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MRNA.OQ - Moderna Inc To Discuss SARS-CoV-2 Vaccine (mRNA-1273) Interim Phase 1 Data

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OVERVIEW:

Co. announced positive interim Phase 1 data for mRNA-1273.

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PRESENTATION

Operator

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

Lavina Talukdar - *Moderna, Inc. - Head of IR*

Thank you, operator. Good morning, everyone, and welcome to Moderna's Conference Call to discuss the interim Phase I data for mRNA-1273, our vaccine against the novel coronavirus. You can access the press release issued this morning as well as the slides that we'll be reviewing by going to the Investors section of our website.

Speaking on today's call are Stéphane Bancel, our Chief Executive Officer; Tal Zaks, our Chief Medical Officer; Stephen Hoge, our President; and Lorence Kim, our Chief Financial Officer.

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

With that, I will now turn the call over to Stéphane.

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

Thank you, Lavina. Good morning or good afternoon, everyone, and thank you for joining our call. One hour ago, we reported positive interim Phase I data for mRNA-1273. Our development candidate against the novel coronavirus as well as its most current data. We believe that these 2 data sets will present an important step forward towards the development of a vaccine candidate against SARS-CoV-2. We are encouraged by the interim data and they confirm our strategy to develop mRNA-1273 as fast as safely possible.

Let me briefly summarize the key takeaways from this morning's press release, before turning over to Tal to walk you through the top line data. After 2 doses of prime and boost, all participants across the 25-microgram and the 100-microgram dose cohort seroconverted with binding antibodies levels at or above level seen in convalescent sera, which is the level of antibody in human blood were being infected by SARS-CoV-2 and recovered from SARS-CoV-2 duly. mRNA-1273 elicited neutralizing antibodies titer levels in all 8 initial participants across the 25-microgram and the 100-microgram dose cohort reaching or exceeding levels generally seen in convalescent sera.

mRNA-1273 was generally well tolerated. The anticipated dose for Phase II and Phase III studies will now be between 25 and 100 microgram. We also announced the outcome of a preclinical mouse challenge study. It is typical in the development of a successful vaccine candidate to run one or several animal challenged models. This consists of vaccination of animals with assembled regimen as that used in clinical service. In this case, a prime and a boost. These are placebo controlled studies. After vaccination, the animals are exposed to high levels of a SARS-CoV-2 virus in order to mimic a natural infection.

In this mouse range study, we showed that mRNA-1273 provided full protection to 100% remise against viral replication in the lungs of the mice. The totality of the data released today, the interim Phase I data and the preclinical mouse challenge model give us confidence that mRNA-1273 has a high probability to provide protection from COVID-19 disease in humans. We'll know how much protection from the efficacy performance of a Phase III study. Currently, our plan is to start the Phase III study in July 2020. We could not be happier about this interim data.

On Slide 4, we received a progression of mRNA-1273 program. The sequence of the virus was made available to the world only 4 months ago. It is humbling to already have this positive data and to be finalizing as we speak of Phase III protocol with the aim to start dosing in July. With this, let me now turn to Tal.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Thank you, Stephan, and good morning, everybody. Before I review the interim data, let me start with a reminder of the Phase I trial design, which, as you know, is being run by the NIH. The study initially enrolled a total of 45 participants between the ages of 18 to 55 into 3 dose cohorts, 15 participants each in the 25, 100 and 250 microgram dose levels. The study was also recently expanded to include 2 additional age cohorts, 55 to 70 year olds and 71 and above. Enrollment into these cohorts is ongoing. And the vaccination regimen is a prime-boost regimens, a month apart totaling 2 vaccinations per participant. The first injection is given at day 1, and the second vaccination was given at day 29. The primary endpoints of the trial are safety and reactogenicity and tolerability and immunogenicity at day 57, although immunogenicity or titer levels were evaluated more frequently starting at day 15, day 29, day 36 and day 43.

Today, we're sharing the top line interim analysis from the trial. Safety and immunogenicity data from the 25- and 100-microgram dose levels are available after 2 vaccinations and safety and immunogenicity data for 1 vaccination at day 29 for the 250-microgram dose level. So let me start with the safety and tolerability profile.

Overall, mRNA-1273 was generally safe and well-tolerated with a safety profile that's consistent with what we've seen in prior Moderna infectious disease vaccines in clinical studies. One incidence of a grade 3 adverse events of erythema or redness around the injection site was reported in the 100-microgram dose cohort.

The most notable adverse events were 3 participants with Grade 3 systemic Grade 3 symptoms at the 250-microgram level that followed the second vaccination at that dose.

We do not see any of these after the first dose. And so I believe these flu-like symptoms are really an indirect measure of a strong immune response. That said, all adverse events have been transient and self-resolving. No grade 4 adverse events nor serious adverse events have been reported.

Now let me talk about the immunogenicity. Similar to our other infectious disease vaccines, we observed a dose-dependent increase in tighter levels, both across dose levels and between the prime and boost injections within a dose level.

All participants in the 18 to 55 age cohort across all dose levels, seroconverted by day 15, the single vaccination, such that we could see antibodies in their blood. For the 25-microgram dose at day 43 or 2 weeks after the second vaccination, the level of these binding antibodies that the vaccine generated reach level seen in convalescent sera from people who have recovered from COVID-19 disease. In fact, if you look closely, they're already above the median or the halfway point of the levels induced by -- or seen in convalescent sera.

