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# EDITED TRANSCRIPT

MRNA.OQ - Moderna Inc to Discuss Phase 1 Interim Analysis for mRNA Flu Vaccine - Conference Call

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**OVERVIEW:**

MRNA provided an update on the first positive interim data from the Phase 1 study of the Co.'s quadrivalent seasonal flu vaccine candidate, mRNA-1010.





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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 of Investor Relations at Moderna. Please go ahead.

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

Thank you, operator. Good morning, everyone, and thank you for joining us on today's call to discuss Phase I interim analyses from our first seasonal flu program, mRNA-1010. You can access the press release issued this morning as well as the slides that we will be reviewing by going to the Investors section of our website. On today's call are Stephane Bancel, our Chief Executive Officer; Stephen Hoge, our President; and Jackie Miller, Senior Vice President, Head of Infectious Disease.

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.

With that, I will turn it over to Stephen.

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**Stephen Hoge** - *Moderna, Inc. - President*

Thank you, Lavina. Good morning and good afternoon, everyone. We're excited this morning to share an update on our quadrivalent influenza vaccine, mRNA-1010. I'd like to start with a little bit of an overview of the influenza epidemiology and current market landscape and then a reprise of our vaccine strategy for the influenza market. I'll then turn it over to Jackie, who will walk you through some of the interim analysis from our quadrivalent mRNA-1010 program before Stephane closes with his closing remarks.

So on Slide 4, just briefly to remind you, the seasonal influenza market is driven by epidemics that occur every year, which varies substantially in severity and generally cause a respiratory syndrome with the symptoms and complications described on the right. Worldwide, influenza leads to 3 million to 5 million severe cases of flu every year and between 300,000 and 600,000 flu-related respiratory deaths annually. About 8% of the U.S. population will experience symptoms every year with approximately 0.5 million hospitalizations and up to 50,000 deaths each year. Peak flu activity tends to come in the fall and winter in temperate climates and increases the number of outpatient visits, urgent care visits and hospitalizations dramatically.

Now on Slide 5, just to remind you, there are 2 major surface glycoproteins on the influenza virus: hemagglutinin and neuraminidase. Hemagglutinin is the primary target of current influenza vaccines. It is, as you can see from the image, the major surface glycoprotein and experiences significant antigenic drift and antigenic shift. It is a key component of both influenza A and B strains that drive the majority of the pathogenicity in humans.

Neuraminidase is the second antigen also present, although less frequently on the surface, and it is variably included in some influenza vaccines currently. It does experience a lower rate of antigenic drift compared to the HA head and independently antibodies to neuraminidase have been shown to correlate with protection.

On the next slide, just to remind you of the disease burden, influenza A strains are the major driver of influenza-related hospitalizations and deaths. As evidenced on this image, which is adapted from a recent publication looking at the drivers of hospitalization and mortality per 100,000 people in the United Kingdom, you can see that influenza A, on the left, leads to the majority of hospitalization and death that is more pronounced in older populations with a smaller amount, fortunately, in younger populations, particularly those under the age of 4. Influenza B, which are present in the vaccines and do circulate does not lead to a substantial amount of hospitalization or death, as you can see here.

Now recent studies of vaccine efficacy over the last couple of decades have found that the average VE or vaccine efficacy against H3 strains, 1 of the 2 strains in influenza A, has been lower, approximately 33% against illness and that is compared to approximately 61% for H1N1 and 54% against the influenza B strains. So lower vaccine efficacy against H3 strains may contribute to the higher medical burden for the -- from the Influenza A family.

Next slide. Briefly, an overview of the current market of vaccines is represented here. In the U.S., the estimated average economic burden of flu is approximately $11 billion each year, and there are 0.5 billion doses of seasonal influenza vaccines that are administered globally in 2019. And the currently approved vaccines are 40% to 60% effective and face significant challenges from both strain mismatch and antigenic drift. An improvement in the vaccine efficacy has the potential, we believe, to substantially increase this already quite large market.

Now improving the efficacy, I'd like to talk to you for a moment on Slide 8. If you look over the years at seasonal influenza virus vaccine effectiveness in the United States using data from the CDC, you will note as these gray bars denote here the variability in the efficacy of the vaccine against Influenza. Approved vaccines vary between 40% or 40% to 60% efficacy in well-matched years, but that efficacy can drop substantially into the 10% to 20% range in years where there is substantial strain mismatching.

Now the gray bars here represent the efficacy vaccine in each year and each season as denoted underneath. What you see in the purple line is the amount of strain matching that happened in the vaccine. And as you'll note, in substantial mismatch years, efficacy significantly declines as low as 19%, for instance, in the 2014, 2015 season.

Now the last point I'd like to make is the prevalent strains changed dramatically year-over-year, as denoted by the pie bar -- pie chart at the bottom of each of these years. In some years, H1 is a predominant strain. In other years, H3 is a predominant strain and the B strains make up a minority in

any given year of the then circulating prevalent strains. The important thing to know is that H3, H1 and the B strains all change in composition each year and the amount of mismatching directionally correlates with the decreases in vaccine efficacy that are observed.

The last thing I would note is that in the last 4 or 5 years, vaccine efficacy has been substantially lower, approximately between 29% and 48% across all of the then circulating strains. If you look at the next slide, some of the reason for this may start to emerge. So if you look at seasonal influenza virus vaccine effectiveness across the different strains, one thing to look at is what's happening in terms of global epidemiology. And in particular, I'd like to focus on the H3N2 strain.

As evidenced here in this image from nextstrain.org, a resource we have all become familiar with through the COVID pandemic, the global circulating H3N2 virus strains over the last 5 years shows a dramatic amount of heterogeneity. In fact, data from Nextstrain showed that over the past 6 years, there have been co-circulation of multiple different clades of the H3N2 viruses each year.

In fact, as you look to the right and you ask, at the beginning of the COVID pandemic, the very beginning of 2020, before things were substantially disrupted epidemiologically for influenza, what was the most common strain in early 2020 for the H3N2 line? And in fact, as you can did not, the most common strain was different across many of the largest countries in the Northern Hemisphere. The U.K., Switzerland, United States, Japan and Canada all had a slightly different strain that was more predominant.

One of the challenges of the current vaccine regime is that a single clade is picked. Often, however, in the H3 category, it represents less than 40% of all circulating H3N2 viruses, creating a high likelihood of mismatch at least in some countries. This, we think, represents one of the most significant opportunities for improving vaccine efficacy.

Now on the next slide, I'd like to remind you of the 3 legs of our strategy for seasonal influenza vaccines. The first is that we have moved forward with a quadrivalent vaccine. And that is a seasonal quadrivalent for flu vaccine, mRNA-1010, using the WHO-recommended strains. This has the benefit of using an established regulatory pathway, although it will be subject to discussions that we have yet to have with regulators.

The second is we are looking to expand coverage beyond quadrivalent flu vaccines. We announced today include the 2 new development candidates in the 1010 line, 1011 and 1012, which add additional hemagglutinin antigens of the Influenza A line H3 or H1 to expand strain matching. This provides an enhanced antigen selection opportunity for public health officials and authorities and the potential for further regional variation to address any regional mismatches.

The third pillar of our strategy previously announced is that we will look to expand the immunologic breadth of our vaccines. This includes broader antigens, as we've already previously announced with the mRNA-1020 and 1030 vaccines. We will accomplish this by adding neuraminidase antigens, which has the potential to improve immunity by targeting antigens that are more consistently conserved and subject to less antigenic drift over most years.

With that, I'd like to turn it over to Jackie to walk you through some of the interim analysis data from mRNA-1010 quadrivalent flu program.

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

Thank you, Stephen. Good morning, good afternoon, good evening, everyone. My name is Jacqueline Miller, and I'm the Senior Vice President and Therapeutic Area Head for Infectious diseases. It's my pleasure this morning to walk you through some of the safety and immunogenicity data from the first interim analysis of our Phase I study, P101.

