like we want it.

And you can imagine this as a -- although eOD-GT8 is not going to induce bNAbs by itself, it's not even going to induce neutralizing antibodies by itself. For a different virus, you could imagine making a nanoparticle whose job would be to actually induce neutralizing antibodies and the fact that you can use Moderna mRNA to generate self-assembly nanoparticles in humans and induce very high serum and at least antibody binding titers, I think is very encouraging as a general thinking of it as a general model antigen. And that data, sorry, and I'd really like to thank the people responsible for that data, Georgia Tomaras' lab at Duke and Amanda and Allen at the Fred Hutch for VISC.

And so the main aim of the study is to find out, well, does the mRNA version of this immunogen induce VRC01-class memory B cells in blood? That's what we -- that was the big readout in G001. So we want to know in G002 and the answer is, yes, it does. And what I'm plotting for you here in this graph on the Y-axis is the percent of IgG positive memory B cells in a person's blood that are VRC01 class, and we measure that through B cell sorting and sequencing the receptors on those B cells and doing a lot of bioinformatics after that. And this data is generated from our collaborators with the VRC and also Jordan Willis working with me at IAVI and Scripps. And you can see, although the exact technical details of the assays used in G001 and G002 are not the same, the readout is intended to be the same.

So we're plotting it on the same graph. And you can see, again, the data in blue from G001 was -- is exciting all by itself. It was groundbreaking 2 months ago, and you can see what we get from G002 is like at week 8, it's about sevenfold higher VRC01-class memory B cell responses, which is fantastic. And so clearly, 100 micrograms of RNA is performing extremely well compared to protein plus AS01B adjuvant. And I would say, in the way we think about it, we'd like to immunize sort of every 8 weeks. We like 8 weeks as it gives the germinal centers time to run and generate mutation. So week 8 is sort of the time point we think about. And in group 2, we're boosting with core at week 8. So that's -- this is the population of B cells that are -- that need to be triggered by core. We talked about somatic hypermutation. We need the vaccine to induce somatic hypermutation to make bNAbs. From the prime, we don't expect a whole lot of somatic hypermutation, but we want to see some.

And what I'm showing you here are for the VRC01-class memory B cells that we've isolated at weeks 4 and week 8 in the 2 trials, how mutated is the heavy chain V gene, which in this particular kind of response is extremely important. And you can see at week 8, which is the important time point here, the antibody, the B cells responding to RNA have at least as much mutation as they did responding to protein plus AS01B, which is a super strong adjuvant and maybe more. It looks possibly like the G002 and I don't think it's statistically significant, and I haven't tried to do that here, but it certainly isn't worse. So that's also very encouraging. And finally, a key readout is if you make the antibodies, how well do they bind. And so we did that a lot in G001, and we're doing that.

We've started to do that for G002. For G002, we've only made antibodies from the first 6 participants. So this is limited data. On this graph, I'm plotting on the Y-axis, the association constant. So lower numbers are titer binding. And you can see at week 8, the distribution, the median is certainly a lot better for G002 than it was for G001. So if anything, maybe there's the same, but it looks like the affinities going along with potentially higher mutation, it looks like the affinities might be higher. And so preliminary conclusions and next steps from the IAVI G002, RNA vaccination induced stronger serum antibody responses compared to historical data from G001 protein and AS01B immunization.

GT8 mRNA induced stronger VRC01-class memory B cell responses compared to G001, although there were differences in laboratory methods that could contribute to those differences. If anything, the methods in G002 are just more efficient at recovering sequences. VRC01-class memory B cell responses induced by GT8 mRNA have higher or similar SHM, somatic hypermutation and affinities at week 8 compared to G001. And so overall, mRNA delivery of this priming immunogen appears promising for HIV vaccine development, but we have to deal with the dermatologic adverse events. We need to better understand them and the implications of potential mitigation strategies. The next step in this trial is to determine if the heterologous boost increase maturation toward bNAb, as I explained, and we're excited to get there.

We don't have any data on that yet, but we should be getting it on the next like 6 months. And the next step for this priming immunogen delivered as RNA, we think, is to test lower doses to see if we can decrease the adverse events while retaining sufficient bNAb precursor priming. And I've shown you that as far as immunogenicity as far as the signal we were looking for, it's a lot stronger than it was in G001. So we feel like there's room to dial down the immunogenicity a bit by lowering the dose, potentially eliminating the adverse events and still having as strong priming as we got in G001, which we thought was good enough already. So we're really excited to be in this position and to move forward. And finally, I would just say, as I mentioned, I think this is the first human data on mRNA delivery of a self-assembling nanoparticle.

That's a general technology that the field has shown can induce much stronger responses than monomers or smaller oligomers. And so I think it's encouraging overall that we could use this technology for vaccines in general. And I'd like to thank all the partners involved, there's many partners involved in all these studies, but particularly IAVI, Scripps, NIAID, the Gates Foundation, the HIV Vaccine Trials Network, Vaccine Research Center and Duke. And there's obviously tons of people involved in these -- in this work. And I'd just really like to thank Jordan Willis for making the immunogenicity slides that I showed, Georgia Tomaras' lab at Duke and the team and Sarah Andrews' team at the VRC for doing all the B cell sorting and sequencing that allowed me to show this data today, and I'll stop there. And Jackie's next emerging programs.

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

Okay. So the last portion of the scientific part of the morning is to talk about some of our newer programs that are emerging towards the clinic. And what's really exciting about these programs is that they're actually in a new space from where we are. So I hope I've convinced you this morning that our respiratory portfolio and our latent virus portfolio are really maturing and moving assets towards Phase III and hopefully potentially licensure.

But we're looking at other ways in the Infectious Disease space that this technology could make an impact. So one place that we're looking are in the enteric viruses. And my background is actually as a pediatrician and I can tell you every winter, 2 out of 3 kids, they either have a respiratory infection in hospital or they have gastroenteritis in hospital. So this is kind of a natural progression for our pipeline given some of the successes that we've seen in the respiratory space. Then, bacterial pathogens are obviously another scourge and while COVID has kind of trained us to think about the viral apocalypse as part of pandemics.

Actually, in a normal setting, it's really the bacteria that land patients in the intensive care units. And just like viruses, our proteins with an envelope, bacteria also produce a lot of proteins for their biology. So we're interested to see what we can target there as well. So enteric vaccines. They multiply locally in the intestinal tract. The analogy with respiratory vaccines as they replicate locally in the respiratory tract.

And unlike respiratory vaccine, enteric vaccines follow a fecal oral route. And what does that mean? That means if you're not washing your hands very well and you touch a surface and then touch your mouth or other mucus membranes, that's how it spreads. So you can imagine especially if there are little kids around who are kind of teething and drooling over everything, spreads like wildfire through houses and other kinds of settings like daycares and schools, and at the other end of the age spectrum also can spread like wildfire in nursing home settings.

Norovirus is a leading cause of acute gastroenteritis, and it results in significant morbidity and mortality worldwide. Again, it really impacts the 2 extremes of the age spectrum, and that's because newborns haven't yet developed their full immunologic potential and older adults, as you saw on earlier slides, begin to lose it over time. So we have been able actually to demonstrate you can prevent gastroenteritis due to viruses. And rotavirus vaccines are the big example of that. So we're looking now to broaden coverage with another important cause of gastroenteritis.

So it's associated with about 18% of the overall cases of gastroenteritis worldwide. And I mentioned to you that it's really impactful in very young children, older adults and then also in the immunocompromised. So just like with respiratory pathogens, the immunocompromised population has a hard time clearing these infections and can also suffer from more severe disease. And the burden in older adults is expected to rise over time. Again, a society ages and more and more people are in group living settings.