At the 100-microgram dose, also at day 43 or 2 weeks after the second vaccination, the level of binding antibodies now significantly exceeded the level seen in convalescent sera. Now I should say that convalescent sera used to benchmark these results were obtained within a month or 2 after the disease. Neutralizing antibody data are available only for the first 4 participants in each of the 25- and 100-microgram dose cohorts. Consistent with the binding antibody titers, mRNA-1273 vaccination elicited neutralizing titers in all 8 participants as measured by plaque reduction neutralization assays against live SARS-CoV-2 virus. The levels of these neutralizing titers at day 43 were at or above levels generally seen in convalescent sera.

Now I should say, this is a difficult assay to perform for a live dangerous virus, and we're really indebted to NIAID and its academic partners for setting these up and running them. The important element here is that in general, neutralization correlates with total binding antibodies once you're above a certain threshold. So the relevance of these results for us is not just the direct confirmation that in these first 8 subjects, indeed, we see neutralizing activity, but they really allow us to extrapolate what we expect to be achieving in all 45 subjects. Let me touch on the preclinical results from the viral challenge in mice that was conducted also in collaboration with NIAID and the institutes academic partners. The results from the challenge study in mice show that mRNA-1273 completely prevented viral replication in the lungs of animals challenged with SARS-CoV-2. Importantly, in neutralizing titers that we see in Phase I clinical trial participants at the 25- and 100-microgram dose levels are consistent with the titers that were protective in the mouse challenge model.

So since early this year and in rapid succession, we, along with our collaborators at the NIH went from selecting the antigen for mRNA-1273 on January 13 to vaccinating the first participant on March 16, a mere 63 days later. The FDA has given us clearance to proceed to Phase II on May 6 and the top line intro -- the top line interim results today boost our confidence to move into Phase II shortly.

Now I have plans to have these and full data from the Phase I trial in the public domain prior to the start of the Phase III, which we now anticipate will start in July of this year. As mentioned previously, we will start the Phase II study in this quarter and it will be evaluating the safety reactogenicity and immunogenicity of 2 vaccination, the prime and boost regimen of mRNA-1273 at 50- and 100-microgram. Based on the data that I've described, the study protocol is being amended and will no longer include a 250-microgram dose R. Since we are already potentially there at the lowest dose of 25-microgram there really is no need to go to 10x that level. And especially when in the context of a pandemic, we expect demand to far outstrip supply and the lower the dose, the more people we expect to be able to protect. We intend to enroll 600 participants in 2 age cohorts, 300 participants in adults aged 18 to 55 year old and 300 in older adults aged older than 55 year olds.

Finalization of the Phase III protocol is ongoing, and we expect to begin the trial, as I said, in July, we'll come back and update once we have complete alignment on that protocol between us, our collaborators at the NIH and of course, the FDA.

Let me now turn it over to Stéphane for closing remarks.

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

Thank you, Tal. We're excited and humbled by the opportunity to bring forward a vaccine against SARS-CoV-2. The development of mRNA-1273 potentially accelerates our overall mission to develop a new class of medicines for patients. I would like to thank the entire Moderna team who have been working 7 days a week literally for 4 months now and the NIAID team who helped us get to this place and all of our partners and suppliers.

I would like to especially thank the many people who participate in our clinical studies, including patients, healthy volunteers, the physician and nurses who work tirelessly to conduct this important clinical study in a very complicated environment with a pandemic going on.

With that, we're now happy to take your questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from the line of Matthew Harrison from Morgan Stanley.

Matthew Kelsey Harrison - *Morgan Stanley, Research Division - Executive Director*

Thanks for sharing these data. I guess 2 parts from me. First, if you're willing, could you provide us maybe a little bit more specificity around the specific titers you were seeing whether that's what the titers you were getting with the vaccine? Or maybe specifically what the titers are that you're thinking about when you compare against convalescent sera? And then second, can you maybe talk a little bit more in detail about the longitudinal results here, where you're seeing clear increase in titers after the boost? And how do you think about the need for a boost versus being able to use 1 vaccination?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Thanks, Matthew. This is Tal. Let me take these 2 questions. I don't think we're being specific yet about the actual titers. I think we are going to defer to NIAID and its academic partners to; publish these results. And I think, of course, the relevant part here is not the absolute level of the titers, but actually how they correlate across between what we see, the convalescent sera and any data and animal models. I think the other point that is worth noting is that these are still relatively early days, both for characterizing and standardizing clinical assays as well as for characterizing and standardizing what one sees in convalescent serum. So many people in many groups across the world are busy working at this. I think there's a concerted effort by NIAID that we are supportive and part of to standardize and qualify these assays. And I think all of that should emerge in the coming weeks and months.

So I don't think it'd be appropriate to just give a number out there because what's relevant is not the number, it's our confidence in context of what that number means in terms of standardization in assays. In terms of longitudinal results, thank you for that question. Indeed, as one would expect from basic immunology of a prime-boost. The prime is clearly seroconverting people and getting antibody levels that you can clearly see that are real. And there is a clear dose response among the doses. When you come in with a boost, that's where you really see an additional significant increase in those titers. The early data that we have for neutral -- for neutralizing activity, these are the first 4 in each of the dose cohorts that we have. And so we focused, obviously, on the end game here, which is 2 weeks after the boost. And at that level, if you look at what you get with the 25, as I said, you're already above the median and at the 100, there's no overlap in the confidence interval. If your question is where do you get after just 1 dose? I think you're starting to get antibodies at a dose of 100, you're starting to get to the level that you can see in convalescent serum, but I think we anticipate, going forward, at least at the doses that we're talking about today with a prime-boost regimen into Phase III.

Operator

Our next question comes from the line of Salveen Richter from Goldman Sachs.

