Investor Day – R&D and Business Updates

September 12, 2024

Stéphane Bancel:

Good morning everybody. Thank you so much for joining us. On behalf of the team, I would like to welcome you to our 2024 Moderna R&D Day, which I think makes it the sixth R&D Day that we have done as a company. Before I start, let me remind you, we'll be making forward-looking statements. You can find those on our website.

What is very exciting for us is that our vision is becoming reality. As you know, Moderna was established using mRNA as an information molecule to prevent and treat disease to help people around the world. We're very proud about what the team has been able to accomplish in a pretty short amount of time thanks to our platform. And I really want to thank our colleagues in research, in clinical development, and in CMC for having this possible. If you got our pipeline, look in just in the last few years, the pipeline has not only grown in size, but especially moved to a lot of late-stage assets now 18 in programming phase two and seven in programming phase three, additional of course to approved products.

Another piece I will talk about today, you see basically updated numbers for probability of success of our drugs compared to industry. We've shown that comparison in the past, we've just updated the numbers with the latest studies. You can see that consistently across phase one studies, phase two studies and phase three studies, we have a much higher probability of success compared to the industry average. And if you combine all those things by multiplying those numbers, looking at the probability of a drug, starting at phase one to be positive in the phase three, we're actually around 6x higher of any industry average. And this productivity or platform, of course, has a big impact on patients.

We'll be spending a lot of time through the last month and for the summer and through Board reviews to look at our strategy. And what we are doing basically is adapting our business strategy shaped by both our successes and our challenges. The success, as you know, is the broad clinical pipeline that the team is going to talk about. You are aware of the commercial challenges we faced trying to estimate or guestimate what the world will be in the endemic setting versus the pandemic. As you know, a few years ago, the COVIID market was a $50 billion annual sales market, it has of course shrunk to around $8 billion now. And we were like everybody trying to estimate what this is, also trying to work on vaccination rate.

So what we've announced this morning is we're basically focusing on delivering 10 products for approvals in the next few years, in the next three years precisely. We'll show you more details in the coming slides, and what we're going to do as a consequence is spacing our R&D investments.

The three priorities from the company are pretty clear. As you can imagine, the party number one is to drive the use, to drive the sales of Spikevax and mRESVIA. If you look at COVID, it's important to remember that in this endemic setting, looking at just the season that finished in the spring, the '23/'24 season in the people above 65 years of age, you see that is a very, very high hospitalization rate of COVID compared to flu is actually 3x higher as per reported by the CDC, 3x higher. And what is

interesting to note is that around 95% of the people that get hospitalized for COVID didn't have any record of being up-to-date on their vaccine annual update. And that's a really important fact that we need to continue to educate and educate and educate to make sure people get protected against COVID.

Many of you in the room are still young and do not think about hospitalization as being a big deal because when you're 20-year-old and you get hospitalized, you should get out of hospital pretty quickly and you're in pretty good shape without huge impact on your life. But for somebody who is 65 or 70 or 75, it's a huge impact. And for all of us that have had parents have been hospitalized, we know. If you look at the data, somebody was hospitalized for around seven days will lose around 10% of a muscle mass in the age group 65 and above. 10% of loss of muscle mass drives around 30% of people indicating that they have a decline in the quality of their life and the independence after hospitalization. But it doesn't stop there. Around 30% of people that are hospitalized are re-hospitalized within six months, and unfortunately around 20% of those and of dying after six months after hospitalization.

So hospitalization is a huge medical impact on those people, on those families, and we have a tool that is available to protect people, it is called a vaccine. So we need to continue to work and educate the doctors and the population about the vaccines. That's for people about 65 and older. You have the same increased risk profile for adults with comorbidity factors, as you know.

Another population that I think is really important to get protected is younger adults because of long COVID, it has been reported that as one has more and more COVID infection, the chance of getting long COVID goes up, as you can see on the graph. But also it's important to know that it has been shown in studies that vaccine can reduce up to 70% the chance of getting long COVID. So if you look holistically between the elderly or people at high risk and ability to reduce hospitalization through vaccination and the ability to reduce long COVID through vaccination, we need to continue with public health leaders and doctors to drive a better vaccination rate across the world and across the country. Stephen and the team will spend more time on this, but as I say, the priority number two is to get the 10 products approvals in the next three years to drive sales growth of a company, you'll see a much bigger graph in a few slides.

And the third one is to drive this with financial discipline. As you know, we talked about it for now almost a year, we are driving cost efficiency across the entire business in manufacturing, in R&D, and also in SG&A. We are announcing this morning that as you'll see for the numbers for Stephen and Jamie, we're going to be reducing our R&D investment to around the tune of 1.1 billion over the next few years, around 23% versus where we are today.

So with this setting, I'm going to turn over to Stephen, then we're going to go into respiratory vaccine with Jackie and her team. And then later on the vaccine, we'll take a small break before going back with Cal and the team on rare disease oncology. Then Stephen will come back, talk about portfolio and Jamie about financial review and key metrics and frameworks. Before I close with a few slides. With this, let me hand over to another to Stephen.

Stephen Hoge:

Thank you Stéphane, and good morning, good afternoon everyone. I'd like to start with just a little bit of a recap of our R&D strategy, where we are in the strategy that we laid out several years ago and what we think the next few years bring. And then I'll, as Stefan said, turn it over to the key scientific leaders here to walk through what we've been doing across that pipeline.

So just a bit of a reminder, in 2021 with the COVID pandemic now starting to recede, but the approval through EUA of our fresh product, we started to generate substantial proceeds, substantial profits from our COVID vaccine. And in the '21/'22/'23 period that resulted in an almost $20 billion benefit windfall

that we chose to then invest in building a pipeline. In 2021, we did not have any other late stage pipeline assets, we were still mostly a COVID company.

So we started building that pipeline across a wide range of therapeutic areas. And as you look forward to the next period, '23-'26, where we're in the middle of right now, what we've been starting to realize is the first product approvals from that investment. Now those happen to be respiratory vaccines because respiratory vaccines were able to leverage both the technology and science that we accelerated with COVID, but also the fact that while those studies are very large, they can often be done in one year because they're seasonal products. And so we're now heading towards a five product commercial portfolio as a part of that strategy. But we always intended to diversify away from that. We always knew that while might take a little bit longer to advance our medicines in oncology in latent and in rare diseases, that those would start to come online and ultimately we'd start to deliver substantial non-respiratory approvals from 2026 forward.

Now, if you just look at this middle of the period where we are in 2024, just in this past year, as the R&D leader, I am incredibly proud of the productivity that we've shown. It is remarkable for a company of any size, but certainly ours, to have accomplished the things that we did in this last calendar year. Let me give you some of those highlights.

So we actually had two major approvals in the last year. Our first ever SBLA seasonally for Spikevax was actually a year ago this week, and then obviously we had our mRESVIA RSV vaccine approved. We had four positive pivotal phase three readouts in our respiratory franchise: the next generation COVID product, our flu COVID product for over adults, the first combination of flu and COVID, the RSV younger adult high-risk population, 18 to 59, and our seasonal flu program, mRNA 1010 where we showed higher immunogenicity than even high dose flu vaccines. That by itself would be remarkable, but there's more. We had three key proof of concepts in our middle stage pipeline. In our rare diseases, that was propionic acidemia and MMA, both of which we were seeing in clinical improvements and biomarker improvements. And as you'll see today, those responses deepened and actually remain durable now one more year, one year forward, exciting progress. And then of course there's the INT melanoma program where we saw the three-year follow-up data presented at ASCO, again showing remarkable durability to that benefit. So the three key mid-stage proof of concepts actually got stronger in the last year.