So what does that mean just in terms of the numbers, in terms of infections, and I'll talk about the U.S., but you can see the numbers globally as well. There are 20 million infections in the U.S. and nearing 700 million infections of norovirus globally each year. In the U.S., there are approximately 900 deaths and 100,000 hospitalizations with \$2 billion of associated health care costs. And that translates to about 200,000 deaths that we know of worldwide and about half of those occur in children because they dehydrate so easily and \$60 billion worldwide in terms of health care costs.

So why -- if it's such an important health consideration, why don't we have a vaccine already? Well, this is a complicated virus. It is classified into 10 genogroups and then 49 genotypes. And so like Dr. Schief was explaining to you for HIV given the diversity of the pathogen like we've seen with COVID, given the diversity of the pathogen, one of the challenges is making a vaccine that's going to cover enough of the serotypes, which by the way, they change over time.

So you see where I'm going with this, again, proof of concept with COVID and the ability to change strains and follow viral evolution over time. We hope to protect about 70% to 80% of norovirus associated acute gastroenteritis in young children and older adults. And to do that, we are going to need a multivalent vaccine because these genotypes really vary worldwide. So you just heard a bit about some of our proof-of-concept data in the HIV space with virus-like particles.

We also have a vaccine in Phase II development, our Zika virus vaccine, which is made through delivering a sequence that translates into a protein chain that self-assembles into secreted virus-like particles. So that's what we're going to do with our norovirus vaccine. They're structurally similar to native virions. And that's important. You may have heard a phrase in biology, structure determines functions. So we think if we can get structurally close to a native virion, we can induce an immune response that's close to our response to wild-type infection.

And as we've shown with our COVID program, our platform is actually able to pivot. If the evolution of this virus moves in a different direction, we can change the composition to follow that evolution. So you see that iteration in Update 1, Update 2, Update 3 on the right side of the slide. Okay. So we have 2 vaccine candidates. They're comprising the virus-like particles. And one, we have a trivalent composition, and that's 1403, so get it. It's also followed with 1405, and that's a pentavalent composition.

We're going to test both and see where we can optimally titrate safety as well as immunogenicity looking, of course, for immune interference. And like our respiratory vaccines, we're utilizing exactly the same lipid nanoparticle, again, building off of the platform that we've developed. So shifting gears into bacterial pathogens. We are going to investigate Lyme disease as our first bacterial target. And why? Well, there are 120,000 cases of Lyme disease each year in the U.S. and Europe. And there's currently no approved vaccine on the market.

Our strategy is going to develop 2 vaccine candidates in parallel and I'll explain the strategy why. In the U.S., there's one predominant serotype, serotype 1, but in Europe, there's a diversity of serotypes, ranging from serotype 1 to serotype 7. So if out of the gate, we're successful with a heptavalent or 7 serotype containing vaccine, happy days. That's the vaccine we'll develop for both the U.S. and Europe. If, on the other hand, there are some immune interference issues we need to work through, we can still move forward with a monovalent vaccine in the U.S.

And so maybe just to say the reason why we're really excited about this bacteria actually much more complex than viruses. They contain many more antigens. They have a cell nucleus. It actually though allows us maybe multiple targets that you can pursue. We happen to know the target in Lyme disease, the outer surface protein A could lead to an effective immune response. And so that's really also behind our choice of Lyme disease. So let's see if we can develop an approach to address all Lyme disease in U.S. and Europe.

The infection follows a bimodal age distribution again. It's mainly in children and older adults. There are about 35 cases per year in the U.S. and 85,000 cases in Europe. And this infection is known as one of the great pretenders. It can produce a rash. It's the classic target rash, although and we'll say many patients can have different kinds of rashes. It's very easily mistaken for other entities. And they have this sort of syndrome where they develop fever, headaches, fatigue, and they can get an arthritis with joint pain and swelling and headaches.

Longer term, if untreated, this infection can lead to some pretty significant cardiac dysfunction. So I mentioned to you the different serotypes. We have developed 7 sequences of the outer surface protein. We know that the serotype one would cover almost all of the infection in the U.S. But ideally, we can use the same vaccine in both the U.S. and Europe. We know that in the past, A-based vaccines have led to the induction of high levels of neutralizing antibody levels.

So the way it works is you inject the human who develops the antibodies when the tick bites the human and begins its blood meal. Actually, the antibodies are able to kill the bacteria in the tick's cut. So the tick actually is essentially getting passively immunized from the human being that we've vaccinated.

So with that summary and teaser of things to come, I'm going to hand the floor over now to Arpa Garay, our Chief Commercial Officer, who's going to talk about commercial opportunities with vaccines.

Arpa Garay - Moderna, Inc. - Chief Commercial Officer

Good morning. As Jackie mentioned, I'm going to give the commercial overview of how we believe all of the vaccines in our portfolio will translate into commercialization. Okay. So you heard this morning about the significant unmet needs across all these different disease areas as well as the health care burden associated with them.

As a result, from a commercial perspective, we believe our portfolio addresses large target markets. If we start with the respiratory vaccines and looking just at flu, RSV, COVID and our combinations, we believe this portfolio will grow to about \$30 billion a year. And then from a latent vaccines perspective, if you look at the vaccines that we have in our portfolio, we believe they will play in the \$10 billion to \$25 billion addressable target market. And then from an emerging vaccines portfolio, as Stephane mentioned, there still is significant unmet needs when it comes to infectious diseases.

And as Jackie just covered, some examples of our emerging portfolio, we believe our future vaccines will address important target markets going forward. Sorry about that. So as we think about just the next 2 to 3 years or 3 to 4 years, in fact, you see we have multiple potential vaccine launches. So next year, we do anticipate RSV to be launching around the world. We also expect to have a seasonal flu vaccine.

In 2025 is when we believe our combination vaccine portfolio will start launching around the world as well as our next-generation COVID vaccines that Jackie mentioned. As we go beyond 2026 and into 2027, we do believe our next-generation influenza vaccines as well as combination vaccine and our CMV vaccines will come to the market. Sorry, I've something stuck in my throat. So as we look specifically at the respiratory vaccines market, we believe 2023 as COVID enters an endemic stage will be the reset year going forward.

And in 2024 and beyond is where we believe the COVID market will continue to grow. As we look at 2023 as well as 2024, there's multiple variables that are really impacting the volume that we're expecting in the endemic market. First and foremost, it will be the medical need associated with viral evolution. So what are the continued sort of healthcare burdens around the world as well as associated public health recommendations. So what do we expect from different (inaudible), public health authorities in terms of vaccination recommendations. And last but not least, which we're seeing quite significantly right now is consumer motivation to vaccinate.

We have seen over the last several months, a lot of COVID fatigue from our consumers. But as you know from a health care burden perspective, we are seeing even in the most recent fall/winter season of COVID, we're seeing almost actually more than double hospitalizations coming from COVID than from flu. So as consumers continue to get educated about the disease burden and as different health authorities around the world continue to update their recommendations, we believe 2023 will be a reset year and then growth will come beyond that. From a global market perspective, the way we're estimating the total addressable market for COVID is really based on 2 key factors. First and foremost is really looking at flu as a surrogate specifically in the elder population. So the 50 to 65 as well as 65-plus, where we believe over time, the vaccination rates will approach flu vaccination rates.

For those who are younger in age, we are seeing lower uptakes and believe over time, the younger population will not fully reach the same level as the flu vaccine. But given the health care burden and the number of hospitalizations, we are -- we do believe, from a price effectiveness perspective, the pricing of the COVID vaccines will be at a premium to flu, resulting in about \$15 billion total addressable market going forward.

From an RSV perspective, we are very excited about the data that Christi shared. External estimates approximate the RSV market to be about \$10 billion in the future and you'll see about \$6 billion to \$8 billion of that total addressable market is coming from the older adult population which is the data that we shared today. Over time, as we think about where the significant unmet need is, we do believe there is significant unmet need in the pediatric populations.