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

Nice to see this data. So 2 questions for me. How do you get confidence here as to what is protective for at the binding and neutralizing antibodies level you've seen in convalescent serum? And then secondly, based on everything you've seen to date, what do you see as the risks on the forward as you look to the Phase II and Phase III?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Thank you, Salveen. So what is -- how can we get confidence as to what is protective? I think it is a measure of really 2 elements, one is understanding the -- how they correlate with convalescent serum. I think while these data give us great confidence that we've got now the right dose range for Phase III, just being at convalescent sera could be enough. We know or at least we believe and I think most experts would agree that once you've had disease, at least as we know it in the past 5 months, it's relatively short follow-up. But once you've had disease, we've not seen really cases described with getting disease again.

And I suspect we would have seen those descriptions if that were a real problem. So we anticipate, I think, like most experts that having diseases protective and therefore, having antibodies by extrapolation is likely protective. And so if you get to the level of people who had disease, that should be enough, that the other point that I think is going to give us confidence is the various animal models. We're describing just the first one here today. I should qualify and say that the virus here is actually a virus that had been slightly altered so that it binds to the mouse Phase II receptor. But it's a valid model in the sense that you see the full gamut of replication in the organs you care about, which in this case is lung. And to the degree that you can correlate generating antibodies to the same level and consistent with that, you then challenge animals, and they do not get replication of the virus in their lungs. I think that all increases our confidence. I think what you'll see in the weeks and months ahead is more data, both in terms of animal models and in terms of the validity and standardization of these assays that would allow this confidence to continue to increase.

Ultimately, we're going to have to pick a dose for Phase III. And as I said, we believe that it's going to be somewhere between 25 and 100. I think whenever you're a vaccine developer, you always want to make sure that you've got a margin and that you've got a higher immune response than what you absolutely need because you expect to see some variability in the population, there inevitably always is, but here, we're going to have a very difficult math because the higher the dose the fewer people were going to be able to immunize. So I hope I've answered that. The risks going forward? Well, it's a good question. I think the biggest risk, as I see it, is actually in being able to see enough cases.

So what do I mean by that? The success of the Phase III trial depends on only 3 factors: number one, can we -- or 2 factors? Can you get enough cases in the placebo arm such that in the vaccinated arms, if you avoid those cases, you can actually speak to it statistically, and that's a function of how good is the vaccine and how protective is it to immunize against this spike protein. I think the totality of science tells us that this is the right antigen that we should be protective. The challenge for me then shift to how do I ensure I have enough cases to be able to demonstrate that as quick as possible. And I think that's a function of being able to conduct a Phase III trial that's large enough but more importantly, that actually goes and vaccinate people who are then at risk for getting disease in the ensuing months. Because if I vaccinate a whole bunch of people, it doesn't matter how many, if there is no circulating virus in the places that I chose to vaccinate, then we won't have the cases, and it will be a long time before we know. So I think really, as I look forward, I think these data today take off the table the risk of not being immunogenic or the risk of the antibody type being wrong? No, it works. And it's -- you see demonstration of neutralizing activity. So I think the major risk, as I look ahead is just operationally being able to demonstrate clearly that there's safety and efficacy in a large randomized trial. So we'll get there. It's just -- it's really a question of time.

Operator

Our next question comes from the line of Cory Kasimov from JP Morgan.

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

And really great to see this latest very encouraging step. So 2 questions for me as well. First, can you provide additional details around the systemic grade 3 safety events that we're seeing at the 250 dose? And was there any evidence of this in lower dose cohorts, even sub-grade 3? And then secondly, how much do you want to see to select for that go-forward dose in Phase III? Will this be coming from -- will this information come from Phase I since you've now including the 50-microgram dose, or is it going to be based on preliminary Phase II data as well? I guess what else is left to finalize that decision?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Cory, it's Tal. Thanks for the questions. The systemic grade 3 were sort of your typical solicited adverse events. They -- I think it was a case of fever. We had some muscle pains, a headache, fatigue. Among those symptoms is what you see, they were all gone by the next day, and there's sort of typical solicited adverse reactions for vaccines. We didn't see anything that we didn't expect, frankly. You do see some grade 1s and 2s, we haven't reported the exact numbers, you'll see that all come out in the table, but nothing surprising and nothing that we believe would prevent one from fully developing and deploying the vaccine.

What additional data do we expect prior to Phase III? I think it's going to be the totality of the data from the Phase I. It's going to be the emerging safety, the very initial safety profile from Phase II to just confirm safety profile. And I think that's it. We're talking a matter really of weeks before we hope to be launching the Phase III. There will continuously be data coming out of this Phase I. And of course, we'll do our best to accelerate any learnings we have from the emerging Phase II. I also think it's important to continuously look at the effort or performance and continuing to characterize and standardize what convalescent sera is so that we're all comfortable with the choices that we're making here.

Operator

Our next question comes from the line of Geoff Meacham from Bank of America.

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

This is Alec on for Jeff. One question from me. In the Phase I study for CMV, neutralizing antibody titers were around 10 to 40x that of seropositive patients. And for the COVID-19, Phase I it seems to be much lower. So could you provide some color around this and what it means in terms of conferring protection? Particularly, since the patient staging an active immune response may yield higher titers than what can be assayed in convalescent plasma?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Thanks, Alex. Let me try and answer that. I think the salient comparators as we look at the data is that at the 100-microgram after the boost, we far exceed what you see in convalescent serum, the confidence intervals do not overlap. I think at the 25 microgram, as I described, we're already at that level, I think the relevance for me here is the convalescent sera, we're still only with a few months of history from this disease. So we're talking about convalescent serum that were obtained at 1 to 2 months after disease, which is sort of their peak. So I think I think it's an appropriate benchmark. I think CMV is a different story because CMV, you're talking about a chronic latent infection and these are antibodies that people live with them constantly. So I don't -- I think you're comparing apples-to-oranges here.

