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MRNA.OQ - Moderna Inc to Discuss Vaccine Against COVID-19 (mRNA-1273) Phase 1 Interim Results Publication Corporate Call

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OVERVIEW:

Co. updated on the Phase 1 interim results publication of mRNA-1273, MRNA's vaccine against COVID-19.

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PRESENTATION

Operator

Good morning, and welcome to 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, Investor Relations at Moderna. Please proceed.

Lavina Talukdar - Moderna, Inc. - Head of IR

Thank you, Shannon. Good morning, everyone, and welcome to Moderna's conference call to discuss the publication of our Phase I interim analysis 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.

On today's call are Stéphane Bancel, our Chief Executive Officer; Tal Zaks, our Chief Medical Officer; and Stephen Hoge, our President. Also on the line for the Q&A section is David Meline, our Chief Financial Officer.

Before we begin, please note that this conference call will include forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

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

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

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Lavina, and good morning or good afternoon, everyone. Thank you for joining the call. I hope everyone is in good health.

We are very happy to announce that The New England Journal of Medicine published yesterday the Phase I interim analysis of our vaccine against COVID-19, mRNA-1273. We are very excited and encouraged by the interim data as they confirm our strategy to develop mRNA-1273 as quickly and as safely as possible.

Let me briefly summarize the key takeaways from the press release before turning it over to Tal to walk you through the detailed data.

The interim analysis of our Phase I study evaluated a 2-dose regimen, a prime and a boost, 28 days apart, of mRNA-1273 across 3 dose levels in 45 healthy volunteers aged 18 to 55 years old. The dose level were 25, 100 and 250 micrograms.

After vaccination with mRNA-1273, 100% of evaluated participants are neutralizing antibody titers. In the live SARS-CoV-2 PRNT80 assay, the Day 43 geometric mean factor levels at the Phase III selected dose of 100-microgram were 4.1-fold above those seen in reference convalescent sera, n=3.

In pseudovirus neutralization assay, ID50, the Day 57 geometric mean titers at the 100-microgram dose were 2.1-fold higher than those seen in convalescent sera n=38.

We also published T cell responses and our vaccine-elicited Th1-biased CD4 T cell responses. mRNA-1273 was generally safe and well-tolerated. These results reaffirm and expand upon positive interim data announced on May 18. The data also supports selection of the 100-microgram dose for Phase III expected to start July 27.

Let me now turn it over to Tal to take you through the data in more detail. Tal?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Stéphane, and good morning, everyone. Let me start with a quick reminder of the data generated to date with our vaccines as they give us confidence that this data is consistent and seen across our vaccine platform to date.

As many of you know, mRNA-1273 is our 10th vaccine in the clinic, and its development was enabled by the learnings we've amassed with the other vaccines that we've taken to the clinic today in over 1,900 healthy volunteers.

We reported 8 positive Phase I data sets against 9 different viruses. For those keeping count, the discrepancy is because we were able to immunize against 2 separate respiratory viruses, hMPV and PIV3 with a single vaccine containing 2 separate antigens. In these trials, we've seen a safety and reactogenicity profile that is consistent with those of marketed adjuvanted vaccines, and we've been able to elicit an immune response in the form of neutralizing antibodies time and again.

mRNA-1273 is our second vaccine to fully enroll a Phase II trial, with CMV having fully enrolled in late February.

Slide 5 lists out the 8 Phase I trials and the level of immunogenicity achieved with each. While the biology for each virus varies, you can see a strong and consistent neutralizing antibody response that our platform is able to elicit.

So as a reminder, mRNA-1273 encodes for the full Spike S protein in its prefusion stabilized form that, when administered, produces the transmembrane trimeric Spike S protein. While the full-length intact protein is recognized by T cell receptors and ultimately elicits antibodies that recognize the

3-dimensional protein, the fact that our mRNA vaccine translates the viral antigen from within the cell is what enables bits of the full-length protein to get processed into peptides that are ultimately recognized by T cells. And thus, we are eliciting a full immune response comprised of both B and T cell responses.

Slide 7 now shows the actual 3-dimensional structure of SARS-CoV-2 using electron microscopy. Now here you can see both the S1 and S2 regions that make up this full Spike protein, which mRNA-1273 encodes for.

Now in red, you can see just that receptor binding domain with which the virus binds to the ACE2 receptor. But in green, you can also see the N-terminal domain, which is adjacent to that RBD or the receptor binding domain. It's notable that neutralizing antibodies have also been described to bind not just the RBD, but also the N-terminal domain. So by encoding for the full Spike protein, mRNA-1273 has the potential to illicit neutralizing antibodies to both the RBD and the NTD domain as well as potentially other domains on the full-length protein.

So let's turn to the Phase I trial design. Let me just remind you of that, which, as you know, it is being run by NIAID, part of the National Institutes of Health. 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. And these are the data that I'll be reviewing.

Now the study has since then been expanded to include 7 additional age cohorts. Enrollment is complete for these cohorts, and these data are expected to be published separately. The vaccination schedule is a prime boost regimen given a month apart, totaling 2 vaccinations per participant. So we start at day 1 and then the second vaccination is given at day 29.

You will note that 3 participants, in this case, 2 in the 25-microgram group and 1 in the 250-microgram group didn't receive, for various reasons, their second or the boost vaccination. And there were an additional 3 missed time points. We are reflecting the total and the data tables that provided the blood draws for the analysis at each time point.

Now the primary end points for the trial are safety, reactogenicity and tolerability. And the key secondary end point is immunogenicity as measured in day 57, although we did measure the immunogenicity or the titer levels more frequently. So you will see data for days 15, 29 after the first dose and then days 36, 43 and 57 after the boost.

So let me begin with an overview of the safety data. At a high level, mRNA-1273 was generally safe and well-tolerated with no serious adverse events reported through day 57. Adverse events were generally transient and mild to moderate in severity.

And on Slide 9, you can see the frequency and severity of the local adverse events, which, when present, were mostly mild or moderate. All participants at the 100-microgram dose level reported mild to moderate injection site pain.

If we look at the solicited systemic adverse events listed on Slide 10, these were also generally transient and mild to moderate in severity.

Now let's just step back, these are really the anticipated flu-like symptoms that you expect from the administration of a vaccine. In fact, their occurrence and severity is scored according to a specific FDA guidance developed for this purpose.

The systemic adverse events graded as severe, in our case occurred in the 250-microgram dose cohorts with 3 participants experiencing one or more events. It is notable that systemic adverse events were more common after the second vaccination, suggesting that they correlate with systemic and specific immune activation. They occurred in 7 of 13 participants in the 25 micrograms, and then all participants in the 100 and 250-microgram groups.