And as we continue to grow our portfolio and our indications, that is where we believe the commercial market will expand. As Christi mentioned, we do have the unique opportunity to have 1 platform and 1 vaccine covering the entire spectrum of the population. From a flu perspective, this is, again, another opportunity from a respiratory perspective, where the current influenza vaccine market is about \$6 billion. If you look at the chart on the right, what you'll see is the enhanced flu vaccines as they brought to the market, increased effectiveness. They have driven significant growth for the overall flu market.

Over time, with the introduction of newer and more effective flu vaccines, we do believe this market will grow to about \$9 billion. So again, the introduction of new, more effective vaccines as well as in the future of combination vaccines will allow us to get to that \$9 billion total market for flu.

From an overall volume perspective, what we have seen over the last several years, is globally, we're seeing about 500 million to 600 million doses. As we think about combinations that we've talked about today, we can bring increased value to health care systems, increase compliance rates, increase consumer convenience as well as potential increased effectiveness of flu vaccines, which will grow the overall volume of the market in the future.

From a latent vaccine perspective, what you'll see here is we have a number of latent vaccine candidates that we believe individually, all address very large addressable markets. From a latent vaccine perspective was different here versus respiratory is we are targeting viruses that have very big and long-term consequences from lymphomas to multiple sclerosis, as Jackie and team have covered. And these different areas as you'll see from the right-hand side, examples for both Gardasil and Shingrix have opportunities for multibillion-dollar franchises.

So 2 things to note here, you'll see not only the multibillion-dollar franchise opportunity, but also as you look at latent vaccines, they do have continued growth over time. So in the example of Gardasil, which launched in about 2006, we still continue to see that franchise grow as the market understands the long-term benefits of addressing latent vaccines.

So just to look at CMV for a moment since we're in Phase III for CMV. CMV, we do have the opportunity to be first in the market. Again, here, we expect the market to grow to about \$2 billion to \$5 billion annually. We will start with the high-risk populations that Jackie had mentioned around women of childbearing age as well as transplant patients but over time, as we think about the potential for eradication, similar to the rubella approach to eradication as we grow beyond the adult population into adolescents and into younger populations, this is a real opportunity for us to eradicate CMV.

So in summary, as you think about -- as we think about respiratory as well as latent, we believe our portfolio targets large addressable markets. The respiratory franchise, we believe will be significant and add more of an annual seasonal basis. From a latent vaccines perspective, we do expect that to be more of a long-term growth with multiple multibillion-dollar opportunities. And as we think about launch readiness and getting ready for the commercial opportunities and bringing about 7 new launches over the next couple of years, we will have the opportunity to build on our existing commercial and medical infrastructure to be able to launch these successfully around the world. So with that, I'm going to ask Jamey, our Chief Financial Officer, to come up. Thank you.

James M. Mock - Moderna, Inc. - CFO

Well, good morning, everyone. We're coming up on good afternoon. And thank you for joining us today, either live and in person or on our webcast. I know we've been going at it for a little over 2 hours. So I'll wrap this up here before handing it over to Stephane for some closing remarks. So as all the speakers have noted today, vaccines play an incredible purpose for patients in the health care system as well as the overall economy. They can save lives, reduce morbidity, save health care costs, increase the economic output for an individual or an economy at large. And so that's all wonderful, but I am the CFO, so I'll walk through the business side of things as well, which I'm here to tell you that the vaccines business is an incredible business model.

We'll walk you through -- I'll walk you through what those characteristics look like for us and why we think we are well poised to take advantage of the vaccines market. And then we'll lay out why we think we have a great return on investment. So we'll walk you through our investment strategy over the coming 2 or 3 years. And then we'll try to give you a little bit of a lens to what the return might look like, come 2027 as it pertains to our respiratory franchise only to show you that return on investment.

So I think COVID is a great place to start, both from an example from an ROI perspective as well as what the themes are when we look at the vaccines business. And as most of you know, even before the pandemic hit in early 2020, Moderna invested over \$2 billion in our platform. Combined with the \$4 billion that we invested over the last 2 years, both in development costs as well as capital expenditures, that led to a terrific economic return. So you can see that we've sold over \$36 billion in product sales over the last couple of years. And then we generated more than \$18 billion in cash, but just to give you a simple data point that you can tie to. We have over \$18 billion in cash for future franchise investment at the end of 2022. As importantly, if not more importantly, we delivered well over 1 billion doses to patients across the globe. And not only that, we've set up a long-term tail, unfortunately, for mankind, probably will be around for a very long time.

And fortunately, on the business side of things, though, we believe that, that has a long tail from a revenue perspective. So the key themes you'll hear today is the speed of development of how we brought this to market. How we delivered over 1 billion doses over a period of 2 years. It's not on this page, but that platform cost, I'll talk about in the future will continue to shrink in any single category.

So once you've made the investment in respiratory, as an example, the next vaccines will be cheaper from a platform perspective. Yes, there is substantial development costs, and that's the investment that we're prepared to make, and I'll talk you through today. But after that, it has a phenomenal return and a long tail from a revenue perspective and that's what we really want to hammer on today, and I'll walk you through. So when we think about any vaccine or any opportunity, we think about 3 things, and I'll use what we hope to be our next commercial product, RSV as an example, as I walk you through.

First, we think our platform can demonstrate very high efficacy. And in the case of RSV, we achieved 83.7% in lower respiratory tract disease as the team walked you through today for 2 or more symptoms. We want a large addressable market and serve a large addressable market. And in the case of RSV, we think just for older adults, that \$6 billion to \$8 billion, if you add maternal and pediatrics, that's another \$2 billion to \$4 billion, so you get to a roughly \$10 billion market overall.

And then it's very -- as I already mentioned, it's a very durable -- we don't think RSV is going away either. So then once you've made that development investment, we believe that we have a very long tail of revenue and we believe our peak sales will be in the \$2 billion to \$3 billion range for RSV. And we believe that our platform has inherent benefits that we will help us capture the vaccines business and help us perform well. And Stephane and Stephen walked us through today, Stephen mentioned the speed of development. So if you look at the big 3 in respiratory, as we call them, as Jackie mentioned, it's anywhere between 1 to 2 years that we can bring a Phase I product through Phase III readout.

We talked about flexible manufacturing. I'll elaborate on that a little bit more. Steven mentioned how the heart of our internal manufacturing is in Norwood, Massachusetts. And then we've broken ground in 3 countries across the globe. So we now will have 4 sites across the globe. And we've invested over \$900 million to date. There is more to invest, but by the end of 2025, we think that our manufacturing footprint for the respiratory franchise will be permanently set.

And externally, we've invested -- we have 5 partners who have delivered for us in the last 2 years, all across the globe, and we've invested over \$600 million in them as well. So we feel well set up. We talked about high biological fidelity and the ability to do combination vaccines. So let me

just elaborate that on that a little bit more. So when we think about one shot having two or more vaccines, I think there's 2 substantial benefits that can come from that. On the left-hand side of the page, we think that could expand the market for many reasons. But if you use flu as a proxy, there's 500 to 600 million doses per year and a \$6 billion TAM. If we have everything in one shot, then I think there's 3 ways that it could expand.

One, it's better for payers and more effective and good for the overall health care system from a cost perspective. I think it's an easier administration for patients. And then if there's one or more that are highly effective, then I think you'll expand the overall reach of combination vaccines, and that \$500 million to \$600 million could grow to \$700 million, it could go to \$800 million and so on and so forth. So we believe the market could expand. Subject to regulatory approvals, we believe that our investment in a combination vaccine could be cheaper than a single vaccine.

And so that's through immune bridging studies as opposed to having to do a more expensive efficacy study. To prove a vaccine, we think we can do a mute bridging to the standard dose. Lastly, I added a fourth benefit to this, and I call it category investment, and this is what I mentioned earlier. So we have invested a lot in our platform to date. And you can see until 2020, we invested a little over \$2 billion. In the last 4 years, combined for infectious disease overall, not just respiratory, we've invested \$400 million. So I think for that category, our continued research on the platform side will go down. Development costs will be there, and I'll walk you through that on the next page. But overall, you can pull from what we've built in the overall platform to date when you look at a new candidate.