Your second question, I think, is the one that everybody is sort of wrestling with, which is, okay, what level are you shooting for and what is protective? And as I said, I think that determination is going to be a function of a full quantitation and standardization of the assays in convalescent serum and seeing more data as it relates to the preclinical models. What do I mean by that? Well, if you look at this mouse study that we described, so after a prime and a boost at a dose that completely protects the animal, we see neutralizing activity that is of same, as what we've described here, after a prime and a boost. But one of the salient points is that at that dose in the mouse after just the prime, the mouse was already protected.

And so I think we're getting a comfortable margin here to know that we're at the right level that one needs to be in to protect people I think the question is going to be, okay, how much higher above that do you want to have a margin of safety.

Operator

Our next question comes from the line of Hartaj Singh from Oppenheimer.

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

Great. Really kudos there, Tal and Stephane. Just taking a step back, one of the things that I think some investors are struggling with is how quickly Moderna has moved. I think Moderna has been pretty transparent about how they're moving. You're moving quickly. Stephane, if you can take a step back and maybe talk a little bit about how the platform, all of the manufacturing investments you've made, the persona there have -- that you have gotten you to a point where you could essentially do in 1 year that normally takes 5, 10 years, of course, the pandemic and the regulatory authorities are being more helpful? And then secondly, how this new sort of approach using this platform approach with this investment and all the preclinical work you've done across all the modalities could also help in different modalities in there?

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

And thank you for the good question. If I think about kind of how did we get there, how could we go from the sequence in January to having the interim Phase I data in May, a green light from the FDA in May and saying that we believe our current path is to start a pivotal Phase III in July. I think there are maybe 5 things that come to mind. The first one is, of course, the platform. Messenger RNA being an information molecule. We could not have done that to our other technology, like in our recombinant, live attenuated virus technology [cohorts].The fact that we are really dealing with an information platform that we can work directly from the genetic information of a virus and literally drop that into our vaccine cassette from the sequence of a virus. I think is really a unique feature that creates extraordinary leverage and the growth effect.

The second piece for me is that this was not our first vaccine. I think there's been a lot of questions we'll have asked ourselves, a lot of scientific unknown process, unknown caring in manufacturing. That -- I think one of the place where we got lucky but we were prepared for it is the (inaudible) vaccine in clinical trial before that. And so we have been actually doing vaccines, first-in-human our H10 influenza December 2015. That's more than 4 years ago before we started 1273. And as you can imagine, we've been working on a couple of years on the science and CMC readiness for manufacturing on the vaccine. And we always keep on learning. We keep on working, the teams in the science develop new lipids, more potent mRNA construct.

And on the process side, Juan and his team keep on inventing new processes, getting new process with better yield, more potent mRNA. And as you know, we will never stop, we still believe we're in the early days of mRNA science, we still believe we have a lot to learn, and we still believe we are the best company positioned in this space to keep growing and keep learning and keep making better and better product. The third thing that enabled us to move very quickly is that we were prepared because we had been working with NIAID Dr. Tony S. Fauci department on the Middle East Respiratory Syndrome, which is another corona which as you can imagine, in those few hours when we saw the sequence of SARS-CoV-2 and the team had to really kind of analyze and understand which protein to pick, how to go at developing the vaccine. And those are, of course, fundamental decisions because if you get these wrong then the vaccine is not going to work. We were, of course, massively informed by all the work that has been done by our teams and NIAID over the last couple of years. So that's also very important. I think it might have been a very different situation. You could never work on the coronavirus.

The fourth one is Norwood. As I've said many times, and I won't stop repeating because I believe it is a competitive, strategic advantage of our company, having our own manufacturing facility. From raw materials to shipping wise to clinical trials. Having own teams who understand the process, who can make judgment about decisions is really fundamental. If we had added contract manufacturers, we could never move so fast. Because, one, we would have to call 4, 5 CMOs around the world and the chance they all had an empty slot falls waiting was, of course, very small. And so being in Norwood, we have own team, own equipment, our own facility allow us to tell the team, this is very important. This one is to move through the system much faster than usual and people knew the importance of this.

And as the virus was spreading our determination just grew stronger with the days. And the last thing for me is the team. We have been very fortunate over the years to assemble a team across the company, I'm not talking only about the executive, you've got the entire company. A team of scientists, engineers, clinicians, women and men who I think, believe in the mission of the company. This is once in a lifetime opportunity that we have in our carrier to be able to collectively together figure out how to build the new technology that could help so many people. And I think today, the company is 9 years old, is just getting to a place where all those pieces are coming together. So it's more of a network effect of all the investments we've made of the science of what we have done before. That got us prepare for this moment.

Now many of us wished, we already had a big manufacturing plant where we would be able to make 20 million or 50 million doses in the first month from January, that will have been amazing. Unfortunately, this caught us a bit too early in the company's history. But this is what I think has made this opportunity unique. And to your second question, I think the read across the platform is going to be extremely valuable, both internally in how we think about study design, how we think about translating products from preclinical to clinical. There are a lot of learnings. As you can imagine, this is a very special moment for the company. And if you look at it at a more global basis, assuming we start in July as planned in our Phase III for 1273.

