Investor Event - R&D Day and Business Updates

September 13, 2023

Stephane Bancel:

Thank you for those joining us here, and thank you for those joining us online today. Before I start, let me just remind you that we'll be making forward-looking statements, and of course investing Moderna [inaudible 00:00:13] risk. Please look at this document online on the SSC website for your information.

10-plus years ago, we started Moderna believing that mRNA could be a very powerful molecule, an information molecule to make a new class of medicines. That was really exciting to us. Having spent years in pharma, having suffered from the small molecule failure rate, large molecule and their limitations, the notion that you can use an information molecule to make medicines was really, really exciting. As you know, because many of you have seen this slide for now 10 years, what excited us is a few things. The first thing was the opportunity to have a very large product opportunity sets, the ability to go and do secreted proteins, or combinations of secreted proteins, the ability to transmembrane proteins, or very complex transmembrane protein like what we have in our CMV products, the ability to get inside the mitochondria, or any other compartment of a cell.

It seems like science fiction for all of us making medicine, but that technology could enable us. The second piece that was really exciting is it'll be a true platform using the same chemical blocks to build the molecules. This, to us, would imply a much higher productivity or R&D, because you don't... Every time we start everything from scratch, dealing with a new molecular entity that you don't understand what it's going to do in human, especially in term of side effects.

The third piece was speed. The good news is for 10 years I had to explain that we should go much faster. Nobody believed me. I think COVID showed that we could go really fast, and that was also a very important piece, because use the same chemical building blocks of the mRNA, the semi lipid system. If you were to invest heavily in process development, automation, robotics, you should be able to go extremely fast, to go from an idea of a scientist, into a drug being tested as a candidate into an animal, and then if you like what you saw in animal, going very quickly, as we saw during COVID, 60 days, from a concept of a drug in animal into a human setting.

And last but not least, great capital efficiency. Why? Because in the same reactors that we make COVID-19 vaccine, we've already making RSV, soon be making flu, and then we're making MMA and P and all the products can be made in the same reactors, in the same manufacturing suites, by the same teams. That flexibility is extremely interesting from a capital efficiency. What was interesting is since the beginning, we believe if we could be successful, this will be a true platform. As you know, in pharmaceutical industry, there's no platform. This is analog drugs, where every drug is different and you go again at learning everything. So we said this should lead to a lot of medicine.

To us, it made no sense this will be a one-drug company. If you go back and talk to our early investors, I would tell them, this will be zero, or a lot of drugs. I used to tell, I don't know the probability on both

scenarios, but it make no sense it's one or two drug. Would be zero ,or a lot. So we build our company assuming a lot, because of course we don't build a company assuming zero. So the strategic imperative was quite simple. Build a platform, invest in science so that you keep exploring and understanding what this technology can do over time. Invest in delivery systems, because like any nucleic acid technology, getting the nucleic acid in the right cells was clearly going to be a very important challenge of ours. And then manufacturing as I spoke about. That's what we do spend in the last 10 years building, and we're not done. We're just getting started.

Our investment in science are really important because we believe there's so much more to explore in the field of mRNA. So how are we doing so far? I think what we're very excited about this R&D day today is if I had told you the positive data that we have so far, including those disclosed this morning, five years ago when we're around today in New York City in September, 2018, you most probably would not have believed us. And I'm sure somewhere in the room I saw Salvin earlier, were with us back in 2018. We basically are standing to a great opportunity for patients. If you look at infectious disease vaccines, with a positive data on flu that Rafael and team I'm sure are excited to share with you in a minute, we're now three out of three positive phase for data. COVID, RSV, and flu.

If you look at latent viruses, we're announcing this morning that were fully enrolled for CMV. Were already accruing cases and so we cannot look, we cannot wait to get that data and to share it with the world. If you look at what we've done in cancer so far is quite amazing. The phase 2 data is really, really impressive. Sometimes we have to pinch ourselves when we look at the data, because as you know, most companies when they get five, ten percent improvement versus standard of care, they throw a party, and what the team has showed at ACR and at ASCO is much better than that, and they're going to go back through some of the data with you.

As you know, we're very excited to be able to launch a phase 3 study melanoma ahead of schedule in July of this year. This morning, we're announcing that we should be able to start the phase 3 before long, before the end of the year. That's quite exciting.

Another thing we're announcing today is we believe we should be able to share new interim data on the phase 2 study in melanoma by the end of this year as well. So the next few months are going to be quite exciting. Then, last but not least, and Kyle his team will share with you some data, with new MMA positive biomarker data, we're now three out of three rare disease. We're showing either clinical or biomarker improvement of those kids that are on all medicines. Three out three, PA, GSD1a, and MMA. So if you think about where we are today and you step back for a minute against Salvin and others, if I had told you in September, 2018 when we're here in New York for only there, that those things will happen, I think the probability that you'll have put on all those things happening together will have been very, very small.

That's where we're standing now, and that's why we're so excited about these product, but even more excited about what's coming next. So, today, we're giving you a bit of a sense for what we think the next few years will look like. We believe we could launch up to 15 products in the next five years. If you look at the next two years, '24, '25, as you are highly aware of, we're on file for RSV across the world. Seasonal flu data is positive now for 1010, 1283 for the next-generation COVID, which is fridge-stable COVID product. And then we're very excited. We believe we're going to have, by the end of this year as well, clinical data on 1083, which is our next-generation COVID combined with 1010, as a COVID plus flu combo, and that data should come out before the end of the year.

Once we have that data, as you know, we need to run a bridging study which is not very long, six months of safety data and fight this over regulator, which means that for the season of '25, we should be able if the data is positive on 1083, to have a launch of a flu-COVID combo.

Then if you look at the next three years, '26, '27, '28, I won't go through all of them because that's a long list and the team will do that much better than I will in the next few minutes. We have a lot of over vaccine in respiratory coming, over combinations of a product. Then if you look at latent, with CMV leading the charge in term of the phase 3 being fully enrolled, there's quite an extensive portfolio of latent vaccine and new vaccines like Norovirus, and also lyme, our first bacterial vaccine in addition to VZV, EVV, and HSV. The team will talk a lot about oncology and the exciting programs we are going to have in oncology. We believe there's a possibility based on the data, as they mature, to have discussion with regulator, of course it'll be subject to regulator decisions to potentially file before that for an accelerated approval.

And of course the rare disease, we've now three rare disease for which we'll have data. We also announced this morning that PKU has now in open R&D, and we'll be dosing very, very soon in the clinic.

That's what's coming over the next few years. It's quite exciting. We're very proud of what the team has achieved, and we can't wait to get those important medicines to patients and help either prevent disease or treat disease for all those important conditions.

So the agenda very quickly, we're going to start between now and the break to talk about infectious disease, both respiratory and latent. After Steven gives a bit of development strategy update, we'll take a coffee break, and then we go into therapeutics, with Kyle and team talking to us about rare disease first, then oncology. Jamie will try to get some financial frameworks for all those investments and all those franchisees that are emerging. And I'll come back for two or three slides to close, and then the team and I will be happy to take your questions. With this, let me turn over to Steven.

Stephen Hoge:

Thank you, Stephane. So I will try and cover very quickly our full scope of work that we're doing, and in particular spend a little bit of time talking about research, which is a really important part of the foundation of the company, as most of you know, but one that we just can't fit into this agenda. So at some point we'll have to come back and do another research day. But for now, I just want to quickly reprise something Stephane spoke about, which is Moderna, at its core, has been founded as an mRNA platform company. What that means to us, what that's meant for over 10 years as we built it is we prioritize our investment in the basic science areas that build our platform. We build a singular platform that then allows us to bring many, many medicines through. The key here is if you use a singular platform for all of those medicines, it allows you to move incredibly quickly when something is working.

I hope as you look through our late-stage pipeline conversations throughout the rest of the day, you get the impression that both things are working, many of them, and that we are really delivering on that vision of being able to bring many medicines forward quickly.

Okay, so how does that work as we do that? As we create that platform and those medicines, we create versions of our technology, we call them modalities, that are different approaches to different types of diseases. You're all very familiar with one of those modalities, our infectious disease vaccine modality. As Stephane mentioned and as we're quite proud of right now, we are three for three in being able to get to meeting our primary endpoints in phase 3 studies. One of those is approved, actually an SBLA for COVID yesterday as well, RSVs now filed, and flu not far behind it. We think we've really demonstrated the power of that modality with multiple products.

Cancer therapeutics, in particular, our individualized neoantigen therapy approach, has now hit proof of concept in INT for adjuvant melanoma, and, as the team will share, we think we've gone three for three in demonstrating early evidence of potential clinical benefit in patients with rare diseases. So those three modalities are moving very quickly, but by no means are we done.

So where have we been? Just a little bit of looking forward and looking backward to look forward. Where we are in the last three years, leveraging that singular platform, is we have gone from the company described on the left here in 2020, 25 development programs, but most of that, a large portion of that preclinical. In fact, we had only one phase 3 program, three years ago today. We all know what that is. It was COVID.

We had a relatively small phase 2 pipeline and a lot of potential in preclinical. Now you move forward just three years, and yes, the numbers have almost doubled, from 25 development programs to 43, but that late-stage pipeline has matured pretty dramatically. In fact, now we're looking at five programs, enrolling or enrolled in phase 3, and a very large phase 2 pipeline and phase 1 pipeline right behind it. We really are just getting started in building this company as we look forward.

Now I do want to say, as I set up in the beginning, a bit about our approach on the research side before we get into that late-stage pipeline, which will be the focus of most of the day. We are going to continue to make the investments in our platform necessary to expand the frontier of what mRNA medicine could be. It is core to who we are. That's what it means to be an mRNA platform company. We will always want to bring those medicines to patients and that's a huge focus of today's conversation. But let me assure you, we have not changed our mission or who we are at our core. We're going to keep pushing the boundaries of what that platform can do.

here's a couple of ways I might like to exemplify that. You've seen these, and we won't talk about these in great detail, but as an example, we're continuing to expand the diversity of applications we're bringing forward in oncology, and our cancer pipeline. Just a few recent deals that you've seen us announce, on the far left-hand side, a partnership with Immatics, where we're working to bring in completely novel proteins. These are T-cells, TCR engager proteins, quite complicated to make recombinantly, really fit well for messenger RNA, and require a diverse range of different approaches across HLA types. So different patients may need slightly different products. Really fits into our wheelhouse in so many ways, and we're proud to be partnering with Immatics on that.

And look at cancer vaccines. We've actually had two announcements, CARSGEN recently this summer, and as well as another part of pillar of our relationship with Immatics, where we're using our platform's ability to promote cell expansion in two different in vivo cancer cell therapies. One is a traditional CAR-T with CARSGEN, and the other is a TCR T-cell therapy with Immatics. Again, something you've seen us do actually as a monotherapy with our INT program, but that we're now doing to really bring, we think, durability and power to cell therapies, to new products that are moving forward, and a totally new concept.

Then on the far right-hand side, just as another example, we did do a deal with Carisma. That's for in vivo myeloid cell therapy. And you've seen this express proteins in the myeloid cells, but we're now moving to try and do that for the purposes of driving those myeloid cells into solid tumors, and hopefully adding one more arm to the armamentarium by which we fight cancer.

Three completely different product concepts. We're not going to talk to them today, but given where those deals are in those announcements, you can see that we're moving very quickly and expanding the frontiers of what we're doing in oncology. We are literally just getting started.

There's another example real quickly I'll flip through, which we've also talked about, and you've seen us do deals on, and that's why I'm comfortable covering it quickly, which is how we're using our rare disease platform and capabilities, which we're increasingly getting very comfortable in the safety and pharmacology of to expand into the frontier of gene editing.

We've founded a group internally called Moderna Genomics that's been focused on how do we use that platform technology to try and address individual mutations or groups of mutations in the rare disease space, with the potential, again over the long term, to maybe offer cures to these patients.

We've done two deals, two partnerships there, that have been announced and others that haven't. One with Life Edit and Metagenomi, and both of those are moving forward towards in the preclinical space, ultimately, we think, towards clinical candidates. So I can tell you there are many, many other such things going on. These are some of the ones that are already public in our research space and I wanted to highlight, but please do rest assured, we continue to invest in that space and expand.

Now, we also prioritize. You saw in the announcement today, there are four clinical programs in various stages of development that we've discontinued, and they're listed here, and we'll continue to look at that pipeline and determine whether or not there are opportunities for us to focus our efforts as we move forward. We have a blessing and a curse in terms of how productive this platform is, and anytime we see an opportunity to focus our energy on programs that we think are the most important to move forward, we'll do so.

Okay, so here is that pipeline. Broad, deep, and increasingly late-stage. In fact, if you look at it, we are really pleased that we now have a therapeutic, and Kyle will talk about it, and Michelle will as well, down to the bottom in the peach color, that's in phase 3, late-stage development, and a couple of others that are moving into phase 2 in the rare disease space. We are really excited about the progress there and moving this forward to pivotal. As you look up, you can start to see the latent pipeline is now increasingly moving in the middle stage development. Phase 2, huge pipeline there and ultimately hopefully moving forward to phase 3. And then, of course, our respiratory franchise, which we'll speak extensively about, I'm sure, but a place that we're really proud of the impact we've had and believe actually the impact we're about to have have is even more impressive.

As that pipeline matures, we do expect we'll be launching many products. I think the same things are true, which is while in the next couple of years, that is a lot of respiratory vaccines or the four that Stephane mentioned as potential product launches. If you look just a few months beyond that, and years beyond that, and you say over the next five years through 2028, what you see is a broad and diverse pipeline across many different therapeutic areas, not just infectious diseases and respiratory diseases and latent viruses, but cancer and rare metabolic disease. In almost every one of these cases, we're going to be sharing some data today on why we're so enthusiastic about it, and why the data we're seeing in patients gives us great optimism for this plan. So what's the focus of today's update? As I said, we have a large pipeline, we can't talk to all of it, so we're going to focus on these things. We're going to talk in the respiratory space about COVID-19 and the exciting recent news in the season of flu space. I'm sure we'll face questions on all. On CMV, we'll provide an update of where we are in that study. It's our lead phase 3 program in the latent virus space. Very exciting.

The three rare disease programs, PA and MMA, we've got clinical updates in patients with chronic data there, and want to let you know about where we're going in PKU, because we think that could move pretty quickly.

Then last, we'll spend some time in INT, which is our individualized neoantigen therapy. I imagine everybody's heard about it. Lots of questions about it, lots of momentum behind it, in the phase 3 studies there. We'll find a little bit of a link back to some translational data that we've had along the way. It'll help you understand why we think we're just getting started with that adjuvant melanoma and soon non-small cell lung cancer studies.

Okay, so with that, I'd like to invite Jackie Miller, the comparable Jackie Miller who you all are familiar with, to come join me on the stage and start us off with the respiratory vaccines.

Thank you.

Jacqueline Miller:

Thank you, Stephen. Good afternoon. It's really nice to see all of you today. Thank you for coming out to hear a bit about the science that we're doing in the vaccine space. So as Stephen mentioned, my name is Jacqueline Miller, and I lead the development group for respiratory vaccines.

I've been now participating in the R&D day. This is my fourth R&D day. We've actually made quite a bit of progress on this slide since I joined the company in 2020. As Stephen just mentioned, three of our programs are either at commercial stage, ready for BLA submission or in the early negotiation stages with FDA about what that BLA will look like, and that's of course COVID, RSV, and flu. But we also continue to work in parallel with improving the vaccines we already have.

We're really looking forward to sharing with you some newer early-stage data from our next generation COVID vaccine. We continue to actually improve on our flu vaccine as well, with additional antigens, either additional hemagglutinins to expand strain coverage, or neuraminidase to hopefully improve immunologic protection.

Then, now that we really are at a place where we have multiple monovalent vaccines that are close to their licensure, our strategy always has been to combine those. The reason for that is really the potential benefit both to patients in terms of convenience but also public health in terms of making vaccination easier to accomplish. So let me tell you a little bit more about how we've been able to do this and move so rapidly in the last three years. Well, it's really because we are building off of what we learned constantly. The SARS-COVID-2 vaccine, mRNA 1273 or Spikevax, was really our first proof of concept that our platform can really work in terms of protection against respiratory pathogens.

RSV now has added some additional support to that hypothesis with its positive phase 3 data. I hope to convince you today, through the presentation of Raffael Nachbagauer, that influenza were there as well. Then the other thing that we have really benefited from is the fact that these pathogens really have similar epidemiology. So the greatest impact of these infections is in the very young and the very old. That's allowed us to get comfortable very quickly with how to conduct clinical trials both in the older adult population where we've been able to move a bit faster, but also in the pediatric population where we've learned a lot from our COVID development and now are applying that to pediatric development and RSV and human metapneumovirus as well. Then finally, the fact that we have been able to increase the number of antigens in this vaccine, so the bivalent COVID vaccine of last year being one example, really gives us confidence that we can begin to combine and see success there as well.