On Slide 12, you'll see a depiction of our clinical development time line. And we actually announced the start of our Influenza vaccine development program last January. So this has really been a very rapid development year for us in the influenza space. We conducted our IND-enabling studies between January and May. And then in July, we had our first participant dosed in our Phase I study. By September, that study was fully enrolled and now we're happy to share some of the initial results with you today.

On Slide 13, you see the depiction of the mRNA sequences that are included in mRNA-1010. mRNA-1010 is designed as a quadrivalent seasonal influenza vaccine with 4 mRNA sequences, which represent the 4 hemagglutinin molecules from the selected each year by the WHO, FDA and other regulatory agencies. The transcripts each represent the full length of the hemagglutinin antigen, and these are membrane-bound proteins.

So if you go to the next slide, on Slide 14, you see an overview of our ongoing study P101, which has a Phase I and Phase II component. Today, we're here to talk about the Phase I component. And this study overall is evaluating the safety and immunogenicity of different dose levels of the messenger RNA influenza vaccine. As you can see in the box to the left, we investigated 3 dose levels of mRNA-1010 with 45 subjects in each group. The dose levels were 50 micrograms 100 micrograms and 200 micrograms, which were compared to a placebo control.

Safety and immunogenicity have been assessed at day 29. And we now are able to announce that we have selected our 50-microgram dose as the lead candidate for conduct of our Phase III studies. As the selection of a dose is always a balance between safety and immunogenicity, I'm going to review those data with you in detail in the following slides. But first, I'd like to talk about the Phase II study that we have moved on to.

So in the Phase II study, we have adjusted to the data that we have received in Phase I, and we are looking to confirm that 50-microgram dose. This time, we are bracketing that 50-microgram dose with 25 micrograms and 100 micrograms, and we will be comparing to a licensed flu competitor. And this study will certainly give us more precision in our safety and immunogenicity estimates as there are 150 subjects in each group.

So now let's jump into the data on Slide 15. And what you see on this slide are the solicited local adverse events. And these are the aggregated reporting rates of injection site pain, injection site erythema, injection site slowing and axillary or underarm tenderness and swelling. So very similar safety reactions to those you've become used to from our reports on 1273.

You'll see that the data are presented by the younger cohort and older cohort. We do this because the safety profiles can differ between age groups. And you see in the younger cohort, which is over 18, but less than 50 years of age, we have between 21 and 23 subjects per group that received mRNA-1010 and similar numbers in those who are over 50 years of age. The 50-microgram data have been highlighted in the pink box on both tables.

Overall, we see reactogenicity that was -- tended to be lower in the older age group, but showed reporting rates of 82.6% in the younger group and 63.6% in the older group. The majority of these reactions were injection site pain and axillary swelling and tenderness were also commonly reported, although the sample size is really quite low, and we expect additional precision in our Phase II study.

Please note that there were no grade 3 events reported at this dose level in the younger age cohort, and there were -- was only 1 grade 3 event in the over 50-year-old group. No grade 4 events were reported in the entire study. And one final point to leave you with, we had 20% of subjects in both groups who received a saline placebo report adverse events, including 1 grade 3 adverse event in the older age group.

So now on Slide 16. Let's look at solicited systemic adverse events. And again, you see the 50-microgram box highlighted in pink. There were reported rates of any events, 78.3% of younger adults and 54.5% of older adults. The most commonly reported reactions fatigue, myalgia, arthralgia and headache, an adverse event profile that we have seen consistently with respect to the mRNA vaccine platform.

Again, grade 4 events were not reported in this study. And we saw grade 3 events in 3 subjects in the lower in the younger age group and 2 subjects in the older age group. And once again, I would point out that we had approximately 1/3 of subjects in the placebo group in both age cohorts reporting systemic adverse events, including 1 subject reporting grade 3 adverse events in the older age cohort.

So now on Slide 17, let's switch gears to the immunogenicity data, and I'm going to present to you the immunogenicity data first in the younger age cohort and then in the older age cohort. So on this slide, you see the geometric mean titers in terms of hemagglutinin inhibition for the 4 influenza strains in the younger age cohort. The 50-microgram dose is the 1 in the blue bars. And so what you can see is that pre vaccination, antibody titers were relatively high. So the geometric mean titer was around 40 for influenza A titers, A strains or H1N1 and H3N2 and was actually closer to 160 for the influenza B strains.

Then what you can see in the 50-microgram group is that there was relatively little discrimination between different dose levels. And that really is the rationale to continue to explore even lower doses. At the lowest dose level, we see geometric mean titers that were around 530 for the influenza A strains and then 261 for the Victoria lineage and 467 for the Yamagata lineage.

And again, I would point out that the starting antibody titers were extremely high for the influenza B strain. For the influenza A strain, we saw increases that we're reassuring to us as we compared to results from recent other clinical trials, which I'll explain in subsequent slides.

So now please go to Slide 18, where you will see the data in terms of the older adult cohort for geometric mean titers. And once again, the 50-microgram dose are in the blue bars. We see a similar pattern in pre-vaccination titers for the older age group with approximately titers of 40 for the influenza A strains and approximately 80 to 160 for the influenza B strains. Once again, the post-vaccination geometric mean titers had little dose response between the 3 dose levels with HAI titers of 263 for H3N2; 310 for H1N1; 215 for Victoria; and 305 for influenza B Yamagata.

If you go to the next slide, you now see younger adults in terms of geometric fold rises or one of the key regulatory criteria for licensure and seroconversion. So let's start with the seroconversion rates on the right. And once again, in blue, you see the 4 influenza strains with seroconversion rates of 77% to 82% for H1N1 and H3N2, respectively; and for 18% in the Victoria strain; and 41% for the Yamagata strain. This translated into fold rises of about 2.5 to 3 for the influenza B strains. And importantly, in the selected dose level, a meaningful rise of eightfold for H3N2 and tenfold for H1N1.

Now if you look in the older adults, the seroconversion rates were 57% and 81% for H1N1 and H3N2; and were 43% and 10% for Yamagata and Victoria, respectively. Again, titers were two to threefold for the influenza B strains and sixfold geometric fold rises for the influenza A streams.

So what does this mean on Slide 21 with respect to comparison to other influenza vaccines? And we had the opportunity to participate in a clinical trial sponsored by Sanofi Pasteur this past summer, investigating the concomitant use of High-Dose Fluzone or a vaccine intended for the older adult age cohort with mRNA-1273. And the reason why these are important data is because they represent testing of an influenza vaccine during a time when the seroprevalence of the various influenza strains was similar because it was taken at the time that the seroprevalence was represented by pre-vaccination titers in our study. And also because the strains that were used were the same, except a difference in the H3N2 strain.

And so this really allowed us to compare, although must compare cautiously because the assays utilized are different and these data were collected in different studies. Nonetheless, we see some similar patterns to what I've just shown you.

So on this slide, you see the older adults with mRNA-1010 on the left, Fluzone on the right. And if you look at the H1N1 titers, you see larger seroconversion rates with approximately comparable geometric mean titers around the level of 320 with sixfold rises in H1N1 and H3N2 and an eightfold rise for H1N1 for Fluzone but below a fourfold rise for H3N2, one of the strains that causes the most morbidity and mortality in older age groups.

If you look at the influenza B strains in terms of geometric fold rises in the Fluzone High-Dose arm results were also less than 4. We think it's going to be critically important to compare the results in our Phase II study to the licensed comparator, and that will really give us confidence in our dose selection for the Phase III study.

So let me now give you an overview of the next steps we will take in clinical development. As I mentioned, our Phase II study is fully enrolled with 500 participants. There are going to be 3 dose arms at 25, 50 and 100 micrograms with 150 subjects in each arm. And we are looking to compare to a licensed U.S. seasonal flu comparator. The interim analysis data are expected early in 2022. And in this study, we'll be testing the Northern Hemisphere strains for the '21-'22 influenza season.

In terms of Phase III, we're continuing our study preparations. And importantly, now that we have clinical data, are prepared to discuss pathway to licensure with regulatory agencies. We are looking to talk not only with the FDA but regulatory agencies worldwide. The active comparator arm in the Phase III study will allow us to assess noninferiority, and we expect to start this study in 2022.