The most commonly reported systemic adverse events, looking specifically at the 100-microgram dose, were fatigue, chills, headache and myalgia. Of note, clinical laboratory values and unsolicited adverse events didn't show any patterns of concern.

So overall, based on these Phase I data, mRNA-1273 appears to be generally safe and well-tolerated, and these safety data would support the choice of 100-microgram as the recommended Phase III dose.

So let me now turn to immunogenicity. I will take you through 3 data sets, 1 on binding antibodies and 2 describing neutralizing antibodies from 2 different assays. Each of the data sets are compared to convalescent sera from patients with COVID-19.

Binding and pseudovirus data were compared to convalescent sera from 38 individuals with confirmed disease, 15% of which -- of whom were classified as having severe COVID-19 illness requiring hospitalization, including ICU care and/or ventilation. 22% had moderate symptoms and 63% had mild symptoms. Their sera was collected between 23 and 60 days after the onset of symptoms, and they're taken from individuals of the ages 22 to 84 years old.

For the live SARS-CoV-2 virus assay, due to the time-sensitive nature of this assay, the convalescent group was comprised of data from only 3 individuals. Importantly, all 3 assays orthogonally supports robust immunogenicity activity, and there's a pretty good correlation between them.

So with that backdrop, starting with binding antibody titers, on Slide 11 you will see a table with the geometric mean titers of binding antibodies at various time points for each of the 3 dose levels. The geometric mean binding antibody titer value for the convalescent sera group of 38 individuals is listed at the top of the table and is approximately 142,000.

Now looking at the tables, you will see that mRNA-1273 induces dose-dependent increases in binding titers across the 3 dose levels and between prime and boost vaccination readily seen at the increase between day 29 and day 36 within the dose cohorts. Of note, all participants' sera converted after 1 vaccination already at day 15. After 2 vaccinations at day 57, the geometric mean titers exceeded those seen in convalescent plasma across all dose levels. And in fact, the 95% confidence intervals are nonoverlapping at the 100 and 250-microgram dose levels.

Slide 12 shows you the graphical box plot representation of the distribution of these titers, and it's useful as it helps to visualize the median binding antibody titers and the maximum and minimum values below and above the median range for each dose level relative to infection as seen in the convalescent sera group.

After 2 vaccinations at time points of day 36, day 43 and day 57, the median antibody titers for all doses were well above the median for convalescent sera. What is notable is the relevancy, is the tight distribution of titers in vaccinated individuals. This vaccine produces a robust and consistent immunogenicity.

Additionally, note the red dots in the convalescent sera box plot; these red dots represent those 3 additional individuals with confirmed COVID disease that were used as comparators for the live SARS-CoV-2 neutralization assay, which we'll talk about in the next slide.

So here, you see at -- the table showing the neutralizing antibody titers from what's called the plaque-reduction neutralization to 80 or PRNT80. Now the way this is done is that you measure the ability of the blood to limit the virus' ability to infect cells. And the curves are plotted using successive dilution, starting with relatively undiluted blood that would provide 100% neutralization compared to background and ending up with dilutions that can't be distinguished from background level. The PRNT80 thus corresponds to the dilution titer at which the blood from a vaccinated individual can reduce the infectivity of the live SARS-CoV-2 by 80%. And people interchangeably use PRNT80s or PRNT50s that time -- that point estimate at 50%. The PRNT80, in this case, was a more accurate and stringent representation of the neutralizing activity.

In the table, you will see the mean values from the PRNT assays at day 1 and day 43 for the 25- and 100-microgram dose cohorts compared to the convalescent sera group, again, consisting of 3 individuals with confirmed COVID-19 disease. The geometric mean titers of neutralizing antibodies for both doses are above the mean for the convalescent sera group. As a reminder, the convalescent sera group is representative of that larger convalescent sera of 38 additional subjects.

Now Slide 14 shows the graphical representation of the PRNT80 responses. At the 25- and 100-microgram doses, mRNA-1273 was able to induce neutralizing titers against the live virus in all participants. The median values represented by the horizontal lines across the box plots were at or above convalescent sera levels from those 3 individuals.

Finally, on immunogenicity, we look at neutralizing antibodies in a pseudovirus neutralization assay. This assay is designed as a single-infection cycle, high-throughput assay that correlates well to what we can learn from a live virus assay. And the titers were scored at the 50% mark, i.e., the titer at which the blood still diluted can reduce infectivity by 50%.

Comparing the geometric mean pseudovirus neutralization assay results to the mean values from convalescent sera here with 30 individuals, we can see a 2.1-fold increase in titer levels at the 100-microgram dose at day 57, above the mean convalescent sera.

Slide 16 now shows the box plots for each dose as compared to the box plots for the convalescent sera group. In this presentation of the data, it is easier to visualize that, again, after the second vaccination at time points 63, 43 and day 57, neutralizing antibodies were detected in all vaccinated individuals. At the 100- and 250-microgram dose cohorts, the responses were fairly consistent between individuals, and we don't see a significant further difference between 100 and 250 microgram. Both dose levels elicit neutralizing antibodies comparable to values that are in the upper half of the distribution of convalescent sera.

Overall, the immunogenicity data I've described from all 3 assays taken together support the choice of the 100-microgram dose level as the optimal Phase III dose.

So let me turn to T cells. As Stéphane mentioned earlier, in this study, T cell responses against the S1 and S2 regions on the Spike protein were also assessed for the 25- and 100-microgram dose cohorts.

On Slide 17, CD4 T cell responses against the S1 region for the 100-microgram dose are shown. And you can clearly see the expression of Th1 type cytokines, including TNF alpha, interleukin-2 and interferon gamma were predominantly expressed at day 43. That indicates that what we see is a response that is of Th1. We do not see the expression of the Th2 cytokines.

Similarly, on Slide 18, you can see CD4 T cell responses against now peptides from the S2 region. And again, you can see the same observation. These are Th1 cytokines at day 43, with minimal to no Th2-type cytokines demonstrated.

So to conclude on the findings from the data from this interim analysis of mRNA-1273, our vaccine against COVID-19, we found the vaccine to be generally well tolerated with no serious adverse events recorded. mRNA-1273 induced binding antibody titers in both a time- and dose-dependent manner above those seen in convalescent sera. We observed high neutralizing antibody responses that were dose-dependent. And after 2 doses of the 100-microgram dose, mRNA-1273 elicited robust neutralizing titers, with a geometric mean above those seen in convalescent sera as measured now by 2 different assays. Vaccination with mRNA-1273 further has been demonstrated to elicit a Th1-biased T cell response.