So to summarize for you, our strategy really is to bring forward the best possible monovalent products and continuously improve upon them. So I mentioned COVID vaccines in terms of bivalence. We're now looking to also improve on some of the technical attributes like refrigerator shelf life, and potentially also higher immune responses and improve safety profile as well. I'll share those data with you in the slides that follow. Influenza, while we're very excited to initiate our discussions with regulatory agencies about our pivotal phase 3 data, we continue to iterate and improve even as we were improving on our influenza B antigens. And then finally with RSV, again, learning from the COVID program expanding very rapidly down to not only children two months of age, but even down to children five months of age, and actually beginning to investigate combination vaccines in that age group as well.

So the data that we will share with you today from the respiratory portfolio include an update that I'll provide to you with respect to the next generation COVID vaccine or mRNA 1283. Then I'll hand over to Darin Edwards, who is our program leader for COVID-19 vaccines, and he's going to tell you a little bit about the process we went through this year to update our vaccine and also the data we've generated,

not just against the XBB strain against which the sequence is targeted, but also how we have assessed potential cross protection of that vaccine as well. Then finally, Raffael Nachbagauer, who is our program leader for influenza vaccines, will take you through our newly announced pivotal phase 3 data.

So to start with mRNA 1283, this is a program that currently is in its phase 3 program, but as part of another development program, we actually had two study arms where we looked at a randomization, it's one-to-one, in two age cohorts, both a younger age cohort, 18 to 64 years of age, and an older age cohort above 65.

In this study, we enrolled approximately 50 subjects in each age stratum and in each treatment group to receive a single booster dose of the previous year's vaccine. So this is the BA.4/5-containing vaccine. We're in the process of following these individuals for six months for the extended safety follow-up. What I'm going to share with you are the initial reactive genicity data as well as the immunogenicity data.

This slide depicts the adverse reactions that were reported in terms of local solicited symptoms as well as systemic solicited symptoms, and this is in both treatment groups in the two different age cohorts. So the older age cohort is on the left, the younger age cohort on the right. What you see are the local symptoms in each bar graph on the left, systemic on the right, and they lead with the 1273 or Spikevax bivalent vaccine. The investigational group is on the right in each comparison.

Taking the younger age cohort first, what you can see is that the frequency and the severity of the systemic adverse reactions is approximately equal between the two vaccines. When you go to the local adverse reactions, we see both lower frequency as well as lower severity reported in the younger age cohort.

Now looking, though, at the older age cohort, in this case, for both local and solicited symptoms, we see lower rates overall of reactions in the 1283 group. This is important, because as we're collecting our data for the phase 3 program, really gives us confidence that the modifications we've made to our COVID vaccine will lead to a acceptable safety profile, comparable at least to that of Spikevax.

So now let's review the immunogenicity data. What you see on this slide are the geometric mean ratios in both of the age cohorts to the neutralizing antibody titers against the BA.4/5 Variant. The geometric mean ratio is dividing the 1283, or investigational vaccine candidate titers over the licensed vaccine. So any GMR that is above one is good in this case. So taking the younger cohort first, there's a GMR of about 1.2. Importantly, the lower bound of the 95% confidence interval is 0.76. In this small cohort, we already see a lower bound that's above the regulatory criterion for successful licensure.

If you go to the older age cohort now, we saw a GMR of 1.8, and here, the lower bound is 1.23, meaning that 95% confidence interval excludes one. All of this gives us confidence that we should be in a good position with phase 3 to be able to meet our pre-specified non-inferiority criteria. We're looking forward to an interim analysis with the 1283 study that should be occurring before the end of the year.

Let me tell you a little bit about the phase 3 study that's currently ongoing. At the moment, it is fully enrolled. We've enrolled 11,500 subjects, randomized them one-to-one to the two different vaccines. This, again, is a single-dose booster, and it's in individuals as of 12 years of age. This is really designed to match the BLA that we currently have approved for Spikevax, and if successful, we'll be launching then the next generation COVID vaccine in pediatric populations as well. The study is currently ongoing in the US, UK, and Canada, and we're also going to be assessing relative vaccine efficacy as we go into this fall season.

Okay, so with that, I'd like to introduce my colleague, Darin Edwards, to talk a little bit more about Spikevax and this year's vaccine update.

Darin Edwards:

Thanks Jackie. [inaudible 00:29:44] COVID vaccines, given that on Monday, we received FDA approval, and we're actually actively conducting our launch readiness plans at this moment. Speaking for myself, I can say that my family and I are really excited to get that appointment at our local pharmacy and to get our updated booster. In addition to the US and the FDA, we've received approvals now in Japan, Health Canada, as well as in Taiwan just today. In addition to that, the CDC did provide their broad recommendation for use across all age ranges that have received either approval or authorization for our updated vaccine. So very exciting time to talk to you. But today, as a part of the launch of our updated vaccine, I'm going to share with you the process that we went through to update our vaccine. I think it's a topic that we haven't provided much focus on previously.

This is a kind of cool process that we've had to develop as the need arose. The original vaccine obviously targeted the ancestral sequence. As variants arose, we had to develop a process and combine that process with the work that was being done at agencies in order to allow for the approval process as well as the data to be collected, to enable us to update our vaccine.

We all know variants arise. We've all seen them, they're in the news, they've been consistently assessed by academics, by us, and by others. We've seen them as they have arisen, that data has come up that has shown that some of them have had a significant impact on viral neutralization, for example, or potentially even the performance of the vaccine. What that required then was a process to update the vaccine. When Omicron arose, that really led to a very rapid determination of a need for an updated vaccine. In August of 2023, we got our updated bivalent BA.4/5 vaccine approved for use as the booster up until two days ago. Now we've seen that other variants have arisen as well. That has caused us to optimize our update process, and it really now has really three main components. The first part of it is we perform continuous monitoring of the virus, and do assessments of the impact of risk associated with those variants. The second part of the process is we provide that data, both data from our assessment as well as from animal and human results for updated vaccines, and provide that to regulatory agencies to enable the strain selection process process. But even at that point, our job is not yet done, and it will continue on an ongoing basis, because even after a strain is selected for inclusion in a vaccine, variants will continue to emerge. That requires us to continuously monitor and perform additional assessments to determine if there is an impact, potential impact, on the performance of our vaccine. So what does that process look like? I'm not going to take you through everything, but I'm going to provide you with some key aspects and some key elements that we utilize in the process of monitoring and assessing variant viruses. So we do perform continuous epidemiological monitoring and for those variants that we identify, we assess their antigenic changes in key regions on the spike protein.

Now what you see on the right-hand side is a view of our initial assessment where in the column on the far left, you see Wuhan at the top all the way to XBB 1.5. Those are different variants that not only emerged but started to circulate broadly, highlighting a need to perform very detailed assessments of those variants. On the bottom, you see a number of amino acid locations on the spike protein. Those are key sites that antigenic that are known to be targeted by monoclonal antibodies in order to neutralize the virus. So those are key sites of neutralization on the spike protein.

Now at the top, you see in yellow, Wuhan, that's the original sequence. But as you start to look down, as variants have emerged, more and more mutations are being found in those regions that are key to driving neutralization. BA.1 was the first that had a large number of mutations and then BA.4/5 assumed additional mutations. And all the way at the bottom you see XBB 1.5 where you see very little yellow left. And if you look very closely at the light reds and the oranges, you see additional mutations versus BA.4/5 as well.

So understanding that, two steps happen after that point. One, we've developed a risk assessment toolkit that allows us to take the antigenic changes, those mutations, and assess the potential impact of risk. And that risk scoring toolkit that we've developed allows us to very quickly perform an assessment to see what the potential impact on immune escapee is. And the second part of our response is what's displayed here, is we take sera that we have banked from our clinical studies of updated vaccines and perform direct neutralization assessments against the variants included in the vaccine as well as new variants that have emerged. So in this case, this was performed prior to the FDA VRBPAC back in June in order to give us a sense of, from our perspective if updated vaccine composition might be needed.

So on the left-hand side in blue, you see the neutralization in these participants against BA.4/5 and both those with prior infection and those without you see a very potent boost and a very high level of neutralization after the booster against BA.4/5. In concurrence with our risk assessment, which suggested that XBB 1.5 had a high potential for immune escapee, direct neutralization assessment also showed the same story. And that was that XBB 1.5 while boosted by our BA.4/5 bivalent vaccine had much lower neutralization titers than we previously had seen against other variants that circulated prior to it. So that gets us to the next part of our process and that is development of at-risk variant vaccine candidates. So building up to the selection point in June 15, 2023, we prepared a number of at-risk vaccine candidates and assessed them in animals, but also for the compositions that we thought were the most likely to be selected, we produced GMP material and ran a small clinical study to prepare the most relevant data that could be used for that strain selection conversation with regulators.

So this is the design of the trial that we ran. It's 101 participants randomized between two arms. One where we vaccinated with a monovalent XBB 1.5 candidate and the other with a bivalent BA.4/5 plus XBB 1.5 candidate. As at that time the conversation was really around if a bivalent would continue to be needed or if a monovalent candidate would be all that would be required for this season. So these participants had previously received four doses of COVID-19 vaccine, an initial primary series of 1273, a third dose of 1273, and then a fourth booster dose of mRNA 1273.222, which is the BA.4/5 bivalent. So what's listed here for these individuals, they had received a fifth dose of either the monovalent or bivalent XBB candidate, and I'll be showing some data and the data that I'll be showing comes from what is now the authorized vaccine or the approved vaccine, which is our monovalent XBB 1.5 fall 2023-2024 seasonal booster.

So starting out with the data that was presented to the VRBPAC committee, which directly informed on strain selection. So we did present our animal data, but most informative to the conversation was the clinical data that we obtained from the subjects that I just described, from the individuals that I just described.

So first, this is from the Monovalent XBB 1.5 vaccine arm, and on the left-hand side you see the direct comparison of the strain that's actually included in the vaccine, XBB 1.5. But a question at the VRBPAC, a question that was in the field is, given that at the time that we're selecting a strain, there were multiple variants co-circulating, could a monovalent candidate cross neutralize to those other variants? And as you can see from the data, they did, and they did that very well. So XBB 1.5, XB 1.16 and XBB 2.3.2 were all co-circulating and all three were effectively cross-neutralized to the same degree as the variant that was directly contained in the vaccine. Gave us confidence, gave the FDA VRBPAC committee confidence and the recommendation was then made by the VRBPAC, by the FDA, the WHO, the EMA that the seasonal composition for the 2023-2024 season would be a XBB monovalent vaccine.

And as I mentioned when I first started talking is a very exciting week. The fact that we are now post-approval and now in a position to make our appointments and get vaccinated makes me very excited not only for myself but also for my family. But our work doesn't end there. We still have a commitment to the community and that is to continue monitoring the evolution of the virus and to continue to assess

and report on the impact of these new variants against the fall 2023-2024 vaccine composition to make sure that we are staying abreast of the evolution of this virus and also to make sure that we're continuing to provide the best data and the most informative data, not only to agencies, not only for the selection process, but also to the public so that they know what we know.

Now, part of this assessment really falls into two categories for two types of variants that do emerge. The first category is we've all heard about I think EG 5.1 and some of us FL 1.5.1. These are two sublineage variants of the XBB family and they now have become amongst the most globally dominant variants out there.

So there's a lot of interest in determining if there's any impact on the performance of our vaccine against these new variants. Now, our risk assessment suggested that these variants had very low impact versus our XBB 1.5 vaccine, but because they became globally dominant, we performed neutralization assessment and now have put those results out in the form of a pre-print so that it's public. Now the second example is BA 2.86, which emerged about a month ago. It's currently circulating in very low numbers, but at the same time, based on the antigenic changes present on that variant, it has created a lot of concern about its potential to escape immunity that would even be provided by the updated vaccine.

So this is the other scenario where there's a high potential for immune escape, but low circulation triggers our neutralization assessment. So we use the sera that we collected from the clinical study I described in order to perform an assessment of cross-neutralization against these new variants. This information was presented to the CDC ACIP Committee this past Tuesday and also has now been put out into another pre-print so that it is public and available. But what it shows is that when you're comparing these new variants, EG 5.1, FL 1.5.1, and also BA 2.86 cross-neutralization versus the neutralization that we see for XBB 1.5, we see efficient cross-neutralization of these newer variants. So this not only gives a demonstration of how we perform an assessment, but also these very promising results against these new circulating variants at the time that the vaccine is approved and launched.

So what I've hopefully shared with you is a brief description of the process that we go through to performing preparation for strain selection and also the type of data that we provide to regulators to enable them to select the strain on a seasonal basis, and also our continued commitment to monitoring and providing data. And I just want to highlight that this is a process that we'll be going through year over year as variants will continue to emerge. Hopefully a little bit slower, I need a vacation. But we will be performing this in order to enable us to have the most effective vaccine in the future.

And I think we're ... Go ahead.

Darin Edwards:

Yeah. Okay. We'll take questions at the end. So thank you very much. That actually concludes my talk. So now, I'll pass it to Raffael to talk about influenza.

Raffael Nachbagauer:

Thanks so much, Darin, and I'm really excited to share an update today on our mRNA-1010 program. To start out, I want to give a little bit of a summary of what we have really rapidly learned in the last 15 months alone. In May 2022, we started our first pivotal phase three study in our seasonal influenza program, P301. It was a safety immunogenicity study conducted in the Southern Hemisphere, and it was intended to give initial accelerated approval based on immunogenicity. However, those types of approvals generally come with the requirement to demonstrate efficacy post-marketing.

In 2022, we started to see influenza pop up again, and so we decided to get a headstart on fulfilling that post-marketing commitment, and we initiated the P302 study in the Northern Hemisphere during the 2022-23 Northern Hemisphere flu season while P301 was still ongoing. As you all know, we have in the meantime received interim data from both P301 and P302. However, we did not have those data until both of those studies were enrolled.

The first data we got from P301 was the day 29 immunogenicity data where we saw that we met our non-inferiority endpoints for the influenza A strains and even superiority for H3N2, but we did not meet our endpoints on influenza B strains. For P302, we had DSNB assess the interim analysis and it didn't show early success for efficacy. And since that interim analysis, we accrued 48 more cases and we were not able to demonstrate protocol defined statistical non-inferiority. With those data, rather than continuing P302 into another season, we decided to rapidly pivot to P303 to test an improved formulation of mRNA-1010 to demonstrate immunogenicity and safety of that updated vaccine.

I want to give a brief summary of what the P303 study looks like. It's a randomized observer-blind, active-controlled study where we one-to-one randomized mRNA-1010 to 50 micrograms against Fluarix, which is the same comparator that we used in all three pivotal studies. It's a standard dose influenza vaccine comparator.

We enrolled approximately 2,400 participants in the April-May timeframe in the United States exclusively. And when we look at the local and systemic adverse events, we see the graphs here on the right side. Overall, the safety profile was in line with prior clinical studies where we evaluated mRNA-1010. And mRNA-1010 showed an acceptable reactogenicity profile with the majority of solicited adverse events being grade one and grade two in nature. The reactogenicity was higher in the mRNA-1010 groups compared to the standard dose vaccine comparator group. However, we saw a trend of reactogenicity in older adults being lower than in the younger adults. Now, with that, going into the immunogenicity. And importantly and most excitedly, we met non-inferiority against the standard dose influenza comparator for all eight co-primary endpoints, which include geometric mean titer ratios and seroconversion rates for all four strains. Maybe I shouldn't have said most excitedly because the most excited part is that the titers, if you look on the right side, it's a similar graph to what Jacqui had previously described that shows the geometric mean titer ratios of mRNA-1010 to Fluarix.

And just to briefly describe, again, the line of one indicates that the vaccines would be the same. Anything above means that mRNA-1010 performed better, anything below would indicate that it would perform worse. And there is a line indicated NI, which would demonstrate non-inferiority. So that's the bar that we needed to meet for the licensure criteria. And you can see that the bars are obviously substantially above that. And in fact, all the lower bounds of 95% confidence intervals are above one compared to the standard dose comparator.