So on Slide 23, the key takeaways from this presentation are that the mRNA-1010 Phase I results indicate that the lowest dose tested achieves high geometric mean titers and reaches some of the immunogenicity endpoints, which have been set by regulators for current flu vaccines. The mRNA-1010 shows similar immunogenicity, at least in a side-to-side comparison of not identical studies as a current enhanced flu vaccine.

There's no dose response observed between the 50-, 100- and 200-microgram doses. And so there may be a potential in the evaluation of lower doses. In terms of preparations for Phase III, our Phase II study, which evaluates 50 -- or 25, 50 and 100 micrograms is fully enrolled. We expect to report interim analysis data in 2022 and the active arm comparator will allow for the head-to-head comparison. And these Phase III data are really critical because they will enable us to feel even more confidence in our Phase III dose selection.

So with that, I'll conclude and hand over to Stephane Bancel to finish the presentation.

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

Thank you, Jackie and Stephen. Good morning or good afternoon, everyone. With today's new flu critical milestone, we have one more component of our pan-respiratory annual booster vaccine. You recall our RSV vaccine is already in Phase II. As you know, this is our company's #1 priority. We now have a line of sight for an annual booster that could contain COVID plus flu plus RSV in a single shot.

Next slide. Because of the modularity of our mRNA platform, don't think of mRNA-1010 as our ultimate best group products. We think of 1010 as our first step into a fast iteration development cycle. 1010 is our first step towards regulatory approval, and it already looks noninferior to the most efficacious flu vaccine on the market. As Stephen explained, we are working to expand through flu strain coverage with 1011 and 1012, adding more HA antigen like H3N2 or H1N1. And we're also increasing immunologic breadth by adding NA antigens to HA antigens.

Our vision for our pan-respiratory annual booster vaccine is a combo of COVID plus flu plus RSV with best-in-class performance, best coverage and immunologic breadth on flu. One of the additional uniqueness of our strategy is we can adapt the annual booster to a country or a region of the world. Why would Canada use an Australia flu strain if we can incorporate the relevant strain to protect people in Canada?

We believe a pan-respiratory annual booster vaccine will present a large opportunity for Moderna. We believe we can create a lot of value for the health care system and should be able to capture premium pricing. A single vaccine took over multiple viruses, starting with a sum of the part, COVID cost, flu cost, RSV cost.

Compliance with a pan-respiratory annual booster will drive value for payers. Convenience to the consumer, everybody will prepare 1 shot to 3 shot every fall. And of course, reduction impacting administration costs in health care systems. As you know, in many countries, it is more expensive to administer the vaccine than the current cost of a COVID-19 vaccine. We also believe that post-COVID, the pan-respiratory market will be much larger than the flu market. We believe Moderna will be the first company to market with COVID plus flu and then a COVID plus flu plus RSV booster.

Millions of people suffer each year of pan-respiratory infection. We get disease, some of us and get hospitalized, and the most unfortunate die. We believe we have a unique opportunity to have a profound impact to prevent these diseases, these hospitalizations and these deaths. Our strategy is very clear. We, as a company, are laser-focused on execution. And this focus is well exemplified by the Moderna team having already enrolled the Phase II study for flu. We have a unique opportunity to profoundly transform disease prevention and help hundreds of millions of people around the planet each year.

With this, we'll be happy to take your question now. Thank you.

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## QUESTIONS AND ANSWERS

**Operator**

(Operator Instructions) Our first question comes from Salveen Richter with Goldman Sachs.

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

Two questions for you. One is when we look at the HI titers here -- or actually, I'm sorry, I'm going to ask a different question. But when you look at the younger adults and older adults, you observed a threefold GMFR change for the Yamagata strain in a twofold for the B/Victoria from baseline versus higher fold for other strains. Why might that be the case? Do these strains have higher prevalence which could lead to higher titers from pre exposure? Maybe you could just help us understand also what's driving the confidence that a lower dose may work.

**Stephen Hoge** - *Moderna, Inc. - President*

Yes. Thank you for the question. So first, as you noted, looking maybe just at the younger adults, we saw eight to tenfold rises in GMFR for the influenza A. And as I tried to cover in the epidemiology, that is where the burden of disease is particularly in older adults. And so there where we saw 8 to 10 in younger adults and the six-fold GMFR rise in the older adults, we think it's going after the current epidemiology, the morbidity mortality.

Influenza B, as I covered, is predominantly seen as a disease burden in younger patient populations, it's actually children. And in that case, it is -- has generally been seen, as Jackie presented, that boosting in the influenza B category. For instance, with Fluzone this past fall, GMFRs and titers have been slightly lower.

As you noted, I would also note that the baseline titers are higher. And so many baseline titers are well above 1 to 40, both in our study and in the Fluzone HD study that Jackie presented, often above 10 to 160. And it's just a simple function of math that you can't get to a higher boosting if you start with a higher baseline titer.

Now the question you asked about why is that. I think it's a fair question about whether there's a burden of disease or whether influenza B is circulating pretty regularly in adult populations without creating disease and therefore, maintaining higher titers. It could also be a function of just a hemagglutinin, the antigens on those viruses. And particularly the 2 influenza B strains that were most recently included in the vaccines. That may change as other influenza B strains are changed. So that may change year-over-year and really be a function of the antigen. And I think the evidence for that could come from the fact that both the enhanced premium Fluzone HD vaccine and Moderna saw similar type responses in terms of the boosting of the GMFR against those viruses.

Now lastly on your question of 25 micrograms. We did not see for any of these antigens a significant dose response which I think leads us to conclude that we can go even lower than 50 micrograms if we were to choose to. Now this is looking, though, at neutralizing antibodies. And one of the other considerations you always want to have is obviously boosting T cell responses and other forms that are not captured in the measurements that we're doing at this point in just this Phase I study.

And so in order to be sure about that choice, as Jackie said, we really want to evaluate the 25-microgram dose, but also the 50- to 100-microgram of dose in the Phase II against a licensed comparator. And that will probably be the first time that we have a real direct comparison head-to-head in that study. It's also been powered to 150 per arm, which will give us much more consistency in terms of the data and the individual performance.

It is possible that looking at that data, we will see that 25 micrograms is more than enough as a dose. And ultimately, we think we want to have a look to know for sure. But as Jackie said, our ingoing assumption is that the 50-microgram dose will be more than sufficient to achieve very high immunogenicity and at least through first approximation, an immunogenicity response that looks as good as the best enhanced premium vaccine in the market today.

**Operator**

Our next question comes from Matthew Harrison with Morgan Stanley.

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

Great. I guess 2 for me. So first on dose response. You haven't discussed seroconversion. It does look like with the exception of H3, you do have somewhat of a dose response on seroconversion. So maybe you could just discuss how that goes into your thinking when thinking about dose?

And then secondly, just on overall titers and fold increases that you can achieve, could you maybe comment on how you're thinking about that with additional constructs or adding different antigens and just your thoughts on the ability to potentially increase the folds that you can achieve with this?

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

Thanks, Matt, for the question. So on your conversion, I think you're correct that seroconversion rates were technically a little bit higher at higher doses, particularly I think in the older adults, if you look at it in the H1N1 line. But that wasn't consistent. And in fact, in the H3N2 seroconversion rates, you'll see that, that wasn't the case, and we had very high 81% of 50 micrograms seroconversion.

So I think the short answer is we need a larger N and in the study to be able to resolve whether those are, in fact, differences that are real. There are hints in a couple of places, for instance, in H1N1, as you point out, but we wouldn't make the decision based just on this data. And so we'll look into Phase II to increase the N and try and sharpen that, and we'll know for sure whether we think there's a benefit there.

The thing one would say about addition of antigens is that part of our strategy has always been in vaccines and including in the flu vaccine program, is to move forward with a product with the quadrivalent vaccine, the mRNA-1010, that is, we think, is hopefully going to be as good or better as what's out there in the enhanced vaccine market, and we're on that path with this data today.