And then we've had six early proof of concepts. These are often immunogenicity or viral shedding or in some cases clinical responses, three of which we talked about with you just six months ago. So in the Vaccines Day presentations, we covered the progress of our Epstein-Barr virus vaccine, EBV, showing decrease in viral shedding, VSV T-cell responses in that case in norovirus, the ability to neutralize norovirus infections with neutralizing antibodies. All of that was previously shared. We won't even be able to do justice to the next three today because of so much to cover. But we have early proof of concept in terms of immunogenicity in our LIME program already and in our EBV therapeutic program. That is a program that we hope to take into early multiple sclerosis patients to see if we can modify MS progression. And our checkpoint program in oncology where we're starting to see some interesting clinical responses and look forward to looking at moving that program forward.

So across the last year, just in the last 12 months, our investment in R&D has produced two product approvals, four positive phase threes, three deepening proof of concept experiences and six new ones. We really are proud of that diversity and that progress in the last year. But as Stefan mentioned, we also have to recognize this starts to become an incredibly large body of work and we need to continue progressing things forward.

So now how do we progress things forward? Looking at our R&D strategy again, those three phases, we've built that pipeline, we're starting to really realize that in clinical data now and we're starting to deliver those respiratory product approvals. We have the two product approvals that I just mentioned

we are all familiar with, Spikevax and mRESVIA. And we're announcing today that the next three submissions are happening this year. And in fact, in each of those cases we will be using a priority review voucher to try and accelerate those approvals. That includes two BLAs, our next-gen COVID vaccine, Jackie and team will be presenting some of that data on 1283, the first flu COVID product for older adults, that's 50+ and that's mRNA 1083, and then a really important SBLA for our RSV vaccine, expanding that population to 18-year-olds at high risk all the way up to 59 at critical addition to the strength of mRESVIA's label.

But as you look forward just a little bit, say starting in '26, what you'll see is there's now five non-respiratory products that are in pivotal development, right? That includes the two rare diseases I talked about and two now, latent virus vaccines, CMV and norovirus. We'll share a little bit why we're so excited about all four of those, I should say, today. And all of those have the potential to be launching and diversifying as you look to '26 forward our overall commercial footprint. And then the INT adjuvant melanoma program where we have moved very quickly in enrollment in that phase three. In fact, we are substantially enrolled at this point. And while last year we thought that might achieve its full approval, full approval based on that phase three by 2028, we now see that moving in a year and possibly even happening as early as 2027 based on the progress.

There's even a couple of programs on there I didn't get to mention, our flu program and lower dose flu-COVID combo for 18- to 49-year-olds. It is an incredible body of work, and I hope you can see why we're proud of the launches, but also why we're daunted by the commercial challenge of launching all of those products really just in the next three years.

And that causes us to want to actually start to pace ourselves. We recognize this productivity needs to then be turned into commercial success, and we're trying to now recognize the work that lies ahead and slow ourselves down in some key ways. And so in addition to focusing on these 10, we're going to make sure that we don't advance further latent vaccines or rare programs into pivotal development until we've shown we can get these out the door. That's how we deliver on our commitment to the patients that can benefit from those programs already right now.

Now, another way to look at those three periods is in terms of our R&D investment and how has that evolved over time. If you go back to that '21 to '23 period that I mentioned, when we were generating tremendous profits as a result of our pandemic response, we began rapidly investing, as you saw, in rare disease, in respiratory vaccines I should say. And that's represented here by the red, right? So you can see in the early periods, '21, '22, '23, the overwhelming majority in red of our investment in R&D was in respiratory pivotal studies. Those are now translating into product approvals and launches. And as you can see, as you move forward, '24/'25, we are not starting new respiratory pivotal studies. And as that naturally sunsets, there will be a reduction in our respiratory R&D investment. We've succeeded in that strategy, we've got the pivotal phase threes, we're going to go launch those products.

You also see that there's been some growth over that time in our efforts to diversify our pipeline, as was our strategy. And so in the lightest blue color there, you see our latent and other vaccines, that is our early pipeline, all of those proof concepts and now those two phase threes, CMV and norovirus. We will slow down though the pace of that growth and be steady about it because those programs will take a little bit longer to develop and we want to make sure we succeed, as I said, in launching them over these next few years.

You also see the growth there of our therapeutics pipeline, including in oncology in the darkest blue, our INT programs. Now, a little bit of a note on that one, that is 50% of the costs of the INT, the other 50% are borne by our partner Merck. And so you could double that to get a sense of the overall investment on a like-for-like basis.

And then rare diseases, which is a relatively smaller sliver from an investment perspective across our pipeline, but one where we are deeply committed to the potential benefit for those patients. CMC R&D are the clinical supply and the necessary investments to launch products commercially. And then as you can see, a sustained investment in our research pipeline.

Now if you pull back, we have moved through that initial phase over the first three years of growing our overall pipeline, big investments, and where we are right now in that '23 to '26 window that I described is in a key pivot point for the company. We are launching multiple respiratory products, we're preparing to launch multiple non-respiratory products in cancer, rare and latent vaccines, and we are slowing down the pace of our investment in R&D. And the effect of that will be about a 1.1 billion reduction in our R&D investment annually by 2027. That reduction starts next year and will proceed in 26 and we'll hit its full scope by 2027.

That pacing we think is essential because if you come back to the size of the pipeline that we now have to launch, it is an incredible body of work. Take a step back, this company intends to launch 10 products in three years across three therapeutic areas, some first-in-class medicine, some transformational things like INT and the largest respiratory vaccines portfolio that we think anybody has. It is a really daunting task. Three launches a year on average for three years in a row. And we recognize that we have to show we can make progress on those launches before starting the pipeline and the engines again with the next part of the business.

So with that, I'm going to invite Jackie Miller to come up and walk you through first the infectious disease vaccine starting with respiratory. And then as Stefan said, after a break, we'll pivot to our therapeutics pipeline with oncology and rare. Jackie?

Jacqueline Miller:

Okay, well good morning everyone. It's such a pleasure to be with you again to talk about the progress that we've made in the infectious disease space. As Stephen mentioned, we're going to start actually with the programs that are nearing the end of their first phase, the regulatory submission stage. And you'll hear first from me about COVID-19, then Raffael Nachbagauer is going to come and tell you about our flu program, and then Kristi Shaw will conclude by talking through our combination program and RSV. And then I will come back and talk to you a bit about cytomegalovirus and norovirus, which are a bit earlier in their iteration. So let's get started because there is a lot of phase three data to cover.

So Stefan mentioned that COVID-19 actually now is an endemic disease. And while it doesn't have the dramatic headlines that it did during the pandemic, it actually continues to be responsible for a large burden of hospitalizations and deaths, particularly in adults over the age of 65. And tragically, 95% of those adults who end up hospitalized did not get their fall booster for COVID-19. And you can see on the graph actually it's a very underappreciated burden, so people are quite good if they are committed to vaccination at going and getting their flu vaccine each year, but that's really ignoring that the greater risk actually for detriment to health is from COVID.

The other aspect of COVID that's underappreciated is the burden of long COVID. So I was taking a cab yesterday from the train station to the hotel, and I heard on the news that the cab driver had on that there is a study actually ongoing in New York to look at the burden of long COVID in children. And again, I think that's quite tragic because there are licensed vaccines that could prevent this really long-term and very impactful illness.

So where are we for the fall? Well, the KP-II variant vaccine if you live in the US is available now in the pharmacy, I got mine last weekend. And in the rest of the world where they have agreed to license the JN-I, we have the approvals that are listed there on the slide. So we every year, I think, get a bit more streamlined and efficient in how we go about getting those annual strain approvals. And what's really

important about that is it's going to be something we're going to leverage for influenza, that expertise in making rapid strain changes. Completely necessary in order to get to that combination vaccine, and it's actually something we can leverage in later parts of the pipeline as well, for example, norovirus, which we'll talk about a bit later.