Importantly, this also holds true for seroconversion rates, which are now shown on that slide, and we see it consistently in all our age groups that we evaluated in this study, which was 18 years and older. And importantly in the 65 years and older group where we know that enhanced vaccines are preferential recommended, we also saw that improved benefit, which is really in line with what enhanced vaccines have generally shown in that age population. Now, talking about enhanced vaccines. We also had data from a smaller phase 1/2 study where we enrolled approximately 50 participants in Fluzone high dose, which is an enhanced licensed influenza vaccine that's preferentially recommended for older adults and mRNA-1010. And here on the right side, you can obviously see that the confidence intervals become a bit wider because the sample sizes are smaller. However, even with those wide confidence intervals, we've seen some really encouraging data, which is that the titer was similar or numerically higher than Fluzone high dose for all of the strains, especially for the A strains, you can actually see that the lower bound of the 95% confidence intervals still exceeds one. And these data

importantly support future phase three studies where we're planning to go head-to-head against enhanced influenza vaccines to actually demonstrate how we compare to those vaccines in these types of larger studies.

So to summarize, we've seen mRNA-1010 demonstrate a consistent acceptable safety and tolerability profile across all three phase three studies. In the most recent phase three study, mRNA-1010 has not only met all of its immunogenicity endpoints, but it also demonstrated higher titers compared to a standard dose influenza vaccine. And the meeting of the non-inferiority for the eight co-primary endpoints are what the licensure criteria are based on for immunogenicity. And we also showed you some data for mRNA-1010 against Fluzone high dose and enhanced influenza vaccine, but the titers were similar, numerically higher compared to that best in class vaccine.

This really highlights the rapid progress that we've made in our seasonal influenza program. So I mentioned the last 15 months of learning, but we truly are only two and a half years out from our initial IND filing this program. And we have generated a wealth of data at this point and really made some substantial improvements. And it really demonstrates the power of the mRNA platform. And it shows that when you understand your platform well, you can rapidly innovate and improve upon your vaccines continuously. And last but not least, we have started consultations with regulators on the initial approval package for mRNA-1010. And with that, I'm handing it back over to Jacqui.

Jacqueline Miller:

Okay, well, thank you so much Raffael and Darin for that great overview of our emerging data. So now, I have just two more jobs with respect to the respiratory portfolio, no more new data, but I wanted to give you a brief update about our current regulatory progress with the RSV vaccine and then talk a little bit about where we are with combinations.

So I'm really excited that we have now submitted our BLA license application to the FDA for mRNA-1345. That's our RSV vaccine, and it's targeted for an indication in older adults as of 60 years of age. This BLA submission joins regulatory submissions that are ongoing elsewhere in the world from earlier this summer, and that's including in Europe, in Switzerland, Canada, Australia, and the United Kingdom. So as we move forward, we're hoping to hear some indication from the regulatory agencies about how those files are received.

Just a brief summary of the contents of that package. What we observed in our primary efficacy analysis was that there was 84 and 83% respectively vaccine efficacy against lower respiratory tract disease due to RSV with either two or three symptoms, at least two or three symptoms I should say. There was also a secondary analysis that was performed. We actually performed many subgroup analyses in these studies, and we looked at patients who had no medical comorbidities, and comorbidity was defined as a few specific conditions like chronic obstructive pulmonary disease, diabetes, asthma, congestive heart failure, things that tend to lead patients to have a higher risk of serious complications from RSV. And what we observed was that whether you had one of these medical comorbidities or not, the vaccine efficacy was generally consistent with 88% vaccine efficacy in those with comorbidities.

From a safety perspective, we saw a really consistent safety profile with what's been observed with other mRNA vaccines with pain, the most frequently reported local reaction, with headache fatigue, myalgia, arthralgia, the most common systemic reactions and most reactions were grade one or grade two. I should say overall the percentages are lower with the RSV vaccine than with COVID, although with the caveat that it's difficult to compare studies that were not conducted head to head.

From a safety profile perspective, we see no new safety concerns, and specifically we did not see cases of Guillain-Barre or acute demyelinating encephalomyelitis in this trial. And that is in a phase three trial that is actually amongst the largest of those that have been conducted with RSV vaccines. We now anticipate that we may hear as early as second quarter of next year about the outcome of our submissions.

So now taking a step back and reviewing our strategy overall for this portfolio, I would say we're well on the way of the pillar in the strategy on the left side of the graph, which is we really aim to bring best in class vaccines. We know that these infections can cause serious complications, and we are willing actually moving to the right side of the graph to begin to innovate and improve as we learn from our clinical trials to make a better vaccine while that development is ongoing. And I think that's the development strategy that makes us a bit unique. We are going to continue to do that now as well with combination vaccines. And we are beginning to put these different antigens together into a portfolio of combination vaccines.

So we currently have ongoing studies with four of these combination vaccines. Why four? Why not do them one at a time in series? The reason is as the epidemiology of these viruses change, it's unclear to us actually what's going to be the most fruitful combination for the general public. And while we're furthest along in our flu COVID program, we're also anticipating results with flu RSV and an early formulation of flu RSV COVID later this year.

And then finally, we don't want to leave children behind. So children actually are the first group that are being evaluated with our RSV and hMPV vaccine. And so with that, I'm going to hand it over to Arpa Garay, our chief commercial officer to talk about the commercial opportunities of these vaccines.

Arpa Garay:

Thank you, Jacqui. Good afternoon everybody. So as we think about the respiratory vaccines, which are our near term launches coming very, very shortly, what's exciting from a commercial perspective is we already have a footprint and we already have capabilities in this space that we can build upon for both the RSV launch as well as flu launch and future launches. From us contracting and a seasonality perspective, we do anticipate all three of the big three vaccines will be the same exact season as COVID. From a customer perspective, we're also looking at contracting with pretty much the same customer base. And from a patient perspective, significant overlap obviously with flu and with RSV. We wouldn't be looking at the pediatric population just yet, but we really are looking at more of a portfolio approach and everything that we do from a commercial perspective.

Overall, as I think about the respiratory vaccines, we are now participating in what we would consider the big three respiratory diseases that have significant burden of disease, not only in the United States, but also around the world. So when you look at the unmet needs and the burden of disease, what you'll see is overall we believe the total respiratory vaccine market can reach up to $30 billion, which we will be a part of.

From a COVID perspective, we have communicated in the past, we think that market could be about a $15 billion market as we get into more of an endemic phase. From an RSV perspective, it could be anywhere up to the $10 billion size as we think about, again, the burden of disease in that group. And last but not least, with flu right now, we see about five to 600 million doses worldwide at about a $6 billion market today that we believe with more effective flu vaccines could actually grow to closer to 9 billion.

So I'm going to start with COVID. Similar to Darin, this is a really exciting week to be in front of all of you with Monday getting our vaccine approved and just as of yesterday getting the ACIP recommendation in

the United States. What you'll see here on the left-hand side, which should be very familiar to all of you, is when we looked at the data of hospitalizations in the last season, you can see that COVID continues to be about three times more hospitalizations than flu and RSV. So this is not during the height of the pandemic, this is just the most recent season.

In the United States alone, we're also seeing COVID actually even in 2023 as a top four leading cause of death. So COVID is still here. It is still creating significant burden. And importantly, you'll see on the chart on the right-hand side, which we have collected a sample of data from a US claims database that's been robust and shared with the CDC. And what you'll see here is despite some misinformation that may exist, the hospitalizations are actually significantly higher than flu across all age groups. So COVID is not just a vaccine for the 65 plus or high risk, it really is a vaccine that's relevant across all age groups, and that was what was reflected in the ACIP recommendations to align it with the flu universal recommendations for anyone over six months.

So what are we doing from a commercial perspective? The first half of this year has been very, very much focused on securing contracts. I'm very happy to report that we have actually secured contracts across every segment of the US business. We're working with the CDC, with the DOD, with the VA and federal programs where we've secured contracts. We have secured contracts across all retail pharmacy chains, including the independent chains, and we have also secured contracts with integrated delivery networks, regional networks, as well as GPOs and smaller clinics. So we are feeling really comfortable about having our contracts secured and in place. As of this week, we are also now actively shipping our doses to these different sites. So as early as later this week, we will have some sites that actually have the new vaccine ready and available for those who are coming in to get vaccinated.

So for the remainder of this year, really, this is now all about vaccination rates, how many Americans are going to come in to get their COVID vaccine. We're feeling good about the contracts, we're feeling good about supply. And now what we're really delving down on is how do we continue to partner across the ecosystem to make sure consumers are educated on the need for the vaccine based on the burden data that you just saw so that we can really help from a public health perspective.

So we're doing this in four different ways. Again, trying to really work within the healthcare system versus as Moderna alone. First and foremost, we have been working very closely with the medical community throughout the pandemic and since then to continue to really reinforce the importance of vaccination and the burden of disease, particularly in the 65 plus higher risk groups. And that medical community is very, very well-educated and ready to recommend for their populations.

From a customer perspective, we're also working closely with retail pharmacy chains and with larger integrated delivery networks to give them all of the education that we have to make it easy for them to recommend vaccines to their patient base so that it's a simpler conversation on when you come in for your flu shot, you should also get your COVID shot because COVID continues to actually be a higher burden of disease than even flu is today.

Thirdly, we are now looking to expand and go directly to consumers in a bigger way than we have. We will be re-engaging the consumer through social channels as well as broadcast TV. Again, the real focus here will be any adult who has gotten a flu shot, we believe is the ideal target for us, for them to come in and get their COVID shot as well. And that's what we're hearing from customer feedback, that's what we're seeing in all the surveys, is that those people who are willing to get their flu shot are going to be more willing to get their COVID shot. It's just a matter of simple, clear education and making sure that it's available and convenient.

Last but not least, we are partnering with different professional organizations, whether it be specialty groups in the high risk populations or underserved communities. So we've also worked pretty closely with underserved communities to make sure that there is clear access to our vaccines in the rural areas

and different demographics in the United States. From an RSV perspective, as Jacqui mentioned, we're really excited about the product profile that we have going into launch season in 2024. First and foremost, what we're seeing is very consistent high effectiveness across different subgroups and different populations. Secondly, as Jacqui mentioned, we're seeing a very well established safety and tolerability profile, which gives us confidence. Importantly, we will be the only mRNA RSV vaccine, and it's built on the same mRNA technology that has now been used in over a billion people during COVID. So we're feeling very good about the safety and tolerability profile.

And then last but not least, which is extremely important from a customer perspective, is our ease of administration. So we will be the only vaccine that is a ready-to-use prefilled syringe. What that does for customers, not just in the United States, but around the world, is it helps them save a lot of time, which is extremely valuable to retail pharmacies, for example, and doctors. But it also has the ability to reduce medication errors, which is certainly something that many countries are looking at around the world to make sure that medication errors are kept to a minimum.

Now, from a flu perspective, I mentioned earlier the flu market is about $6 billion today. As we continue to get more and more data about our profile, what is exciting on the right-hand side is you'll see that over the last several years, the flu market has been growing based on enhanced flu vaccines. So as we launch into more of an enhanced market, we believe we can expand and grow the flu market with more effective potentially flu vaccines and grow the overall flu market.

Last but not least, as a consumer but also as a commercial leader, I'm very excited about is the potential for combination vaccines. We've seen a lot of vaccine fatigue. We've seen a lot of people just tired of going back in multiple times or hesitant to get two shots at once. And the combination vaccines, we think can have a pretty dramatic impact, both from a healthcare system perspective in creating efficiencies, but also from a consumer perspective in creating convenience. So with that, I'm going to ask Jacqui to take us through the latent and other viruses.

Jacqueline Miller:

Okay, so now to shift gears into the rest of our vaccine portfolio, we actually have an expanding portfolio of latent virus vaccines, which are shown on this slide. And then we're also emerging into new areas. So we have our first gastrointestinal vaccine, which is norovirus, and I'm going to be telling you a little bit more about that one today, as well as our first bacterial vaccine Lyme disease. And so why are these two programs so important to us?

They really enable us to further investigate and expand the impact we can have with the mRNA technology. Most of our trials are still in phase one, so what I'll mostly share with you today from a latent perspective is an update on our CMV program. I did want to highlight that we are bringing forward a couple of novel programs, also first-in-human this year. So we have two therapeutic vaccines that we've started first-in-human since January 2023.

The first is an EBV vaccine that's enhanced not only with the lytic antigens, that's the same as the 1189 program designed to prevent infectious mononucleosis, but T-cell antigens and latent antigens, as well, that should be able to help us prevent the longer term complications of EBV infection, including complications like multiple sclerosis and some cancers like non-Hodgkin's lymphoma, gastric carcinoma, and nasal pharyngeal carcinoma.

The second therapeutic vaccine for which we've started a phase one this year is our herpes simplex virus vaccine. This is a vaccine that's actually intended to treat patients that already have herpes and have frequent recurrences. These patients currently are often on antiviral prophylaxis or treatment, and the idea is to enable them to have more convenient therapy with hopefully fewer exacerbations over time.

The focus of this discussion today is going to be on CMV, which is currently in our phase three program, and then the initiation of norovirus, which is our first product that's targeting a gastrointestinal virus.

So starting with CMV. CMV is the most common congenital infection worldwide, and it results in billions of dollars in annual healthcare costs. The sequelae at birth most commonly includes sensory neural deafness. It's actually the most common congenital cause of sensory neural deafness. And the longer term complications are often neurologic in nature as well, and include things like cognitive impairment, seizure disorders, and cerebral palsy. One in 200 infants actually is born to a mother who has passed along a CMV infection, and of those infants, one in five will turn out to have severe, life-altering problems. So we think that cytomegalovirus is an incredibly important infection to address.

Our vaccine includes six mRNA sequences. They encode two antigens. One is the GB antigen, which has been used in other CMV vaccines that have been shown to have some vaccine efficacy. Five of those mRNA sequences naturally assemble into the pentamer antigen, which is actually the immunodominant antigen in humans, so we're hoping we can build upon past success. Our phase three program has recently completed enrollment of the adult cohort.

So while enrollment is still ongoing in younger women 16 to 17 years of age, we have completed the enrollment of over 6,900 women of childbearing age. Why are the adolescents so important? We think they're important because this is a three-dose vaccine and one of the ways to increase uptake can be to include it in a vaccination schedule with other routinely recommended vaccines. 16 is a big age when children are still going to their pediatrician prior to college entry, and so we think this is really an opportunity to take advantage of the adolescent platform for vaccination.

The participants in this trial are at a higher risk for acquiring CMV, so they all have contact with younger children as of the age of 20. And the reason for that is to really enhance the likelihood that we will capture cases of primary infection. So again, learning from the development we've done in the past, this is a case accrual study and we're now in that point of time where we are waiting for those cases to begin to accrue. We have approximately a quarter of the cases that we need for our first interim analysis. So let me talk a little bit about the statistics and what will happen at that first interim analysis.

When 81 cases of primary infection have accrued in the study, we will perform our first analysis. And we've talked through this graph before, but I'll take you through again. The dotted line represents study power as a function of the true vaccine efficacy at the time of the interim analysis. The dotted line is the first one, the solid line is the final one, which we will conduct when we've accrued 112 cases. So if you just look at the dotted line for a moment, if the true vaccine efficacy is 60%, we have about 60% power, so a little better than flipping a coin of demonstrating successful vaccine efficacy. Another way to think about that is the lowest possible efficacy that we could see and still meet that objective is 57.7%.

But now, look at if this vaccine has 70% vaccine efficacy. We're already at a place where we have 90% power to be successful, which is why we built in this interim analysis. However, if we are not successful, that doesn't mean that this won't be an efficacious vaccine. It just means that the particular case split will not allow us to conclude the study early. So now, I'm going to pivot a little bit and speak about our norovirus vaccine program. And for those of you that haven't heard of it, norovirus is one of the most common causes of diarrheal disease each year, and it impacts, like respiratory viruses, primarily the very young and the very old.

It's also an infection that's taking place at an epithelial surface, so not so different, actually, than respiratory vaccines, which is what really gives us confidence that the mechanism of action that's working in respiratory can also work in gastrointestinal infections. The highest incidence is actually in children, and we will be, as part of this program, deescalating our dose ranging into children relatively early. But older adults and immunocompromised are actually at the highest risk of severe outcomes from disease, and that's typically dehydration and its further complications.

The burden among older adults is expected to rise with societal aging and the increased need for institutionalized care. So what you can see on the right-hand side of the graph is a comparison of the infections and deaths and hospitalizations, as well as costs in the US versus the rest of the world. And I think even in the US alone with $2 billion in annual healthcare costs, this is a program well worth targeting. So how have we designed our vaccine? This is a vaccine that actually, like our Zika virus vaccine, rather than being cell-surface expressed actually expresses a virus-like particle that is excreted from the cell. And this is really to take advantage of how the immunity at mucosal surfaces can occur.