Overall, the safety and immunogenicity data supported advancement in the later-stage clinical trials at the 100-microgram dose level. And I'm super proud of all the Moderna and grateful to the NIAID teams that have worked so well and fast and collaboratively on this program, and I'm extremely thankful for the participants in this Phase I study.

So let me now change gears to quickly talk about the clinical development plan for mRNA-1273, where are we and what's ahead? Given the urgency of the global pandemic, we, along with our collaborators at the NIH and with the close support of FDA, have been moving the plan along in a parallel fashion with making sure that we expand the safety database for this vaccine carefully. As such, we started the Phase II trial after Phase I safety data were available, and we expect to start the Phase III trial on July 27.

As it relates to the Phase II, last week, we announced that both age cohorts in this trial are fully enrolled. 300 participants in the 18 to 55 year old age group and 300 participants in the above 55 age group have been enrolled. And this trial is basically designed to confirm the safety, reactogenicity and immunogenicity as seen in the Phase I, with further exploration of the 50-microgram dose level, while we carefully expand the safety database ahead of Phase III.

So let's talk about the Phase III in our late-stage development. There's been a lot of understandable interest in this trial, and I'd like to take this opportunity today to transparently provide you with some relevant details around the trial design and the endpoint definitions to help everybody understand what we're hoping to achieve and how we're going about it.

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The Phase III protocol has been reviewed by FDA and is aligned to their recent guidance on clinical trial design for COVID-19 vaccine studies. We plan to randomize 30,000 participants, 1:1 between vaccine arm and placebo, with a primary endpoint of prevention of symptomatic disease. The primary efficacy analysis will be event-driven based on the known

(technical difficulty)

target efficacy against COVID-19 for powering assumptions here to a point estimate of 60%, and a 95% confidence interval meant to exclude a lower bound greater than 30%. The data will be reviewed on an ongoing basis by an independent safety monitoring committee led by NIH, and this trial is expected to have 2 interim analyses at approximately 53 and 106 events prior to the final event-driven analysis at approximately 151 events.

We define the prevention of symptomatic disease as the following: a participant must have experienced at least 2 of a systemic symptom, whether it's fever, chills, myalgia, headache, sore throat or new taste or smell disorder; or at least 1 respiratory sign of symptom, which include cough, shortness of breath, difficulty breathing or clinical and radiographical evidence of pneumonia. And of course, in order to be classified as a case, the participant must have at least 1 demonstration by RT-PCR of positive viral infection.

Now that being the primary endpoint, the key secondary endpoints would include, on one hand, prevention of infection, even asymptomatic of SARS-CoV-2, and on the other hand, prevention of more severe disease, in this case as measured by such things as hospitalization.

In terms of the plans for filing, I can tell you that we've received Fast Track Designation, and the team is actively preparing indeed for a rolling submission for the BLA so that we're ready once we have the first interim data that supports safety and efficacy.

Let me spend a few minutes just on the trial recruitment. We are working closely with the Operation Warp Speed colleagues and the NIH, including NIAID's COVID-19 Prevention Trials Network that has recently been launched to conduct the Phase III COVE study with the hope to achieve our shared goal that the participants in this trial are indeed representative of the communities at highest risk for COVID-19 and representative of our diverse society.

You can see some of the specific measures we're taking on the right-hand side of the slide. We've approached this challenge really at 2 levels: first, picking vaccination -- vaccinating centers and experts in areas of current and anticipated exposure to infection, think of this as figuring out what the right ZIP code to go after or to go to; and second, working with the local investigators and communities in those ZIP codes so that we can enable those who are at highest risk for both infection and disease have the opportunity to enroll. As announced, we expect to begin vaccinating volunteers on this trial by the end of this month.

With that, let me turn it back to Stéphane.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Tal. With the clinical development plan right in place, the team at Moderna has mobilized quickly in order to manufacture as many doses of mRNA-1273 as we can do, with high quality of course. We believe that Moderna has a good plan to manufacture 500 million doses annually at 100-microgram as a base case. The new projects that our manufacturing team are executing as we speak are designed to take our capacity up to 1 billion doses annually. We have designed our supply chain to ensure we can supply the U.S. market from a U.S. supply chain, and we can supply outside the U.S. markets from outside the U.S. supply chain.

For the U.S., formulated mRNA is being made at our Moderna Technology Center in Massachusetts and Lonza site in New Hampshire. Catalent will do our fill-finish for the U.S. market from Indiana. For outside the U.S., formulated mRNA will be made at Lonza site in Switzerland. ROVI, our latest partner, will do our fill-finish for the outside the U.S. market from Spain.

As many of you are aware, we raised \$1.3 billion in equity capital in May primarily to fund mRNA-1273 stockpiling at risk prior to Phase III data or approval. The Moderna Board decided to do so to ensure that if mRNA-1273 is approved, we will have hundreds of millions of doses available to

protect as many people as we can at launch. That equity capital from our investors has started to be deployed in Q2 to put all the pieces in place to make hundreds of millions of vials, buying raw material, buying capital equipment to be installed and validated at Moderna Technology Center in Massachusetts as well as Lonza in New Hampshire and Lonza [in] Switzerland. And of course, hiring and training personnel. We have already started to make material at risk in preparation for commercial mRNA-1273 doses.

We are moving as quickly and as safely as possible with our mRNA-1273 program in order to generate as much data as possible to enable a risk-benefit assessment of our vaccine for a potential BLA filing. The key upcoming next steps are nonhuman primate challenge model publication. As we shared before, a nonhuman primate model has been run, and we expect this data to be published in the near future; the start of the Phase III trial with site initiations starting as soon as next week; the Phase I interim data for age 55 to 70 and the group of 71 plus; the Phase III interim data; the Phase III interim analysis; the BLA filing upon evidence of Phase III safety and efficacy.

It is difficult to believe that it is only 6 months since the sequence of SARS-CoV-2 virus was made available online. We published encouraging interim Phase I data in The New England Journal of Medicine, showing after vaccination with mRNA-1273, 100% of evaluated participants had neutralizing antibody titers. We are now days away from starting to recruit healthy subjects for a 30,000-participant placebo-controlled randomized Phase III study.

Everyone at Moderna understands the responsibility we have to deliver on the promise of mRNA science and to create a new generation of transformative medicines. And we strive to meet this goal every day.

Our effort in the mRNA-1273 program truly exemplify what the Moderna team strives for on a daily basis.

I am very grateful to the team for all their efforts and commitment to our mission. I am thankful for our team dedication. It has been a 6-month intense, 7-days-a-week effort by hundreds of colleagues at Moderna. I would like to especially recognize and thank the participants in our clinical trials and the clinical trial site investigators and nurses for their help and dedication. I would also like to thank our collaborators at the NIH and NIAID in taking this journey with us. I would also like to thank the many suppliers and partners helping us to scale at this unprecedented pace in a 12-month time frame.