So now I want to talk about the next generation vaccine, and I hope I've convinced you that there remains a remaining unmet medical need against this pathogen. And this next generation COVID, it's important not only because it will enable us to reduce the dose and therefore amount of antigen we give to people. As you'll see in a minute, we believe it will help us better address the remaining health burden against COVID-19, and it also has been a critical component in helping us accelerate forward our development of the combination vaccine.

So how did we study this vaccine in phase three? Well, it actually was both an efficacy and an immunogenicity trial. And we randomized one-to-one in an observer blinded fashion participants to receive either the next generation vaccine or the original 1273. And the important point there is 1273 Spikevax, that already is an extraordinarily high bar. So to do better than Spikevax really means you're having an impact against COVID-19. There were over 5,700 participants in each group, and these were medically stable individuals who were over 12 years of age. And we studied this at the time that the bivalent, the first BA45 Omicron strain was the prevalent strain and there was half of the dose given as the original Wuhan, and we studied this vaccine in the US, UK, and Canada.

So here you see the efficacy estimates. And because relative vaccine efficacy means something slightly different than establishing efficacy versus placebo, I'd like to take a minute or two just to walk you through the table you see on the slide. So what you see first are the number of cases, 560 cases in the 1283 group, 617 in the 1273 group. And maybe the first thing that strikes you is the large number of cases it took to actually conclude successfully on this trial. That's because as I mentioned before, it's actually really difficult to get better than something that's already as good as Spikevax. So we really needed quite a few cases in order to see that we were having an impact with this next generation vaccine.

Then you see the incident rate between the two vaccines. We actually followed them for quite some time. So this was a study that lasted through the entire season, we had actually done most of the vaccinations between April and June and then followed through about February. And then you see the overall relative vaccine efficacy based on the hazard ratio, and that was 9.3%. The statistical criterion required that the lower bound of a 99.4%, so this is much higher confidence than we normally have at 95%, we're 99.4% confident that the result we see is real. The lower bound had to be greater than minus 10%, it's greater than minus 6.6%. And the overall estimate was 9.3%. So that means on top of the efficacy that you already see from Spikevax, you're getting 9% higher with 1283, and that's why you get a highly significant p value of 0.0005.

So I mentioned to you that we had quite a broad age range in this trial ranging from adolescents 12 to 18 all the way through adults over 65 years of age. And we were quite intentional actually about enrolling primarily the population in adults. If you look at the top of the slide, you can see we had about 1000 adolescents evenly split between the two groups compared to at the other end of the age spectrum over 1600 participants in each group. And we were really pleased to see that that group I was telling you about, the older adults who really have the highest burden of hospitalization and mortality actually have the highest point estimates. So they are likely to benefit the most from switching out to this next generation vaccine. And I want to point out that the adolescents have a very, I would say, inaccurate point estimate because we saw very few cases in adolescents, and that really matches what we know about the epidemiology of this disease. So I mentioned that this trial also had immunogenicity endpoints, and that actually continues to be helpful for us. One of the things that we've been able to do

from a development standpoint is investigate things that maybe are more difficult to investigate because we know that those neutralizing antibody titers correlate with protection. And one question was would we see something similar with 1283? And in fact we do. So we are targeting the aspects of that protein that really are leading to the most important protection that people get from their vaccination.

So here you see primary immunogenicity endpoints, and again, because this was a bivalent vaccine, we had hypotheses in place for both the original Wuhan strain as well as the BA45. This was done in an immunogenicity subset. And what you can see on the slide is the non-inferiority margin. So there had to be a lower bound that was above 0.667. And we actually had key secondary endpoints that define superiority, meaning statistically significantly higher, superior, antibody responses. That was a lower bound of 1.0. For both of the components of the vaccine, we exceed that lower bound, and the ratios, as you can see, are depicted by the dot on the slides so point estimates. That in addition to a second immunogenicity hypothesis for each antigen also showed superiority so response rates were higher than -10% and in fact ruled out a lower bound of zero. So really consistent with what we see from an efficacy perspective, we are seeing higher neutralizing antibody titers with 1283. All of this is telling us that we have an opportunity to further improve upon vaccination against COVID-19, okay?

And as before, I wanted to give you a sense of the immunogenicity responses across age groups. And what you see here is that while the immunogenicity was approximately equal to 1273, so remember again, a very highly effective vaccine approximately equal in adolescence, it's a bit higher and certainly ruling out a lower bound of zero in those 18 to 64. In 65 and above, we see the highest point estimate. And again, this is just further corroborating evidence that we are really hopeful by launching this vaccine and particularly target older adults, we can really address the remaining unmet medical need.

So now a word about the safety of this vaccine, because you might ask yourself, okay, if you're getting additional antibody response and you're seeing at least a point estimate of higher vaccine efficacy, what is the impact in overall safety? And so we'll go through that in the next few slides. But the other remarkable thing about this redesigned vaccine is that we can deliver these benefits in a much lower dose. So the dose of Spikevax that you can receive in the clinic today is 50 micrograms. The dose that we will file for regulatory approval of 1283 is 10 micrograms. And so here on the slide, you see the safety results.

And with respect to the local reactogenicity and in particular pain, we actually saw lower reported rates in the 1283 group. And from a systemic reactogenicity standpoint, so including the symptoms like headache and fatigue and myalgia, we saw very comparable rates. And that's rates both in terms of frequency but also in terms of severity. So the safety profile of this product is really comparable to 1273, but delivering better benefits, particularly to the oldest adults.

Okay, because I want to give you a picture of how the reactogenicity looks overall per age group, here you also see the greater than 65, 18 to 64 and 12 to 17 years of age. And in each of the bar graphs local are on the left, the systemic are on the right. And a similar pattern is actually observed throughout all of the age groups with lower local reactogenicity than Spikevax and similar systemic reactogenicity. The greatest benefits are actually seen in the older adults and, like with Spikevax, we also see the mildest reactogenicity in the adults over 65.

So in summary, 1283 was well-tolerated and its safety profile was really consistent with the known profile of Spikevax. There were no deaths or discontinuations of vaccination that were assessed by the investigator as related to vaccination. Myocarditis and pericarditis have rarely been reported with Spikevax and are important identified risks for that vaccine. So we are obviously, as we work with regulatory authorities to submit our approvals, going to be following this very carefully once we launch

1283. But we did not see events of myocarditis or pericarditis reported in the mRNA 1283 group in this trial.

So our pre-specified relative vaccine efficacy objective has been met, and that relative vaccine efficacy was demonstrated to be non-inferior to Spikevax. The point estimate was highest in those greater than or equal to 65 years of age. The immunogenicity objectives were also met and really highly consistent with what we observed for efficacy, again, with the highest hiders in the oldest age group. Local reactions tended to be lower than with mRNA 1273, and systemic reactions were comparable, and there were no other safety concerns identified. So we are anticipating submission of this regulatory dossier in 2024, and we intend to use a priority review voucher for this program.

Okay, so that concludes the discussion on 1283. I'm going to invite Raffael to come up and speak about influenza. Thank you, Raffael.

Raffael Nachbagauer:

Good morning. I'm really excited to share an update on mRNA 1010, and our seasonal influenza programs today. As you all know, despite the availability of influenza vaccines, there still a substantial health burden provided by influenza every single year. And we actually think that mRNA vaccines are uniquely positioned to improve on the current vaccines by not only providing better immunogenicity that will hopefully translate into better efficacy as well, but also based on the fact that we can quickly reformulate and optimize our vaccines, which year over year could allow for future better strain matching, which is a consistent problem in influenza field, as we have seen for COVID as well.

Last year at R&D Day, we presented an update on our phase I-II study that compared mRNA 1010 against high dose, that made us quite excited. And we announced that we're planning to formally compare this in the phase III study, which we now did. So to this end, we enrolled 3000 participants, one-to-one randomized mRNA 1010 versus fluzone high-dose in older adults where this enhanced vaccine is licensed. It was a single dose, the study was conducted last fall.