We have the VLPs that are structurally similar to the native virus, and we think that really will help to mimic immunity from a natural infection similar to what we've done with COVID-19 and RSV. And unfortunately now you still can't see what I was speaking about, but I'm going to continue from there and hopefully, they'll get the tech back up and running. So we now started our phase one norovirus study last month. We are investigating both a trivalent and a pentavalent formulation and we will, based on that result, pick one of those formulations to take forward into phase three development if we see acceptable safety and immunogenicity.

So I think that was what I really wanted to share with you about norovirus, and Arpa is here to come up and talk about some of the commercial implications for our latent portfolio. I'll leave it to her to decide if she speaks without slides. Oh, it's back up.

Arpa Garay:

Thank you, Jackie. So from a latent perspective, you'll see while still vaccines and with similar contracting and buying and purchasing customers around the world, there are some distinct differences as I compare it to the respiratory portfolio. First and foremost, I think from a diversification perspective, latent viruses typically do not follow a seasonal pattern, so we will see more of an even selling cycle across a latent portfolio. And as you look at other latent vaccines that have launched like the Gardasils or the Shingrixes of the world, what you also see is upon launch, they don't have significant uptakes that then stabilize, as you may see in maybe a respiratory vaccine.

But rather, you see more of a trend towards expansion and growth as these vaccines are expanded to different patient populations. Overall, and Jackie touched just briefly on the number of latent and other viruses we're looking at, if we look across all of the different areas, we think this total market could be as big as $10 to $25 billion just given the ongoing burden of disease. And for us, as I mentioned earlier, with the portfolio that we have, we do see significant commercial opportunity, as well. We'll be competing similar to the HPV as well as the VZV landscapes into multi-billion dollar opportunities with each one of our candidates.

And then last one not least, I did want to just touch on norovirus, as Jackie had teed up. Jackie shared there are about 200,000 deaths globally from this virus. There is a significant unmet need. I can tell you from a patient perspective, there is a significant interest as well in actually preventing a lot of this disease. And while you'll, see particularly in the US, the real burden of disease is in the very young as well as the very old, it is actually still quite prevalent across all age groups.

As someone that does not fit into either category, I just had norovirus last week and it is not something that anybody wants. So we are seeing significant interest in norovirus from a consumer perspective. And if you look at the pediatric population and compare it to a rotavirus, what you'll see is norovirus actually has more burden of disease than even rotavirus does, which today is a multi-billion dollar opportunity around the world.

On the right-hand side, as we look at norovirus versus RSV, you also see significant burden of disease in the above 65. Again, another multi-billion dollar potential commercial opportunity. So, we're very

excited about the overall latent portfolio. I will not go through all of them today, but really just to touch on, from a latent vaccines perspective, we see more of a steady sort of growth with expansion. And then with some of our other vaccines like norovirus, we do see significant burden of disease, unmet needs, and interest from a public health perspective. So with that, I am going to give us all a break. I think we have a break before we come back for the therapeutics section. Thank you.

[BREAK]

Kyle

…talking about how platform can be leveraged for our therapeutics pipeline. Similar to what our ID pipeline colleagues talked about, we can leverage the platform in multiple ways for therapeutics [inaudible 01:19:16] by utilizing common LNPs, we can match these LNPs to different indications. We can leverage the information within the LNP and we can start at higher dose levels, we can accelerate our dose escalations, we can utilize information to have smaller packages for IND and even for BLAs.

So there's a lot of information that we can use to leverage across our platforms, and we're doing just that. We also have similar trial design elements, so by that I mean we're using the same types of infusion procedures, we're using the same dose schedules, we're using lots of common endpoints. All of this can really help us accelerate our programs across the therapeutics pipeline. This is just a quick snapshot of our therapeutics pipeline, and I'll go over some of these molecules with you right now. So the PA and MMA programs are programs that Geoffrey Rezvani will talk to you about a little bit later and do a deep dive on those programs.

GSD1a is also a program that's in clinic, so PA, MMA, GSD1a are all our programs that are in clinic today. And then on the right side of the slide, we have programs that... well, the CF program, VX-522 is also in clinic. At the bottom of the right we have a couple of programs that hopefully will be in clinic shortly. And as we announced earlier, the PKU program just received our Safe to Proceed letter from the FDA, so we'll have that program in clinic shortly.

What's really exciting about the PKU program is this is a program where we'll be starting our phase one trial in patients, and so hopefully we'll see proof of concept relatively quickly as soon as we start dosing our first patients. I'll also mention very briefly our CF program. Really excited about the CF program. We're doing this in collaboration with Vertex. As you know, Vertex is the world leader in cystic fibrosis, they're experts in the disease. And I think we're really solving a significant unmet need here in the patients with missense mutations who really have no other available options. So I'm excited to see the progress of our CF program, as well.

So these are the three programs that all use a common LNP: our MMA program, our PA program, and our PKU program. Our MMA program and PA program will have updated data that we'll share with you today. And hopefully, we'll start generating some similar data with PKU. The information that we've gathered from MMA and PA will be used to help support our PKU program because they share the common LNP. And on this slide I'm sharing with you the two different LNPs that we have in clinic. LNP 1 for the PA and MMA program, we have almost 30 years of patient experience of dosing in those products. It's been very well-tolerated, very infrequent allergic reactions, very encouraging signs of clinical benefit, and we hope we'll see very similar effects with our PKU program.

And then in with GSD1a, we haven't had quite the extensive experience with GSD1a in clinic. However, to date, we haven't seen any dose limiting toxicities and it's been very well-tolerated and we hope to see similar effects with our OTC program that we'd like to bring into clinic early next year. So with all of

these rare disease programs, we're excited to share with you that we think we'll have product launches for four of these programs within the next five years. And the reason why I can say this is twofold.

One, because regulators around the world have become very interested in rare diseases. Regulators have told us that they want us to bring these programs forward, they want to help us get these products to patients because they've been neglected in the past, and they see the value of our platform across all of these different rare diseases. So with propionic acidemia, MMA, glycogen storage disease, phenylketonuria, all of these programs we think are programs that can proceed to a product launch within the next five years. But this is not the end. So there are between 1,000 and 1,500 inborn errors of metabolism, and I believe that our platform can help solve all of those inborn errors of metabolism. So, stay tuned. We'll have many other programs that we'll announce over the coming years. And with that, I'd like to turn things over to Geoffrey Rezvani, who will talk to you a little bit more about our PA, MMA, and PKU programs. Geoff?

Geoffrey Rezvani:

Thank you very much Kyle. I am the program leader for our PA and MMA programs, and I'm happy to be here today to share some updates on our PA program. The first data that we're going to be sharing on our MMA program, and I'll talk a little bit about PKU as well. So I'm a pediatric endocrinologist and I had the opportunity to take care of patients with inborn errors in metabolism when I was in practice. And I've seen how devastating these diseases are for the patients with them, as well as their families. And I couldn't be more excited for the opportunity that we have with our platform to address some of the unmet medical needs that still exist in these patients with these diseases and beyond.

So I'll start out with a quick update on where we are with our PA program. So this was our first program testing an intracellular protein, and we've presented a little bit of data on this in the past and we continue to expand our experience with the program. Propionic acidemia and methylmalonic acidemia are both inborn errors in metabolism of the same pathway, one that's responsible for metabolism of certain proteins and the amino acids in them and fatty acids that are in almost everything we eat.

And it's necessary for the body to change these into energy in the mitochondria. So with PA, you can get abnormalities in this PCCA or PCCB gene causing this. And with that, you get a number of issues. So you get chronic disease issues, such as severe neurologic issues like seizures, developmental delay, and you also get acute problems on top of that. You can have strokes and you can have metabolic decompensation events, which we'll talk about quite a bit more as we go through this program here. Those can be severely debilitating and deadly. Now, our approach to treating propionic acidemia is to replace that intracellular enzyme using mRNA to code for that enzyme. We presented some data on this last year, some very early data on our Phase 1/2 program, and then we presented more in-depth data for this at the American Society of Gene Cell Therapy meeting in March. So there's a deeper dive there, and we've continued to build on that experience over the last months. So again, this is our paramount trial, Phase 1/2 study. Safety and PK are our primary endpoints.

We're also though looking at clues towards efficacy in this program and we've made great progress in this. So at this point, we've now enrolled all of our dose finding cohorts, and we have moved on to dose confirmation. In fact, we only have one more patient that we need to enroll in this trial at this point, so we're hoping to get that patient in soon and be able to select this dose and move on from there. So far, we've dosed 20 patients. We've got 12 patients who've had more than one year, 19.1 patient years of experience. And we've given now over 433 intravenous doses.

The majority of the patients have additionally chosen to remain on our drug in our open-label extension, and it's generally been very well-tolerated with no dose limiting toxicities. Importantly, I also want to note that we've only seen mild and moderate infusion-related reactions for the most part, and of those

433 doses, we've seen this in less than 10%. So I think that's really important to know that the patients are tolerating these infusions very well over time, also. And as we learn more about our LNPs and infusing them, we hope to see that number go down even more. Now, metabolic decompensation events that I mentioned earlier are our main clinical outcome that we're looking at here. These are serious, clinically significant events that you see in both PA and MMA. These commonly present shortly after birth in these patients, and they can be a major contributor to mortality and long-term problems in these patients, and they can kill them as well. So these can be objectively measured, and in our discussions with regulators on PA, they've provided initial support for using MDEs as a clinical meaningful endpoint.

So again, we showed you some information in the past on MDEs. We continue to collect that information in more patients and over more time. And so far, what we've seen with this is the relative risk among patients with prior MDE, which is the main group that we're likely to continue to follow for this endpoint. We've seen an overall reduction of over 70% of that relative risk. And if you just look at the patients who are on the regimen where we think we get efficacy, the two-week dosing regimen, that goes up to 80% relative risk reduction, so a really robust reduction in these terrible events.

So overall, we're expanding our experience with this drug in the clinic in PA. It's been generally well-tolerated with no DLTs, and this early information continues to support a reduction in MDEs. The majority of patients stay on drug in the open-label extension, and the next steps are to get that last patient into this trial so that we can finish this up, confirm our dose, and move on to the next stages of development, so stay tuned for that.

Now, methylmalonic acidemia. We talked a little bit about this last year and kind of previewed where we were going with this, but this is going to be the first time, now that we've collected more data, that we're sharing some information about this. As mentioned earlier, MMA is a disorder of the same metabolic pathway that I just talked about with PA. This time, you're talking about a different enzyme further down that pathway, that methylmalonyl-CoA mutase enzyme. This disease, again, just like PA, because you're looking at the same pathway there, has very similar problems to patients with PA where you get those neurologic problems.

These patients also tend to have kidney failure that you don't see quite as much in propionic acidemia, and they still have those acute events that can be deadly or severely debilitating in strokes and MDEs. There's no current treatment available for this, no medical treatment that addresses the underlying problem. These patients are treated with protein-restricted diets or sometimes with liver and kidney transplant.. Those have their own problems, so even with that, there's still a really large unmet medical need in these patients.

I'll say this over and over, and you've seen this slide before. Same approach to treating we use with our platform. We replace that abnormal enzyme by delivering that mRNA to the liver to code for that enzyme. So our landmark trial, this is analogous to our paramount trial in propionic acidemia. It's our first-in-human Phase 1/2 study looking at safety and pharmacology of our mRNA-3705 in these patients with MMA. We're also looking at some secondary endpoints of... I'll talk about in a minute, of methylmalonic acid levels. And again, as an exploratory endpoint, those MDEs as a clinical outcome.

We've now fully enrolled the first three dose finding cohorts, and importantly, we're getting up to a range where we might expect to see some efficacy out of the doses that we're at. We've also enrolled two patients in cohort four, and we'll continue working through these dose finding cohorts to select a dose. So good progress there, to this point. The patients look like you might expect for a fairly diverse inborn errors of metabolism trial, but what I want to point out and note is that we started out in patients one year and above, and that's really important in these trials, because these are diseases that very much affect children disproportionately and obviously, they're born with. So we've got to get our

drugs into these patients early on in life and figure out how they work, find the right doses for those patients early on. And as you can see, we've already enrolled a wide age range in this trial.

So as of now, we've dosed 11 patients so far with a total of actually now over 221 doses with a total cumulative treatment of 10 and a half patient years. It's ongoing. We're looking for that final participant in cohort four. We're hoping to enroll them in the next couple of weeks. And just like in PA, this has been generally well-tolerated to date with no DLTs to this point. And in this trial, all of the patients who have completed so far have chosen to continue on for treatment in the open-label extension trial.

In terms of the primary outcomes of the safety that we're looking at, we've had no deaths or discontinuations due to safety-related reasons. We did have one discontinuation due to a site closure, though. We haven't had any DLTs and only one serious AE, which was an event of body temperature increase. Patient continued on treatment and it resolved. Drug-related adverse events have mostly been mild and moderate, and again, importantly, less than 5% of those 221... 223 doses that have been administered as of this data cut were associated with any infusion-related reaction, and the ones that we have seen have generally been mild and easily managed.

Now, MMA presents an interesting opportunity for us, and that's that there is potentially a biomarker that we can use here as a surrogate for those clinical outcomes. And that's methylmalonic acid, one of the molecules that builds up in this pathway when you have this disease. Now, this is not a clinically validated biomarker yet, but what we find is that changes in concentrations of methylmalonic acid generally correlate with disease severity, and the natural history data suggests that changes there also may be associated with clinical events.

So what do we see in our trials with this? Well, we see exactly what I think you would hope to see with the little bits of data that we're collecting at this point. Now on the right side, you're looking at methylmalonic acid. On the left side, another potential biomarker of 2-methylcitrate here. And each of those columns represents one of the cohorts starting at our lowest dose, moving up to 0.4, which again, is the earliest doses where we would think we might see some signs of meaningful efficacy.

And what you're seeing there is as you go up in the doses, a dose-dependent decrease in that biomarker of methylmalonic acid on the left side, and we're starting to see clues with 2-methylcitrate there, as well. So more to come on that, but we're excited that we potentially have a surrogate there as well. Now you'll notice that I didn't include the cohort four patients in there. Again, we've only enrolled two patients there so far, and as of this data cut, they only received a handful of doses and we only have a handful of data points. We haven't seen a decrease yet in the methylmalonic acid levels for them, but we'll continue to follow that and continue to enroll patients.

Now, our clinical endpoint of the MDEs, just like in propionic acidemia, we're following those and we don't have quite as much data here yet. We'll continue to follow this, but what you'll see is just like what we showed in propionic acidemia last year. The early data there shows exactly what we would hope, which is that when you get up into those doses that we think would be efficacious, we're not seeing, so far, MDEs in the patients who are on treatment. So that's really exciting for us as well.

So in summary, we're building our experience with this drug. We're up to over 10 and a half patient years now. It's generally been well-tolerated just like in PA just as you would expect. And as Kyle talked about, we are building our overall experience with our LNP here. There's encouraging initial pharmacologic data as well as clinical data, and we'll continue to follow that. And from here, we need to continue to enroll those last cohorts, choose a dose, and then move on quickly from there to getting this drug to patients who I believe will benefit from it.

Now, I'll briefly touch on PKU as well. So we're very excited to get our Safe to Proceed letter, so we're going to be kicking off that trial soon. Now, PKU is a rare, inherited metabolic disease, another inborn

error of metabolism that has to do with protein metabolism, in this case, phenylalanine. This has analogous problems to the other inborn errors of metabolism that we've been talking about, so you get developmental delay, brain damage, and while there are a couple of medical treatments available for this, they're not perfect and there's still a huge unmet medical need in PKU and a need for better drugs here. So, we're hoping that our mRNA therapy will be able to meet that need. The other thing that you'll notice about this in that target population, some of these diseases you're talking about a few thousand patients worldwide, potentially. PKU is on a little bit of a different scale. You're talking about potentially 40,000 patients worldwide. So again, many more patients, huge unmet medical need there. We're going to be very excited to get into that population. Again, same approach to treating these patients. Use our mRNA to encode for the enzyme that's abnormal in these patients. Stay tuned for more data coming out on our PA and MMA programs and the first emerging data in PAH in the near future. Thank you very much for the opportunity to tell you about these three programs. With that, I will hand it over to Arpa.

Arpa Garay:

Thank you. From a commercial perspective, rare diseases is pretty much the exact opposite of all of the vaccines' world from a commercial perspective that we've been in, but we see this as a really exciting commercial opportunity. First and foremost, there's a really, really high unmet need, as Jeff just described. Oftentimes in these diseases, there's no option at all for these children as well as for their families. We also see very high levels of diagnosis, either through newborn screenings or just early symptomatic events. And because these are life-saving therapies for the most part, you see very high compliance rates. You've got very motivated patients and very motivated caregivers and very motivated healthcare providers.