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

QUESTIONS AND ANSWERS

Operator

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

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

Thanks for the significant detail on the data and the Phase III design. Two questions from me. I guess, first, can you comment broadly on durability of the neutralizing titer response? It appears that the average neutralizing titer declined a bit from day 43 to 57. And I'm wondering specifically if you could comment on patients that you followed outside of the study period that you published here and if you're seeing stability in that neutralizing titer level.

And then second, I was also hoping you could comment on CD8 responses and how important you see those or not in the data. I think that's a question that I've gotten a lot from people around the lack of CD8 response.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thanks, Matthew. This is Tal. Let me take these. The -- we don't have any more data on durability. I haven't seen beyond what's there. In fact, these data are fresh and they emerged so that you can see a lot of time points here almost weekly after the boost. I think it's very early days to talk about durability. And as we will see the data, of course, we will share them. There have been recent descriptions, I think, coming both out of cohorts from the U.K. as well as China, whereby the neutralizing antibodies may wane over time. I think my takeaway is that it's entirely plausible, but it also seems that those who start with asymptomatic infection or start with lower levels of antibodies, they seem to lose them more quickly, which probably speaks to the quality and type of the immune response to begin with. I think with that in mind, for me it's reassuring to see that we achieve neutralizing antibodies that are consistently above what you see from people who've actually been sick and who we expect are going to be protected.

Now the antibody levels are naturally going to wane over time. The higher you start, the longer the durability you will see of protective levels in the blood. That's just math and kinetics. But I think the other element here, which you allude to, is the T cell response because that is really -- I think for this -- I think of it as the master coordinator of the response, if you will.

My understanding of the data that is emerging is that neutralizing antibodies are really carrying the brunt of the weight of an immune response against this virus. And in any case, I think of them as sort of the ultimate thing that we can measure that tells us that the right immune response has occurred. And I think that's based on a number of strands of science, both the ability to vaccinate effectively against just the Spike protein a whole bunch of preclinical species and show you could prevent viral replication, and that correlates very nicely with neutralizing antibody levels, as well as the utility of -- potential utility early in disease of the transfer of convalescent plasma. We can come back to that, I'm sure.

So as I look at the T cell responses here, the CD4 is clearly evident and quite robust. It's enough to tell you that you've got the right kind of T cell for 1 phenotype. And indeed, I think people have recently described -- there was a paper from Alessandro Sette's group a couple of weeks ago showing that you actually have in people who've been sick, everybody gets a CD4 response against the Spike protein. And those responses correlate very nicely with antibody, with neutralizing antibodies.

So our vaccine also in that regard elicits what has been described as the relevant immune phenotype for people who have been infected.

CD8s are an interesting question. The -- they're an effector arm against intracellular viruses, as we know them, and against other intracellular changes. And so I think it's not clear to me what the effect of CD8 cells are in viral clearance. Now that being said, we do see some low but significant elevation. If you look carefully at the data out to day 43, the T cell immunologists, they'll tell you that day 43 is far from the ideal time at which to look for T cells relative to the infection. I think it's early data. It's hard to say. And for me, it's harder to pin what the relevance of the CD8 response is against this virus to begin with.

Operator

Our next question comes from Ted Tenthoff with Piper Sandler.

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

And congratulations to everyone on this data. It's just incredible how quickly you guys are moving forward and all the pieces are coming together.

I had a question with respect to the manufacturing side. Can you give us a little bit more of a sense in terms of how many vaccines or doses would be prepared by the time of potential approval around year-end? And what are some of the steps that go into expanding that capacity with Lonza?

Stéphane Bancel - Moderna, Inc. - CEO & Director

Ted, it's Stéphane. Thanks for the question. So on the manufacturing front, as you know, we have not guided precisely in terms of what will be available by the end of the year. We are working very diligently, and the team are doing really a remarkable job just to make as much product as we can. As I've stated on the call today, we have already started to make commercial product at risk, and we'll continue to do so every day, every week, every month.

The way to think, I think, about the ramp, which I think is behind your question, is as we've said in the past, the ramp will increase. So the capacity will increase every month on a forward-looking basis from now on to next month to the month after. So you can -- most model a ramp that will get us to an annual run rate, what we said today in the call, and as we've said before, when we're assuming 50-microgram for the dose a few months back, as you recall. At the dose that we're doing the Phase III 100 microgram, we have a very solid plan to deliver 500 million doses, and we feel very comfortable with this number, again on an annual basis.

You can almost assume kind of almost a linear ramp. And the team has many actions and plans in place to get this up to 1 billion. So it's not in the budget, which is why we characterized it as we did on the call in our remarks. But I wouldn't bet against the team. As you know, Juan and the team all come from experience in large manufacturing organization. For those of you are not aware, Juan used to run manufacturing for Novartis worldwide, including the vaccine business when Novartis had the vaccine business. And so there's still a lot of work to do, which is why we want to be cautious. But you want to think about it in that way. So we will not communicate the year-end exact number because there's so many things that could move around that we want to be cautious. But be reassured that the team is pushing hard, again with a big focus on quality, because this is a product to be injected in people, so quality is very important. But the team is working very hard to make as many doses as we can to help protect as many people as we can, assuming the product gets approved.

Operator

Our next question comes from Salveen Richter with Goldman Sachs.

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

Congratulations on the data. Two questions for me. So one, can you comment on the meaningfulness and the insights you've gained regarding your neutralizing antibody data, just given the lack of consistency with assays across the trials?

And then secondly, given the need to enroll a diverse population in the Phase III and the moving infection rate, how long do you think it will take for you to get to these interim events?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Salveen, it's Tal. Thank you for your 2 questions. Obviously, both are top of mind. So let me start with the neutralizing antibodies.

I think you point to a problem that we're all facing that hopefully in the near future we will see some standardization of these assays. I know it's a top priority for my colleague at the OWS and the NIH, and, I think in that regard, really grateful for our ability to collaborate with them from the get-go here. So I anticipate some of these assays are forming the basis for what will end up being harmonized.

That being said, people have described neutralization, live virus micro neutralization, pseudovirus neutralization. So there's a variety of assays out there. I think the way I think about it is the live viral one should give you roughly in the ballpark of the similar range of responses. And I think for me, the telling bit is to look at the FDA guidance for how do you characterize donor plasma if you want to use plasma from somebody who was sick -- convalescent plasma as treatment. And there, the FDA basically says that you should look at titers of at least 160, in some cases maybe as low as 80, but 160 is what's in their guidance based on a live virus assay. And this is typically thought to refer to the ID50s or the PRNT50s. And

what you see for us, I think, on the live viral assay, is that we get to a geometric mean at the 600 range, 640 or so, and that is at the PRNT80. Now mathematically, the PRNT50 should be even higher.