But that is just the entry point. And what we would want to do over time is add even in that 1010 framework additional antigens. And what we're -- we said with the 1011 and 1012 programs is particularly additional HAs for the influenza A lines. And why does that matter as it relates to seroconversion? We think additional strain coverage in both H1 and H3 will improve matching and potential coverage of circulating strains and deal with some of the pressure that gets put on the virus circulating intraseason as a result of vaccines. There will perhaps be some benefit -- cross benefit to increasing the number of antigens that we put in the influenza A state. We'll have to look at that, but that would also increase your conversion rates.

And so the question around -- to tie the 2 halves of the question together around whether we should explore higher doses to push to even higher north of 80% seroconversion rates, we actually think, first, we need to look at that from a dose perspective and make sure there is a difference there. But the second, if we do want to go down that path, does it make more sense to add more diverse antigens to improve that across a range of strains? Or does it make sense to do it through dose escalation against individual strains? And we will evaluate that as part of the 1010, 1011 and 1012 programs.

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**Operator**

Our next question comes from Michael Yee with Jefferies.

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

We had 2 questions. One is maybe a high-level strategy question, which is to hear you clearly say whether you're similar or differentiated to the high-dose high-efficacy vaccines and how important it is just to get the product to market, and to really just try to enhance all of this stuff in the future.

And as part of that, the second question is the combinability question, which I think has always attempted to be a differentiation. And when you look at your high doses here, there is clearly some differentiation in terms of more side effects. So how confident are you that you could actually combine a couple of different diseases and get up to 100, 150 micrograms and still be okay on side effects as you combine vaccine?

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**Stephen Hoge** - *Moderna, Inc. - President*

Thank you, Michael. Both great questions. So let me try and cover them first. So as a strategy matter, just to be clear, I think you asked a question about whether we are a superior/inferior to Fluzone HD. Obviously, the data is not head-to-head. We can't make a direct comparison. We present it as a benchmark, but only as guidance. I think the best place we will start to have data, as Jackie said, is from the Phase II study, where we include an active license comparator head-to-head in the same population at the same time against the same strains in the same assay. So that is an important caveat.

But as a strategy point, as I tried to lay out at the beginning, our view on mRNA-1010 from the beginning has -- we want to be -- we want to aim at being as good as the best enhanced vaccines in the market, those that achieve premium pricing for older adults, like Fluzone HD does with the highest market share in the United States and that we want to use that as the starting point for what we then go build off of in our overall flu franchise.

The reason we want to aim at that right now is many of the things that we're talking about doing in our platform, for instance, adding additional clades in influenza A line, the 1011 and 1012 programs and adding different additional antigens like the neuraminidase antigens to broaden protection, those are not precedented in the current market. And obviously, for that reason, we have the benefit of previous regulatory pathways and clear guidance around that.

And so in order to work within the existing framework, we are prioritizing moving quickly forward with the mRNA-1010 program, a quadrivalent influenza vaccine and ultimately, hopefully, going down more established regulatory pathways more quickly while we bring in the second, third and subsequent generations of product improvements that we really do think will drive efficacy improvements and close some of the gaps from mismatch and other challenges in the flu market.

Now why push forward with that 1010 product as rapidly as we are? First, we think that there's an opportunity to -- in the enhanced vaccine space for an mRNA vaccine. But second is, as Stephane said, our overall strategy is eventually to do combinations, and maybe to get to your second question, which is we do believe that there's a substantial value to be created by combining a very strong influenza vaccine, seasonal influenza vaccine platforms, mRNA-1010 with COVID and eventually COVID plus RSV boosters.

And we think that will manifest itself not just in the combination with a very -- we believe, a very strong COVID booster, which is mRNA-1273 and subsequent generations of that product but also to facilitate better clients and lower cost for administration health care systems, which no doubt will be an issue as we go forward.

So we're big believers in that and that's ultimately the role that 1010 programs play for us. We want to be as good as we're seeing with enhanced vaccines with that program, and then what we want to do is do combinations, and then use 1010 as the foundation to build even taller with the addition of additional antigens.

1010 also does have the opportunity to do more regional tailoring, as Stephane described, because we've all seen the flexibility of mRNA manufacturing processes, for instance, in terms of the variance in the response to COVID. And so that does provide an immediate opportunity to also create value where we do see regional suboptimization in the selection of antigens today.

Now on the question of reactogenicity. I think your point on the influenza vaccine study presented here, 1010, which is that we did see a trend towards higher reaction, higher doses, that is consistent. And although these are low end, generally, and as Jackie pointed out, we saw quite high reactogenicity even in the placebo arm, which is probably just a function of in these Phase I studies, you work really hard solicit that day 7 reactogenicity. You put in place tools that are even more aggressive because we want to make sure that we characterize and understand it. But it

makes it very hard to compare that reactivity against other standards until you do something like what we're doing in our Phase II which is you bring in an active comparator control. And therefore, you really do know what you're up against and how it compares.

And so subject to that data, I don't know for sure where we are on that spectrum. But I do agree with the general trend that we've seen, which is that higher doses do elicit those sorts of increased solicited reactogenicity tolerability questions over the first week.

Now how -- what drives that? We -- the ultimate answer is we'll have to run the combination studies and show that we do not see any sort of synergy or additive effects as we go combine vaccines and boosters across many different strains. That data will be dispositive. We are doing -- we are running those experiments as we speak with -- we are running combination studies with approved vaccines as we speak right now for the mRNA-1273 program. And -- but what we really need to do is show that combinations for instance, our mRNA-1073 program, which is a combination of flu and a COVID booster, shows similar comparable or better, but we have to evaluate the reactogenicity in that vaccine context.

Most of the reactogenicity I think you see here and most of the reactogenicity you see as we increase doses in our vaccines is, we believe, related to the antigens. And so in particular, as you push up in doses, you tend to see higher responses to the antigens and not specifically to the technology, the mRNA and the LNP. And there's evidence of that, I would say that you see this emerge in different dose levels across different vaccines and for different dose frequencies, right? First dose versus second or third dose in our CMV vaccine.

And so I think what we would -- what I would say in summation is I don't think we can look at a mass number and make that hard determination today about whether 200 micrograms or 150 micrograms is going to be the right answer. It is likely going to be a combination of what amount of antigens and what kind of immunogenicity against those antigens. We also think it's 1 of those things, therefore, that you have to evaluate clinically to know for sure. But we have reasons to hope and believe that we're going to be able to combine things and achieve good protection, good boosting as we would hope to do, and ultimately, an acceptable safety and tolerability profile for an annual vaccine.

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**Operator**

Our next question comes from Gena Wang with Barclays.

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

I have 2. One is regarding efficacy and the other is regarding safety. So thank you for sharing the data compared to Fluzone, but I think a much better cross-trial comparison should be seroconversion rates. And since those also will be the approvable endpoint and GMP full change. So when we pull out the data and we did see your number showed quite high or better compared to a few strains. However, B/Victoria seems a little bit lower compared to Fluzone.

And I wanted to know that if you're -- for the 50-microgram or each dose cohort, what's the ratio of each 4 sequences? Would these -- 1 to 1 to 1 to 1? And if that's the case, given the overall low seroconversion rates for B/Victoria, do you need to increase RNA concentration for this strain?

And my second question is regarding the safety, and you did share some high-level reactogenicity rates. But just wondering, regarding only for your 50-microgram cohort, how's your -- the injection site pain, headache, fatigue, myalgia compared to the other flu -- or the Fluzone's rate. We know that the 47% for injection site pain, headache is 16%, fatigue at 11%, myalgia is 24%, that's for Fluzone and how that compared to your 50 microgram? Was yours also comparable to Fluzone or was it higher?