We have not yet shared the size of the study because we have to discuss and align with the FDA, as everybody can appreciate. But this is going to be a large study because as Tal said, the biggest risk of the study is the attack rate and how quickly are we going to get enough people infected to get to efficacy data. Well, one of the way to solve for that is you just have a lot of people enroll in the study because they just not. And so that is going to enable us to get a very big safety that, obviously, is going to benefit all the vaccine programs. And then the question because, so far, if you look at it, we have said we are in 18 to 55 years old, 55 and 70, 71 and above. There are still a lot of subpopulation that we have not talked about yet that might be accelerated through the Phase III study. And this would be, of course, extremely valuable across the platform. So I think I hope this answers both of your question.

Operator

Our next question comes from the line of Yasmeen Rahimi from Roth Capital Partners.

Yasmeen Rahimi - *ROTH Capital Partners, LLC, Research Division - Former MD, Senior Research Analyst & Co-Head of Biotechnology Research*

Congrats team on the amazing progress, and thank you for your tremendous dedication for working on this incredibly urgent matter. 2 questions for you. The first question is, can you share with us what was the median age of the cohort that just read out. Did you look at each dependency on neutralizing antibodies and immunogenicity data? And maybe some color on reasons for moving forward with the 50-microgram dose group and the new cohorts add of the Phase I study? And then I have a follow-up.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

It's Tal. I don't have data yet on the median age or any of those other analyses. These, I think, are things that we'll be looking at it in due course, I think the salient point for age is going to be very deliberately testing the immunogenicity in older and elderly adults, which is part of the Phase 1 that has been amended by the NIH. You asked about reasons for moving forward in the 50. I think as we described, we think the Phase III dose is going to be somewhere between 25 and 100. The question is how much of a margin do you want above already exceeding the median of convalescent serum. And with that in mind, the Phase II is really meant to expand the safety database and enable us to start the Phase III. So that's why we have amended the Phase II instead of 100 and 250 to be 150, there's no reason to go higher. But it is important to continuously expand our understanding both of safety, tolerability and eventually immunogenicity of the dose range that we think is the relevant one for Phase III in eventual deployment.

Yasmeen Rahimi - *ROTH Capital Partners, LLC, Research Division - Former MD, Senior Research Analyst & Co-Head of Biotechnology Research*

And then another question is, can you shed some light in regards to maybe the level of viral load reduction you saw in the challenge model or to an extent to the T cell responses in the mouse model?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes. So when you look in the mouse models, I think the relevant organ where you want to see decrease in viral replication is the lungs, right? That's where the virus causes its pathology. And there, we see complete elimination of viral replication at the dose that we described that has the same level of neutralizing antibodies. Don't have any T cell data yet to share, I would make 2 observations. One, whenever we look across our platform, whether it's preclinical or in clinical trials, we do see strong T cell activity and you would expect that based on the fundamental scientific principles of how an mRNA vaccine works because it teaches the body -- our body's own cells to make the protein from within the cell, and that's how you stimulate T cell responses as well. It is not a recombinant protein.

The other element is when you see such a strong, what we call, anamnestic response with a boost that is your -- you mountain immune response faster and stronger when you boost, that tells you that you've got T cell help that's how the immune system works. You have a collaboration between T cells and B cells to stimulate the second response to happen quicker. So I think based on places where we have other data, based on the fundamental signs and based on the magnitude and kinetics of the immune response that we see here I have little doubt that we are listening T cells. Measuring T cells is a tricky thing, especially in clinical trials and often is not very useful as a way to either predict immunity or find a correlative protection. And so we're really focusing here on the antibody assays as the relevant measures of what we're achieving.

Operator

Our next question comes from the line of Alan Carr from Needham & Company.

Alan Carr - *Needham & Company, LLC, Research Division - Senior Analyst*

Congratulations on your progress. Tal, can you go into a little more detail about the target group to be enrolled in Phase II and Phase III? You mentioned at risk in a view in government agencies come to any conclusions on which groups maybe it's by age? And then also, can you give us an update on manufacturing capacity and the -- do you think you'll be entering into more production agreements? And then where do you -- what sort of production pressing do you think you'll have towards the end of the year?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Thanks, Alan. Let me take the first question then I'll defer it to Stephane, who want to take the second one. The Phase II is still subjects that we anticipate not being at risk, at least as far as the local epidemiology of the centers where we're going, although that's, of course, very hard to predict these days in the U.S. and it will have both old adults and older adults. The expectation for the Phase III is that we will enroll people at risk. We will enroll people at risk, both based on their age, based on their comorbidities and based on their occupations and other sort of parameters that put people at risk.

I think the goal here is to have a fairly large trial that will look across different ways of how one defines that risk and leave some of that decision-making to the local investigators who understand their local population better. But the exact discussion on what that would look like from a protocol perspective, and then in real life, I think is still ongoing between us and the NIH and FDA. I think FDA has an expectation that the Phase III trial will indeed include people at risk and will include a population that would be representative of the population where we ultimately expect to apply this vaccine. And of course, that should include everybody.

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

Thanks, Tal. This is Stephane, let me maybe take a step at the manufacturing capacity question and whatever I miss, I'm sure Juan will add to it. As we've said in the past, we are currently scaling up our manufacturing capacity as fast as we can. Partnership with Lonza, help us to be able, assuming the 50-microgram dose to potentially get to 1 billion dose per year. And as you understand, we are basically expanding from the Norwood plant, which was our only manufacturing capacity, with our Lonza partnership to enabling GMP suite at Lonza with new CapEx, new teams and so on.