From an overall perspective, from a metabolic rare disease perspective, we think the market could be as large as $10 billion across several different companies studying rare diseases. But importantly in the programs that Jeff just talked us through, we see quite a variability. Now, these are just US numbers, so the numbers are actually larger as you look globally, but in some of the different disease areas, you see very small concentrated populations. In others such as PKU, we see that growing quite significantly around the world.

Now, while the populations are concentrated, what we also see is it's also concentrated based on countries as well. Many of these rare diseases are just specific to a handful of countries that are driving the majority of the disease. So from a commercial perspective, it is a very targeted commercial play in terms of what countries do we operate in with our rare disease programs, and then how do we think about this very narrow prescribing base and academic hospitals, but also very narrow patient communities. You've got a lot of advocacy groups in the rare diseases that are very willing to partner with companies like ours to make sure that their patients are aware of different therapies and that they're able to get access to them in the best possible way.

Beyond the very concentrated base, because the rare disease portfolio is such high unmet need, what we see generally is higher value assigned to rare disease products, so higher pricing in general across countries. Like I mentioned, it's typically an easier way to identify patients and most other therapy areas just given the high burden of disease in small numbers. And then also from a regulatory perspective, as both Kyle and Jeff had mentioned, we do see benefits from a regulatory perspective given the high burden of disease and unmet needs. So from a rare disease perspective, we're really excited about the commercial opportunity. Obviously, we treat rare diseases very, very differently from our vaccines portfolio, but we think it's a very exciting opportunity for us to make a difference but also do it in a very lean and efficient way across our different metabolic diseases. With that, I'm going to ask Kyle to take us through oncology.

Kyle:

Thank you, Arpa. Okay, last but not least, one of my favorite topics to talk about is our oncology pipeline. As a medical oncologist, I just couldn't be more thrilled with our pipeline and the potential that this pipeline has to really make a meaningful impact on patients. Let's walk through it together very quickly. Again, we leverage the platform. And what's really, really exciting about INT is that I can't think of another example where you bring to a regulator a billion patients of a safety database with your L&P. Thanks to the work that our ID colleagues have done, we have dosed over a billion patients with our COVID vaccine. This is the same L&P that we're using for INT, and it's remarkable. I don't think there'll ever be an oncology drug with that type of safety information, so I'm super excited about the way we can leverage that information for INT.

We also have specific T-cell responses for our oncology pipeline. What I mean by that is we're not a common IO agent with INT. We have directed T-cells to the neoantigens that are unique to the cancer, so we're telling the T-cells where to go. Unlike a general broad immune activation, which is typically what you see with other IO agents, we have a specific direction for the T-cells to go and attack the cancer itself. This is important because it really changes the therapeutic index of our product. By targeting the cancer cell and not having the same effect systemically, then you can see a much greater efficacy with a more tolerable safety profile.

This is very evident when we start talking to you about INT and the safety data from INT. We have flu-like side effects with INT. When you think about chemotherapy in general for cancer, flu-like side effects is not something to talk to patients about. It's hair loss, it's nausea, it's fatigue, it's diarrhea, it's horrible, horrible side effects with chemotherapy. And with IO agents, you have, again, autoimmune reactions, which can be pretty debilitating. So coming out with a drug for cancer that has a couple of days of flu type symptoms is pretty remarkable.

And that goes along with the self-limited and low grade safety profile, and not just for INT, but we have similar self-limited and low grade profile with our other agents, our checkpoint vaccine, as well as our Triplet therapy. This is a snapshot of our oncology programs. Of course, Michelle Brown, the program lead for INT, will come up and do a deep dive on the data for INT. I'll talk to you a little bit about what's happening with our Triplet program as well as our checkpoint vaccine.

I'll start with our Triplet program. So our Triplet program is a combination of three mRNAs, one mRNA targeting OX40, another IL-23, and the third IL-36. We inject the mRNA directly into the tumor, and we do this to activate the immune system locally and create that immune activation that can have a direct effect on the tumor. Now, you might think this may only be a local effect on the tumor, but what happens when you have this hyperactivation of your immune system is the T-cells learn from that injection and from attacking that cancer, and they can then go systemically and find other tumors. What we call this is an abscopal effect of the local treatment injection. We've already observed some abscopal effects in our clinical trial.

This is a schematic of our study. We start out with a combination of 2752 plus durvalumab. We escalate it in a variety of different solid tumors and lymphomas. After confirming the dose, we've now expanded into checkpoint refractory melanoma, and we're currently enrolling in that dose expansion.

We also have a very interesting study that's ongoing by a physician named Dr. Laura Esserman. She is a very famous breast cancer surgeon who started the I-SPY trial, so many of you may be familiar with her. She has been working with us specifically on a trial looking at women with DCIS and injecting our Triplet therapy into the tumor. What we hope to see with this trial is an effect on the tumor significant enough to reduce the need for women to undergo mastectomies from DCIS. I believe this is a very high unmet need. In fact, relatives and people that we work with at Moderna are significantly affected by the fact

that they have to undergo mastectomies for something that is a local problem. I think we can help solve this problem with the administration of Triplet therapy. We hope to release data in an upcoming scientific meeting hopefully later this year, and Dr. Esserman will be presenting her data at that meeting.

The next program I'd like to talk to you briefly about is our checkpoint vaccine. This works a little bit differently than the checkpoint antibodies that all of us are familiar with. The checkpoint vaccine is designed to activate T-cells against two antigens, PD-L1 as well as IDO. IDO and PD-L1 are very important, as we all know, in immune regulation, but it works differently than the antibodies because it activates T-cell and it directs T-cells to any cell that's expressing these antigens. And so that means not only can it have a direct effect on the tumor, but the T-cells can also help decrease the Tregs which express IDO and PD-L1. So by decreasing the Tregs, we can lift that immune suppression that happens with Treg cells.

So not only do we see direct tumor killing from the T-cells, but we can see a heightened immune activation. And so with this checkpoint vaccine, we think we can have a amplified effect on the tumor, particularly if we administer the checkpoint vaccine in combination with some of the checkpoint antibodies. And we're doing that right now as part of our phase one trial. We started with monotherapy and we dose escalated the vaccine as monotherapy. We then moved on to a combination therapy with pembrolizumab and our checkpoint vaccine. And then later on we hope to open an expansion cohort in both melanoma and non-small cell lung cancer. Both of these populations will be in checkpoint refractory disease.

With that, I'll turn things over to Dr. Michelle Brown, who will... Oh, not quite yet, I got a couple more slides. Thanks. Before I get to Michelle, let's talk a little bit more about INT. As we all know, there are many, many different types of tumors that are currently targeted by IO agents. There are over 20 different tumors across the different labels where IO agents that have shown efficacy, and this is just an example of some of them. Even though IO agents have been remarkable and in fact revolutionary in oncology, they're still really high unmet need. So if you look across all these different indications, you can see that you typically have fairly low response rates. In fact, the cure rates are almost non-existent. So we think we can do better, and that's what INT is designed to do, is to do better than what the standard IO agents can deliver.

But what's interesting about INT is we don't necessarily need to know what tumor it is that we're treating because the way INT is created, and Michelle will go into this in more detail, is we look at the tumor mutation pattern and we build our vaccine based on the neoantigens that are predicted to have an immune response. And so what's most important in that process is understanding the DNA mutation patterns of that particular tumor. Every single cancer has a mutation and a series of mutations, and we can develop our vaccine based on that mutation pattern no matter what cancer it is. So quite frankly, the world is our oyster in terms of the cancers that we think we can have benefit in.

And so then how do you develop a playbook on where to go first? Well, this is an example of the cancer treatment spectrum, all the way from a healthy individual until late stage disease. What we currently are working on is the immediate adjacencies to where we've shown randomized clinical proof of concept, and that is in the adjuvant melanoma space. Now, melanoma is a very responsive tumor type to IO agents. And so if you look at other tumor types that tend to be responsive to IO agents and you look at the adjuvant space, that's the obvious next place to go. And we've announced that we're moving forward with a non-small cell lung cancer study.

But outside of the adjuvant space, I'm even more excited about the space before you get to adjuvant therapy. There's a whole world of opportunity where patients are getting screening tests now to understand their DNA methylation and circulating tumor DNA levels. And if you can screen people very,

very early with ctDNA, you could potentially capture those patients and give them a vaccination based on INT before they're even diagnosed with cancer, which would be pretty incredible.

Not only that, but you can look at early cancer management. So there's a lot of cancers right now that are followed with a watch-and-wait approach. I'll give you some examples of CLL is watch and wait, prostate cancer oftentimes it's a watch-and-wait approach. We might be able to target these cancers as well with an INT type therapy. The reason why we can do this is because we have a vaccine-like tolerability. If you're offering a watch-and-wait approach to someone, and the other option is, well, I can give you toxic chemotherapy, I think most patients would say, "I don't want toxic chemotherapy." But if you give them the opportunity to get a vaccine, I think the conversation might be very different.

So that's the earlier stage of disease. Of course, I'm also excited about later stages of diseases, in particular the surveillance. As you know, there are multiple ctDNA assays currently on the market looking at surveillance after tumor resection in particular for colorectal cancer. We might be able to take a patient very early on in recurrence through the ctDNA and understand how we can vaccinate at that stage. Look, a lot of people don't believe that vaccines can have much efficacy in bulky disease, but I think we're here to prove them wrong. Let's see whether or not we can find a way that INT can help patients with end stage disease too. So all of these pieces on the cancer journey are up for debate right now for both Moderna and our partners in this space, Merck. Okay, with that, I'll move things over to Michelle, and she'll review some of the recent data. Thank you.

Michelle:

Thank you, Kyle. I'm going to apologize as we're going to go into some deep data to show why we have so much exuberance around our individualized neoantigen therapy program. And like Kyle, being someone who has been involved in the field of oncology for my professional career and seeing the impact of cancer on patients and their families, I think we all at Moderna share that exuberance for the potential of INT. I think that it is my pleasure to walk you through the exceptional journey we've been through for the past year and how we plan on bringing this novel mRNA-based, completely individualized treatment to oncology patients.

INT has many names. Right now it's referred to as mRNA-4157, V940, or INT. It really sits at the advancement of our understanding of immunology and cancer biology and at its core is a beautiful interface of technological, digital, and biological innovation. This all starts with the patient. I know that the mechanism has been described in the past, but I do think it's worth us spending a little bit of time on it because it is what sets it apart from previous treatment approaches and is also the foundation of the clinical benefit we're observing and why we think we can aspire to what we're doing. So in the clinic, patients have their blood samples and their tumors biopsied so that we can perform next generation sequencing. This next generation sequencing allows us to identify thousands of tumor-specific mutations. Those are then fed in to an automated proprietary bioinformatics algorithm, which assesses these mutations on a number of fronts. The first is looking at potential expression or protein folding. Another is looking at similarity to self. And then a third milieu is thinking about how that mutation would stimulate a T-cell response.

And taking into account all of those factors and looking across all these mutations, the algorithm produces up to 34 tumor-specific mutations, now we call these neoantigens, that are predicted to train a patient's immune system to better identify tumor cells and then mount an anti-tumor response. Once we have those 34 neoantigens identified, the information is seamlessly sent to our manufacturing facility where it is encoded upon a single mRNA strand, lipid encapsulated, similar to what we see with our infectious disease portfolio, and then shipped to sites for administration. Importantly, this entire

process which took me about five minutes to describe happens with high efficiency, and it can be achieved within about six weeks.

Now, similar to the other assets that we've spoken about today, what we see is that this single mRNA strand that is now completely personalized enters into a cell and is endogenously translated. What is released is now these 34 neoantigens. They enter into the normal processing for antigen presentation and expression to stimulate T-cells. So this is a known mechanism, but it's a very distinct way to stimulate T-cell responses. Not only is that unique for INT, but the way we're using this mechanism is also very unique, because INT is truly targeting neoantigens, and neoantigens are patient specific, just like a fingerprint. And that is amazingly challenging to do without the advancements we've had.

Previous approaches when they've tried to target this type of approach have used tumor-associated antigens. Tumor-associated antigens look like normal cells, but they're just manipulated by the tumor. So they're very generic. Studies using these TAA approaches have largely not yielded clinical benefit. We think that the mRNA technology, our ability to really personalize the neoantigens that are being selected, and tailor that to the antigen-presenting machinery of a unique patient is going to overcome the shortcomings of previous approaches and show us a clinical benefit for patients. And indeed, that's what we saw in our randomized phase two study.

This study in collaboration with Merck enrolled high risk resected stage three melanoma patients and assigned them to treatment with INT or pembrolizumab, also called Keytruda or pembro, or pembrolizumab alone. The reason we selected pembro is because this is standard of care for adjuvant melanoma, so this is what patients would normally receive out in the clinic. And similar to landmark adjuvant melanoma studies, we designed the study with a primary endpoint of recurrence-free survival with the secondary endpoint of distant metastasis free survival. DMFS was pre-specified to be tested if our primary endpoint of RFS was positive. In addition, we're following these patients for an extended period of time to understand the durability of the treatment effect and also look at overall survival.

The study is designed with traditional phase two statistics, so it does have an 80% power and a one-sided alpha. However, because of the transformative potential for the technology, we designed a very aggressive hazard ratio of 0.5. And importantly, the primary analysis was pre- specified to occur after a minimum of 40 events were observed and a year follow up, and we had that happen last year in November. The data from that primary analysis has been presented in a number of forums this year and has really been the foundation of our excitement and our enthusiasm for this approach. What I'm going to walk you through is the primary endpoint of recurrence-free survival. This is a Kaplan-Meier curve, and what you see is essentially the follow-up and the recurrence events that happened on the study. The red line is the INT/pembro combination arm. The gray line is the pembro control arm.

What you see based off the 0.56 hazard ratio is that patients that were treated in the INT combination had a 44% chance of risk... sorry, a reduced risk of recurrence or death. And when we look at landmark timing, what you see at the 18-month mark is a delta of about 16%. That's really important because when pembro was first approved, it was compared to placebo, so nothing, and it actually showed a 16% delta as the foundation of its approval. And importantly, what you see in this gray arm as well is that the pembro arm here performed like it did in its historical keynote 054 study. So although this is a small trial, it gives us much more confidence in the treatment effect we're observing in the combination arm.

Now, one thing that's been pointed out with this curve is how close the lines are for the first couple of weeks. What we see is that would make sense because we have a pembro lead-in, INT is being manufactured. But this is also true because of the mechanism of action. It's going to take a little bit of time to stimulate our T-cells and mount a robust anti-tumor effect. But what you would expect if INT is working is a separation over time. And so what we see here is this separation of the curves would suggest a T-cell effect, a durability of response that is maintained for disease control well after patients

are done with their treatment. This theme is very similar to what we saw with our secondary endpoint of distant metastasis-free survival.

So here, very similar to the RFS, we see a clinically meaningful benefit for patients on the combination arm, again displayed in red compared to the pembro arm displayed in gray. In this situation, when we're looking at distant events, we see that those treated in the combination had a reduced risk of recurrence by over 65%. And notably, when we look again at landmark analysis, what we see is that over 90% of patients treated with the combination... free from distance events or death. So again, supporting this profound ability to impact clinical outcomes for patients. In addition, you also see that there's not a lot of events happening in the very beginning. But again, we see this separation of the curves suggesting that INT really does induce a durability to control the distant disease over time.

This has potential to really positively impact patients because those that have distant events tend to have increased morbidity and mortality. So again, what we believe here is what you're seeing is clinically meaningful outcomes for patients. In addition to benefit we're seeing off of the efficacy outcome, we did thoroughly look at the safety and tolerability. This is a busy slide, and the key theme here is that when we put INT on top of pembrolizumab, the combination doesn't necessarily change the safety profile compared to pembro alone. So the majority of our patients had grade one or two adverse events. There was very few increased grade three or more serious adverse events. And when we characterize the types of adverse events patients are having, it's very similar to what has been described across our mRNA platform. So again, as Kyle alluded to, flu-like symptoms, infusion site reactions, very low grade, self resolving, clinically manageable with standard of care, and importantly, these decrease with repeat dosing. So overall, very well tolerated compared to the known agents for oncology.

When we think about pembro, if you look at the two columns, essentially what we see is that pembro behaves similarly in both arms, and it behaves similarly to what would be expected across its indications. Further, when we think about immuno-oncology agents as a whole, we think about their immune media adverse events. What we saw was the addition of INT on top of pembro did not change the nature of the immune media adverse events. And this is really important because generally when you combine two immunostimulatory agents, you see an increased frequency and an increased severity of the itises, and these have clinically meaningful impact because they require hospitalization or long-term steroids or long-term disease management. And so we're not seeing that with the combination.