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**Stephen Hoge** - *Moderna, Inc. - President*

Thank you, Gena. Both great questions. So let me try and take and then I'll invite Jackie to comment on anything I get wrong here. But just first on the seroconversion rate, thank you for pointing that out. Seroconversion rate is also another important endpoint. And if you look at the seroconversion rates particularly in the older adults, and we focus a lot of our attention in the older adult population because as we've talked about, that's where we think the pan-respiratory vaccine need is the most significant.

And if we look at those older adults, as you noted, in Influenza A, we saw actually higher seroconversion rates than have been reported elsewhere, particularly in the H3 lineage, which is exciting. And as you noticed, in the influenza B/Victoria strain, we saw slightly lower. We did see higher in the, I believe, when you compare against the published rates in the B/Yamagata strain. So it is a bit of a mixed picture and strain-specific, but we are pleased with the strain in Influenza A and obviously, with Yamagata. And we do know, as you said, the lower seroconversion rates in Victoria.

I would note though that generally, people have reported quite low seroconversion rates for Victoria, particularly in the older populations, including for Fluzone HD. And so we have to be careful about over interpreting whether there is -- those differences, any of them, candidly, are significant when we're dealing with such a low end in our current study. The answer to that question really has to come from the Phase II study, where we've increased that end quite dramatically at these dose levels and will help us drive that resolution.

But on the specific question of the relative math is -- it is 1 to 1 to 1 to 1. So you can divide the dose mass by 4 and you get the representative mass math for each of the strains. Again, that is consistent with approaches taken with general -- in general in influenza vaccines.

And on the question of whether we think we should increase the mass for B/Victoria strain. I think the answer there is complex because -- you might say if we were managing to that result, just the B/Victoria's seroconversion rate, you might say, well, sure, why not increase it.

But that is -- maybe just solving for that 1 value. If you kind of pull back and say, well, where is the epidemiology? Where is the disease that will ultimately show up in a vaccine efficacy measure? And ultimately show up as a decrease in cases and hopefully, then in the market morbidity and mortality.

It is really not in the Victoria strain that you would go do that. It would be continuing to focus on having the highest possible responses in influenza A. And so I think a difficult challenge for us would be the decision to increase the mass in Victoria and perhaps to do that at some expense to what's happening with influenza A. We really do believe the epidemiology says we should be focusing on H1 and H3.

And then the last thing I'd say is because there's so much uncertainty about any of the current vaccines' ability to effectively boost or seroconvert against the Victoria strain, I think there's an open question as to whether or not that strain is actually from an antigen perspective, suboptimal; and whether subsequent strain evolutions that happen, for instance, in the coming year, might obviate that need. Again, these are strains that are getting updated in the current vaccine as we speak.

So we are not, at the present time, planning to change that mass or ratios. We're going to continue to look at additional strains of B as we go forward, and we're quite pleased to focus on the influenza A strain where we think that -- influenza A virus is where we think that the opportunity for improvement on current vaccines is most important.

Now second question on the safety tolerability profile. I would really caution against direct comparisons. We have to provide that data, but we think it has to come from the Phase II study where we have an active comparator. And the reason I would say that is we are dealing with incredibly low numbers, we have 20 subjects. In many cases, when you're looking at a grade 2 or grade 3 difference versus placebo, it is a single subject difference. And again, we are soliciting quite substantially in a Phase I study, those results for that first week.

And so while you -- there's a tendency, and I'm sure it will happen for people who want to sort of directly compare these numbers, we, on our side, we're going to wait until we have an active comparator in the same regime before we feel like we can feel confident about it. I would point out what Jackie said before, which is the rate of solicited adverse events, both systemic and local for the placebo were actually very high. And you even saw grade 3 events in the older adults.

And that just is, again, a sign of the types of solicited reporting that we're doing in these Phase I studies to make sure that we're appropriately monitoring safety and tolerability and can be a confounder. So we would not recommend direct comparison of that yet.

Intra study comparisons are acceptable, and that's where we conclude. We don't think we need to go higher on dose towards 200 micron. There's no dose response, and we see more reactogenicity. But actually, between study comparisons are really something we should hold off from doing and wait until the Phase II results, particularly on something like tolerability, which is so subject to stimulation.

And that's why we're pleased with the Phase II study. It's fully enrolled. There's 500 people in it, 150 in each of the dose arms, which gives us good resolution. And we have, as I said a moment ago, in the same study, blinded, an active comparator, which is a licensed influenza vaccine. That will be the first time we really can make a comparison about tolerability.

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

And Stephen, it's Jackie. Maybe just to conclude on the immunogenicity point, I think it's important to remember that while immunogenicity is an important end point, it's not exactly the same as efficacy. So there actually are licensed flu vaccines that have failed on the regulatory criteria from an immunogenicity perspective for B strains. And in particular, Flublok, one of the most recently licensed vaccines, they missed on their GMTs for the B/Victoria Strain in 1 study and missed on seroconversion rates for H1N1 and B/Victoria in the second study.

And the other thing I would say is that while the hemagglutinin inhibition antibodies are an important marker of how these vaccines work, there are also other elements that we know that messenger RNA as a platform are capable of inducing. So we've seen particularly in the 1273 program, the induction of cell-mediated immunity, and we will be studying that in our program as well. So there may be components that we're not measuring here that will ultimately contribute to efficacy. And certainly with Flublok, despite missing some of those immunogenicity endpoints, it's a quite efficacious vaccine.

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**Operator**

Our next question comes from Andrew Galler with Wolfe Research.

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**Alec Warren Stranahan** - *BofA Securities, Research Division - Associate*

I just said to -- so first, I just want to know, if you had any data on an IgA response in mucos immunity? And then secondly, just on reactogenicity. I just wanted to see how you think the grade 3 events compare to licensed vaccines.

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**Stephen Hoge** - *Moderna, Inc. - President*

Thank you for the question. So first on the IgA, in the Phase I study, we did not sample that. We do have data from our other [respiratory] vaccines, actually specifically 1273, but we've also looked at, preclinically, across our range. And we have seen mucosal immunity from this platform. Now obviously, both in humans to prevention of infection with [SARS-CoV-2] and in animals, but not in this study.

And, I think on the question of reactogenicity in comparison, I just referenced that we're still dealing with the Phase I study. It's a very different, small number of end.

And so we would advise against direct comparisons because it is, ultimately, a very sub-selected group of people that we go look at this (inaudible) the Phase I, we need larger end to be able to make direct comparisons, we believe, in the future.

And then the other thing I'd say is that, obviously, protocol is all different. This, as a dosing regime, is a single booster, in the context of current fall, where some of our other vaccines were studied, we've seen multiple doses and other regimes. So it just makes direct comparison quite difficult.

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**Operator**

Our next question comes from Cory Kasimov with JPMorgan.

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

Two for me as well. So in terms of the Phase III design, should we assume the comparison versus an established standard of care will be designed as non-inferiority and not superiority. And then second question is kind of thinking about the newer 1011 and 1012 programs. Is there any sort of expectation for added safety liabilities, as you add additional strains? Or would you anticipate the profile to look similar, overall?

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**Stephen Hoge** - *Moderna, Inc. - President*

Great. Thank you. Let me -- I'll take the first one. The short answer is, the established regulatory pathways due or are based on non-inferiority. The accelerated approval pathways and guidances that are out there. However, our ultimate design for that study, is going to be dependent upon regulatory consultations that are up and running now and that we have clinical data, as Jackie said.

So I can't answer that question for sure. But I would -- I would point to the precedented pathways that exist and the fact that our objective with the Quadrant 1010 program is to move quickly, so that we can eventually move to combination, quickly, there.

The reacto profile as we add additional antigens. In general, the profile we see, as we added antigens, I mean -- not to be lost in this moment, is this is a quadrivalent influenza vaccine, which in more mRNA (inaudible) vaccine, has not happened before. And it is quite comforting to us to see the balance of reactogenicity and immunogenicity that we saw in this study.

As we look add additional strains in the future and do additional combinations, we will evaluate that. Obviously, we've done that preclinically, but there's limitations to the ability of preclinical to sort of guide those suites.