So I think both based on what we see with our -- with the internal reference set of convalescent plasma in our study and what we understand is sort of the ballpark numbers that are being used out there for similar live viral assays, I think this puts us in a really good place with our vaccine.

The second question is how long will it take to understand safety and efficacy and see an interim? As you rightly point out, that's a function of infection rates and the infection rates in the people whom we vaccinate. And I think the truth here is I don't really know, and I think different people are going to have different opinions. So rather than give you my own crystal ball here, what I -- what we chose to do is be very explicit and transparent about the underlying assumptions powering our study. So you've got the full details for our statistical design. You have an understanding of how many events we're going to be looking at at the first interim, second interim and final analysis.

The -- calling it a success will follow fairly conservative O'Brien-Fleming type crossing rules. It will all be done by an independent data safety monitoring committee looking routinely at the data as they emerge. Now when these events happen, I think it's a function of what will end up being the infection rates at the sites we go. As you point out these very widely, we're doing our best with our collaborators and the sites where we're setting this up to make sure that we're in areas that are seeing infection rates that are significant, and that we are enabling the participation of those individuals who are at highest risk of getting infected.

I hope with those parameters in place that in the coming months, we will be able to demonstrate the safety and efficacy based on an interim analysis of this trial.

Operator

Our next question comes from Cory Kasimov with JPMorgan.

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

Great. Great to see the continued progress here. So 2 questions for me as well.

First one is just given everything you know today, what do you see as the biggest risk at this point to the Phase III trial? And then my second question is putting the cart before the horse a little bit. But curious if you would contract with the government prior to Phase III data and/or approval to supply doses of the vaccine? We saw AstraZeneca already engaged in these types of deals, so I'm wondering how you're thinking about that going forward.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Cory; let me take the first question, and I'll defer to Stéphane on the second.

I think the biggest risk to the Phase III is that -- which Salveen alluded to in the prior question, which is the attack rate in the -- the population that will get vaccinated. If we -- with the current attack rates we're seeing in the U.S., we should be able to vaccinate people, some of whom, ultimately by chance and disposition are going to be at risk and will end up being exposed to the virus. And to the degree that we're able to see those events, the trial will read out sooner and with a robust data set.

To the degree that we are unable to capture those individuals and we end up vaccinating people who do not get exposed, I think it will be very hard to make a determination. We'll have a great safety database, but it will make it challenging to demonstrate efficacy. So I see that as the greatest risk right now.

And with that, let me turn it over to Stéphane to answer the question about contracting.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Thank you, Tal. Cory, so yes, as you know, we have a very close partnership with the U.S. government from OWS, Operation Warp Speed, of course NIAID, BARDA, the FDA. And with all of those agencies, we have sometimes daily, sometimes several times a day discussions. As you can appreciate, it will not be appropriate for me to comment on this. Our goal is obvious. We are making product at risk, and we want to be helpful, starting, of course, with the U.S. government and U.S. citizens.

Operator

Our next question comes from Gena Wang with Barclays.

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

I also wanted to add my congrats on the data. So I have 2 questions. And first one is regarding the convalescent data. Just wondering, did you see any correlation regarding severity and versus the GMP number? And for the live viral, the PRNT80 test, 3 patients, 1 had a close like to 500. Was that patient was more severe versus the other 2 patients that was roughly around 100?

And then my second question was if you can make some comments on the comparison between your pseudoviral neutralizing antibody test versus the BioNTech one.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you, Gena. Appreciate the sentiment and questions. I think on the convalescent data, we -- or more accurately, I think our colleagues at the NIH are looking at this. I don't have any explicit data to share as to the 1:1 correlation of where each of those dots falls relative to disease severity. But I think the field, at large, is informative on this point. And so I would expect that what you're seeing is a range that roughly would correlate. I think the important part here for me is to understand the totality of the data because the relevant point is sort of the geometric mean, if you will, of where that convalescent reference ends up. So I think it is a representative cross-section in terms of the illness or the burden of disease that we have the convalescent sera from and, therefore, I'm comfortable that the geometric mean represents a relevant reference for judging how good our neutralizing antibodies are, how good with the vaccine, at eliciting high titers.

Comparing it to data from others, as I said before, I think it's still tricky. I think if you're looking for a number to latch on to, I think the best comparator to be done is probably looking at live virus versus live virus. I think they used a live virus that's been engineered to give a more high-throughput reporter which allowed them to demonstrate it. I think our live viral assay is sort of the gold standard here. It's the virus as exists in nature. It hasn't been tampered with and what we're measuring is the plaque that it actually induces in cell monolayers. And so I think if I were to pick a number to compare, it's probably the absolute number and the relative performance relative to convalescent plasma of a live viral assay versus another live viral assay.

I think there is a correlation between the pseudovirus neutralization. That's a single-cycle replication assay. So there is a correlation. And if you pull up the supplemental figures from The New England Journal, you can roughly kind of draw that line and see the correlation between the 2 assays. But I think numerically those numbers are probably a tad lower just because of the assay characteristics. I hope that answered your question.

Operator

Our next question comes from Michael Yee with Jefferies.

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

Congrats on the progress. I have 2 questions. One was in thinking about the Phase III data that's enrolling, or Phase III study that's enrolling, I mean, is there any sense that infection rates could actually be very high and the interim data could actually come very quick? And is there any thinking about what would be needed in terms of amount of follow-up or amount of safety or amount of people that have actually been dosed in the sense that it was the opposite scenario where the infections actually come very fast? How would you think about that scenario?

And then my second question was a little more detail on the Phase III. I appreciate that the primary endpoint is actually symptomatic infection. Could you just maybe make a comment about why the endpoint is not actually SARS-CoV-2 infection, and whether that's important too because you could still be infectious if you are infected with SARS-CoV-2?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Thank you. Great questions. So I think the first one, if we do see a signal very soon, then as you rightly point out to, the duration of follow-up of safety is going to be commensurately short. I think the answer there is going to lie not with us, but actually with the FDA. And we've had a pretty close dialogue with them, and I'm super grateful for how they've stepped up to support not just us, but every and many sponsors of vaccine trials, both with individual support and then with a consistent guidance across the industry. They've already sort of -- we've had initial discussions on that in terms of expectations, but I think as you rightly point out to, once we cross that rubicon, it will be up to a dialogue with them to understand how we can translate that first signal into a safe deployment for the population given that we're already manufacturing supplies and hope to have a significant amount of supplies on hand by that time.