And if you look at the immunogenicity, which were the eight co-primary endpoints, so geometrometer ratios on the left for each of the four strains and seroconversion rates for the forest strains on the right, we saw that not only did we meet non-inferiority against influenza for all the strains, we actually had superior immune responses seen both in the geometrometer ratios and seroconversion rates against all of the strains. So this is really exciting because it's something that is quite hard to achieve for a vaccine to improve on the current market leaders as well. So for us, that was really exciting data to see.

In terms of the reactogenicity, we saw consistent with previous studies that mRNA 1010 has an acceptable tolerability profile in older adults. And while the reactogenicity is higher than the majority of the events were grade one and grade two in nature. To expand on the safety, we saw the unsolicited adverse events that were reported similar rates between [mRNA 1010 and the active comparator groups. We didn't see any myocarditis or paracarditis events in the study. The rates of SAEs up to the end of the study were similar for mRNA-1010 and the active comparator. And we overall did not see any safety concerns for mRNA-1010.

Now, as another update, we want to introduce the study design of our upcoming efficacy trial. We're planning to start this efficacy trial later this month. And as you all know, influenza vaccines have to demonstrate efficacy, either pre-licensure or in the case of accelerated approval post-licensure. And so, this efficacy trial is supposed to not only support mRNA-1010 licensure, but also a licensure of our combination vaccines and our next-gen vaccines.

This is a randomized observer-blind active controlled study for mRNA-1010. It's one-to-one randomized against Fluarix, a standard dose comparator. And it is designed to be enrolled over two seasons.

However, with the possibility to declare early success after a single season, in which case the second season would not be enrolled.

In terms of this efficacy trial, it obviously depends on the accrual of cases. And this is a part that we cannot control beyond the study size effectively since the influenza epidemiology will play into it as well. But as a point of reference, the first season of the study is actually similar in size or larger than efficacy trials that have previously successfully demonstrated efficacy. This study is financed by the project financing through Blackstone Life Sciences that we announced earlier in this year.

So, in summary for mRNA-1010, we consistently saw throughout all our studies recently that immunogenicity criteria are not just met for non-inferiority, but also superiority against standard dose and enhanced vaccine comparators. We see an acceptable reactogenicity profile with the majority of solicited adverse reactions being grade 1 and grade 2 in nature. And no safety concerns were identified for mRNA-1010.

As next steps, we're planning to conduct a confirmatory efficacy trial for mRNA-1010 in 2024. And as I said, this is funded by Blackstone Life Sciences. And based on some exciting updates in the combination program that Christy is going to talk about in a minute, we are now internally prioritizing the submission of mRNA-1083, our combination program. So, we're no longer planning to file mRNA-1010 this year for accelerated approval. And with that, I'm going to hand over to Christy.

Christine Shaw:

Good morning. Excited to be here today to share updates on our combination vaccine, respiratory combination vaccine, as well as our RSV vaccine. So first, our combo vaccine against seasonal influenza and COVID-19.

There's still thousands of hospitalizations from these two diseases every week in the United States. And as you can see from this graph from CDC, the rates of hospitalizations for COVID actually exceed that for flu in many times of the year. So, why is this considering we have such good vaccines for these diseases?

Well, that is partly due to the suboptimal vaccine coverage that we see against COVID and flu. Some numbers are shown on the right side of the slide here where individuals 65 and above, about 74% of them got a flu vaccine last year. This is pretty good. Could be better, but not too bad. However, as you go down in age, so the 50 to 64 range, you can see only 52% got a flu vaccine last year. Now, the rates are even substantially lower for COVID-19 shown above that.

So, even in the high-risk 65 and above, only 41% of individuals got a COVID-19 vaccine last year. And then we go down to only 25% in the 50 to 64 range. The numbers below that age are even lower. So, we think this highlights the urgency to develop a vaccine, a combination vaccine against both of these diseases. And why is that? We think that this combo vaccine would be very effective at increasing the coverage rates, particularly for COVID-19. So, if we're able to pull those numbers on the top, they're up closer to flu, that would go a long way to addressing the burden of disease. And how might this work? Well, an individual going to their doctor who's used to getting a flu vaccine, if there was a combo vaccine available for COVID as well, they could still go get their flu vaccine one shot, but also be protected for COVID-19.

Because of this, we are actively working to develop a vaccine against COVID and flu in a single shot. This is called mRNA-1083. And I'll walk you through the pivotal data from our study. This vaccine, first though to give you some details, it is encoding the antigens, the same antigens that are in our next-gen COVID vaccine 1283 that Jacque just described, as well as the antigens in our 1010 influenza vaccine that Raffael just described.

So, in this study, individuals are dosed with the vaccine and we are measuring immunogenicity and safety. We divided the study into two completely independent age cohorts shown on the right. There's those that are 65 years and above. And then the second cohort, Cohort B, is individuals 50 to 64 years of age. In both cohorts, about 2,000 individuals received the 1083 vaccine.

We also have in the cohorts a second treatment group which is the co-administered licensed seasonal influenza in COVID. So, those control cohort received one flu vaccine in one arm, COVID vaccine in the other arm. We split the study into these two age groups so that we could compare 1083 to an enhanced flu vaccine, Fluzone HD, in the above 65 and to a standard dose flu vaccine in the age group below 65.

This is an agreement with the recommended vaccine for these two age groups in the United States. The comparative group in both age cohorts received Spikevax as the COVID-19 vaccine. So, we monitored safety for six months in these individuals and immunogenicity at one month was primary endpoint.

So, those immunogenicity data are shown here. And again, there's different analyses for the two different age groups. So, in both cases, we calculated the geometric mean ratio. And what that means is the ratio of the titer of antibodies to the combination vaccine compared to the titer of antibodies in the individuals who had the co-administered license comparator vaccines.

So, we measured the response to the four flu strains in the vaccine using hemagglutinin inhibition assay and those data are shown in blue. And we also measured the response to the SARS-CoV-2 strain in the vaccine and that by neutralizing antibody and that shown in red.

So, in all cases in both age groups, we did meet the predefined success criteria for non-inferiority. And by that, I mean the lower bound of the confidence interval was above 0.667. And what you can probably see from this figure here is that we actually did better than that and 1083 was inducing higher antibody responses for the clinically relevant flu strains. By that, I mean H1N1, H3N2 and B/Victoria.

And by higher, specifically, I mean the lower bound of the confidence interval was above 1.0. And this includes a higher response compared to Fluzone HD. Similarly to what Raffael just described for the COVID standalone vaccine ... I mean, sorry, for the flu standalone vaccine 1010. B/Yamagata is no longer circulating. WHO does not recommend inclusion of that strain in vaccines anymore. We also are achieving similarly higher antibody responses to SARS-CoV-2 compared to Spikevax. Again, lower bound above 1.0. So, summarizing this 1083 vaccine in both age groups, higher antibody responses than co-administered licensed seasonal vaccines for the clinically relevant strains.

The vaccine 1083 is also well tolerated shown here. In the two age groups separately, you can see the data for both local and systemic adverse reactions. Most are grade 1 and grade 2. There is a bit higher reaction in the younger individuals compared to the older. This is something we have consistently seen across our platform. And there's slightly higher in the 1083 group compared to the co-administered comparators. However, overall, very well tolerated grade 1 and 2 and short duration effects.

A bit more on safety, not only was this vaccine well tolerated, but it had a very safe profile. In some details, the rates of unsolicited adverse events were similar across the groups. There were no deaths, serious adverse events or adverse events of special interest leading to steady discontinuation that were related. We had no events of myo or pericarditis reported related to the vaccine. And so overall, no safety concerns.