In addition, it also speaks to the fact that INT and pembro have distinct mechanisms of action. So those are the phase two data that really made us very excited for the potential for INT. In addition, this really is the first randomized study to show a clinically meaningful improvement for this type of individualized cancer therapy. Further, it shows the potential benefit that we can bring to patients with a high unmet need in a well-tolerated forum. And lastly, it's these two factors that allowed us to receive breakthrough therapy designation by the FDA and prime designation by the EMA.

So the question becomes, we have this data, where do we go from here? First and foremost as been alluded to, we're a learning organization, so we will continue to follow these patients, we'll continue to develop data, and we'll continue to learn. We do have additional analysis has been announced that will follow the patients for an extra year so we can assess the long-term durability of the responses. In addition, we'll do additional translational assessments and immunologic assessments to learn more about the true mechanism of action of INT. In addition, we are continuing to have discussions with health authorities, and these discussions involve teaching them about INT, learning how they view this novel modality, and then also soliciting their feedback for how to develop this new paradigm. Because as we've heard, our mission and our belief based off the data you're seeing is that we have an obligation to develop INT as expeditiously as possible to positively impact patients with high unmet need. And for those reasons, we are truly pursuing accelerated opportunities.

Now, a large step forward has been the initiation of the phase three study that achieved first patient first visit in July. We keep hearing about speed, but if you actually think about it, our top line data came out in December, and we have our first phase three in July. That's seven months from proof of concept to phase three initiation, which generally does not happen in oncology. So We're truly developing this agent in an expeditious fashion.

In addition, this study is building upon the learnings of the phase two study. So V90-001, in collaboration with Merck, is a robust phase three trial. It is double-blind, it's placebo controlled, and it seeks to enroll about 1100 patients. It has the same endpoints as what we just walked through with the phase two trial. In addition, the study has an expanded patient population so that more patients are able to receive INT. And so here we're including stage 2B, 2C, threes, and fours.

Now, the initiation of this study is important for Moderna and the INT team because it represents the first phase three trial for an individualized neoantigen approach, it represents the first phase three study for Moderna Oncology, but it also shows that Moderna has built an infrastructure that's actually capable of delivering a completely individualized therapy to patients across the globe. So this is truly really a profound moment for us on the INTT. Now, in addition to expanding our global footprint, we are also expanding our development strategy beyond melanoma. And as Stephen said, we have to look forward or backwards to look forwards. So, we have announced we are planning a trial in non-small cell. And the reason for pursuing non-small cell lung cancer is both from a biologic level but also embedded in our P101 study results.

So, P101 was a traditional first-in-human dose escalation study of INT as a monotherapy and in combination with pembro. And the goal of the study was to assess mechanism of action, characterize primary safety, and look at preliminary efficacy signals. And not surprisingly, the first types of patients that could enroll were those that were IO sensitive patients.

What you're seeing here is a swimmer's plot from our cohort A. So, this was the group of adjuvant patients who received INT monotherapy throughout dose escalation. And the swimmer's plot represents the patient journey over time and their relapse events. And if you do a quick tally of the non-small cell lung cancer patients on the Y axis, you'll come out to 11. And what you'll notice is that these 11 had relatively early non-small cell lung cancer.

Now, historically, about one in five of these types of non-small cell lung cancer patients will have a recurrence event in about two years. Again, if you look at the swimmer's plot, what we saw is that zero of our 11 developed a recurrence event while on treatment or throughout their entirety of their study. And what this suggested to us was that INT may actually have a role for patients with non-small cell lung cancer.

In addition, if we delve into what's happening in one of these adjuvant non-small cell patients, we looked at their T-cell profile, and what you see here is a graph that depicts T-cell responses in that patient. On the X axis, it's [inaudible 02:14:32] neoantigens in their INT, and what's seen with the red bars is that we have T-cell responses across the litany of neoantigen pools. And if you look at the grade to the red bars, what we see is a threefold induction of T-cell responses.

So, what that means is that INT was able to induce robust T-cell responses and potentially clinical activity in patients with non-small cell lung cancer. And this is important because non-small cell cancer remains an area of high unmet need. And as you hear, that's a continual theme for Moderna. We're trying to transform and generate medicines for patients that have high unmet need.

So, non-small cell cancer is one of the most common forms of cancer worldwide. About 50% of patients are diagnosed with early stage disease, and those numbers are expected to increase over time with the advent of additional screening techniques. Now, generally, a lot of people say these patients tend to

have good outcome, but if you really look at their five-year overall survival rates, what we see is that those with very early disease, one in three of those patients will not be standing here after five years. And if we look at those with stage III disease, only one out of 10 will still be alive after five years. So, we have room to improve and we can do better we believe with INT.

In addition, if you think about the biology, we believe that non-small cell is a biological adjacency to melanoma. It's a immune sensitive tumor that has high tumor mutational load. It has an inflamed tumor microenvironment, and it basically says here is a tumor type could respond well to a neoantigen based therapy. So, you take that in conjunction with the results from our phase 1 study, and it's not surprising that we plan on having our adjuvant phase 3 non-small cell studies starting this year. Importantly, again, this represents two phase 3 studies within less than a year from our proof of concept.

In summary, we've had quite the journey for INT. So, encouraged by the phase 2 study, we have proof of concept for mRNA technology and the impact of an individualized therapy to positively change care for oncology patients. And so, it's not surprising that we have a very bold development strategy, and it's not surprising that we're very excited based off of the mechanism of action and the clinical benefit we're seeing. And because of that, we plan on doing a lot of different things with this therapy as Kyle alluded to.

So, the first is to start exploring tumors that have established IO sensitivity, and we've talked through that with non-small cell and the rationale, but with melanoma. But we're also looking at other tumor types that have the same type of biologic features, so high tumor mutational burdens, high inflammation scores. And these tumor types, if you look at them and think about them, these are what's normally the litany of checkpoint approved indications. And so, we're looking at those and those tumors would include things like cSCC or RCC.

In addition, we know that oncology is a very fast-moving field and we're watching the treatment landscape shift from adjuvant settings to earlier lines. And so, we are looking at tumor types that have perioperative approaches coming into play, and those tumor types would be reflected as non-small cell lung cancer or gastric, but we're not going to end with just those that tend to be IO sensitive. We are, because of the unique mechanism of action, also anticipating evaluating the potential of INT in those tumor types that have been historically challenging for immunotherapy agents. And so, that's why you see PDAC listed here.

So, in summary, what I can say is that it's been a great journey for the past year. We're very proud of our accomplishments with INT. We're very excited for the future of this program and the impact it can have in patients. And across Moderna, we're dedicated to bringing the mRNA platform and mRNA technology to generate transformative medicines. Thank you for your time. And with that, I'll hand this over to Jamey to talk through the franchise.

Jamey Mock:

Thank you, Michelle. Thanks everybody for joining, either live, in person or sticking it out on our webcast. I'd like to cover three things today. The first is the benefit of our platform, how we actually use that to run the business, and then how it manifests itself into financial benefits in each one of these franchises. The second thing is we have a large investment profile, particularly in R&D over the next five years, which I'll share with you, and then I'll share what the return on that investment looks like from a revenue standpoint. And then third, while I have you, I thought I'd talk about the shorter term in 2023 and our COVID business as well.

So, we'll get started here. As you all know and heard of today, we are a platform company. And so, what does that mean? Financially, that brings a lot of synergies and it brings synergies in terms of how we run

the company for every single function. And I've laid out three, but it touches all the back office functions as well. And then it shows up in financial benefits, which I'll touch on, and then I'll show you how they translate into each of our franchises.

So, at research, Stephen talked about a little bit, but we operate at the intersection of the technology capabilities that we've established, what we call modalities, and then we run that across all areas of biology. And so, as we de-risk a modality, we then apply that to many different therapeutic areas, which is why what you see today is that we believe we have four different franchises. In development, we talk about rapid and iterative development, and I think Jackie and Roth did a great job today explaining that.

So, if we talk about rapid development, Jackie laid out for COVID, RSV and flu, from the start of phase 1 to the end of phase 3, that took us one to two and a half years, or two years on average. In terms of iterative development, Roth talked about what we did with flu, just from Vaccines Day till now, the improvements we've made, which I guess is four months. And so, that iterative development allows us to develop a terrific pipeline.

And then we built an incredible clinical trial structure, both internally and externally with our partners. And we learn from it every single time we run a trial through it to become more efficient from a cost standpoint or to actually enroll faster so that we can bring our pipeline to market faster. And then commercially, Arpa talked about it. Particularly in our respiratory business, we call on the same customer base. We built a respiratory sales force across the globe, and this all manifests itself into three large areas: greater sales, lower cost of goods sold, better capital efficiency, and then better R&D efficiency as well, which I'll touch on in a couple of pages.

So, we take those three things and say, "Okay, well, how do they manifest themselves in each of our franchises from a financial synergy perspective?" So, starting with sales, as I've talked about before, we are trying to build large recurring revenue streams. And we've talked about the respiratory franchise, how there's over 500 million vaccinations across the globe in flu right now. In the United States, over 150 million. And as we develop our portfolio across all three different vaccines and then add combinations, we're hoping to expand that 500 million because of the value that it brings. And we also look at it from a growth story perspective. The population's growing, and the older adult percent of the overall population is growing at a faster pace as well.

And in rare, as another example, as our patients live longer on our therapies, that becomes a recurring revenue stream. And the more successful we are, the more patients we'll be able to treat. So, we think that that becomes a larger recurring revenue stream as well.

When we talk about manufacturing, you can see three of these franchises use the same manufacturing footprint, and I think Stephane might've mentioned that earlier today. The only one that doesn't is oncology because we miniaturize to individualize our therapy for mRNA. And so, that leads to overall better efficiency in terms of cost of goods sold. Also, capital efficiency because we have to invest less with more franchises using the same infrastructure.

And then further on, optimized manufacturing, as we come out with our combination vaccines, that will reduce the highest cost of our cost of goods sold, which is the drug product filling step. If we can take out one or two of those steps, that's a significant improvement in terms of our cost of goods sold and our overall margin rate.

And then in terms of R&D investment, we talk about getting through the first phase 3s. That's a significant hurdle for anyone. And as soon as we get through those, you actually have a growing franchise with less R&D, and I'll talk about that a little bit more. But this is the most important part in terms of R&D efficiency, it's our high probability of success. And if you look at this page, we're

comparing ourselves to industry standard. And the higher probability of success means that we should invest more R&D dollars in it because it'll actually come to fruition.

If you look at phase 1 versus the industry, we are 2X. If you look at phase 2 versus the industry, we are 3X. And then if you look at overall phase 3, we're actually on par. But those two events that did not happen were P301 and P302 and flu. So, all three of our programs actually came to fruition out of phase 3, flu, RSV and COVID. So, we believe that the higher our POS is, that's what gives us confidence to invest more dollars into R&D and actually believe that it's in a very efficient manner.

So, we want to invest organically to grow this business for a long period of time. And to do so, we're going to invest $25 billion over the next five years. And so, there's a few points I'd make on this. Number one, that's obviously on average about $5 billion a year, which is not too dissimilar than what we're spending in 2023. And we believe that we've achieved the scale of our R&D organization to actually fulfill our ambition.

Number two, you can see the spend drivers. So, I mentioned this at Vaccines Day, respiratory, I said at the time we have to invest another 6 to $8 billion or on average about $2.5 billion a year. And you'll see that continues in 2024 and 2025, but then it goes down by 2027 to be 10% of our overall revenue. That's what we said is the routine maintenance portion of our R&D investment for our respiratory franchise. And then you'll see latent and oncology start to pick up over time. And those franchises, we will invest more in.

And then underneath all of this is our research in the platform. And Stephen talked a little bit about it today and it doesn't get enough airtime, but it makes up about 10 to 15% of our investment and includes our collaborations, much like we just announced with Immatics earlier this week. And that 10 to 15% of this overall R&D spend advances the science, advances the technology, and increases our pipeline. And when we say we're going to come out with 15 new products or when we say we're going to come out with 15 new products and 15 new pipeline candidates in the next five years, that's where this money goes to, is to help improve that.

The last couple of things I'll mention are on the right-hand side of this page. It is quite diversified. I already gave you how much research will be, if it's 10 to 15% of this overall number, and I gave you basically what respiratory will be. So, that leaves the other three that are basically the rest of that 50%, roughly 50% of this spend. And the last thing I'd say is we will always, and we have always monitored our capital and the strength of our business. And our core underlying business right now is only COVID. In a couple of years, it'll be flu, RSV and combinations, but we always monitor that, and we have a high ability to flex this spending.

So, right now, our base plan is $25 billion to invest organically to grow our company. We think it's the right thing to do, to bring 15 new products to market, not just from a revenue standpoint but also for our patients. And that's what we plan to do, but it can be flexed up or down based upon the success of the underlying business. And the return on this we think is substantial. So, we already laid out at Vaccines Day the respiratory business by 2027 will be 8 to $15 billion in revenue.

And essentially, these 15 new products, ex the ones that are in the respiratory column, will almost double that, are worth another 10 to 15 billion as well. And we can talk about that a little bit more, but we think we're building a 20 to 30 billion-dollar top-line company actually just on what we've established to date, but the additional pipeline will come and we will have other franchises that we add to this.

So, while I have you, I thought I'd just touch quickly on 2023 and talk about the COVID product line. And I use the word "line" because it's not a business. We have an overall business that we're investing in across all four of these franchises, but I think we want to make sure everybody knows it's just a product

line. And we are hard at work focused on making it a profitable and sustainable product line. So, in 2023, we still feel confident into the 6 to $8 billion of revenue, highly dependent upon the US vaccination rates. Arpa talk through what we're doing in terms of education all across the system. We also mentioned that our supply chain teams are hard at work and we are already shipping millions of doses. So, a quick shout out to them.

And then on the right-hand side of this page, we recognize that our cost of goods sold in 2023 was elevated, $3.5 billion to $4 billion. And there's a couple of reasons for that that I think will improve and it's important for you to understand as we believe we will expedite our way to this 75 to 80%. Number one, as we transition from a pandemic to an endemic market, it was a difficult exercise to understand what that volume will be. And based upon our current estimates of what we think that volume will be, we probably overproduced a little bit too much this year, which is why we have excessive unutilized capacity and excessive materials, and that will come down.

And the second thing is, over the last few years, we built for a pandemic environment, and that also means that we have too much of a manufacturing footprint. We are hard at work resizing that right now as we speak, to try to get that right sized for the next couple of years, so that you should see that cost of good line come down. But those are the two reasons, and what we're working on right now. So, what I would just end on is COVID is a very valuable product line of business and will continue to be, and we'll make it more profitable. And it helps fund the 25 billion of R&D.

So, we have $15 billion of cash at the end of the second quarter that we talked about already, and ex the $ 5 billion of R&D every single year, this business kicks off cash and that's what we will continue to monitor and make it a most sustainable and profitable business as we can. And after that happens, then we will have four additional terrific franchises that are all sustainable and sizable and valuable as well. So, with that, I will turn it over to Stephane.

Stephane Bancel:

Thank you, Jamey. I would like to thank the team of presenters, but also, importantly, all the colleagues at Moderna that have been working relentlessly, some of them for many years to make this science possible, to make those products possible. So, just a couple of slide to close, I hope for those presentation and those new data, you understand why we're so excited with our three modalities for which we believe we have clinical data showing that they are working. And that's really a very strong foundation for where this company is going.

And as Jamey just shared, we believe as we've said for many years now, that because we use the same chemical matters to make all of our products, the probability of technical success of our drugs is going to be way higher than industry. And that's going to be really important as we think about investment in the business.

The team has shared with you the way that we're thinking about the company right now, waiting for more clinical readout in things like pulmonary and our applications is four product franchise. We'll keep investing in those four product franchise, and we're going to be excited to launch a lot of product in the coming years. The manufacturing team, the late stage development regulatory team, and the commercial teams are busy making this a reality. In '24, '25, we should launch RSV, flu 1010. We should also launch flu/COVID combo 1083 and the next gen COVID product. And that's going to be really exciting.

We could also, as we discussed, potentially have an accelerated approval of INT in that timeframe, and that will be transformative for patients as well as for the company. And then you look for the next wave, the '26, '27, '28 launches. There's a lot of exciting things happening across the entire pipeline. I won't go

back through every product. I'm sure we'll have questions in the session to come, but this is a very exciting time for Moderna. The platform is working. We have the right resources to scale it in terms of both a cashflow generated by COVID.