Now that brings me to a second point, which is, I think no matter how long the duration of safety follow-up is here, I think it's incumbent on us to make sure that deployment from the earliest start occurs in a manner that allows us to continue to understand the safety profile of this vaccine. This will be the first mRNA vaccine ever approved and -- if we're successful-- and so continuing to collect that safety data will require continued close collaboration with those branches of the government that ultimately, we expect to be responsible for deploying this vaccine early to those who need it the most. And so that as well will require ongoing work, and we're starting to have those conversations.

Your second question was about the endpoint of symptomatic infection and why not include asymptomatic infection. So for me, there are 2 reasons why we -- and we had considered it, and we've had a very robust dialogue with our colleagues at the NIH and as well as with the team at FDA on what is the right endpoint and how one defines it. And this has not been easy. I think if you put it all on balance, I think what's important for us is to demonstrate, first and foremost, the ability to prevent disease. Now there's no doubt that there could be -- and there would be a secondary benefit if one can demonstrate prevention of infection. But I think there are 2 reasons why prevention of symptomatic disease rose to be the sole primary endpoint.

I think the first is, as it relates to the population to whom you want to vaccinate and bring this benefit, it is a much more readily understood by the public know what this does is prevent me from getting sick, that's why I am getting the vaccine. And I think that's a very powerful endpoint for people to be able to understand what we're trying to achieve.

But I think there's a second element that's just as important. If you look at the history of vaccines against respiratory viruses, it is interesting that what they do the best is actually protect from disease. And in fact, the worse the disease, the more effective they are. If you will, even if they don't prevent full infection, they are -- they can blunt the infection by prewiring your immune response to rise more quickly to the challenge should you get infected. And in that regard, I think we're -- it's just scientifically more likely that you can demonstrate a higher level of efficacy against the prevention of disease.

Now you should still -- or we hope we would see some prevention of infection as well, but given there's going to be a higher likelihood and therefore a higher point estimate of prevention of symptomatic disease, and that is what people readily understand to care about, I think it made sense for us to include this as the primary and let the other endpoints be the secondary such that the analysis and our ability to quickly understand the data is solely driven off the prevention of symptomatic disease.

Operator

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

Geoffrey Christopher Meacham - *BofA Merrill Lynch, Research Division - Research Analyst*

Thanks for the question and all the detail and data. I just had a few on the Phase III design. So when you look at the data so far, it's clear that the boost dose confers better protection from infection. And so will the Phase III measure the endpoints from the first or the second dose? And can you speak to your assumptions on age, knowing that it has a big impact on hospitalization risk?

And then real quick, just want to get your thoughts on emergency use authorization, the potential for that prior to getting Phase III results.

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

Thank you, Geoff. Let me take these in succession. So the Phase III, the primary endpoint is being measured -- we're starting to count cases 2 weeks after the boost, because I think that's when you will achieve the maximum ability to protect. Now that being said, we will, of course, be counting cases and following everybody very closely from day 1 as soon as they step into the trial. And so we will be able to look secondarily at the ability of the vaccine to prevent cases from earlier on, and that's from the get-go. But the primary endpoint here, case definition is that which occurs 2 weeks after the boost.

In terms of the age, I think you're right. We believe that older people are the more vulnerable. We are making sure, as part of the trial design, that there's a significant portion of the trial that is going to be people who are either older or have comorbid conditions such that we can ensure that we're not just bringing an effective vaccine to those who are more likely to get infected. We're also making sure that we understand the safety and efficacy in those who are more likely to get sick should they get infected. And so the trial will definitely be geared to look at that.

Emergency use authorization, look, I think that question should probably be directed to our colleagues at FDA. Ultimately, they've given guidance so far in public that expect the bar for an emergency use authorization to be the first clear demonstration of safety and efficacy. I can't speak to their behalf. It will be a conversation with them as our data matures and emerges as to what is the right point to trigger that. I think we have the advantage, I believe, of working very closely with several branches of the U.S. government, including our colleagues at BARDA, the CDC and the NIH. So obviously, as manufacturing gears up, we being the sort of first trial out there and the leading company to be collaborating with the OWS, we expect to be at the tip of the spear here in terms of the eventual deployment once we're able to show that this vaccine is safe and effective.

Operator

Our next question comes from Hartaj Singh with Oppenheimer & Company.

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

Great. Thank you for the questions. And again, a really great, robust data set there. Just a couple of questions post the Phase III. Vaccine distribution is -- has a higher degree of complexity than most other therapeutics. So just how to think about that in terms of, is it going to be administered in the doctor's office? Could you get a broader distribution maybe in the pharmacy? Also, cold refrigeration? And then lastly, the various U.S. and ex-U. S. organizations you have to work with, for example, the ACIP in the U.S. or [WHA] to get further certification. Any initial thoughts on that? Thanks for the questions.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Well, let me take it from a clinical perspective, and then I'll defer to Stéphane to talk about how he's thinking about distribution in the U.S. and ex U.S. I think we expect here the initial deployment to really be one that is handled very closely with the appropriate branches of the government. I would defer to them in terms of the settings in which we will ultimately be able to distribute it to the last mile and make sure that the people who need it the most have access to it. I think that dialogue is only beginning now in terms of getting prepared for that eventual distribution. I'll let Stéphane sort of speak to how we think about the supply chain in its totality and from a global footprint.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes. Thank you, Tal. Yes. So I think Tal started to frame the question correctly, which is, in this first phase, post launch or in the case either will be during BLA review, an emergency use approval in different geographies, that, of course, will be at the decision of local authorities.

We see partnering with the governments as being very important to make sure that people who will need the vaccine the most get it first because, obviously, as we understand the disease more and more, we can now appreciate that an elderly person with comorbidity factor should be earlier in line versus a young person who has no comorbidity factors and so on. And we do not think this is a decision that the company should make. It's really the public health system that should make those decisions. So we could see, in the case of the U.S., potentially working hand in hand with the CDC, where we will ship from our filling facilities finished product to different depot centers across the country for the U.S., where then they will do allocations to hospitals or pharmacies and/or schools or other locations that they will decide to do the deployment.

As you have read, I'm sure, through Operation Warp Speed, the Department of Defense is very involved. It could mean a thing for supply chain reasons. So this is kind of what we anticipate for, I would say, the first few months, where we know across the industry that there is going to be a very tight supply of the vaccine. And I think as we move over the following quarters into more of a normal setup, I think the more traditional channels will come into play. But what we think is very important, and this is really again public health decisions to understand who gets the vaccine first. This is not for a private company to make those decisions. We will not have the right data to be able to make those important decisions. So that's how we think about it.