So, summarizing this study and program, we are pleased to share that the 1083 combination vaccine against flu and COVID did meet all of the primary immunogenicity endpoints. It also elicited a higher antibody response than the comparator licensed vaccines against both SARS-CoV-2 and the clinically relevant flu strains. And this is true in both age groups and including higher than Fluzone HD.

As you likely know, antibodies both for COVID and flu are known surrogates of protection against disease and, therefore, we think that these results suggest the vaccine will be effective at preventing

disease by both pathogens. And as I mentioned before, we think this will ultimately help increase the vaccine coverage rate for COVID and, therefore, reducing the burden of disease due to COVID and to flu.

The vaccine is safe, well tolerated. And as Stephen shared earlier, we do expect based on these data to submit the dossier for licensure this year in some regions. And we do intend to use a priority review voucher.

All right, moving to the second program I'll discuss with you today, our respiratory syncytial virus vaccine. This is mRNA-1345, also known as mRESVIA. RSV continues to cause substantial respiratory disease and hospitalizations in particularly older individuals as you can see by the figure here. Our vaccine mRESVIA is now licensed for 60 years and above and we think will be part of the tools that we can use to reduce burden of disease in these older individuals.

As shown on the plot here, there is less frequent hospitalizations in younger age cohorts, age groups. However, what's kind of buried underneath these figures here is that there's a population, a subpopulation of younger individuals that have underlying comorbidities which put them at higher risk for RSV disease. And we next wanted to really develop a vaccine that would protect these younger at-risk individuals. So, I'm going to share some data from our phase 3 study in 18 to 59-year-olds in a moment.

First, a quick update on the approvals of our mRESVIA vaccine in 60 years and above. As you know, we have recent licensure in the US and the vaccine is available on the market. We also recently received approvals in the European Union and just recently in the state of Qatar.

So, back to the younger at-risk population, we know that there's substantial burden in those individuals with underlying comorbidities. So, we wanted to advance our mRESVIA vaccine to help protect these individuals as well. So, we conducted this study, it's in 18 to 59-year-old individuals that are at high risk for RSV disease. The definition of high risk in our study is shown in small print at the bottom. Covers those with coronary artery disease, congestive heart failure, chronic lung disease, and type 1 and 2 diabetes.

So, this was an immunogenicity and safety study. We enrolled about 500 individuals that received 50 micrograms of mRNA-1345 shown in the dark blue. The 50-microgram dose is the dose that was tested in our pivotal efficacy study in 60 years and above and that's licensed for use in that population. We did test a second dose level as kind of a backup and, however, we are not sharing data on that dose level today.

The primary endpoint of the study was the 50- microgram dose comparing the immune response in that group of individuals across back to our study in the older adult, the efficacy study. We wanted to show the immune response was the same in the younger adults compared to the older adults where we demonstrated efficacy.

So, individuals got a single injection of this vaccine, we monitored safety and the immune response after one month of this one injection. So, those immunogenicity data are shown here. We measured the immune response to both subtypes of RSV, the A subtype and the B subtype. And we determined the geometric mean ratio of the response in the 18 to 59-year-old high-risk individuals compared to the response we saw in the pivotal efficacy study in adults above 60.

And in both cases, we met the predefined success criteria, meaning the non-inferiority criteria, sorry, were met. And that is that the lower bound of the 95% confidence interval was greater than 0.667. And you can see that's the case here. So, we think these data give us confidence that the vaccine will be equally immunogenic in the younger at-risk individuals as it was in the older adults.

The 50-microgram dose of mRESVIA was also well tolerated in these younger at-risk adults. The systemic and local reactions are shown here with each set of bars. The first one is the data or are the data in the 18 to 59-year-olds. And the second bar are the data from our pivotal efficacy study in 60 and above.

In all cases, you can see the reactions are mostly grade 1 and 2, the local reactions are primarily pain and the systemic headache, fatigue, myalgia. However, the type of reaction and the frequency are quite similar between these two age groups. So, we do believe that these data show the vaccine is well tolerated in the younger adults.

So, not only was the vaccine well tolerated and with a similar type of response to that in older adults, but we also through a month after vaccination saw no related unsolicited adverse events that resulted in study discontinuation deaths, AESI, adverse events of special interest, or related serious adverse events. We saw no anaphylaxis related to the vaccine, no thrombocytopenia, no Guillain-Barre syndrome, and no ADEM reported after vaccination. So overall, we saw no new safety concerns in this age cohort compared to what we've already reported in the 60 years and above.

So, to summarize the RSV update, we completed this phase 3 pivotal study in 18 to 59-year-olds at high risk for RSV. And we're successful on all the primary immunogenicity endpoints. We were able to demonstrate non-inferiority of the response compared in these young at-risk individuals compared to our pivotal efficacy study in 60 years and above. And thus, we're able to infer effectiveness of the vaccine, the 50-microgram dose in the 18 to 59 high-risk population.

The 50-microgram dose was also very well tolerated and safe in this younger adult population. So, based on these promising results, we do intend to plan to file a supplementary biologic license application to FDA this year. And we do plan to use a priority review voucher for this program as well.

So, I think I'm turning to Jacqueline next to take you to Latent.

Jacqueline Miller:

All right. Well, thanks to both Christy and Raffael and actually all of the people on the teams that they lead who are actually back at the mothership currently working very hard at delivering these regulatory submissions.

So, we are about to try something unprecedented actually in the 24 years that I've worked in this industry, which is submit two BLAs, one sBLA by the end of the year in this four-month period. So, I just really wanted to give a big shout-out to all of the teams that are behind the amazing data that I have the privilege of sharing with you each of these events.

We're going to now shift gears to one of our emerging therapeutic areas and we call it Latent and Other. It's a little bit of a combined group of viruses. We have one latent virus we'll talk about today, cytomegalovirus, and then one of the newer emerging disease areas for us, gastrointestinal viruses.

So, cytomegalovirus and apologies for those of you that have heard this before, but I find it useful to go through every year because I think if you're new to this field, cytomegalovirus, unlike influenza may not be something that you've heard of before.

So, this is one of the classic latent viruses. What that means is you get an infection. Typically, most of us are infected by the age 30 or 40. And actually, your infection can be like a mononucleosis-like syndrome. It can also be completely asymptomatic. But the problem with this virus is that it has the ability to intercalate itself into your DNA, and then reactivate in moments of time in later life that can be really difficult to predict. This virus unfortunately has a much worse phenotype or clinical picture when it occurs in infants that are gestating inside of their mothers. So, it is really the source of a terrible congenital syndrome called congenital CMV. It is the most common infectious cause of birth defects in the US. And it costs several billion in annual healthcare costs. And as you'll see in a minute when we talk

about frequency, it's nowhere near as frequent as something like COVID, flu or RSV. The reason it causes several billion a year for very few subjects is because of the intense impact of that infection.

So, the sequelae for these babies include microcephaly or a small head and all of the attendant developmental challenges that come with that. They also get chorioretinitis which can be a cause of blindness, as well as seizures and sensory neural hearing loss is actually the very classic congenital defect associated with this virus.

And then long-term, these children can have cognitive impairment, cerebral palsy, other types of neurologic deficits. And the real tragedy about that was this was a normally developing fetus until the moment that mom became infected and passed that infection through the placenta to her baby.

So, about one in 200 babies are infected each year in the US. And about one in five of those infected babies will have lifelong really life-altering health problems. So that's about one in a thousand babies when you do the math. And so again, going back to the enormous impact that this infection can have on a single baby and their family members, it's really incredible. So, what can we do about it? Well, we can actually look to vaccinate moms to avoid passing that infection onto their babies. Moms who have not yet been infected are at the highest risk of passing an infection to their baby, but actually the majority of infections come from mothers that have already experienced one infection. And why? Because most of us have gotten infected by the time women reach their typical childbearing years. You can get reinfected with a strain that is not the same strain as your original infection. You can also reactivate, as I mentioned, your earlier infection. And any one of these ways can lead to congenital CMV.