And as Jamey say, we're going to resize it with our manufacturing footprint to get back to the right gross margin that we should have. And we're going to also invest heavily in research to keep building the platform and development to bring all those product to market and recycle those [inaudible 02:32:36]. But I think the probability of technical success is what's going to make this company different from the other biopharmaceutical companies. So, with this, I would love to get the team up here. So, we'll be happy to answer your questions. Kyle, Arpa and Jackie.

Stephen Hoge:

All right.

Stephane Bancel:

I suppose if you have a…

Jeff Beacham:

Hi, guys. Jeff Beacham, B of A. I have a couple of questions. The first is on the combo with COVID and flu. As you've de-risked the combination, how has your thinking evolved to comp the price? When you look at flu, obviously, it's pretty well-established. It's not particularly a high bar, but you're offering a lot of value with the COVID piece, but that's sort of a less certain market. That's the first question. Second question on the oncology piece, I think that you guys have a pretty productive platform, you go into phase 1. How important is it strategically to look at new novel targets in oncology that you could combine? I feel like the INT, the personalized piece of it, is pretty straightforward, but the target discovery is obviously a pretty big research effort.

Arpa:

I can take the first question on combo pricing. Obviously, we're still working through the pricing, but the way we're thinking about it is the value that the combination provides back to the healthcare system. So, it would not just be priced at flu or at COVID, but really the totality of the COVID and the flu benefit. So, it will vary by market. It will also be taking into consideration the total cost because in some cases, based on administration fees and office visits, the total cost of getting two injections is actually significantly higher than getting one. So, we'll be looking at total, and we'll be looking at price for value versus tagging it to a monotherapy.

Stephane Bancel:

Just to add one piece. I think depending on what we get for the flu comparator, if we get really 1010 and the following product, because remember, 1010 is just a first stepping stone to a flu strategy. But if 1010, as we've started to see early data is as strong as Fluzone HD, it has an impact on pricing versus a standard flu vaccine. And as time evolves, as we get more and more data by adding more express, by adding also the NS antigen, we might also be able for efficacy data to actually capture even more value.

Stephen Hoge:

Thanks for the research question. Scary question. Look, I'll be honest, we are a platform company. So, we start with a question, what does the platform do? What do we know it's capable of doing biologically? And then we go out, and in some cases, find other people who have knowledge about the target biology. So, if you look at the deals that I was talking about before, we're doing T-cell vaccines and CAR T-cell vaccine with the same platform technology that we were talking about in infectious diseases with a couple of companies, Immatics and CARsgen, that we think have really terrific cell therapies. So, pretty straightforward how one plus one could actually be three there.

That's a place where we didn't have to work out the Claudin18.2 biology or the TCR T-cell therapy approaches. We actually just looked at somebody who was doing something and said our platform combined with that could do something really special in terms of the durability of solid tumor responses. I'd say the same is true with Carisma. Carisma is going to be an example of a company that's worked out myeloid cell therapy. They're in the clinic with it. It's hard, complicated thing to do cell therapy, but we already know based on what we've been doing with the rare diseases that we can actually chronically dose safely. Even at high level of doses, we can transfect those cells if we want to. We can make proteins on them and in them.

And so, for us, it's another one of the technologies that we don't need to go become Carisma-like experts on CAR macs. We need to go apply the technology that brings them to another level. So, that's where we start in many of our cases. Now, there are examples where we will look at a biology and say, "Gosh, nobody's solved that and the technology can do it." And those are places where you'll see us build more discovery biology in the more traditional way, getting deep on pathways and targets. But it'll be more the exception than the rule in our approach.

Kyle, I don't know if you want to add anything to that.

Kyle:

No, I think that's exactly what you said. We need to go where the platform can tell us to go. And yes, oncology is a very complicated field and there's a lot of target discovery happening all over the globe. And so, if we can leverage that information and use our technology to help create a better way to target that specific protein, then we'll do it. And I think that's the best path forward.

Michael Yee:

Hey, guys. Michael Yee from Jefferies. Maybe an easier question and then maybe a slightly tougher question. The easier question is just on flu. I noticed that you said you still need to talk with regulators. What do you need to get agreement on? When would we know that? Is there absolutely any risk at all that they wouldn't let you file accelerated on flu? Maybe talk to that and the chronology of when we would know about flu.

And then the tougher question maybe is just there was obviously a lot of discussion around your confidence in jabs, in vaccines' utilization. Obviously, it's very sensitive to the vaccine rates. Under what scenarios do you think if that didn't come in at where you think that's going to come in this year or even next year, that you guys feel right-sized about your expenses and the growing expenses? This year is a year where there is supposed to be EPS negative. Maybe that gets tougher next year. So, under what scenarios do you think about that, or it doesn't really matter?

Stephen Hoge:

I'll take a first crack at the flu stuff and then ask Jackie to correct me when I get it wrong. But as a general point, so we're following established regulatory guidance of what we're doing. We've had

conversations as we've run through these phase 3 studies. But in any study, when you get to an end of a phase 3 and you've met your endpoints, the appropriate next step is to, in the US, to have a pre-BLA meeting and other jurisdictions has their own version of that. We say, "Here's the data. Now, can we talk about what the package looks like?" And that's, ultimately, the process that we're engaging in right now. Those are pretty quick conversations that'll be going on through the fall.

And in the background, you can be rest assured that we're doing the work to prepare everything to file. But until we have that feedback of how they want to see the package come together, how much follow-up they want to see even in the P303 study, we won't have the answer on filing timelines. Rest assured we're using every minute we can to get it happen as fast as possible, but we have to have those conversations.

Jacqueline Miller:

Yeah, nothing to add. I think that's it. So, we're in the process of having those conversations now, and you'll know more, I guess, when we do.

Stephen Hoge:

What's clear is we've met the regulatory guidance for accelerated approval in terms of immunogenicity at our P303 study, which was the thing we were looking to do.

Jamey Mock:

Yeah. And to the second question, I think that's exactly what I was trying to articulate earlier, which is we look at our capital and we look at the strength of every annual business here, and we have scenarios. Our base plan is $25 billion. Should it not be, should the strength of this core business not achieve what we think, it's probably lower than 25 billion. Should it be higher? We actually might invest a little bit more than $25 billion. So, we definitely look at those plans. And right now, we think we feel comfortable that that's our best guess in terms of the R&D investment.

Evan Wang:

Hey, Evan Wang from Guggenheim, exciting data in flu. Great to see improvements on B strains. So, I guess, how are you thinking about this combined with P302 data, which I think still had primarily A cases? Should this updated formulation translate to improved efficacy in the real world versus standard flu or hand flu? If not, how you guys think about next steps towards evaluating that, the head trial with either mRNA 1010 or next gen program? And a second question on oncology, following the data from ACR and ASCO, if you're approached by regulatories on what would be required for accelerated approval, both for adjuvant melanoma and to support approvals in lung cancer and the undisclosed candidate? Thanks.

Stephen Hoge:

Great. So, I'll start us out. So, first on 303, because we've met the regulatory guidance on immunogenicity for accelerated approval, that's the phase 3 that can right now go forward, and that's the basis of our current thinking and strategy for engaging with regulators. 302, as you know, as we said today, we didn't accrue enough cases. We'd said previously we need probably something like 400 and we didn't get there in that season. The next step in that study logically, we'd enroll a second season.

That would take longer. In the 303, in our hands right now, it feels like the accelerated approval path on that is the faster path to market.

But Jackie, you want to speak to the questions of what we might do alternatively or what we might do to follow up and build on the success of 303?

Jacqueline Miller:

So, I think as we reported earlier, one of the key things in any regulatory submission process is successfully meeting your endpoints that you pre-specified. P302 was an incredibly successful study for us in terms of learning. It was not as successful for us in terms of meeting that criterion. We actually did have a positive point estimate on the overall vaccine efficacy. And you pointed out earlier that really was on the basis of the strong efficacy of the A strains. And we observed that from the immunogenicity perspective in the P301. Where we fell a bit short was on meeting the lower bound. Anytime you don't have enough cases, you have wider confidence intervals.

And the other thing we observed was that our B efficacy wasn't what we want it to be in the product that we're going to put forward. And so, I would say the other piece of that was deciding to really invest in improving and developing the best possible flu product that we can bring forward. And so, that really is why we did the additional study and why we're going to go with the accelerated approval, and I'm sure we'll have the opportunity to demonstrate the effectiveness of this vaccine in the real world moving forward.

Stephen Hoge:

I think the other part of your question, just to hit it, is you mentioned maybe even being superior in terms of efficacy. Look, scientifically, we're excited. We see really high GMRs here. Even in our smaller studies, we're excluding one. So, there's a reason for some optimism that those higher titers will translate. We have to go prove that though. For now, we're just pursuing the accelerated approval path for the P303 study.

Kyle:

And in terms of your question about oncology, trust me, we've had lots of discussions with regulators. I can't, unfortunately, share with you the discussions that we've had with regulators, but we're excited about the data. We've even heard excitement from regulators about these data. And so, it's an ongoing discussion. When we're able to share with you what they've said to us, then we will do so. Trust me.

Salveen Richter:

Salveen Richter, Goldman Sachs. Just to follow up on that last point, I think you've talked about the three-year data coming by year-end for the INT program, but also the interim look that'll come at, I believe, FiftyOne Events. Do you have a sense of what the regulators want to see from those two data sets? Or is it the first one gets you to that discussion point? And then just a broader question, when we think of this oncology vertical where historically you've talked about how you would really need to unlock a vertical before you fully invest in it and cancer is risky, talk to us about the INT work and how that translates to your triplet as well as the checkpoint vaccine, and then why you're now starting to do these partnerships that are a bit more peripheral. Thank you.

Kyle:

Sure. So, let me

Kyle:

Let me follow up on that question about INT and regulators. So we need to follow our statistical analysis plan for our randomized phase two trial. So we will be following that plan, waiting for our events, making sure that we're doing our analysis as written by our protocol and by our statistical analysis plan. And when we have those data, we hope to share them not only with regulators, but hopefully at upcoming scientific congresses.

The discussions around accelerated approval are complicated, of course. There's a lot of things besides just data that I think regulators want to see. They want to make sure that you have a commitment to moving forward with large randomized phase three trials. They want to make sure that you have robust safety data. And so all of these things are things that we're trying to pull together to make sure that we've got the best package possible.

But in terms of the criteria that you're asking about, like what are the exact criteria that regulators want to see? I can't answer that question because those are discussions that we continue to have with our regulators.

Stephen Hoge:

The one thing I'd add though is obviously we have a intermediate goal of filing, but that's not really the objective, right? The objective is to get the product to market. So even the objective isn't the approval, it's to get the product to market. And so the other piece of the puzzle that we're working on right now that will be a part of any licensure package is manufacturing. Global manufacturing to supply this product to thousands of people, tens of thousands of people pretty quickly. And so what you see us doing, and hopefully we've been consistent about is we do believe... It's our perspective. We do believe there's a path towards accelerated approval.

We do believe that it requires that the responses continue to deepen and remain durable. The signal gut has got to get... It's been strong, it needs to stay strong as we fall over time. We believe we've got to demonstrate the commitment that Kyle mentioned, which is we've got to be in that phase three study we're in, we're enrolling fast. And then we've got to build the infrastructure to provide that product to patients in the real world. Because that's ultimately, what gets licensed. It's not a file, it's not a clinical study, it's a product. And so those are the things you see us doing.

Can that happen by 2025? Clearly, we're trying to signal. We do believe that, but we've got work to do across those three things to get there.

Kyle:

And whether that happens, the accelerated approval or not, we're going to have to run the phase three study. So it's really important that we focus on that phase three study, get patients in that study, and make sure that we have that fully enrolled and executed. So that's very, very important.

Stephane Bancel:

I just want to add to Steven's point on CMC for INT, because as you said, getting approval is great, but we want products to reach patients, obviously. And so for that, as you saw in the Q2 press release, we

have been buying a new site in Marlborough, which is 20 minutes drive from Norwood, which many of you have visited. And that site is dedicated for INT commercial. So we're doing the phase three INT out of Norwood. And as you know, we've been scaling up Norwood pretty drastically because if you go back in time, the phase two was a 100 patients on INT, the other 50 were on placebo. The phase three that you saw a thousand people for melanoma, a thousand-ish for lung. And you can start doing the math and you already see right there, 20x, 30x capacity need.

And as the team was saying, we want to enroll those very quickly because we believe there's potential benefit for our patients and to get the data. But at CMC, we're moving a bit like we did with COVID. So if you look at what the team has done when COVID happened and the incredible manufacturing scale of that happened in 2020, that many of you followed very closely. It's actually the same team with the same mindset. And actually one of the thing we said internally, it's a COVID-like moment, which is like, "Oh geez, the data is so good on INT, we cannot have manufacturing the bottleneck."

But today as we have a data [inaudible 02:48:55] Q4, manufacturing is at bottleneck. And so what we're doing is investing aggressively, the board has given us the resources we need to be able to really scale that new site. And we need that to also, as Steven said, put out the manufacturing part of the file into the discussions regulatory. It's all happening and we're pushing as hard as we can.

Kyle:

Just one other thing I'll add is, the important part of this is making sure that we have consistency across endpoints. And so we've shown consistency in RFS DMFS, a tumor inflammatory score, a PDL 1 status. No matter how we look at the data, we see consistency across the data. And I think that gives us more confidence and certainly would give regulators more confidence.

Stephen Hoge:

We could talk all day about this.

Kyle:

Sorry.

Stephen Hoge:

No, I want to say, and it was globally run. It was randomized. We're seeing this in multiple countries and we're following it over time. The short version of it is we believe this medicine will get to patients quickly if we do a bunch of things right. We're focused on getting this done. You asked the how do we expand in oncology on that. Again, thank you for that question.

So specifically, we've got programs like our intratumoral programs, you mentioned the Triplet, which we've seen some interesting early data. And we're still waiting for that confirmatory proof of concept study that absolutely clear, well-powered signal that like, oh, that's doing something. And we have to advance quickly there.

So I think in the other modalities that we have in clinical development right now, we have not yet seen that. Checkpoint is in between we know our vaccines generate T-cell responses, we have a biology question about those targets and whether we can demonstrate a benefit in those tumors. And so we're running that study. And then as you look at the other programs that I mentioned, what we're doing with Carisma and cell therapy, what we're doing with the T-cell and CAR-T booster vaccines and even what

we're doing with the T-cells. I think they're all categories that are somewhere in between those two, right?

So places where we're still looking for proof of concept, trying to understand can the platform do a lot there? And what we're doing is partnering in the biology or in the case of the checkpoint vaccine, advancing it ourselves to try and see whether or not that's a proof of concept. And so when we hit one of those, while those are all in the same therapeutic area, view them all as related, very adjacent modalities. And if we hit one of those, then of course we'll be doing a lot more, whether it's in cell therapy, In Vivo cell therapy, supporting CAR-Ts-

Speaker:

Intratumoral.

Stephen Hoge:

... or alternatively doing intratumoral work like we're doing in the Triplet. So that's I think just exploration still. Still waiting for the proof of concept.

Ginawan:

Ginawan from [inaudible 02:51:25]. I have three questions. The first one is [inaudible 02:51:29] you show very impressive data. I'm wondering, will you be able to share that improved formulation and what is that, if you can share with us? And second question is regarding the combo vaccine. So has FD already aligned with you regarding the approval path? What exactly kind of data you need to show?

And then lastly is the INT non-small cell lung cancer phase three trial design. Can you share with us regarding the target patient population in terms of a stage of the disease?

Stephen Hoge:

Actually, I'm going to disappoint you because we've literally had competitors come up to us in conferences and say, "We can't wait for you to tell us how to solve that problem." And so we are not right now talking about what we've done in just the last six, 12 months. But as Rafael said, we're really proud of the platform we've built and the ability it allows us to make those quick changes. What really matters is the proof is in the pudding. What we were able to demonstrate just looking at the B antigens, is we think, potentially best in class over time. We'll see.

And we're really excited by those titers. It shows we've-

Stephane Bancel:

The B thing is not a class effect?

Stephen Hoge:

It's not a class effect.

Stephane Bancel:

Not a class effect.

Stephen Hoge:

Science. And so we're very excited by the titers and that's why, as Jackie said a moment ago, we're rolling that product forward very quickly. Do you want to handle the combo regulatory path?

Jacqueline Miller:

Yeah. Well, so the reason why we've been investing so much in developing the monovalent vaccines is really twofold. One is, well, combos will be great. Not every country actually wants to implement combos and some physicians like the flexibility or patients like the flexibility of getting one at one time. But what that also allows us to do is really have an anchor to which we can bridge back. We've actually capitalized on this with COVID, the immuno bridging strategy. So we've managed to expand the age indication by doing some immuno bridging work. And we've also managed to license the bivalent and now the monovalent for this Fall.