So this is the investment that we want to lay out, particularly on the R&D side. I already mentioned the capital expenditure side. This rounds it out. This is a much more substantial driver of investment for the next 3 years. And we have more to do to round out our respiratory franchise. We've invested a lot in COVID. We've invested a lot in RSV and in flu, but you'll see here a few things. One is the future investment options on the bottom, which we believe total \$6 billion to \$8 billion for the years '23 through '25, maybe some of this trickles into 2026. But I think more importantly, you see the spend drivers. You can say COVID and how it peaked in 2022, and then we'll do 1283 in 2023, and then it will become a nominal amount in terms of the priority you spend.

Take RSV. RSV, we began and completed our first Phase III trial in 2022. It will now go up in 2023 as we look at duration and boosting as we look at maternal, as we look at pediatrics, everything we've talked about to round out the RSV portfolio. But then in 2024, it will go down and then 2025, it will be the #3 spend driver, and then you can see it go away because the investment hasn't made. And then the same is true for flu. And then the same will be true for combinations, and then we'll get into next-generation vaccines.

So I think it's this concept that you have to invest early, which we did on COVID, we will on RSV, we will on flu. And then after that, you have a long recurring revenue stream that is here for years to come. And so if you look at 2023, for just the respiratory budget, we've already said that our overall R&D is \$4.5 billion. If you look at respiratory, that makes up the lion's share of it. It's about 60% of it. It's \$2.5 billion. And then so we think that will be relatively consistent and might be some puts and takes over the next 2 or 3 years, but relatively consistent, it will start declining in 2026.

And then by 2027, we really just have a maintenance amount of R&D expense. And we actually can't even assume a dollar to that. We put it as a percent of revenue, which I'll walk you through on the next page that depending upon the size of the P&L, you have more or less to invest in it, but we think 10% of respiratory revenue is where we'll hit in 2027. So COVID was a terrific return, \$6 billion of investment, at least \$18 billion in cash. It definitely generated more than that when you factor in other items. But that's a 3x return just to date, and it has a long franchise. If we look at respiratory, all that investment that I just talked about on the prior page, we want to show what that return can look like come to 2027.

And I'll walk you through the P&L. There's a fairly broad range on revenue on product sales. \$8 billion to \$15 billion, and you can see the drivers on the right. How effective are vaccines? What's the vaccination rate that Arpa just talked about? How quickly will combination shares grow? We think that is a total game changer, as I mentioned, in terms of increasing the market size. And I would say that, that even this \$15 billion, whether it happens in 2027 or beyond that, the market will continue to grow in our opinion for many reasons.

One, the combination I talked about. Two, I think, the global population will continue to grow. The percent of older adults in the overall population grows faster than the overall population growth right now. So that will become other driver. So this isn't an endpoint. The entire market will continue to grow as will we. And as I walk down the P&L, we've already talked about 2023, our COGS are elevated as we move from pandemic to endemic. For many different reasons that we can get into, but this year, we'll be at about 35% to 40%. We think this will settle out at a minimum at 25% COGS or 75% gross profit.

And if we're on the higher end of this range, it's more like 20% COGS and 80% gross profit. And so we feel great about that. I've already talked about R&D being 10% of revenue. So you can kind of back into what SG&A is in either of these scenarios. So overall, that gives us a \$4 billion to \$9 billion overall operating profit with tremendous cash flow generation. And we like the characteristics of this business. It's a leverageable cost base that will be fully invested in by 2025. It's highly flexible from a cost perspective. And then it requires a limited amount of capital. And a reinvestment ratio for those of you that don't know it, is the amount of capital you spend over your depreciation.

And we think ours will be below 0.5x by 2027. So in summary, what I hope you take away is we are hopefully building a terrific respiratory franchise. I think we've already evidenced that in COVID, but the big 3 are next as well as some of the things that Jackie and the team went through today. We believe our platform is extremely well positioned to capture and has inherent benefits that would advantage us versus others. Yes, our -- take some development costs over the next 3 years, and then we try to lay that out for you, but we think the return is well worth it. And that by 2027, this is a substantial franchise that continues to kick off cash and we'll hopefully fund the next franchise beyond respiratory. So with that, I'll turn it over to Stephane for some closing remarks.

Stephane Bancel - Moderna, Inc. - CEO & Director

Thanks, Jamey. Well, Dr. Schief, thank you so much for this exciting presentation. Team, thank you so much for the great presentation. And most importantly, for the work that happens every day at Moderna, you only see the tip of the iceberg and you see how we're excited about it. So I just have 2 slides to close. As you can say, we are so excited to be able to launch up to 6 products in the next few years. Of course, RSV should be the next one, as the team said, we are on track to file the BLA this quarter. And flu, we are very excited about flu. Of course, we'll have hope we made the cases and be able to announce that today. But I hope you got from the great presentation that you got today that the data on the immuno is very exciting. The As are very strong. The Bs, as we shared with you, we know how to fix.

This preapproved study that's going to start very soon is going to able us very quickly (inaudible) to get that data, get single-dose booster to get that immunogenicity data, and we believe we're still on track to the original plan, which has to launch in '24. Even if that have been positive today, we would have missed the fall of '23, so you have to prepare the BLA, file it. If this will view it, go to (inaudible) it will not have happened by September. The math did not work. So we're still on track for a '24 launch, which was the plan. So I was always so excited and then the combos are coming and much more.

The COVID-19 is a great base for us to grow, but as Jamie showed you, as we looked at the data with the teams, country by country, product portfolios, single's combos, pricing, we think there's something really exciting for us to come.

The platform allows us to keep growing in respiratory, in latent, you saw what Jackie presented to you on noroviruses, Lyme and there's much more. Andre and his teams are not standing still. They are working. Jamie should do increased research investment. The infectious disease team is going after a lot of exciting opportunities that we think can have a great impact on patients and as a return, create value for the company and shareholders.

And I think also, Jamie give you a good sense of how this size, we believe after a few years of investment could create very long tail revenues because those respiratory virus are not leaving the planet. I've not seen with several scientists who believe that COVID is going or RSV is going or flu is going. We're going, unfortunately, for us as a species, we to live with those viruses forever.

And as you see the aging of population and you saw massive of a T cell, this is not a good combo for disease. And so we believe the financial characteristics of this respiratory franchise and beyond that of infectious portfolio is really exciting.

We believe Moderna should be a key vaccine player in the next few years and for decades to come.

So I know it's a vaccine there, but I have one slide that is not about vaccine just for micros because this franchise and this platform we've been building for 10-plus years has always been because we believe it's a new tool to go and invent new medicine. It's a new age of medicine enabled by this very exciting platform.

For the first 9 years of Moderna, I went around saying, I believe mRNA will change over the world. And some people have mocked me. Some people call me names in print and in media. Some scientists thought are you crazy? This will never work. And we put our head down and we did the work.

In the spring of 2020, I said, "I believe we'll have a vaccine working by the end of the year." And people call me names, some pharma CEOs went on TV saying it was irresponsible to the world to say that we could have a vaccine approved by the end of the year.

Well, one of the things I would like to tell you today is, I believe, the impact we will have in oncology is going to what a lot of people are going to know us for in 3, 5, 10 years. Some people will forget in 3, 5, 10 years, what we did with COVID, what we're doing every year with a combination vaccine that gather their CVS or other doctors because in fact, I believe this company and this technology is going to be in cancer is going to be so profound. So I can't wait for you guys to see the data at AACR, which is just this weekend, so just a few more days of waiting.

The team is working really hard to get the Phase III for melanoma up and running. And to get with our colleagues at Merck, the lung study up and running again Phase III. And we have many more studies that the teams are working on. As we get that finalized with Merck, we'll share those studies.