So, we are investigating the ability of our vaccines, mRNA-1647, which is a hexavalent vaccine, meaning there are six antigens in this vaccine. One antigen stands alone. Five of them combine actually to form one of the most important antigens and the most immunogenic antigens in a natural infection.

We're looking to see if this vaccine can prevent infection in seronegative women. And why? Because if you can prevent the infection from occurring, actually getting infected is an important step along the way to preventing that congenital infection in the infant. And then our plan is to really look at congenital infection post-licensure. And again, it's because the infection is not as common as things like influenza or COVID-19 in young babies. We really need to evaluate in the millions of children and that will be easier to do in the post-licensure space.

So, we've enrolled nearly 3,700 women to receive 1647 and an equal number of women to receive placebo. And we've completed that enrollment. We actually completed it almost a year ago. It will be a year in October across 290 sites globally. These participants are 16 years of age and above. And those who are 20 years of age and above had to have some contact with young children. Young children actually, toddlers are a really big focus of transmission. So, the women who are engaging with young children are at higher risk of infection. And our primary analysis will be triggered based on two criteria. The first is on the number of cases that we detect. And then the second is we have committed to regulatory agencies that we will follow women for at least six months after their third dose for safety.

Okay. And again, apologies for those of you that have heard this before, but this is a bit of an explanation as to what will happen when we look at that primary efficacy endpoint. And I'd like you to focus on the graph on the right side. We actually have two analyses planned. One in the dotted line is what we're calling our interim analysis. If this vaccine should have overwhelming efficacy, we would like the opportunity to be able to conclude, pull together our regulatory submission and start preventing cytomegalovirus infections by launching our product earlier.

The solid line represents the final analysis. And this is really the fully-powered analysis where at the end of that analysis, if we haven't demonstrated success, we will conclude that we need to go back to the drawing board.

So, the first analysis will be that dotted line. And what you see on the x-axis is the true vaccine efficacy. So, if you look at 60, it means if your true vaccine efficacy is 60%, you see the power or probability on the y-axis that you're going to be successful at the interim analysis. So, at 60% vaccine efficacy, we have a power of 0.6 or about 60% likelihood of showing success at that interim analysis. If your vaccine efficacy is truly 80%, well, then at the interim analysis, that power now approaches 100%. So, you see what I mean about it giving you the possibility to declare early success.

At the end of the study when 112 cases have been accrued, if you look at the black line, now, look at 60% true vaccine efficacy. Again, your power is more like 90% likely to be able to demonstrate success. So, the accrual of cases means more likely that you're going to declare success. So, this is giving us two shots on goal and will allow us the possibility to accelerate potentially.

If you now look at the left, I've already told you about the approximate number of cases in each group. From a statistical perspective, we have to be careful with how many looks we take because every look you take, you have to spend what we call alpha. Meaning once you've seen results, you're no longer completely blinded and those results in the future are no longer completely random.

The vaccine efficacy bound means what is the absolute lowest efficacy we could observe and be successful at the interim analysis. So, you have a sense of where we are. We need an efficacy of at least 57%, for example, at the interim analysis to declare success. All right, so just to review, CMV is the most common infectious cause of congenital defects worldwide. This vaccine is targeting two key antigens with six mRNA sequences. The pentamer is the first antigen, glycoprotein B is the second. Our trial continues to accrue cases and is ongoing. And our DSMB will be intimately involved. This is how we'll be able to stay blinded and continue the study to conclusion should our interim analysis not be successful.

And we're expecting it to be triggered potentially by the end of the year. That certainly is when the safety follow-up we've committed to will be completed. And then it is all a matter of when these cases accrue. Okay. So now, for something completely different, and there is a bit of a tradition actually in medical school that lectures either before or after lunch are always of the more upsetting if you happen to be of the more squeamish variety. So, welcome to the club. We're going to talk about infectious diarrhea and gastroenteritis.

Norovirus, I really don't have to tell you how awful this is. You all know because everybody in this room has had norovirus. It is responsible for about one in five of all viral gastroenteritis. And so, if you've ever been at home miserable, you can at least once in your life have thanked norovirus.

So, the highest incidence actually is in children. And again, children are wonderful but they are vectors of a lot of infectious disease. And the morbidity and mortality of this infection is greatest in children in low-income countries. But in higher income countries actually, the highest burden are in older adults and in immunocompromised patients. And that's because as we get older, our immune systems are working less efficiently. Immunocompromised patients, doctors are making their immune systems work less efficiently to treat other diseases. And so, this leads to a higher risk of hospitalization and severe outcomes.

So, my background was in kidney diseases, particularly transplant patients, what we would see sometimes is patients getting gastroenteritis, getting dehydrated, then their kidneys not getting enough blood flow and there could actually be damage to that kidney graft if they weren't rehydrated quickly enough.

So, this is really why we're focusing first in older adults, we very much have the plan to age deescalate in time and go to pediatrics. And actually, while I'm telling you about the burden in older adults, our trial will actually focus on all individuals above 18 years of age.

So, the burden in older adults is actually expected to rise along with societal aging and the increased need for nursing homes because like many other infections, norovirus passes quite rapidly when you're living in close quarters.

So, what you see on the right are just some statistics. There are about 685 million infections with this virus worldwide each year, 200,000 deaths. In the US alone, 900 deaths and 100,000 hospitalizations. Within the US, societal costs up to $2 billion. And if you've ever had gastroenteritis, we think that not only is this a vaccine that could be recommended, it's a vaccine that at least those of us who know that we've had norovirus want. I will be signing up.

Norovirus also has some similarities with COVID and influenza. So, it has many different genotypes which you can see it represented in a variety of ways in the pie charts on the right of the slide. The point being and I was emphasizing this earlier, we think that there may be a need over time to take the genotypes that are in the original vaccine and update them as the epidemiology may change. And again, this is a place where we think we can really have impact because we are learning very well how to do this year on year with COVID and in the near future hopefully with flu.

So, a multivalent vaccine is definitely needed if we want to protect a substantial portion of disease. And the vaccine that we will be taking forward first is a trivalent and we have a pentavalent candidate that's then waiting in the wings to bring forward next.

Okay. So, this actually works a little bit differently than some of our other vaccines. The mRNA sequence actually encodes amino acid chain that assort into virus-like particles. And those virus-like particles then are the way that the immune cells take up the antigen and express it on the cell surface. They're very similar to native virions and they're actually the way, for example, that human papillomavirus vaccines work, it's the way our Zika virus vaccine works.

So, the trial that we presented some early data from back on vaccines day in March was our phase 1 study. And so, you can see on the slide 1403, that's our trivalent vaccine, 1405 is our pentavalent vaccine. We will be talking about the trivalent component today. We looked at various dose levels and compared to placebo. There were 664 volunteers and we had two age cohorts, so 18 to 49 and 60 to 80. These participants are being followed for 12 months after vaccination and the study was conducted in the US.

So, you've seen some of this data before. On this slide, you're seeing the older adults and the two leftmost bar graphs, you actually saw last time. We now also have the second genotype 2 strain worth of data. And once again, we saw that in all doses, this vaccine was immunogenic if you compare it to the gray bars in each graph. Similar story in those who are younger adults, we see numerically higher titers, as would be expected. Here are the safety data in both younger and older adults. So as we've seen with our respiratory vaccines, older adults tend to have lower reactogenicity. But in both cases, we believe that we have found a dose that we can take forward into the clinic. And what you really see here is that the vast majority of events are grade one, grade two. We saw very few grade three reactions at any dose in the trial. Further summary of safety, we did not identify any safety concerns and we have not seen deaths or AAEs leading to study withdrawal. Within 28 days, we also didn't see serious adverse events or adverse events of special interest. And none of these SAEs or AESIs have been assessed as related to study injection. The clinically meaningful dose-dependent trends in unsolicited AEs were not evident among individuals. So what I'm telling you is that safety is not what's driving our selection of this dose.