And I think outside the U.S. is a similar manner, working with governments that are interested to get access to mRNA-1273 so that they can locally decide who gets the vaccine first. Our plan, given we're going to be in a supply-constrained world, is basically as soon as a lot is approved, to basically ship it to whoever has ordered the lot. So that we're going to be kind of hand to mouth to make sure that we don't lose any day.

Operator

Our next question comes from George Farmer with BMO Capital Markets.

George Farmer - BMO Capital Markets Equity Research - Analyst

Sorry. I was on mute. Thanks again for your time this morning, and congratulations from me as well.

Tal, I was wondering if we could drill down into some of the data in the paper. I noticed that at day 29, you see a pretty robust antibody response to the full length Spike protein as well as the RBD. But the -- based on the data from the pseudovirus neutralization assay, it looks like you're not seeing much activity. What's going on there? Are there 2 different classes of antibodies that are arising here? And what do you see the boost being extremely important here as really generating neutralizing antibodies over just general binding antibodies?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

George, that's a really interesting question. I think the truth is, I don't know. I think what's generally been observed in the field, and I think it's true of our data set as well, is that the correlation -- there's a strong correlation between binding antibodies and neutralizing antibodies, but you have to have a certain threshold of antibodies. In other words, the binding assays, the ELISA has to be more sensitive.

And in fact, if you look at the backup, I think it's plot 5 of The New England Journal, when you see the correlation sort of dots between the binding antibody levels and the pseudovirus neutralization assay, you will see that at low binding antibody titers, you're not seeing much as the titers go up, and that sort of seems to be irrespective of whether you got a prime or a boost. And probably the most telling element there is if you look at the 250 microgram, if you get a strong enough initial response, you start to actually get into neutralizing antibody territories, and you've got very high binders. So I think that tells you it's probably not just an effect of the boost, it's actually -- there is a correlation by the numbers with one assay being more sensitive.

Now that said, I do think that scientifically, it makes sense. And from everything we know in immunology, that a boost weeks later will indeed get you a higher quality response and a higher quality response against SARS-CoV-2 means you've got more ability to generate neutralizing antibodies.

It's a bit of a nuanced answer because the truth is I don't know, but I think there may be an element of it. I think the primary driver though is that you simply have a more sensitive assay when you look at total binding activity.

George Farmer - BMO Capital Markets Equity Research - Analyst

Okay, great. And then regarding the Phase II trial, if I do the math correctly, you probably have your first 350 patients enrolled, volunteers enrolled probably have received their booster already. Can you comment on safety so far? What sort of data are we going to see when the results are ultimately presented? Is it going to be the same type of data that we're seeing in Phase I?

And then maybe could you just comment generally if anyone that has received the vaccine and that has been enrolled in your trials has been down with COVID-19.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Yes. So on the Phase II, your math is right. We're looking at these data as we speak. I haven't seen anything surprising, but I can't really comment yet. We're still evaluating that. It's obviously important data for us to look at. We expect to publish them in due course. You'll see similar data like the ones that have emerged from the Phase I. In terms of the endpoint, I think you -- we expect to have a much more robust understanding of the reactogenicity and safety profile of the vaccine based on larger numbers.

The interesting thing about the immunogenicity is that it will kind of fill out the curve because it will get us another data point at 50 micrograms, but it's really interesting to me to see how tight the individuals cluster within any dose range. I mean, if you look at the spread versus infection, it's pretty clear that this vaccine is giving us not just a response in everybody, but a fairly consistent one at that. And so we'll be able to describe that, but I don't think beyond filling out the curve on the immunogenicity plot at 50 microgram. I think really the main takeaway is going to be a deeper and better understanding of the totality of the safety and reactogenicity profile as it emerges. Did I answer all your questions?

George Farmer - BMO Capital Markets Equity Research - Analyst

Yes. I was just wondering if anyone has come down with COVID-19.

Tal Zaks - Moderna, Inc. - Chief Medical Officer

Oh, yes, yes, yes. I think we may have seen one or 2 cases. I don't -- I think they were -- it's more cases of finding people who have been positive when the antibody titers came in. So I don't think yet I've seen an active case on the trial, on any trial. I think we've seen evidence of prior infection because we didn't make it an eligibility criteria. We just post factum looked at antibody levels on day 1 of people who entered. So I think there may be one or 2 individuals who fall on that bucket, but I don't think that's really informative for what you're interested and as am I, which is the ultimate ability of this vaccine to prevent disease.

Operator

Our next question is from Alan Carr with Needham & Company.

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

Just a quick one around manufacturing. You'd spoken earlier about having plans to manufacture outside and inside the U.S. Can you give any more details around that, around the timing? Is one going to happen later than the other? And relative amounts that you expect to be producing in the U.S. versus ex U.S.?

Stéphane Bancel - Moderna, Inc. - CEO & Director

Yes. So this is Stéphane. So if you go back to the slide where we have a manufacturing pictogram, Slide 24, what you see is the U.S. supply is coming both from our Moderna Technology Center in Massachusetts and the Lonza site in New Hampshire. As you know, we have been making mRNA in Massachusetts at our plant since July 2018. And when we announced the Lonza deal, we were very specific to see that the first tech transfer was to New Hampshire.

And so because those are obviously the 2 nodes of manufacturing capacity of formulated mRNA in the U.S., you will expect the U.S. to be ready first, the Lonza Switzerland facility, the teams are working to make this happen. But because the Moderna Technology Center has been making mRNA for 2 years now, we have supply for the U.S. market first. We have not described in detail the split, but we have said that our intent was to be able to make enough product in the U.S. to be able to vaccinate everybody in the U.S., so it kind of gives you a sense as we kind of said that we're able to make 500 million dose with the current plan, that we're working hard and have very specific projects to take this up to 1 billion dose per year. We will at least be able to cover the U.S. population out of the U.S. if there was enough demand for the U.S. If not, of course, if we have a vaccine made in the U.S. that we're not selling in the U.S. for whatever reason, we'll, of course, direct these to countries outside the U.S. who need them.

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

So that 500 million that you're referring to on annual basis, is that coming just from the Moderna plus Lonza in New Hampshire? Or is that including some capacity from Lonza Switzerland, too?

Stéphane Bancel - Moderna, Inc. - CEO & Director

Well, it's including everything. The numbers we have given, we have not given any split. The numbers we have given, the base case of 500 million that we know how to do and up to 1 billion that we are working toward making happen. This is a global number. But I'm just saying, to give you a sense, is the U.S. capacity will be available first. And that we have designed the capacity so that we can supply the U.S. population out of the U.S. supply chain if this is required.

Operator

Our next question comes from Mani Foroohar with SBV Leerink.