And so the way to think about it is a ramp. Is the ramp between Norwood, which was not kind of fully staffed and without the process of a larger scale that we think we can get to the teams are working on as we speak.

And so the way to really think about it, I think, is that in terms of multi-output. And so as we've said in the past is the monthly output is going to start, obviously, making millions of wise doses, sorry, per month. Going into tens of millions of doses per month and just keep ramping that number until we get to around 1 billion annual run rate on a monthly basis. And that's how you want to think about it. So it's going to take several quarters, obviously, to get there. But the teams are already working really hard both in Norwood. As we said, one is transferring the process to the Lonza and their entire plant in the U.S. as a first step, with a goal to start making product there in July. So we'll give you more update as time goes by. There are so many moving pieces right now. Just be assured that Juan and his team are highly aware that every additional million doses will make a big difference in many people's life. And so we will make sure while not compromising quality because there are people -- products that we're injecting people. So quality is priority #1. While not compromising quality, the team knows the role we have to play to protect a lot of people. So we will get as much as we can out of the system.

Alan Carr - *Needham & Company, LLC, Research Division - Senior Analyst*

One last one. Tal, with respect to animal models, what do you think is there a best animal model for respiratory infections? You've used a mouse one here. What are your thoughts on that? Is there -- might we get -- yes, you mentioned there's more animal models in progress.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Sure.

Stephen Hoge - *Moderna, Inc. - President*

Tal, let me take that.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Sure. Please go ahead, Stephen.

Stephen Hoge - *Moderna, Inc. - President*

So Alan, thanks for the question. I think the answer is always virus specific. And because this is such a new virus, we just don't know. We don't have enough information to say, which particular models are most predictive. There are several under development. Obviously, you start with rodents and there are also primate models that have been put in place. Our intention is to test in a pretty broad set of models, so eventually across most of them just to confirm the activity of the vaccine and its potential to generate protective immunity in those models. But I don't think we have a clear sense of which one is going to be more or less predictive. Obviously, the most encouraging thing to find will be that across any model across primate and rodent models that we're able to show this sort of protective amusement that we showed today or that we announced today in just the rodent.

Operator

Our next question comes from the line of George Farmer from BMO Capital Markets.

George Farmer - *BMO Capital Markets Equity Research - Analyst*

I wanted to talk about the difference between immunogenicity and neutralizing antibodies? I guess the 2 aren't necessarily the same. At what point do you get comfortable with whether immunogenicity is actually predictive of the generation of neutralizing antibodies? Are we there yet? And is it necessary to keep on doing these kinds of high-risk assays on patients to determine such?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

George, it's Tal. Thank you. The short answer is yes, I think we're there. In other words, there is in people who are looking at it, there's a clear linear correlation between total binding antibodies and neutralizing activities. I think that's true once you cross the threshold, we're clearly here at or beyond that threshold with the data that we've described. I think the one caveat is that these assays need a certain level of qualification and standardization before we can just use binding as they correlate. So there are several assay formats that are being developed. There's the neutralization assay, there's a print which is looking at reduction of plaques, that is the one that's most complicated, but it is the gold standard because it's a live virus, and it's the full viral life cycle.

There is on the other end of the spectrum, just measuring antibodies, which is what we are describing here. In the middle, there's something called a pseudo neutralization assay, which is where you develop a pseudovirus, one that has all the components necessary to bind and get into a cell, but don't have the replication cycle or are not dangerous to work with and you can adapt these to high throughput. There's work ongoing by many labs to correlate all of these assays so that the simplest one and the one that's the most high throughput can be put to use to develop a correlative protection, a surrogate of protection, a way to actually be able to say, yes, if you achieve this, then you should be protected and make vaccine development ultimately easier. So I think to summarize my question, I think we're there in terms of the confidence we have that the antibodies we're listening are the right ones. I think there's work to be done to standardize these correlations so that the simpler assays can be adopted for more high throughput use.

George Farmer - *BMO Capital Markets Equity Research - Analyst*

Great. And then a couple more. Recognizing the urgency of developing a vaccine. What is the rationale for layering Phase II and Phase III so close together? I mean, do you need -- don't you need to get some sufficient information out of the Phase II trial before comfortably starting the Phase III? And then also, how do these -- how does the potency of this vaccine compare to what you've seen with the CMV vaccine?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes. So 2 good questions. I think the Phase II was envisioned with 2 goals in mind. Number one was to substantiate the safety, at least in the initial month or 2 of what we are proposing to take into Phase III in a larger number than just 15 subjects per dose level before you go in vaccinate thousands. So I think that's a reasonable expectation from the agency, and that was always the #1 driver to do this Phase II. Even if the timeline is abridged, it is still some information that's relevant that I think makes us all more comfortable. I think the second reason to do the Phase II is that it will allow us to substantiate and better quantify the immune response and in a world where our understanding of the immune response continues to evolve as to what is relevant and how much is relevant.

There's a potential down the road that the Phase II with the 100 subjects now for arm with very tight air bars will give us confidence as to the level of antibodies that is then relevant as measured both by standardized assays on standardized convalescent serum and animal models that the scientific world is developing and will feel is predictive of what's likely to happen in people. And so the Phase II continues to increase our data, even if the Phase III is launching and ongoing, I think the Phase II will generate data that is relevant for our continuously increasing understanding of what it is we're trying to achieve here.