So we're very comfortable now moving eminently to phase three, and this is our phase three study design. We're going to be looking at 25,000 adults. They're going to be over 18 years of age. And we're actually going to look to demonstrate efficacy both in the overall population, and in the population that is over 60 years of age. And once again, that really is reflecting, making sure that we are protecting

those who are at the greatest risk of severe complications. Individuals will be randomized 1:1, to receive either the vaccine or placebo. We're going to actually follow for two seasons upfront. Obviously, we will be guided by our DSMB as the study is ongoing. And we are conducting this study really worldwide. You'll note that we have quite a few countries participating from South America. That's because the rates in South America are quite high with this infection.

So in summary, we had a robust antibody response observed against the vaccine-matched norovirus genogroup I and II strains, and there were similar antibodies observed in younger and older adults. Older adults again benefit from the multiple infections they've had lifelong, so they boost incredibly well. There were no safety concerns that we observed through our interim analysis and the single-dose was well tolerated and showed the favorable reactogenicity profile. So stay tuned. Hopefully sometime next year we'll be talking to you about phase three results. Okay, the good news for all of you is it's now time for a break. When you come back, you'll get to hear about the therapeutic side of the business from Kyle and his team. Thank you so much for your attention. I really appreciate it.

Kyle Holen:

Thank you. So my name is Kyle Holen. I lead the clinical development for our therapeutics and oncology clinical development group. Excited to be here today because we're just making a really remarkable impact on the lives of children with rare disease. And so I'll talk to you a little bit about how we're making that happen, and then I'll pass over to Dr. Brown, and Michelle Brown will walk you through some of the data that we've generated on INT, which is also of course, really exciting because we believe that INT can have a significant impact on the lives of patient with cancer. So let's start out with the rare disease part of the discussion. And we're going to start with our most advanced program in rare disease, which is propionic acidemia.

So I usually have to start this conversation with a little bit of a background, because it is a rare disease and not many people are familiar with propionic acidemia. Propionic acidemia is a metabolic disorder where there are defects in the DNA that encodes for either the PCCA subunit or the PCCB subunit of a critical carboxylase in the mitochondria. Both subunits come together to create the enzyme, the propionyl-CoA carboxylase enzyme, and this enzyme is critical for clearing metabolites in your system. Without this enzyme, these metabolites can accumulate and they can cause significant sequela.

The clinical sequela unfortunately can be permanent and severe, and therefore it's important that these or controlled as best as possible and that patients don't have the accumulation of these metabolic enzymes. I will say as well, that unfortunately there really aren't any approved therapies for propionic acidemia right now. The only way it can be managed is through diet. And occasionally some patients with severe disease will undergo liver transplantation. Not only are there not any approved therapies, but there also are no therapies in clinical development right now. So we've talked to families who've said to us, "Moderna is our only hope. Please, let's make sure that this treatment can be delivered to our children."

This is a depiction of how we deliver our mRNA intracellularly. And what's particularly unique about our technology is there's no other technology that could deliver an intracellular enzyme like what we do with mRNA. So mRNA is incorporated into the cell. It's encoding both the PCCA and PCCB subunits. As I mentioned, these come together, create the carboxylase that's effective inside the mitochondria. This is a depiction of our ongoing phase I-II study. Our study had the primary endpoint of both safety and pharmacodynamics and efficacy.

We had an assessment of both the incidence and severity of adverse events, as well as some clinical endpoints including metabolic decompensation events, which I will describe in a future slide. We are also looking at some plasma biomarkers. And participants anywhere from the age of 1 to 26 have been

enrolled into this study. We started at a fairly low dose level of 0.3 milligram per kilogram IV, Q3 weeks. And as we recognize that these dose levels were safe, we increased the dose level first by decreasing the infusion time from Q3 week to Q2 week, and then increasing the dose from 0.3 to 0.45 to 0.6, and then 0.9. And after we had safety assessments at these doses, we were then able to confirm the dose with a dose confirmation cohort. We also have other parts of this study. So I just described the dose optimization portion of the study, but we have a part two and a part three portion of this study. Part two is a dose expansion. So the dose expansion, as I mentioned, is a larger cohort of patients all at the same dose, where we can further explore efficacy of 3927 in this patient population. And then part three is a expansion into the very, very young age groups, the infants less than one years of age. And the reason why this is important is as I mentioned earlier, decompensation events can lead to severe and unfortunately irreversible consequences. And so to be able to prevent metabolic decompensation events in infants could prevent them from having irreversible consequences.

So our clinical experience to date, and this is from a data cut that occurred in August just last month, we have 22 patients that have been dosed. This 3927 has been very well-tolerated. In fact, we have now 31 cumulative patient years of experience with some patients on treatment over three years, 722 intravenous doses have been administrated and the vast majority of patients have elected after they've completed their primary study, to move on to the extension study and continue to receive treatment, because it's been well tolerated and they've seen effects clinically.

The study is ongoing and we've defined a dose now of 0.6 milligram per kilogram, with an option to increase or decrease based on clinical signs and symptoms, which means that if a patient has an MDE at 0.6 milligram per kilogram will allow patients to escalate to 0.9, or if a patient has a safety event, will allow them to de-escalate to 0.45. In the subsequent side, I'll show you why we have confidence in this strategy.

So just a little bit more about the metabolic decompensation events. So one thing that many of us in the rare disease field have understood is that unfortunately in rare diseases, oftentimes the end points are not well-defined in clinical research. And so one of the challenges as well as the opportunity is for us to have discussions with regulators to make sure we can define those end points. So we've had multiple discussions with regulators about this endpoint and we've landed on metabolic decompensation events as an end point that's agreed to by both the regulators in the US and regulators around the world.

So now that we have this clear metabolic decompensation event end point, I'll describe a little bit about what this means. It means that patients are having signs and symptoms that are consistent with the metabolic decompensation event, including vomiting, anorexia, lethargy, or even seizures. It also means that on blood testing, they have a metabolic acidosis, and it means that they need acute medical care and that means hospitalization or prolonged admission into the emergency room.

And here is a summary of the metabolic decompensation events that we've observed in our study. And this is an update from what I showed last year. And I'll walk you through this slide because it's quite busy. Essentially what this is a swim lane plot. So on the Y-axis, each subject is identified with their subject number starting at the top with subject number 01, all the way to the bottom of subject number 22. And then on the x-axis you see the points in time that these patients were followed.

Now in the first column, those are patients where we've captured metabolic decompensation events prior to coming on study. And each red dot represents a metabolic decompensation event. And you can see that prior to coming on study, these patients had multiple metabolic decompensation events. In fact, if you look at subject 21, there were one, two, three, four, five, six, seven metabolic decompensation events in the year prior to coming on study. So there's unfortunately a lot of red dots and as I mentioned, some of these consequences can be very severe and all of these led to

hospitalization of these children. And then at the first hash line there at day zero, that's when patients started coming on study and receiving 3927.

Now at 0.3 milligram per kilogram Q3 week, and 0.3 milligram per kilogram Q2 week, you see that patients continued to have some metabolic decompensation events after coming on study, slightly reduced, but we still saw some decompensation events. We believe that these doses were too low to adequately control the decompensation events. But then once you come down to 0.45 milligram per kilogram dose level and higher, the decompensation events almost completely disappear. In the first year of treatment, only one patient with a decompensation event was observed and that was patient subject 12. So this is a fairly dramatic decrease in the decompensation events. And if you look at the overall statistics, we saw 73% decrease in metabolic decompensation events on the entire population. And if you look specifically at the patients who were treated at a Q2 week schedule, we saw an 81% decrease in the risk of metabolic decompensation events.