We do not, currently, believe that there is going to be a limit that is related to the technology, i.e., the amount of mRNA or lipid nanoparticle and really what this is, is a balancing act between the antigens and making sure that we get the right immunogenicity and that any one of those antigens don't over contribute, in terms of reactogenicity.

And again, we think those are, ultimately, clinical endpoints. But we are quite pleased with the direction that we're heading, right now, with the 4 mRNAs that are already there. I believe that we get there with the quadrivalent vaccine in [MRH and 10] that the addition of a fifth or a sixth mRNA around hemoglobin antigen, will not dramatically change that picture.

It feels relatively consistent, as we have now gone from a single monovalent, our prior (inaudible) experiences, to the quadrivalent.

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**Operator**

Our next question comes from Tyler Van Buren with Cowen.

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

I had two topics I wanted to ask on. The first was, with the recent Vaccines Day, Sanofi was vocal in saying that late strain selection is not a solution for improved efficacy in that 2 out of the 10 past years, had strained mismatch. So curious to get your thoughts on those comments.

And if the speed of manufacturing and prediction of accurate strains, is now less of a competitive edge relative to the new 10, 11 and 10, 12 candidates, adding 1 and 2 additional flu antigens. And the second is just, at a high level, why do you think efficacy here seems to be similar to traditional vaccines for flu, when mRNA was so superior for COVID?

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**Stephen Hoge** - *Moderna, Inc. - President*

Great questions. So let me take the first one, which is the strain mismatch point. I mean, if you look at that mismatches as simply -- was it the #1 strain? I think, you asked that question -- that question gets asked very narrowly. If you look at the next strain data across, let's just say, H3 and the evolution of the picture over the last 4 or 5 years, what you see is that there are multiple circulating H3 clades.

And again, clades are defined as having different immunogenicity, often between them. And so the question really is why is, Quadrivalent, in the definition of whether you've got the #1 H3, on average, globally, the success measure here?

We actually -- we understand why it has been, historically, but we believe that providing tools to public health officials to think more broadly about that. i.e., that there are multiple H3 strain circulating that have 20%, 30%, 40% of the circulating epidemiology.

We think that, that actually is the right way to think about this disease. It's just following the epidemiology, rather than following precedent.

And so our view on mismatch and whether or not narrowly, we focus just on whether it was mismatch 1 year in 7 or 1 year in 10, as others may have commented, probably misses that nuance and also misses the nuance that the most prevalent strain in different geographies, might be different and might need some regional adaptation or might need polyvalency and multivalency solution.

So our goal is to bring forward solutions that could work with public health officials. It's ultimately, their decision, particularly, as it is right now, in the groups like the WHO, about what goes into these vaccines, but we want to make sure that we actually advance the science towards something where you can do more, where you can cover more strains. Of course, we also can make later strain selections.

But I think, as you pointed out, later strain selections, or multiple strains, in additions of pentavalent, hexavalent, heptavalent vaccine, actually achieve similar results. And we're quite comfortable using our platform to try and address the problem from either one of those directions.

But if we can actually move beyond quadrivalent, we may be able to address much of that mismatch risk, as well as address the fact that there are regional differences rather than a single, global norm of a single clade or at least particularly with H3N2. I apologize, the second question, could you just restate it again?

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

Yes. It was just -- at a high level, why do you think the efficacy here seems to be similar to traditional vaccines for flu, when mRNA was so superior for COVID? And how should we think about that, when it comes to RSV or CMV or other diseases?

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**Stephen Hoge** - *Moderna, Inc. - President*

Great question. Thank you for reminding me. So first of all, I would remind you that we're not looking at efficacy here. We are looking at immunogenicity. And so there's a desire to extrapolate from this immunogenicity, absolute confidence about what the curve of efficacy looks like. I don't think, that's clearly doable. I know we all wish to do it.

But I think, where we see immunogenicity at a very high level in a well-matched strain, when we match, let's say, on the quadrivalent, we're quite encouraged by that because we do think that a lot of the challenge, in terms of vaccine efficacy, is actually matching circulating strains and, as I said a moment ago, the diversity of the circulating strains, which is a feature that we think, (inaudible) uniquely compete on.

But when you match well, you can get good efficacy. I think, the complaint often around influenza vaccines, generally, is just when we get to those mismatches and also regional- or country-level mismatches. So -- But we are looking, ultimately, at [immunogenictiar], not efficacy. Efficacy will come later.

And it is possible that you would see, even in equally-matched superior efficacy, as a result of the mRNA platform. We, ultimately, need to go prove that with other data. not with just the titers today.

The second thing I'd point to, is that these titers, while we all do compare the HAI titers and assays, and you can look at things like GMFR and 0 conversion rates and try and intuit comparisons between, these are still different assays.

We've all gotten quite accustomed of the idea that looking between different companies and different assays, can be challenging until you have head-to-head in the same assay is, as we're doing in the Phase II, it is difficult to know, for sure.

And so I have not yet -- we have not yet passed judgment, at least internally, on the Quadrivalent [1010] program and what its efficacy might be. I will note, though, as I think one of the earlier questions asked, our goal with the 1010 program, is to be at least as good as the best and move very quickly to establish paradigms and then show how you improve, which we think is about epidemiology not necessarily just technology.

Now, our ability to address that epidemiology, is a function of mRNA technology and the fact that we think we can quickly add 6, 7 strains, if necessary.

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

And Stephen, it's Jackie. If you don't mind, I'll just add, to go back to an earlier point. So hemagglutinin inhibition titers are useful. As you said, they're not the same as full efficacy. There's an entire size of the immune-adaptive respose, the T cell response that we aren't measuring, that will measure in subsequent studies and be able to report on.

But I want to take a step back and just remind everyone that the novel coronavirus was something that human population, as a whole, hadn't seen before and is likely the reason why it has spread so quickly through the population.

And so vaccinating a completely naive population, is very different than vaccinating a highly-boosted and exposed population, which is the case with influenza, where all of us have had multiple flu infections. And if we're good about vaccination, yearly influenza boosters. And in particular, we were running this study at a time when -- If you'll remember in the early summer, everybody was starting to mix again after a long time of social distancing.

So I think, we may be seeing pre-existing titers that maybe, are not the usual pattern. It's why we compared to Fluzone HD in a study that was conducted during a comparable time period. The other thing I would mention is that Fluzone HD is not a standard seasonal influenza vaccine. It's the high-dose influenza vaccine, intended for older adults.

So I think, there's good reason to hope that our mRNA-1010 will be highly efficacious and capitalize on the benefit of the technology. But as Stephen said, we're not relying on that. We're looking at other ways to improve.

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**Operator**

Next question comes from Hartaj Singh with Oppenheimer & Company.

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

I've just got two quick ones and really nice data. One is, Stephen, I think you had mentioned this, but can you just walk us through, when the Quad vaccine and the additional antigens could actually be in the clinic? I mean, would you have to wait for the Phase II data or have a full Phase III data set before we could start seeing those in the clinic? And then just remind us, what the cold chain requirements are for 1010 and the other ones?

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**Stephen Hoge** - *Moderna, Inc. - President*

Great. Thank you for the question. So we are planning and, as Jackie said, intending to initiate the Phase III study for the Quadrivalent mRNA-1010 program next year, in 2022. We will have interim analysis from that Phase II data in the early part of 2022.

And so that will be confirmatory, we hope, and allow the direct comparisons, and if that's the case, we will go forward quickly into that Phase III study. Again, subject to your regulatory consultations on the scope of that and some of the questions that were just asked about what that comparator will look like and what tests will be running in that state. The 1021 and 1022 programs, we expect to move very quickly behind it. We have not yet guided on when we start it in the clinic. But I would note that we do now have quite a comfortable level of safety data with H3 and what we're starting to see here.

And so we will look to add in an additional 1011 and 1012 additional antigens, quite quickly, perhaps even in 2022. I think, the question for us is a little bit of a regulatory one as well, which is what is the best way to move forward in this platform, where we're adding additional antigens.