George Farmer - *BMO Capital Markets Equity Research - Analyst*

And relative to CMV vaccine?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Oh, yes. So I think the dose here if you do the math of the CMV vaccine, remember, CMV has 6 different mRNAs in every constructs. So if you take a look at 180-microgram of our CMV vaccine, which was near the top end of the dose. I mean, the highest dose we've tested was 300 and you divide that the mass by 6 then you realize that the per antigen level in any one of those constructs was between 30- and 50-microgram at the highest doses that we've tested. And here, we're talking about 25 to 250 of just 1 antigen. So that's one way of thinking about it. Of course, that is not all of biology, the -- every construct is going to get translated and expressed depending on the biology of that construct and that mRNA and it's -- the sequence of the promoter, everything else that goes into it. So it's not a one-to-one, but at least it gives you sort of a rough sense of a ballpark estimate of what we think, where we think the potency of this vaccine lands relative to others that we have been developing.

Operator

Our next question comes from the line of Jonathan Miller from Evercore ISI.

Jonathan Miller - *Evercore ISI Institutional Equities, Research Division - Associate*

I guess I wanted to ask more about neutralizing antibody levels in convalescent sera. And I understand that you're not giving numbers here, but when we look at convalescent sera, we see huge variability in the reported levels of neutralizing antibodies. You've spoken a little bit about the need for standardization of those assays, but I just wanted to clarify, when you say you were at or above those median levels, are you using a particular reference or a particular source that's already been published? Or is that internal data taken from patients that hasn't been published yet?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes. Thanks, Jonathan. That's an excellent question. These are internal data that have been generated by our collaborators at NIAID.

Jonathan Miller - *Evercore ISI Institutional Equities, Research Division - Associate*

And you're just looking at convalescent sera, broadly speaking, you're not thinking about, for instance, I know the FDA and NIAID has put out guidelines for the use of convalescent sera as a therapeutic, which has minimum bars for expected neutralizing antibody titers. Sometimes that seems much higher than what we see in the broader population. But you're just talking about observed in the broader population of recovered patients?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

That is correct, although I would note that NIAID does put that far of sort of their monoclonal antibody control. And if you look at where we get to at the 100-microgram post-boost, we're well above that level as well. So if that helps you visualize the graphs than we're above there.

Jonathan Miller - *Evercore ISI Institutional Equities, Research Division - Associate*

No, absolutely, and we look forward to seeing that published. I was also going to ask a little bit more about cellular responses. You said you haven't gotten that data. I think I was confused have you not gotten that data from the animal models? Or do you have any data of cellular responses in patients yet? Or are we still waiting for that.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes, we're still waiting for that. I'm not sure to what degree we actually expect to see cellular responses in the clinical data. It's easier to play around with that in the nonclinical models. I personally find in the clinical trials that these are complicated finicky assays that really for an antigen like this and in a disease like this, I don't expect them to add that much of a significant information as it relates to vaccine development. They're always reassuring to see but you can deduce their presence based on the first principles that I alluded to, and I struggle to see how that data is actually informative to concrete vaccine development, frankly.

Jonathan Miller - *Evercore ISI Institutional Equities, Research Division - Associate*

Makes sense. And one final one. As you talk about the amendment to the Phase II with the new doses being 50 and 100 as opposed to going up to 250. You've spoken a little bit about wanting to get as many doses as possible out of the manufacturable stock, and that makes perfect sense to me. But you also said that there was dose dependency in effect observed across those doses. Do you see a delta in first dose efficacy? Obviously, you don't have boost data, but in prime efficacy between 100 and 250 micrograms? And how big is that?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

It's a very astute observation. The answer is yes. We still see a delta to the 250. I think that delta pales in comparison to the bump you get with a boost, and that's why we're comfortable with the (inaudible), we should be able to go much lower.

Operator

Our next question comes from the line of Geoffrey Porges from SVB Leerink.

Geoffrey Craig Porges - *SVB Leerink LLC, Research Division - Director of Therapeutics Research & Diversified Biopharma and Senior Research Analyst*

Congratulations in getting so far, so fast. Really remarkable in the history of vaccines. A few short questions. First of all, could you talk about -- do you have any information about the number of epitopes that you're seeing antibodies develop too, and a little bit about the isotype though I presume it's still IgG? Secondly, in your conversations with regulators, could you give us a sense of what duration of safety you'll need to see in vaccine subjects both in Phase II obviously, you're moving quickly to Phase III, but particularly in Phase III? And do you envisage needing to give longer-term reboosting particularly if the virus isn't circulating and providing any natural boosting? And then lastly, Stephane, could you give us a sense of whether your expectations are that this vaccine will be profitable for Moderna because the number of your competitors are talking about giving product away. But obviously, if you're at the billion dose level, just wondering how you're talking to investors about what that profitability might look like or whether it should be profitable?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

So, Geoffrey, this is Tal. Let me take your first 3 questions. A number of epitopes, we haven't mapped it yet. Isotypes, this is total IGG we're talking about. Duration of safety, I think in Phase II, we expect just a preliminary climb boost to get a sense of the tolerability as enabling to get into Phase III. I think the duration of safety for Phase III will be your typical vaccines, it will be a total follow-up of I expect a year or 2, the -- I would make a distinction between safety and tolerability, you get a good sense of the tolerability just up to 7 days after the dose. You don't expect anything after that. Safety is, of course, something that you monitor for a longer duration. I think I expect the agency is interested in seeing as long the safety is reasonable to follow these people.

Given the size of the trial that we anticipate to launch and the fact that it will be the largest and first such experiment for our platform. Longer-term reboosting, I think, is a good question. I don't think we have any idea today either what natural infection give you in terms of long-term immunity,

let alone what a vaccine would do and how relevant weighting immunity over the course of months and years is to a pandemic that may or may not circulate. So great questions, but our entire history on the relevance of anything having to do with durability here is no longer than 4 months since we started filing subjects, certainly in the U.S., maybe 5 in China. So these are all good questions that we will need to collect data on, but I think your prediction here is as good as mine. Let me transfer your last question over to Stephane.