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

Congrats on the data. A couple more nuanced ones. You guys mentioned diving into the data and getting a more nuanced perspective on different patient populations and their response in terms of neutralizing titers. Can you comment on any variability in neutralizing titers that you've seen amongst various strains as far as SARS-CoV-2, perhaps the strain is now becoming more globally dominant in some areas? The RBD D614G strain that Regeneron commented on as well.

In terms of -- separately in terms of the Phase III, one of the interesting data that we saw in your Phase I published data is that a few of the patients had missed their second dose because of suspected COVID-19. As you're going to be enrolling the Phase III presumably in geographies with high infectivity rates in a very active pandemic environment, how do you think about it statistically or in terms of the statistical analysis or in terms of clinical trial operations managing around some number of patients, potentially substantial, could miss that second dose? And how do you think of that secondary impact on your statistical powering, on any possible triggers for the IDMC to look to expand enrollment if you have an unexpectedly high number of patients who missed that second dose?

Tal Zaks - Moderna, Inc. - Chief Medical Officer

This is Tal. Let me take them. The first question on strain differences. So as far as we can tell, and I think that's the emerging science to date and it's consistent with some of our emerging data as well, these strains are not immunological escape variants, i.e., they don't allow somebody who's been sick to now get sick again because they get infected by a different strain. And indeed, when you do the in vitro work, neutralizing -- binding and neutralizing antibodies that recognize the wild-type initial strain seem to recognize just as well the various mutations that have been described since then.

These mutations, you speak exclusively about the 614 one, it's outside the receptor binding domain. It's not predicted to -- it's a single point mutation that's not predicted to make a big difference. And when you've got the full-length Spike protein, you're actually -- you're generating antibodies against a pretty large diverse set of epitopes that even if one of them got changed, I think, we would expect the impact on the vaccine to be de minimis. And so far, I think the preclinical data that people have been describing is consistent with that. We will, of course, look at that. And we -- I think we're in the process of testing some of the Phase I share just to ascertain that, but that's also true in clinic. But scientifically and mechanistically, I don't think it's a big concern to date.

In terms of missed second dose, I think you make a very valid point. We're having those active discussions with our investigators. I would make sort of 3 points here.

Number one is there's a very careful and explicit monitoring of anybody with symptoms from the moment they step their foot in the trial. And so that includes also rapid diagnosis to swab anybody and make sure that we understand if somebody is getting sick, so we should be able to identify these people. And, if you will, there's sort of a care package around ensuring a consistent approach to their care or should they get sick, I think it's helpful in that regard.

Number two, still on the safety side of it, there is a -- as you say, there's a data safety monitoring committee. There are routine and frequent safety calls internally that then escalate to that. That body is able, with a separate unblinded statistician, to look at the data as it emerges and help us understand both the performance of the trial from the operational element as well as any safety concerns early on so that we can continue to stay blinded.

Finally, as it relates to powering and statistical design, this has been taken into account. So we already account for a certain percentage of dropouts, people not getting to the second dose or people becoming ill before they reach 2 weeks post the boost to be eligible for that primary endpoint. So the statistical power already accounts for that. That being said, with the support of the -- our collaborators at NIH, both at the level of the data

safety monitoring committee and sort of a harmonized oversight group, if we see that, that exceeds what we had allotted to in terms of the powering, then obviously we'll have a conversation on whether we need to change the sample size in order to react. We're not going to be doing that alone, we're not going to be doing that based on blinded data, but we have -- we put in place the operational mechanisms to ensure that we are able to react in a timely fashion to that.

Operator

Our next question comes from Jonathan Miller with Evercore ISI.

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

If you don't mind, Jon. My question was twofold, if I may. First, the PRNT80 titer you guys published in the paper is 654. The pseudovirus assay suggests PRNT80 is about 2x PRNT50. So is it an accurate analysis? Would it be inaccurate to assume that your PRNT50 on the live virus would have been 1,200 plus? Again, your PRNT80 is 654.

Second was for the live virus, your PRNT80 has 3 patients and there's values on neutralizing antibody response. But on pseudovirus, 2 out of those 3 patients had no neutralizing antibody response. Why is that on the pseudovirus assay?

And finally, if you could speak to the significance of lack of CD8 response.

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

Yes. So I'm just jotting, so I don't forget. Let me start with the end because that's the easiest. I don't think there's a lack of CD8 response. I think the CD8 response, there is a response there. It appears low. It was measured at a certain time point that may be suboptimal, and I've already sort of alluded to what I think is the questionable scientific relevance overall to that response relative to a CD4 Th1 helper phenotype in a robust antibody response.

Working my way back rounds. I'm not sure what you're alluding to. There is -- these 3 subjects who had high levels of neutralizing antibodies, I believe, also had clear evidence of neutralizing antibodies in the pseudoviral assay. So perhaps I missed something, I'm happy to go back afterwards and double check that, and I'll follow up with you if I got it wrong. But I believe that you have a consistent level for 2 of them sort of between the first and second quartile. For the third, it seems to be between the third and fourth quartile, if you look at that.

Finally, your first question about the PRNT50s, I think you're spot on. We expect that if you had tried to calculate PRNT50s here, that numerically, that should be a little over twice the number that you see. So I would concur with your assessment. That's just an estimate.

I think the relevant point here is what I had alluded to in terms of that, which is in the FDA guidance. FDA believes that donor plasma that has neutralizing activity at a titer of 160 or higher is sufficiently good, that one could use it to try and treat and prevent exacerbation of disease in somebody who's already sick.

Now here's an interesting bit of math for you, since your questions revolve on this math. If you take somebody with a titer of 160 as a donor plasma, and you injected, say you inject a unit or 2 of that plasma into a recipient, you've actually now diluted that titer by fivefold. So the effective neutralization titer that you find yourself in the recipient, on top of whatever that recipient may already have, that what you hope will actually help ameliorate their disease is now actually an effective titer of 1 in 30 to 1 in 60, right, because you've taken that 1 in 60 or higher, you've diluted it by giving just the unit into the total plasma volume of that recipient.

So if you kind of start with that math and then you go back and say, well, our vaccine is able to elicit in a live viral assay a geometric mean titer that at a PRNT80 of 640, and as you say, we maybe can guess to extrapolate that it should be over 1,200 if we were to look at PRNT50s, I think that gives us a good degree of confidence that we're eliciting a robust immune response.

Operator

Thank you. And this concludes the question-and-answer session. I would like to now turn the call back over to Stéphane Bancel for closing remarks.

Stéphane Bancel - Moderna, Inc. - CEO & Director

Well, thank you very much, everybody, for joining and for all the questions. We look forward to speaking with you at the latest for Q2 call in early August. Stay safe and have a nice day. Bye.

Operator

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

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