One strategy might be to pursue 1010, all the way through, and hopefully, precedented regulatory pathway towards, perhaps, an accelerated approval, again, subject to regulators agreeing with that. And then using subsequent updates to add additional HA antigens in the influence A line like 1011, 1012.

And that would certainly be our hope. We think, it would follow on precedents, for instance, when vaccines went to Quadrivalent, which was just a few years ago. But ultimately, that's going to be subject to those regulatory consultations over the next month. So it just makes it very hard for me to provide anything other than directional, in terms of how we're thinking about it.

On the question of cold chain and storage. We -- our target product profile here that we'd like to aim at, we want to be acceptable in the existing market, which tends to be refrigerated, single-dosage forms.

We have, as you know, a number of different ways that we've demonstrated that in our past. The mRNA-1273 program, and we are continuing to extend that shelf life and that is a quite large mRNA. But we have actual experience in other vaccines, where we have gone to refrigerated forms in the past. And so we have some reason for optimism help there.

It is a seasonal vaccine as well. And so you do not need many years of shelf life, in that case, or 18 months. In fact, it's going to be updated quite regularly, particularly if we go regional with it. And so we are hopeful that we're going to be able to hit a non-inferior profile, in terms of storage, that, ultimately, we think, will be beneficial in the food market.

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**Operator**

Our next question comes from Joseph Stringer with Needham & Company.

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**Joseph Robert Stringer** - *Needham & Company, LLC, Research Division - Associate*

Can you just remind us on the, sort of, the -- as you look at the inclusion of customized antigens, perhaps on a regional basis, what the turnaround time is on manufacture those and how that compares to, say, the COVID variants.

And then secondly, just more generally, on the Phase II readout early next year. Just help us -- is it -- would you be looking for just non-inferiority, essentially, versus the active comparator? And would that -- or do you need to see more, in terms of efficacy, to give you confidence in your Phase III discussion in this side?

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**Stephen Hoge** - *Moderna, Inc. - President*

Thanks for the question. So I'll take the second one first on the Phase II. Obviously, we'll want to see results that are consistent with what we saw here today. And obviously, we hope favorably in the comparison with the licensed standard-dose vaccine.

I think, if we do see results that we're seeing GMFRs here in older adults of 6 in the influenza A strains and quite-high titer [zero] conversion rates and that sort of -- as we saw here, 60% to 80%. That gets quite encouraging. Obviously, better is better, and we'll hope for that as well, as we increase the end, in terms of that update.

I think, the pathway though, for us, in the 1010 programs, as I keep saying, is principally to in a well-precedented established way, try to get on -- get approvals.

And that -- those pathways exist. They are clear, and we would like to follow them as best as possible, before we, perhaps, bring more disruptive innovations into that framework, which would include the addition of additional HA antigens and neuraminidase, which we are working on in parallel.

Our goal is not to have there be a long delay between moving forward first with 1010 and then those more disruptive innovations. We're trying to move those in parallel. But we recognize that we have some work to do to move forward the mRNA-1010 quadrivalent program.

And we want to make sure that we do that in a way that is most well established and comfortable for both regulators and public health officials. I think, on the question of -- I'm sorry, on the second question, actually, if you could just restate it.

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**Joseph Robert Stringer** - *Needham & Company, LLC, Research Division - Associate*

I'm sorry, just in terms of turnaround time manufacturer for inclusion of the regional...

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**Stephen Hoge** - *Moderna, Inc. - President*

Sorry, It was your first question. I apologize for that. On the turnaround, so we're -- you've seen us turnaround quite quickly in multivalent vaccines, with the COVID space. I will note that the volumes of what we're doing, in COVID, are dramatically bigger than even the entire flu market today. We're talking about hundreds of millions of doses.

And if we, in 100 days, are able to turnaround here, for instance, with an Omicron booster, and that's not subject to today's conversation, but as we've talked about, if we start to do that and producing tens of millions to hundreds of millions of doses, that is very similar to what you might need for a regional variation here.

But I would note that actually, if you look again back at the strain evolutions, there is multiple different strains that are evolving. And they are maybe different at a country level or a regional level, in terms of what's most predominant. But if you look at the top 2, 3, 4 within, let's say, the H3 clades, you actually get quite substantial coverage.

And so maybe, the answer is that you pick up 3 H3 and it actually provides broad coverage. You don't need too much regional sub-specialization. And oftentimes, you have some lead time to those quotes, right? It's not like you need to do it in 100 days, which is something, obviously, we know we can do, based on prior experiences with COVID.

So I think we're quite comfortable, based on the experience of the last 18 months, based on the volumes of our production and based on the number of times we've demonstrated our ability to pivot and maybe even in the coming months, demonstrate our ability to pivot again, that we will be able to -- at the smaller volumes in the flu market, be able to address those issues with some specialization.

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**Operator**

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

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**Alec Warren Stranahan** - *BofA Securities, Research Division - Associate*

This is Alec Stranahan on for Jeff Meacham. Just a couple from us. Just wanted to know, if you commented on what the active comparator will be in the Phase II trial. And also, how will you guys [use safety] and immunogenecy, when determining the dose selection for the Phase III?

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**Stephen Hoge** - *Moderna, Inc. - President*

Thanks for both questions. We haven't commented yet on the active comparator. We may in the future. I just don't think we did today, and so I will refrain from doing so. I think, how will we compare reacted immunogenicity for the 1010 program, out of the Phase II and guide us.

I think, as I said a moment ago, if we see good zero conversion, particularly zero-conversion GMFRs, like we saw here against the influenza A strains, which are the primary strains of concern in the older adult population, the flu market. If we see those look like what we've seen here today in the Phase I, I think we will feel very good about moving forward.

As was noted, zero conversion and GMFR there are quite high and quite good in the H3 line. I think, in terms of reactogenicity, we want to make sure that it's a development profile, it's competitive in the flu market for older adults.

And so the best way we will know that is, again, the comparison against the active comparator in that study, so that we can assess whether there are differences at all in reactogenicity, and if there are, whether a 25-microgram or 50-microgram dose will be the optimal choice for those populations.

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**Alec Warren Stranahan** - *BofA Securities, Research Division - Associate*

Great. And maybe just one follow-up. What are your thoughts on the idea of ideal [valency] for the flu vaccine, when you put it into a combo with RSV and COVID?

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**Stephen Hoge** - *Moderna, Inc. - President*

So we have gone preclinically, into the well north of 10 different antigens, and we continue to see that we see good immunogenicity. So I don't think that there's a technical limit. So the question is maybe around an epidemiologic one, which is at what point does it become more than is needed. And I think what we will be guided, is where is the epidemiology, the different viruses.

Obviously, we want to make sure that we cover RSV. And if there's still a single, dominant strain for COVID, then you could have a single mRNA for that. If there's a couple of strains for COVID, then you could imagine a couple of slots there.

In influenza, we want to, obviously, have the quadrivalent strains that are getting selected and used broadly now by many vaccines. But the question of how many H3s and H1, given influenza A drive most of the morbidity, mortality, is really one that's going to be guided by epidemiology. It does not need to be the same answer every year.

That's another issue, which we think -- the current approach is that mRNA might be able to resolve. In some years, you might choose more diversity. And in other years, you might think, that is less necessary. And that's something that we hope to bring as an innovation to this market.

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**Operator**

Our next question comes from Mani Foroohar with SVB Leerink.

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

I've got a couple of quick ones that will go in series. It sounds like you guys haven't disclosed whether or not you're going to be using the high dose or standard dose, as a comparator, in the Phase II. Should we expect one or the other? What's the rationale not to disclose that?

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**Stephen Hoge** - *Moderna, Inc. - President*

Mani, sorry, with the question. We'll be evaluating a standard-dose comparator in the Phase II. You could choose either standard or high dose. We just need the benchmark in the same study.

And then obviously, you can compare. And so that's why we're -- for now, for the timing of that study and matching the strains, we're using a standard dose, but at that point, you'll be able to compare it against the standard dose.