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

Thank you, Tal. Thanks for the question. So as we've said in the past, we have not finalized our analysis on pricing. As you said, we have moved so fast in January. We have been literally focusing on the clinical plan, and Tal and his team have done a remarkable job and on the manufacturing plan. Because trust me, it was not part of the business plan to be having a line of sight of how we're going to make even $100 million for 2020, '21, not even talking about $1 billion. So that has really been our focus and will remain for the coming weeks. But we want to do a detailed analysis of value. When you think about the health care cost and health care system, we want to understand the value of this vaccine. And when we have this analysis done and buttoned-up, we will, of course, share it with our investors and analyst.

Operator

Our next question comes from the line of James Birchenough from Wells Fargo.

James William Birchenough - *Wells Fargo Securities, LLC, Research Division - MD and Senior Biotechnology Analyst*

Congrats on all the progress. A few questions, maybe just starting with the preclinical data, the mouse model. So SARS-CoV-2 doesn't bind very well to the ACE2 receptor. And I know you referenced a modified virus, but could you speak to the binding affinity to ACE2 with the modified virus? And then did you look for any other areas of infectivity, upper airway as an example? And then I've got a follow-up.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

[Ben], do you want to take that one.

Stephen Hoge - *Moderna, Inc. - President*

Yes, sure. So this is done with an academic collaborator with the NIAID. It's the work I'm describing is theirs. They have modified the SARS-CoV-2 virus, particularly the receptor-binding domain. So there is good infection in mouse, ACE2 receptors have demonstrated that. And so it's a negative control in the study, you obviously have a viral infection, both in the lower respiratory tract and the upper respiratory tract. I think the -- we looked at a range of dose levels.

Across that study, and I'll wait for the day to come out, but we did see suppression of our replication, both in the upper airway and lower respiratory tract. Our primary focus, though, as Tal described, is what's happening in the lower respiratory tract. That's the disease that causes COVID-19 as opposed to sort of just nasal replication or things like that. So the assay itself, at least the negative controls, give us a high degree of confidence that it's replicating a good productive infection in the mice and that the vaccine is able to completely eliminate viral application in the lower respiratory tract in the lungs.

James William Birchenough - *Wells Fargo Securities, LLC, Research Division - MD and Senior Biotechnology Analyst*

And then maybe just on the clinical side, just in terms of confidence in these results being replicated in older adults. Is there anything to reference in your CMV experience that would suggest you can get to immunogenicity that's comparable and older adults to younger? And just wondering,

a bit of a controversial area, but challenge studies. Do you -- is your sense that, that's going to be difficult to pursue and you feel there's enough infection out there to really conduct an appropriate Phase III study?

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes. So the older adults, let me just say that where we have experienced, which was, I think, our first RSV program, we did not see a difference between older adults and adults. So we look forward to carefully seeing the results here. I'm sorry, your second question? Could you please repeat that?

James William Birchenough - *Wells Fargo Securities, LLC, Research Division - MD and Senior Biotechnology Analyst*

Just in terms of regulator appetite for a challenge study.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Oh, the challenge study. Yes. Yes.

James William Birchenough - *Wells Fargo Securities, LLC, Research Division - MD and Senior Biotechnology Analyst*

Yes. And just whether there's enough infection out there to do an appropriate Phase III.

Tal Zaks - *Moderna, Inc. - Chief Medical Officer*

Yes. I guess what you're seeing me is having a bit of a florigen block there. The issue with a challenge study, as I see it is threefold. Number one, for us, by the time it ever gets established, it will likely be irrelevant. I mean we're about to launch a Phase II and will be in an efficacy trial, I think before anybody is to launch a challenge study. Number two, on the fundamentals of it, the challenge study, if you read sort of the expert opinions and people are continuingly looking at this, it's not going to replace our ability or the need, I'm sorry, to do a safety and efficacy trial for a very simple reason. A challenge study is not going to give a good enough sense of the efficacy because you'll be measuring a vaccine's ability to limit -- very minimal disease and relatively healthy people, where what you really want to know is that the vaccine can eliminate really severe disease in older people and people with comorbidities.

That's really the benefit that we hope for vaccine to do. And so you're confident that the vaccine can do it let alone your confidence that you have the right dose, I think it's going to be very hard as from a challenge study. And your sense of safety of the vaccine is also going to be very hard to extrapolate from a limited number of subjects in a challenge study. So it's -- I don't think it's really possible to get the full assurance of safety and efficacy from a challenge study. And if it doesn't eliminate the need to do an efficacy trial than at least for us, the benefit that our development would obtain from putting people in harm's way, I don't think outweighs the risk for those individuals. Now, all that being said, if the right institutions develop and qualify and set up the ability to do such a challenge study and regulators believe that such information would be materially useful to an understanding of our vaccine, then, of course, we would consider it. But I don't think that is the case today.

Operator

At this time, I am showing no further questions. I would like to turn the call back over to Stéphane Bancel for closing remarks.

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

Well, thank you very much, everybody, for being with us today on the quick notice and for your excellent questions. We look forward to talking to you in the coming days. And just to remind you, our next big rendezvous is on June 2, where Stephen, Melissa and the team will share with you all the new things that have been working on the science. It will be a very exciting day. Speak to you soon and stay safe. Thank you.

Operator

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