But as we've said before, the reason we're increasing so much the R&D budget this year is we believe that the data we have seen in oncology were that investment. We are very pleased to partner with Merck as (inaudible), when you have a great product in oncology, being aggressive investing in clinical studies, phase of -- first for patients and 2 for shareholders. And with this exactly what we're going to do with the personal cancer vaccine.

Rare disease, we continue to stay very excited from what we are seeing in the data. We're now moving to expansion phase of a study on (inaudible) because of the data that we have seen.

Colleagues at Vertex are enrolling as we speak, kids that do not respond to their drug in fibrosis because too many mutation on their genes. We believe on inhaled, which is a new technology, a new way to get them on the body as very interesting proposition for the patients, and we look forward to seeing that data. It should also come pretty quickly because it's in patients. So we should see that data pretty soon.

And then cardiovascular, but not least, the #1 killer in the world. We're in Phase Ib study in heart failure patients. So again, we should be able to get the data on Relxin pretty quickly. And if it's positive, again, we'll be very aggressive on time lines to move very quickly to pivotal studies.

As you've seen with this platform, we can do things quite differently. We have the ability to work the disease that you cannot go with recombinant, what the level of efficacy that is not doable with other technologies.

The speed is to keep increasing. The speed is really amazing, but we are not done. Our team are investing in IT. Our team investing in more tools in robotics in AI. So keep shrinking and shrinking and checking the time because when you take a 5, 10, 20 year view on things, every week you can save is going to have huge value creation for patients and as a consequence, for investors.

So we're very excited about what we are we'd like to do today is to please welcome the team back on stage so that we can take your questions.

QUESTIONS AND ANSWERS

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

It's Michael Yee from Jefferies. Two financial questions, if I may. On the 2027 guidance, if I may. I think a lot of people would ask how the heck you could forecast out to 2027, particularly given COVID? And if I may even push a little harder, people not even a lot of confidence about 2023 COVID and where the numbers are going to. Could you just express your confidence level in 2023 in vaccination rates and what part of COVID is in 2027?

And then on the expense guidance, I think I heard you say \$4.5 billion, which is what you're doing now. Did you imply that \$4.5 billion is sort of the range going forward, and that's where it is? So can you just talk to again where the expense guidance is going? That's critically important because people are trying to figure out profitability over the next 5 years?

James M. Mock - Moderna, Inc. - CFO

Yes. Thanks, Michael. We'll start with the forecast for 2027. Of course, difficult. Of course, 2023 is difficult. But we feel like this is our best estimate right now. And if you walk through what Arpa talked through, the \$30 billion market that we play in is a 2023 number.

So the \$15 billion in COVID, there's obviously some puts and takes that you could say that's \$10 billion to \$20 billion, and we can go through the math on that. But the \$15 billion, we think RSV will be about \$10 billion in total and then flu is \$6 billion. So that's a \$30 billion, and that's today. That will grow over time, as I mentioned, with population, both with inflation, maybe with combinations, et cetera, let's just say it's \$30 billion to \$32 billion.

The low end of that range is about \$0.25 share. And even if you were to knock COVID down, let's say COVID is a \$10 billion marketplace and then RSV is \$10 billion flu is \$5 billion or whatever, that's a 33% share. We feel pretty comfortable. And that's before you get into combinations as well. So that's on the low end.

On the high end, it could be a \$40 billion marketplace. You could say COVID might be \$20 billion. As Arpa mentioned, we believe that 2023 will be a low point, and then it will grow over time. So if it's \$40 billion, then \$8 billion on the low end is 20% share. So we feel very comfortable with our vaccine efficacy, what we have. That 20% to 33% market share is a fair number on the low end.

And then that \$15 billion, as I mentioned in my remarks, that we think that's coming. Will it come in 2027? Can't promise that. We will launch the combination, as we mentioned, in 2025, and that can expand the market and hopefully expand our share. And if our efficacy is there, that we think that we could continue to expand. And so whether that's 2027 or 2028, that P&L we believe a coming to Moderna, so that's that.

On the R&D side. So a separate question on 2023. So we didn't guide anything on 2023. I think we've said on 2023, as you know, is the \$5 billion overall signed APAs and \$2 billion in the first half, which we feel we're still very comfortable with.

And then on top of that, which is often lost because that's not our guidance, our guidance is not \$5 billion. It's just what's contracted. On top of that, what we believe we'll have orders in the United States. We believe we'll have orders in other various countries, including in Japan and Europe, et cetera, that will add on top of that \$5 billion. We're not guiding a number, but we are confident in what we said already.

R&D side. So R&D side, \$4.5 billion overall for 2023, \$2.5 billion is respiratory. We're not guiding '24, '25 around what the total R&D is right now. We're saying that respiratory needs to be at least \$2.5 billion. Obviously, we have a lot of exciting things going on with PCV in rare and other areas. PCV is probably one of the bigger variables or wild cards, I would say. So I would anticipate it to go up, maybe not at the rate that we've been going up, which has been 50% a year, and I'll let Stephane comment more, but that's what I'd say right now. I don't know if you'd add anything else to.

Stephane Bancel - Moderna, Inc. - CEO & Director

And maybe just to add one thing to Jamie's comment on the market sales for combinations. The piece we should not forget in combination is the value being created for the payers because of higher compliance because when a lot of our payers are worried, are people going to get free shot of winter through COVID RSV in that elderly population, which is a key part of the market. And if you talk to the payers, today, they already pay the pharmacists or the doctors cost to inject a vaccine. So when you talk to them and you realize that they are willing to pay a premium trend the sum of the parts because how much we're going to be saving on administration costs.

So we have a value process the cost saving and administration. So when you look at this, there's another element to the market, which is the high case scenario of that bar, which is basically the mix between monos and combos. Clearly, in a high case, there's much more combo mix but a combo,

we believe, has a potential to have much higher pricing. And when you look at plus aging population in that time frame around the world, that's kind of drive that number, and we're very comfortable with these numbers.

Unidentified Analyst

So I want to ask about the PCV, considering that you have the data coming up at AACR. So I'm wondering how much do you think the hazard ratio or clinical benefit can improve past a year? And then related, how much follow-up do you think that you'll need to be able to file for accelerated approval based on the Phase II data? And if that follow-up can come at ASCO or ESMO?

Stephen Hoge - Moderna, Inc. - President

Okay. A couple of questions there. Let me try and pull apart. So we haven't shared the data yet, we will on Sunday about what the shape of those curves will look like. And so I don't want to get too far ahead of that. But a feature of immune therapies are obviously what you want to see is durable benefits and really over time separation of those curves that has, as a feature of it, enriching hazard ratios as data matures. And so that's one thing to look for when we present our data in AACR. Obviously, the 44% reduction in the rate of relapse or death signals that there's a pretty exciting trend there. And we would hope as people look at it, that they'll see that same trend towards strengthening responses are differences over time. But look at the yourselves.

As far as the possibility of accelerated approval, it's really too early to go into those sort of speculations. At this point, we are still following that Phase II study ourselves.

We are working hard to start a Phase III study because in the current environment, we do believe we have an obligation to demonstrate that we're working hard towards enrolling that Phase III study before you'd even approach and as that kind of question. And so that's where we're focused with our partner, Merck right now, get that Phase III confirmatory study up and running.

And then as we follow over subsequent analysis, whether they're in June, as suggested or as we move through to R&D a towards the end of the year, will really event-driven basis. And so we'll know when we hit certain milestones in terms of the number of that it's appropriate time to conduct that analysis and provide updates. Obviously, our fingers are crossed that we'll see continuing deepening of those responses and ultimately, even more compelling data.

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

Ed Tenthoff Piper Sandler. So I have two, if I may. Firstly, picking back up on Michael's. When it comes to the negotiations that are ongoing for Spikevax in COVID this year, how big of a factor is this speed or this speed to be able to produce vaccine. So do we think maybe market shares can change from what we kind of saw before as it becomes a negotiated market?