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

Okay. So you cautioned against comparing cross trial after spending about an hour comparing cross trial versus a high dose on efficacy. Doing essentially the same thing now and looking at the prescribing information, your all AEs or Grade 3As, across the board, are between 2.5 to 6x higher after 29 days, then the 180 days captured on the prescribing adulation, for high dose.

Is it rational to move forward into a combo vaccine with COVID, RSV, with 1010? Or is it more appropriate to go back to the drawing board and produce and look for a new flu construct that doesn't have this severe reactogenicity profile?

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**Stephen Hoge** - *Moderna, Inc. - President*

I guess, as I said, I think it's dangerous to make those sorts of comparisons, and we've tried to be measured in our comparisons on immunogenicity and reactogenicity. I think, I'm going to be guided by the Phase II data results.

If you look at our saline placebo, you will probably note that, that is also higher and more reactogenic than the authorized labels that you're looking at, which I think gets to the point that until you get an active control, you really need to be careful at what you're looking at, in terms of solicited, adverse events.

There is a little bit more history of comparing across assays, on things like GMFR and zero conversion rates, in both the regulatory guidance and in literature, which is why we cautiously present that data as a comparison here.

But again, I wouldn't be guided by that either, until we see the active comparator in our Phase II, on immunogenicity responses, I think, it's not appropriate to draw too many conclusions, and that's where we are.

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

I'm sorry. Can you -- I don't think you answer the question about whether or not it makes sense to go to a safer flu backbone or push through with the lower dose of 1010.

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**Stephen Hoge** - *Moderna, Inc. - President*

I don't -- you're asking a question about whether or not we believe the reactogenicity profile is appropriate for moving forward to Phase III. At present, we believe that, from the Phase I data, that particularly the reactogenicity profile of the 50-microgram dose, is appropriate to move forward to Phase II, as we have done.

We're going to be guided by that Phase II data to actively compare it against the flu vaccine. And until you do that, we don't know how to -- I don't know how to answer that narrow question. We see reactogenicity in the placebo arm that exceeds the flu market. If that were the standard, we wouldn't be going forward at all, and that is in the placebo.

So we really do need a direct comparison before you can make any of the statements that, I think, you're making as a present to the question. So we will evaluate it in Phase II. We will be guided by that data.

But as I've said before, I think you run the risk of taking low numbers, a single instance, in the case of a Grade 3, difference between placebo and the 50-microgram dose level and trying to draw too many conclusions from it, including ones that would involve, as you say, going back to the drawing board. I think we want to go see that data.

We are in parallel, evaluating a lower dose, 25 micrograms may achieve the same immunogenicity, as well as have even better tolerability. And that is ultimately, the goal of the Phase II study, is to answer these questions.

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

Okay. That's helpful. You guys repeatedly mentioned the absence of Grade 4 AEs, in combination with your -- with the noted reactogenicity profile of 1273, should we expect an additive reactogenicity profile, i.e., invest some risk of a higher Grade 3 rate or Grade 4 AEs, when you add in the additional immunoactivation of your COVID vaccine as well in an eventual combo vaccine?

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**Stephen Hoge** - *Moderna, Inc. - President*

I tried to answer this question a moment ago. And I think, I did the best of my ability, which is that we do not have any evidence yet, on whether there's going to be additive synergistic or not additive reactogenicity profile. It is not something you can tell from the current data.

In my opinion, you need to go run the clinical study. We have dosed in our platform technology, up to 1 milligram, constantly, in the PCV space. We've gone up to several hundred milligrams in some of our other vaccines including respiratory vaccines like the [165-7653] program.

And we do not believe that this is a limit, in terms of technology. It's a function of antigens, and therefore, you have to actually combine the antigens to know. And that is a clinical trial that we look to run in the future.

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**Operator**

Our last question comes from Emmanuel Papadakis with Deutsche Bank.

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**Emmanuel Douglas Papadakis** - *Deutsche Bank AG, Research Division - Research Analyst*

Perhaps, I'll take a couple, please, as well. First, on the regulatory profit, perhaps I could just push you a little more on regulatory probabilities. I appreciate you've not yet had the discussions in question. But based on your engagement with the FDA today, do you think the Phase II (inaudible) data is likely to be approvable as the Phase III more likely a pre-approval requirement.

And then perhaps more interestingly, what does the regulatory pathway look like for a combined vaccine. I think Stephane said, you have line of sight for a single, combined annual respiratory booster. But from a regulatory perspective, does that need for Phase III efficacy studies? Or again, is early immunogenicity data likely to be sufficient?

And then perhaps, a question on commercial, we've had existing market leaders discuss at length, the importance of (inaudible) efficacy and outcomes data to drive contracting and uptake in the flu market.

Based on your discussions to date, to what extent these in committees, payers unlikely to first want to see long-term outcomes data, for example, around hospitalization and comorbidity outcomes, to really drive significant commercial update of (inaudible) get to the market over the coming years?

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**Stephen Hoge** - *Moderna, Inc. - President*

Thanks for the questions. As you hinted in your question, I will struggle to provide guidance that we haven't gotten yet from regulators. I think, we are -- I will note that the published guidance does call for demonstration of efficacy, even following accelerated approval. We would fully expect to do that ourselves, anyway.

And so we will be looking to demonstrate in clinical studies, either pre- or post-approval, depending upon that regulatory guidance, the efficacy of the mRNA-1010 vaccine.

And we would hope, if we move forward with better matching, that we can also demonstrate over time, improved performance of the vaccine, relative to other comparators. But that, again, is subject to discussions with regulators about whether that's happening before or after.

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

Yes, and I'll take the other one. So we've had a lot of discussions, thanks to COVID. We've been at health ministers, payers, (inaudible), who many governments around the world and private payers as well. And the feedback has been very strong. People are really excited about the idea of having a non-inferior flu product that can be adapted for that geography.

For example, in Canada, we have (inaudible) to build a plant there. One of the key feature of that partnership, which is a multiyear partnership, is to provide adaptive product that will be designed in collaboration with the government of Canada and (inaudible) .

And (inaudible) the addition of COVID. People are very worried in governments that the chance of people getting an annual COVID booster and an annual flu booster, is going to be a big issue. It's a very large (inaudible).

And so when you talk about the combination, this is a piece that people are so excited about. People are telling us, if you can give us a non-inferior flu shot and what is, from a real-world evidence, the most effective COVID booster. People are very excited, and that's exactly what we are doing.

And the piece, I think, that people are not, kind of, getting from where we are today. This is our first iteration on flu. As we've said in our remarks, this is not our last flu product. This is our first one. and our first, short-term flu is not inferior to the best product on the market that people have worked on for 20 or 30 or 40 years in traditional pharma.

So we're going to keep moving very fast. We're going to keep adding components like the (inaudible) antigen, DNA antigen, we're going to keep adapting this trend, as Stephen said, to the country. And of course, it will being COVID. So all the (inaudible) we had with buyers, government or private payers, are very strong, and we anticipate to have a big impact there.

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**Emmanuel Douglas Papadakis** - *Deutsche Bank AG, Research Division - Research Analyst*

Very helpful. And then, just on the efficacy and outcomes data to drive U.S. commercial uptake?

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

Sorry, can you say your question again?

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**Emmanuel Douglas Papadakis** - *Deutsche Bank AG, Research Division - Research Analyst*

Full efficacy and outcomes data, for example, hospitalization, how significant do you think that is likely to be in driving U.S. commercial uptake? Your flu vaccine...

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

So that will be a product, we'll get for the clinical study. That's what Stephen was saying, of getting to write those in the Phase II, that is going to be very important to then drive the [Phase] frames, get all that data up, of course, the governments and the payers are going to be looking for.

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**Operator**

I'd like to turn the call back over to Stephane Bancel for any closing remarks.

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

Well, thank you very much for joining us today. We are very excited about this data, and we think we're going to be able to keep pushing the envelope on respiratory vaccines. We look forward to providing an Omicron update soon. Have a good day.

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**Operator**

This concludes the program. You may now disconnect. Everyone, have a great day.

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