Again, really based on immunobridging. So it's really a similar kind of strategy where we will enroll a certain number of individuals, we will ensure that we have a safety database that the agency considers to be sufficient, and then we also will compare immune responses to those monovalent vaccines that we now will know can be efficacious. And that really is the rationale on which that platform is based.

So what it means is we're able to be a bit more efficient in our development in the sense that the investments we're making now in those monovalent programs actually pay dividends when we then try to develop multiple combos. Because you can imagine those efficacy trials would very rapidly expand if we were going to do that in every instance.

Stephen Hoge:

In some ways, that's also why we've waited for that flu, COVID combo to move forward. We needed to know we [inaudible 02:54:21], right? Because if you got there and you didn't have the monos built up, you might be wasting some effort.

Kyle:

In terms of the design of the lung cancer study, I can't give you specifics around the design because we're waiting with our colleagues at Merck to unveil the specifics of the design. What I can tell you though, it's an adjuvant population. So what that means is you wouldn't expect stage fours and you wouldn't expect stage ones. So that's probably as much as I can share unless, Michelle, you think we should share any more?

Michelle:

I think we can wait a couple weeks.

Kyle:

Okay. It'll be out very, very soon. Thank you.

Tyler Van Buren:

Hey guys. Tyler Van Buren, TD Cowan, thank you very much for the presentation. Have a couple... The first one is with the list price for the COVID-19 booster announced for the fall season, can you give us more precision on what the net price might look like relative to the $6,400 range you guys previously announced? And then the second one is on CMV since it's fully enrolled, not too many investors pay

attention to that program. So what's your best guess when we'll get top line data? And can you describe the magnitude of the opportunity relative to say RSV and why investors should be so excited about it?

Arpa Garay:

Okay. So I'll start with the pricing question. The list price is around the 129, 130 that we publicly announced. As we get from list to net, obviously, it depends on the customer, it depends on the segment. So we don't have an average net price that we're willing to share. Typically, from a vaccines' perspective, you're giving discounts for wholesalers, distributors, GPOs, and then actual customer contracting, right?

We do have separate pricing that is generally public, which I believe is now public for also the federal systems, CDC, VA and DOD. Did I answer your pricing question? I'm trying to remember if there was a second part.

Tyler Van Buren:

You did the best you could.

Speaker:

Thank you.

Michelle:

Okay. And then I think you had a comment around the 64 to a 100. That was from, I believe a year ago where we were talking about global pricing and what that might look like, whereas the list pricing that I'm talking about today is US.

Jacqueline Miller:

Okay. And then for CMV, so we just finished enrollment, but the way that these trials actually read out is not based on enrollment or length of time in study, but how the cases accrue. So CMV accrues a bit differently than respiratory viruses. Respiratory viruses, obviously, have this huge peak in the winter. CMV is a little bit more sustained year round, but I think harder to predict. It's also a six-month vaccination schedule, so you get three doses over six months. So we believe we may have a readout as early as at the end of next year.

We are starting to capture cases. So we're 22 cases there towards the interim analysis at 81 cases. So it could be shorter, it could be longer depending on how those cases accrue. But why you should care about it is an easier question for me to answer.

So I mean beyond the fact that I think this is something that once people appreciate the value in preventing birth defects. So it's not just in the overall cost, I think immediately after birth. It's the lifelong preservation of contribution to society that really matters. There are other things in CMV that we may be able to investigate as well. So we have a study ongoing right now in hematopoietic stem cell transplant. CMV, Viremia is an enormous problem actually in transplant patients, both solid organ and hematopoietic stem cell.

And if we can figure out and crack the code of how to prevent viremia in those individuals, well that not only is a market in itself, but it also opens up the possibility to learn and really work through these other therapeutic vaccines like EBV and like HSV. So I am super excited about CMV. I can't wait to see what those data look like once they occur.

Speaker:

And Jackie, correct me if I'm wrong, but CMV has been the number one priority of the National Academy of Medicines for many, many years.

Jacqueline Miller:

Yes, that's true. So everybody has their own favorite product to develop, but the Institute of Medicine actually has labeled this a public health priority. And again, I think it's because of the number of productive life years lost and really the impact to those children and those families.

Kyle:

Waiting for events. It sounds like-

Speaker 3:

Hey, I'm [inaudible 02:59:03] with the Oppenheimer and Company. First, just want to thank you all for a really nice presentation. I think none of your bio pharma peers actually give the breadth and the depth of presentations you all tend to do 3, 4, 5 times a year. So I really appreciate it. A couple of specific questions. I think that Jackie, you had mentioned earlier that the implementation of the bivalent is going to help you with the combos. And you might've answered this question before, but how so, specifically with the COVID-19 bivalent, how's it going to help you with the combos in the future?

And then follow on to that is one of the gentlemen previously had talked about how you monitor seasonality and variance currently. With the combos, how would that change or how would you be able to shift that into your combo vaccines? Thank you.

Jacqueline Miller:

Yeah. That's a great question, and I'm going to answer twofold. So there's one from a scientific proof of concept, and then there's also a manufacturing piece to the ultimate launch of the product. So from a clinical perspective, I think launching the combos, it wasn't actually obvious that you could put more than one antigen in the vaccine and actually get the immune response to both. So immune interference is something that all vaccinologists have to think through, and our ability to do that and generate specific responses with the bivalent, not only to the Wuhan that people had been primed and boosted two, four years before, but then also to the BA4, five.

So being able to turn that immune response on when there was such an immunodominant favoritism towards the Wuhan I think was incredibly encouraging to us. And then from the manufacturing piece, our ability to launch last year, the vaccine within 90 days from the recommendation of FDA, go with Omicron BA4, five to the bivalent, it's double the complexity of launching a monovalent.

And I think that also gives us confidence that we're going to be able to develop the procedures we need in order to launch, hopefully one day, a COVID flu, RSV. And it actually also speaks to the flexibility of the platform. So part of the reason why we are looking at so many different combos in phase one, there may be in some situations or for some patients, one combo that's better than another. One of the benefits of the platform is being able to pivot from making one thing to being able to make a different thing for another customer, and that's not something that's necessarily as feasible with other technologies.

Jess:

Hey. Good afternoon. Jess [inaudible 03:01:36] JP Morgan. For RSV, can you just talk about what you see as the key differentiating features of your products' profile? And also maybe talk about how you envision that market taking shape in the context of shared clinical decision making?

Arpa Garay:

Sure. So in terms of differentiation, and Jackie can add a little bit more on the clinical side, we have shown consistent high effectiveness data across multiple subgroups, which is a differentiator versus the competition. The second piece, as I mentioned, we are the only mRNA vaccine for RSV, and we have a very well established tolerability and safety profile based on all of our experience with COVID in the real world setting. As Jackie mentioned, we also have not seen any cases of GBS or other severe neurological safety side effects.

And then last but not least, just from an implementation perspective, we will be the only company with a ready to use, prefilled syringe. Both GSK and Pfizer will have to be reconstituted. There are multiple steps involved and that's where, from a customer perspective, we're hearing a preference for ready to use in terms of time-saving and also in terms of reducing medical errors.

So I'd say it's across the three. In terms of the market with the shared clinical decision making, I think there was a little bit of uncertainty. I think you heard from all the companies around what would that uptake look like. What we are hearing in the early days of the launch is actually that the demand has been much stronger than anticipated. So we're hearing this directly from retail pharmacies that the uptake is very strong. Over the next couple of weeks we'll get more data on what does that curve look like, but it's better than expected.

Stephane Bancel:

In addition to pharmacies I think I saw the CEO of GSK is on the record saying that this is a very good uptake and they're very happy with the uptake. So we look forward to seeing the first data when they come out.

Jacqueline Miller:

And I guess, Harper, the only thing I would add is looking to the future, there are really two advantages of mRNA. One is I think we have hundreds of millions of children that have received an mRNA respiratory vaccine, which is not necessarily true for other kinds of platforms. Which is why we're already enrolling in a study of children as young as five months of age to look at actually addressing an even bigger problem, frankly, in RSV disease.

The second reason is, again, going back to the combos, when you have multiple vaccines that are on the same platform, that formulation becomes so much easier than if you're having to figure out ways to combine different vaccines on different platforms. And so we're fairly confident that that's going to help us to accelerate bringing the combo vaccines to market.

Kyle:

[inaudible 03:04:35].

Ted Tenthoff:

Great. Thank you. Ted Tenthoff, Piper Sandler. Just following up on some of the data that you showed with respect to the rare disease franchise. Can you paint what the picture looks like for where we go from here? I know you were talking about dose confirmation, but what could registrational trials look like in those orphan settings, and how different would PA MMA be versus PKU, for example, where there's already some [inaudible 03:05:08]?

Kyle:

Yeah, thank you for that question. So there's a lot of opportunity in rare disease to go quickly with much smaller trials. This has been shown through precedent with multiple other agents that are in that space. And so I think the opportunity we have for MMA is that we have a biomarker that we can use to assess the impact of the drug. And I think if we can show that that biomarker has a correlation to clinical endpoints, I think it might be reasonable to consider that as an accelerated approval, as a surrogate for accelerated approval.

We're struggling a little bit more with PA because we haven't found a relevant biomarker that can really assess whether or not there's a clinical impact. And so I think for PA, we're going to focus mostly on the clinical impact of that program, which takes a little bit longer for us to read out. We see effects on the biomarker for MMA within weeks of dosing, whereas with PA it takes a little bit longer to capture all the MDEs.

So that's our current strategy. But for PKU, I think it'll follow a similar path to MMA where we have a relevant biomarker and there's already a drug that has been approved based on a biomarker in an accelerated fashion. And so I think we can follow that same path.

Stephane Bancel:

And what as [inaudible 03:06:21] might be a bit longer because we have to look at medical [inaudible 03:06:25]. It's an end point as you know, Ted, we've talked about it before, that the regulators have accepted as an preferable endpoint. So it's a timing speed issue.

Kyle:

But regardless, this is where Jackie's world and my world are very, very different. We're hoping for very small studies, 12 to maximum 50 patients in these studies for an approval. Jackie, I can't imagine a vaccine ever getting approved at 12 patients, but she has-

Jacqueline Miller:

MMR actually, way back when...

Kyle:

She gets to enroll many, many more patients than I do in our clinical trials, but somehow she's still is faster than I am.

Stephane Bancel:

Yeah, I was going to say the [inaudible 03:07:08] was pretty fast [inaudible 03:07:11]. Pretty amazing.

Jacqueline Miller:

That's a testament to all of the people in the clinical development operations group that made that happen.

Stephane Bancel:

For sure. Thanks, Ted.

Monte:

Thanks for the very thorough presentation. I'm Monte [inaudible 03:07:26] Partners. A couple of questions on the financial side. You talked about the relevance of US vaccine volumes to the guidance this year. How do you think about what data you gather from [inaudible 03:07:43] volume in the US this 4Q and the extent to which you read that forward into next year and future seasons? Is it fairly linear as Pfizer has suggested on their calls? Or do you think each season has its own character and need to see multiple endemic years before you start assuming what a run rate would be? And I've got one more question.

Arpa Garay:

Okay. So maybe I'll take that one. I think this year will be a good data point for future volumes. I would not say that it's a linear... What we see this year is what's going to happen in the future. I think there are a couple of things that could change year over year. It could be severity of disease. So depending on the variant that's circulating and the hospitalizations and the rate of people getting sick could certainly change that equation. I think the other piece that's different this year versus in future years is the ACIP recommendation and the approval just happened yesterday.

Whereas in future years, this will become more common practice as part of universal recommendations. And then I think the third piece is hopefully starting next year we'll be more in line and in sync with the flu launch timing so that when flu vaccines are available, COVID vaccines will also be available to capture those patients that are going in early. So I think it's a good data point, but I would believe that over time the actual volume could increase. As there's greater acceptance, it's also the first commercial year for the US so there's more experience, more acceptance and more understanding. I think that volume or that market could grow.

Stephane Bancel:

And the other piece I would just add to our past comment is the combo, which is if we could launch 1083, [inaudible 03:09:30], there's 150 million dose in [inaudible 03:09:33] in the US every year. So I believe that a lot of consumers, if a combo product is available early in the season, we decide to go with combo to get more protection, as [inaudible 03:09:47] in the US in COVID [inaudible 03:09:49] and we have a flu.

And so I really think that over time, and as you say, it's not going to be linear and we have to be humble about how does the next couple of years look like, but I think the combo might be yet another thing that help us go toward the full volume, but [inaudible 03:10:03] process.

Monte:

Great. And I'll follow up on the expense infrastructure and the flexing that you talked about around thinking about how to think about clinical trial results, et cetera, different franchises. Can you give us a sense of on SG and A, R and D and COGS respectively? How much time does it take to flex up or down

based upon what we see with the COVID business this year? Does it take a year to flex down because you've got contracts with suppliers on the R and D and SG and A side?

How nimble can you be in terms of scaling up or down? Obviously, you can't just send people home. It takes time to resize your headcount. How quickly could you pivot in either direction?

Jamey Mock:

So maybe I'll start with cost of goods sold and SG and A.

Speaker:

That's [inaudible 03:10:53].

Jamey Mock:

Let's even talk about R and D a little bit. So we believe we can act pretty quickly in both categories. Number one, we use a lot of outside services and partners. It's easier to shut that down. That's a substantial portion, and it's not a long-term contract. On the cost of goods sold side, as I mentioned, it'll take a little bit of time and I think extra volume, the combinations that'll help us achieve our overall 75 to 80% gross margin. But you'll see a market step from 2023 to 2024 in terms of our cost of goods sold percent. So we might not get the entire way there, but we're taking steps to do it. And same thing on the SG and A side.

Stephen Hoge:

Yeah. I think R and D is pretty flexible. We make investment decisions around these programs to try and drive towards the product launches. The overwhelming majority of the budget is dedicated to clinical trials and clinical expense, and the overwhelming majority of that is the late stage. And as you look at the spend drivers, you can see that that drives more towards our respiratory studies right now. That makes sense. Those are very large. As Kyle was joking a moment ago, as they rotate down, [inaudible 03:12:01]. But those studies tend to run a year.

So one way to think of that is that that's probably the gate in which we have really substantial flexibility, but more importantly, we look at those commitments to start a phase three study to get a product launch. As a franchise, a value creation event, actually, it generates financing opportunities in the years ahead. So as we make those investments and as we see those successes, we actually think it allows us to make more investments going forward. But we have a high degree of flexibility, certainly over five years and even a year or two.

Monte:

Thanks.

Steve Chesney:

Hi. Steve Chesney from Redburn Atlantic. Just two quick ones from me. Just thinking about the opportunity in the high efficacy flu vaccine space, what are your thoughts around the need for hospitalization data as you eventually approach payers? And then on the COVID vaccine side, it sounds like you've made a lot of progress on contracting. Could you provide any updated thoughts on the contract dynamics in terms of how returns would be handled, and then just on the cadence of revenue recognition into the third and fourth quarter? Thanks.

Stephen Hoge:

Take it first.

Jacqueline Miller:

Sure. So part of the whole accelerated approval pathway in the regulations is that you conduct a post-marketing efficacy study. So we are anticipating undertaking that study. And hospitalizations would be an endpoint obviously built into that study just like they've been built into COVID-19 and RSV in the original, actually, P302 study. And then I'll hand it off to-

Stephen Hoge:

Well, the only thing I'd add just as we're [inaudible 03:13:38] is generally whether it's ACIP or other recommending authorities when they've created the enhanced categories, there are precedents for accelerated approval products being recommended based on immunogenicity. So while we have the obligation to fulfill that in, we don't see it right now as initially limiting.

Arpa Garay:

So maybe I'll take the first part of the question on contracts. From a contracting perspective, depending on the customer and the segment, we do have different returnability clauses. I'd say this year going into a commercial market is probably the most uncertain year from a customer perspective on total demand that we've been working closely with them, depending on the size of the contract and the customer. In terms of the Q3, Q4 revenue recognition, do you want to take that one?

Jamey Mock:

Yeah, sure. No change. At the last earnings call, we [inaudible 03:14:28] that about 30% of our revenue in the second half would be recognized in the third quarter, which then 70% in the fourth quarter. So still sticking to that.

Speaker 4:

Okay. With that, thank you very much to the panel and for everyone who had questions. We invite all of you to please stay through the hors d'oeuvres and cocktail hour and mingle with management. Thank you.

Speaker X:

Thank you.

Stephane Bancel:

Thank you. Good. Thank you, guys. [inaudible 02:45:00].