And then I do have a question for Dr. Schief if I may as well.

Stephane Bancel - Moderna, Inc. - CEO & Director

Sure. So I'll take this one on timing. I think, thank you. As you heard from the [VA Park] meeting, it seems that the agency is going to do a strength election to end of May, early June versus as Jackie reminded you, was June 28 in 2022. And with our June 28 date, we were still in pharmacies, the Labor Day weekend, which is like a 2-month time frame to develop the vaccine.

So I think what the buyers are expecting through our association right now is that we'll be able to deliver the same thing and it will be for Labor Day, which is what they need so that people at high risk can get vaccinated as they come out of the summer. I think that's what the market expects, which I think is a position that's only the mRNA technology enables. So think about where the market is going and then it's something about

combination or you can do the same for flu and wait much later in the season to be able as Stephen and Jackie talked about is customizing product potential markets or regions because we can do that. (inaudible) on the plant that we're building in the U.K. is the U.K. wants a different strain than the U.S. strain. They can't tell us that's what we want, and we can still in the summer based on AP going on in the U.K. and the surveillance they're doing, get that data for them.

So we think that this ability to grow fast. And if you look at the OriCiro acquisition we made in Japan over Christmas, we think we can even shrink that time lines in a few years when we get that for the GMP setting and through the regulators in terms of changing the manufacturing process to shrink that even further, which I think will allow us to keep the leadership there and to really keep this combination product really as an mRNA only opportunity.

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

Yes, that's really helpful. I appreciate it. And Dr. Schief, if I may ask you a question, I really appreciate the work that you're doing and that was cool early data, the thoughtfulness and the progression of how you're going here. I'm wondering that as you achieve broadly neutralizing antibody proof-of-concept with the mRNA vaccines, including lower doses as you're doing now, how do you really interrogate these multiple antibody classes simultaneously or in combination? It really becomes sort of additive approach, I guess, in this combination. So is there a way to do that in order to maximize vaccine efficacy? How do you envision doing that?

William Schief

Yes. Thank you. Okay. Thank you for that question. Yes. So one, the nice thing about the strategy, as I was saying, is that we're looking for specific sets of genes. I mean, we're looking, we know what the antibodies look like, so if we just sequence the B-cell receptors at any stage, even if it's a combination, we can see we got VRC01 class, we have BG, we have 10 different things. So there, we can evaluate the combination.

But also, we will hopefully be able to do it at a serological level. So if we start to get bnAbs and we start to see broad neutralization against panels of viruses from [Sierra], we know what certain classes, we know sort of the strains that they neutralize so you can get a fingerprint for a certain class. And you could see -- if you're getting 3 different ones, you should see the combination of those fingerprints in the indiscernible. So there are several different ways to tell. Thank you.

Lisa A. Walter - RBC Capital Markets, Research Division - Senior Associate

Lisa Walter here, on for Luca Issi, RBC. just a question for you on flu data today. Can you clarify whether the interim look for efficacy for flu was first superiority or non-inferiority? And if it was for noninferiority, how do we rationalize that? You did hit on superiority for immunogenicity for the strain A in both the northern and southern hemisphere, but that is not translating to at least a non-inferiority efficacy at the first interim look.

Stephen Hoge - Moderna, Inc. - President

That's great clarification. So first, the study was designed as a non-inferiority efficacy study, and so that's what we're looking for. But the first interim analysis of efficacy wasn't -- was a bit of an early look, right? So it wasn't powered with a full number of cases that you will have in the final analysis. And as a result of that, you see -- leave yourself sort of looking to see whether or not there's evidence of really superiority early.

In fact, in order to hit non-inferiority at that early lower case number, the point estimate for efficacy would have had to have been trending towards superior, almost 20%. And that's something you'll do just to see as an early look as to whether or not we've demonstrated non-inferior efficacy technically but because the vaccine was performing even better than we thought.

Given that we didn't see that in this event because ultimately, as we've talked about with 1010, it is targeting a non-inferiority profile against quadrivalent right now, we'll proceed to that second instance or the follow-up efficacy analysis at the end of season with more cases and see whether or not we achieve the more appropriately powered end point of non-inferior efficacy.

Now as it relates to the neutralizing titers, there's a version of the same answer, which is, again, because we were looking at a very small number of cases in that first interim analysis, ultimately, we believe the study was underpowered to really provide a clear signal on the performance of 1010 as a vaccine relative to a license comparator.

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

Go ahead. Sorry, might be way (inaudible).

Stephen Hoge - Moderna, Inc. - President

You might work the microphone.

Lisa A. Walter - RBC Capital Markets, Research Division - Senior Associate

Just for the next interim cut, is there a set number of cases that you need to hit?

Stephen Hoge - Moderna, Inc. - President

At this point, we expect to do an end-of-season analysis and of flu season. And so we don't have a specific number of cases that we expect to hit, and then the study itself would be put power to go up more towards 400 cases in the future if we choose to continue it. But again, right now, we're looking for an end of seasonality for this current season.

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

This is Elizabeth Webster from Goldman Sachs from Salveen's team. question on Study P303, when may we see the first data here. And then if you could remind us of the specific updates made to the candidate versus the original 1010. And then on your work around classifying how differences in the immunization history of the study populations could have contributed to differences in responses. Does this imply that there might be some level of priming required? Just wanted to get your thoughts on that.

Stephen Hoge - Moderna, Inc. - President

Good questions, El. I'll, maybe I'll kick to Jackie on the P303 immuno study. But I'll just say, first, we haven't disclosed for competitive reasons, what the updates are to the 1010 product. But we do have a degree of confidence, a good degree of confidence, as we said previously, that it will achieve non-inferiority and actually will improve upon the B strain we've seen. And in fact, if you look at the data that Raffael summarized, even in the P302 study, we were seeing titers that were consistent with non-inferiority against B. So we're improving on a good base. Do you want to give a sense of the P303 study and...

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

Sure.

Stephen Hoge - Moderna, Inc. - President

I don't know if you're on.

Stephane Bancel - Moderna, Inc. - CEO & Director

Just check on.

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

But I can project. I've been holding back a little bit. So the P303 study actually is designed very much like the P301 study. The thing about influenza is that the vaccines have been with us for a while, and the regulatory agencies have issued very clear guidance about what you need to do to qualify for different regulatory paths of approval. So you'll see data analysis come out of that study that look really similar to what you've seen from P301. And in fact, when we published the detailed P302 immunogenicity data, they look very similar as well.

And then you were asking about priming and about whether that could be playing a role. So I think that's a bit of the story that Rafael was telling this morning.

Any time you see results that you didn't expect, the first thing you do is dig deeper and try to understand why you're seeing what you're seeing. And we noticed right away that the population in Australia was very different than the other Latin American populations. And there are a number of reasons for that. But one reason is that in Australia, you're more likely to have gotten a previous seasonal flu vaccine. But again, flu vaccines change yearly over time. So these specific strains can have an impact.

As Stephen mentioned, there are some upgrades to the vaccine that we're not going to discuss today, but that may also impact in the future. And then I'm fond of saying that people are complicated. This comes from working on the [D] side of R&D. So in research, we work with mice. We tell them who to breathe -- I mean there's not a lot of variability in those mice we use. People on the other hand, do all kinds of things out in the wild. And we often see results that you have to dig into a little bit more. So priming may be part of it, but there's also a possibility that that's not all of it.

Stephen Hoge - Moderna, Inc. - President

If I could just build on the P303 question too, just a little bit. So Jackie pointed to, but for those who aren't familiar with those details, that was a study run last year. P303, the immuno study is really an immunogenicity study, right? So we're going to be looking as a primary end point at day 29 or 1 month after boost with a flu vaccine. And so that is data, even in the case of the P301 that Jackie was referencing, that was a study that really enrolled mostly in July and August of last year. And we were looking at the full 6 month, the data at the end of the year, that year, the immunity results.

We're doing this a little bit earlier in the year. And actually, we're going to be looking at a relatively early time point that day 29 end point, so we think that there's a possibility that we'll be looking at that immunogenicity data, we would hope in the fall of this year or towards the end of this year.

And that's why we have some confidence that if we see what we expect, in fact, if we see what we just saw in the P302 study, that, that would support an approach for accelerated approval following the well-established guidance the FDA has laid out for that approach. So that's kind of our sense of timing and why we think we are still on path for a launch of 1010 subject to data and regulatory consultations, but a launch of 1010 next year.

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

Hello? This is [Huidong] from Gena Wang from Barclays. We have two set questions, so on flu and RSV. So on flu, so can you -- or do you still plan to file with the current data on accelerated approval for 1010?

Stephen Hoge - Moderna, Inc. - President

So I think that I would point to our base expectation at this point is still to file for accelerate approval but on the P303 results that we just talked about and launched the product next year. There are two other possibilities, but they would be subject to data and consultations of regulators that haven't happened yet. One possibility is that the P302 study, the efficacy study that is still ongoing in the subsequent analysis demonstrates efficacy. And if that's the case, then actually, that will be the basis of a full approval filing. And at the end of the season, we'll conduct that updated analysis and update if we're there. But as we've kind of accrued most of the cases, that probably is not the base case assumption that we have at this point for this year.

The other is what you proposed, which is the combination of the current Phase III results, the P301 and P302, would that suffice? Again, that would be subject to continuing to dig into that data and a consultation with regulators about how they would view that. We haven't had those discussions. And again, I think our focus as a company right now is on the things that we know we can control and they're well precedented, which really is this Phase III P303 study we just talked about on the time lines we just talked about and launching next year. None of the others would likely accelerate that launch for the fall of 2024.

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

So for RSV, I just want to confirm, you have not observed any serious adverse events in your trial? And so on -- so I know you don't have the TDS. Have you observed any other immune-mediated demyelinating conditions in the trial?

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

Yes. So maybe just to clarify what Christy was reporting to you. So this is a trial in adults over the age of 60. So we did see serious adverse events in both the 1345 and the placebo group. Rates were balanced. And frankly, I think we'd have some concerns about our safety monitoring. If in that age population, we hadn't seen some serious adverse events when there are 37,000 individuals that we've enrolled.

But in terms of acute demyelinating events, yes, we have not seen Guillain-Barre. We have not seen other demyelinating events, including ADM or acute demyelinating encephalomyelitis.

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

Simon Baker from Redburn. I've got a lot of questions, but I'll try and restrain myself. On the -- going back to the 1283 data, you pointed out that the reactogenicity was comparable. In the past, there's been a feeling that reactogenicity was linked to chain lengths, and that would suggest that's not the case here. So your thoughts on that and the relevance and the reason I'm asking it is if there isn't a clear link between chain lengths and reactogenicity and in light of the science paper that was published in January, what are your thoughts on a universal flu vaccine encoding for 20 A and B subtypes?

And then moving on to the financials. The outlook for 2027, you get Jamie is really, really helpful. The COGS range of 20% to 25% makes a lot of sense. But in that context, the COGS for guidance for '23 of 35 to 40 or 30 to 35x royalty seems a little bit high. So I was wondering if you could give us a bit more insight into the moving parts for '23 relative to that '27 outlook.

Stephen Hoge - Moderna, Inc. - President

I have to say it's like your plant sitting next to rough I had 20 valent flu vaccine. I'm sure he's -- I can see him grinning, like, of course, why not.

Look, I think on the point of reactor, Jackie, I'll invite you to comment. But as it relates to the platform science on it, we have generally seen reactogenicity isn't related necessarily to construct length or even dose level as you look at massive mRNA but more to the on-target immune response that you're seeing against the antigen. And so in that sense, it maybe isn't as surprising.

Now as it relates to how many antigens you can get in there, Rafael already talked about the fact that you got an 8 valent if you count the neuraminidase antigens and valent flu vaccine, we will look to continue to explore that. And at this point, we haven't yet hit a limit when it comes to antigens that are well tolerated and that we can get in there. But at some point, we, of course, will. We can't go all the way up to 20 without some risk, I'm sure.

Jackie, anything you'd add in terms of the reactogenicity data of 1283 to?

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

I think you've basically covered it. Maybe the one thing I will say is that 1273, we did make an attempt to look at whether reactogenicity was linked to the level of immune response. And I will say that link was actually, was there, but it was really weak.

So I think, again, people are complicated and respond to things differently. The vaccine platform has been consistent in the reactogenicity pattern we see, but the magnitude actually does vary between programs. I mean with all of the caveats about comparing across studies and so forth.

So I think the antigens and as Stephen said, the on-target immunity is also playing a role there, but we'll continue to research and look.

James M. Mock - Moderna, Inc. - CFO

And in terms of the COGS question, so it's a great question. And maybe to make it super simple, I'll point you to 2022. And if you look at 2022, our COGS as a percent of revenue was 29%, let's round it to 30%. Half of that was waste. So if you look at what we wrote off from an inventory perspective, we wrote off \$1.7 billion of inventory. We had \$800 million of unutilized capacity out there.

So when we say as we transition from a pandemic to an endemic, that basically means we have to get through that waste. And so what we provided for in this year's forecast is a little bit more of that. We still have a substantial amount of inventory that we assess all the time and believe we can utilize but should we not be able to utilize because of any kind of demand issues or otherwise, we provided for a little bit, an excess amount of waste remaining in 2023, we would hope that starts to drop in 2024 and '25. And that by '27, we're through all that. We should be 1% or 2% of COGS, not 15% of revenue -- not 15% of revenue. So, that's why 2023 is still elevated.

Alexandria Hammond - BofA Securities, Research Division - Associate

This is Alex Hammond on for Geoff Meacham from Bank of America. So how does Moderna weigh capital allocation and clinical investments versus profitability? And should we expect any near-term M&A? And have your interest changed in the space?

James M. Mock - Moderna, Inc. - CFO

So if I heard the question, it's on capital allocation versus profitability and then has our outlook change. So, maybe I'll start with the latter. Our outlook hasn't changed. We still have the same capital allocation priorities. We've been very disciplined about them. First is to reinvest back into the business as evidenced by our investment in R&D as well as capital expenditure, and we laid out the investment that we're going to have to make over the next 3 years.

The second is business development. Most of that comes to collaborations. You asked about acquisitions. We had our first small one that Stephane just mentioned when we were 0, that was less than \$100 million. We don't anticipate or foresee any substantial acquisitions out there right now. So I think if there's any, it's probably more in that smaller range. But we are seeing a good pipeline for collaborations. I think we've announced 4 or 5 in the last 3 or 4 months, actually. So that's number two.

And then the third is to return any excess capital to shareholders, which we've been very disciplined about, as we came into the year, we had \$2.8 billion of remaining authorization on our \$3 billion for share buyback. And we continue to look at what our forecast our and what our excess capital is. And to the extent that we believe it's there, we will return to shareholders, but that's the prioritization hasn't changed.

As it pertains to versus profitability, obviously, a very difficult question for us. We don't take losing money lightly. That is not hopefully our base case. Our base case is to hopefully make money. That said, the market is relatively unpredictable to Michael's question earlier, particularly on COVID-19 as it sits right now. We talked about the \$5 billion floor we have in terms of signed APAs and we hope to win on top of that. But we believe it's the right thing to do for long-term value creation.

And if that means, and I've said this before to people that, if that means that we have to use, I'll say, \$2 billion, \$1 billion in loss, plus \$1 billion in capital expenditures, that's \$2 billion on \$18 million of cash. We think that's the right move. That's the fortunate position that we're in right now, and we hope to continue to be in, in 2024 and if the same situation presents itself, and we still get the same excellent results that come out of RSV, PCV, PA, COVID, I mean we've got a lot of success here. And I think we think that the best thing to do is invest that back into the business.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. And maybe just to add to Jamie's answer, if you can hear me. I think '24 is a very odd year because we're only 1 product. We are expecting to have RSV and to in '24, such mean more sales. And the \$5 billion is not our guidance. It's as carried the floor, those are the signed contracts. As you know, this number assumes nothing in the U.S., like we don't sell \$0.01 in the U.S., which we think we will sell product in the U.S. in a fall. He assumes no new contract in Europe, and assumes no new contract in Japan. That's the \$5 billion just to calibrate it. And as Jamie said, we're comfortable with \$2 billion for the first half of the year.

And so I think '23 was really the situation where we had to understand the move to endemic. I've never managed the business going from pandemic to endemic in my life. I don't think anybody in the room has before. And so we just want to be cautious because we don't want to not make our numbers.

And then there was the PCV data. We got the PCV data came and you guys will see some of it on Sunday. We look at it with a team, we rely with Merck and with a Board, and we like this is not the moment to be shy. We have \$18 billion in the bank. We believe, and I think (inaudible) is a great example of value creation. We believe we can do something really important with PCV for patients and for investors. And so we say, we're going to invest what is required to maximize the value of PCV to patients and investors starting this year.

And so we are investing a lot. We have to scale up manufacturing, which goes into R&D cost for when it's for Phase III because as you recall, we had only either 200 patients worth of product in the Phase II for this melanoma and 2 Phase IIIs we're talking thousands of patients, and we want to do many more studies than that. So we're also ramping up manufacturing, which is part of the R&D investment, but we think, as Jamie said, it's the right things to create value.

Our goal here is to create return for shareholders by creating value. So '23 might not be a great change of how the P&L looks like. but we think it's the right thing to do to create a lot of value in the mid- to long term.

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

Hartaj Singh with Oppenheimer. Just got two quick questions. One is just Jamie, talking about your assumption in 2027. Your competitors, for example, in COVID-19 vaccine space, they mentioned that they have a majority market share in the U.S., ex U.S. Some people, many studies might

argue that you might have a slightly better COVID-19 vaccine, right? So how do you think of market share going forward even with all the other vaccines that you're hopefully going to be launching planning on being first to market, best to market, combination of both? How to think about that? How does that play into your assumptions? And I just got a very quick follow-up on reactogenicity question from earlier.

Stephane Bancel - Moderna, Inc. - CEO & Director

Yes. I can take a stab at this one. So you're correct. As far as I'm aware, most if not over real-world evidence data have shown that consistently the Moderna vaccine performed better in terms of hospitalization and deaths. There are some countries where we have a leading share today. Take the U.K., it takes Switzerland. So some countries have wanted to use that differentiation to drive clinical outcomes, and they have pushed nationally. I've heard from (inaudible) Swiss investors spending at pharmacy and the pharmacy spending half an hour switching somebody was on Pfizer to use Moderna. It's an (inaudible) growth, but it shows in the market share.

In some countries, health officials have decided during the pandemic that they did not want to differentiate the vaccines. So you guys read centric papers, some doctors with papers, not all of them. And so one of the work we're going to be doing in the commercial team and the medical team is to continue to get the message out as we can do that as we move into commercial market.

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

And then just a quick question on reactogenicity. On just the absolute amount that you're giving to patients, 25 micrograms versus 50 versus 150, so thinking forward to the combination vaccines, Stephen. And is the goal to bring that absolute amount down while getting the combination vaccines in? I mean how much does that matter to the reactogenicity profile, just the absolute amount of product you're giving?

Stephen Hoge - Moderna, Inc. - President

I'll take a stab and then let Jackie actually build. So look, I would caution us to think too much about the mass of the dose. Our goal is, for sure, to optimize the overall profile of combination vaccine. You want to make sure that you maintain the expectations for efficacy and you want to make sure that you have a really good tolerability profile and obviously always safety.

But the RSV data that we shared, if you look at it, that's a 50-microgram dose, right, that's the same dose that we're talking about with COVID boosters or other things. It's clearly not the mass because at that level, we're seeing really good efficacy, but a very different reactogenicity profile, one that really is quite comparable to placebo, maybe 1% or 2% on the grade 3 is different.

And so that's why I think it's probably not just mass Hartaj. I think it is about actually interrogating biologically how those antigens perform together, what's the optimal reactivity profile from a clinical perspective. I don't know, Jack, if you...

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

I really have nothing to add other than I think each program has its own unique facets. I mean there is a certain contribution of dose. We know that in the COVID program, for example. We studied the 250-microgram dose level. We stopped it. But in CMV, for example, we were able to go up to 300 micrograms and didn't have to stop the dose level. So to the extent that there is some degree of dose ranging, yes, things like 1283 that we can potentially give at a lower dose are desirable because they may be able to allow us to put additional antigens in the vaccine. It's not really the only determinant of reactogenicity. And that's why I think the data that we generate are so important because each product is slightly different.

Boran Wang - Guggenheim Securities, LLC, Research Division - Associate

Evan Wang from Guggenheim. Just a question for Stephane. I know you said in 3 to 5 years, you may be known as a cancer company. You've laid out some pretty big goals for vaccines. So I guess, longer term, could we see the cancer opportunity being larger than this vaccine opportunity?

Stephane Bancel - Moderna, Inc. - CEO & Director

I mean you guys can do most really better than I can in terms of the size of the oncology market, how we're aging population and immunotherapy, it's growing.

We believe the way our product works from a mechanistic standpoint in terms of educating T-cell is very, very powerful. And so we believe that we're going to build a great vaccine franchise in terms of cancer vaccine franchise in terms of oncology. So when you look at just the size of the immunotherapy market today and what is projected to be in 5 or 10 years, those are pretty big numbers. So -- and some products are going to go generic in the meantime. So could we end up having a material share of the oncology market? We believe so.

Unidentified Analyst

So this is Serena of Wells Fargo here from Mohit Bansal (inaudible). I wanted to ask about the RSV vaccine. Kind of given how differently each company has defined their endpoints based on signs and symptoms. Can you help us think about how to compare the reported vaccine efficacies and what differentiates mRNA-1345? And then also on safety, kind of given the delta from placebo just how you would compare 1345 versus GSK and Pfizer's?

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

Right. Well, so again, I want to really caveat taking different studies, different populations and comparing them, especially when reactor is measured differently. So different companies not only look for different end points, they look at different scales for the same endpoint. So I would really caution against direct comparisons overall.

That said, I would say that the way we addressed vaccine efficacy was more similar to the way Pfizer has addressed vaccine efficacy. The strength, I think, of that kind of case definition is that first and foremost, it relies on RT-PCR. So identification of the pathogen. Secondly, it clearly defined symptoms that we know are statistically associated with RSV and the presence or absence of those symptoms there.

I think what's exciting about our data is the ability to protect against the lower respiratory tract disease. And as was presented at the recent RSV Congress, we had on hospitalization in the study. It was in the placebo group.

We're going to expand on those data coming up. So I'm not going to steal my thunder on Sunday when we're present in Copenhagen. But just to say that I think the maintenance of high levels of protection, so 83% and 84% regardless of 2 plus or 3 plus really implies that we're achieving the high level of protection even in subjects that are have fewer numbers of symptoms. And I think that protection, severe, more severe and milder disease actually really speaks to the strength of maintenance of efficacy. So you'll see more about even milder disease on Sunday. I hope you pay attention there. And I don't know if there's anything anyone else wants to add about it.

Stephen Hoge - Moderna, Inc. - President

That's well said. I think we're really optimistic about our profile, but we'll wait for the data to return.

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

And I think that's it for questions. Thank you very much.

Stephane Bancel - Moderna, Inc. - CEO & Director

Super. Well, thank you very much, everybody, for joining a person or live, and we look forward to continuing the dialogue. Thank you. Have a great day.

Stephen Hoge - Moderna, Inc. - President

Thank you.

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