So we're very confident that we're having a dramatic effect on these patients' lives. We've also talked to the patients and their families after they've come off study in exit interviews, to understand better the impact that this treatment has on patients that we've heard incredible stories from these families. One family told us that because the severely restricted diets that these patients have to have, that they've never had a Christmas meal with their child. And once they started on study, they were able to liberalize their diet and there was the first time they had a Christmas dinner with their child. So it's really changing people's lives. Okay, this is another table showing some of the risk reductions in metabolic decompensation events. And this is an update from data that we showed last August of 2023, where we saw a 71% decline in the risk of metabolic decompensation events. And as we continue to follow these patients, we see a deepening of that decompensation event risk from 71% down to 73%. And again, a similar trend in the Q2 week dosing schedule, where we saw a continued maintenance of decrease in the risk of decompensation events. I can't talk about efficacy without also sharing information around the safety. So as I mentioned, it's been very well-tolerated with infrequent severe adverse events. We have observed not a single dose limiting toxicity in all the patients that have been enrolled. We have had some cases of drug-related serious adverse events. There was a participant who had a vascular device infection, and an infusion site erythema and a couple of patients who had pancreatitis events.

These patients also had pancreatitis events prior to coming on study, but it was difficult for the investigator to rule out possible implication of 3927. So we did have some serious adverse events, but overall, the patients tolerated treatment well, and as I mentioned, I think a testament to the fact that these patients tolerated treatment well is that the vast majority of patients continue on to receive treatment as part of the extension study. We have observed some mild to moderate infusion-related reactions, but they reported in a very small percentage of patients who received treatment. Okay, so to summarize next steps for a propionic acidemia program, our early results are really encouraging where we've seen dramatic decrease in the frequency of metabolic decompensation events. We have built up now a pretty robust amount of data on the patients who've received treatment with 31 patient years worth of data. We will continue to enroll patients in the parts two and parts three to better understand the impact that we can have on the very young children and to confirm our efficacy. And we will continue to have ongoing discussions with regulators about our pivotal program, and we intend to begin to generate pivotal data by the end of this year.

Okay, I'll move on to a related rare disease; methylmalonic acidemia or MMA. Methylmalonic acidemia is an enzyme that's on the same pathway as propionic acidemia. It's a different enzyme. However, this is a mutase. Methylmalonyl CoA mutase. It's further down on the pathway. You can see propionyl CoA enzyme, the carboxylase a little bit higher up in the pathway, but it's also very, very important in clearing metabolites. In this disease, you can see the metabolite that is broken down by methylmalonic CoA mutase is methylmalonic acid. And with that methylmalonic acid, it's something that we can follow

very closely to see whether or not we're having the effect that we'd like with the introduction of the enzyme. Changes in the gene causes this disease because you then have an ineffective mutase that cannot break down the methylmalonic acid. The methylmalonic acid then builds up in the system and it causes fairly severe clinical consequences. This includes seizures, it includes renal failure. There's an increased risk of pancreatitis, as I mentioned, similar to the propionic acidemia program. It can cause cardiomyopathy. It can cause seizures to the point where people have fairly severe mental challenges. So we again, like PA, really want to make sure we intervene early because some of these consequences are irreversible.

The only current therapies for methylmalonic acidemia include diet restriction and potentially a liver transplant for those children with severe disease, something that is really critical for patients who need it, but unfortunately it comes with its own consequences. Similar to the PA program, we're delivering the mRNA that codes for the enzyme. This enzyme then lives in the mitochondria and has its effects inside the mitochondria. We have a similar dose optimization study that we're running for participants with MMA. In this study, we also started with a Q3-week schedule at a dose of 0.1 milligram per kilogram, increasing our dose all the way up to 0.9 milligram per kilogram. And I'll share with you since the data cut on this slide, we have also fully enrolled into a cohort at 1.2 milligram per kilogram.

The endpoints are similar to our endpoints in the PA program, and this includes safety, tolerability, PK and metabolic decompensation events. But I'll share with you, we also are closely tracking methylmalonic acidemia levels, as well as 2-methylcitric levels or 2-MC. Here's some characteristics of the patients that have enrolled into the study. You can see the ages range quite significantly from an age of 2.5 years all the way up to 39.5 years. And the age at onset generally is fairly young. What I didn't mention about the PA program, but it's true for both PA and MMA is these are part of genetic screening tests. So they're standardly diagnosed at the time of birth. And that's important again, because you want to put these children on very strict diets to try and prevent any metabolic decompensation events. There's one patient that was diagnosed at a much older age in cohort four at 0.6 milligram per kilogram. And I'll point out some inconsistencies later about that particular patient.

So our clinical experience to date has shown that we've had 15 patients enrolled with 384 doses administered. Similar to the PA program, the treatment has been very well-tolerated. We're very pleased with our LNP that it hasn't caused significant infusion reactions. We have seen some patients with mild to moderate infusion reactions, but generally the rate of those infusion reactions is quite low. All participants in this study have elected to continue on their treatment in the extension study, which suggests that there are patients that are tolerating the treatment well and are receiving some benefit from the therapy. And both this study and the extension studies are ongoing.

So I mentioned earlier that we have a very clear biomarker in this disease in order to track the activity of the enzyme and make sure that we're delivering the enzyme in levels that can help metabolize methylmalonic acidemia. So we can look at concentrations and changes in those concentrations of MMA, and we can correlate that with a disease severity. We can correlate that also with the clinical consequences of metabolic decompensation events.

So this is a depiction of the changes in the MMA levels. And we're excited to show you that at baseline, there's been quite a wide range of MMA levels all the way from low of in the hundreds, up to almost 3,000. And the majority of patients had a dramatic decrease in their MMA levels. And this decrease in their MMA levels was more pronounced in the patients at the 0.4 milligram per kilogram dose level and above. And I'll point out the one patient at 0.6 that had a dramatic rise in their MMA level. This is a patient with a very unusual phenotype and we're studying this a little bit further to understand why this patient had an increase in their MMA level but ended up having a phenotype called MUT-minus. And we believe that MUT-minus patients, not all of them may benefit from the addition of the mutase enzyme.

But overwhelmingly, all the patients had pretty remarkable responses in their MMA levels after the administration of 3705.

And we followed up with other biomarkers as well, not just the MMA levels but the 2-MC levels, the 3-HP levels and the NPG levels. And across all of these biomarkers, we saw consistent declines after the administration of treatment. And then lastly, I'll share with you a similar slide that I shared with you for PA, where we looked at metabolic decompensation events. And this is a similar slide where it's a swim lane plot. Each patient from the lowest dose level at the top to the highest dose level of the bottom is depicted on the Y-axis. And then time is depicted on the X-axis. The first column between the two red lines represents the time prior to coming on study. You can see multiple decompensation events in those patients who participate in this study, but prior to their enrollment.

And then at the higher dose levels at 0.4, 0.6 and 0.9, there was only one patient with metabolic decompensation event after enrolling in the study. We are going to continue to follow these patients not only in the primary study but the extension study and confirm that we can truly prevent metabolic decompensation events in these patients with MMA.

So to summarize, we have not observed any deaths or safety-related discontinuations. We've had similar to PA, no dose-limiting toxicities in this study. We had one serious adverse event that was potentially related to 37-05 and that was a fever of grade two. But the drug-related adverse events were predominantly very mild grade one or grade two. And the most common adverse events were a fever, a respiratory tract infection and some vomiting. And here, in MMA, less than 5% of the patients had infusion-related reactions. And I'll just add that when patients do have infusion-related reactions, we can usually allow patients to continue to get dosing through decreasing the rate of infusion or with different pre-medication schedule.

I'll also share with you, since last year, some exciting news that we were selected as part of the FDA START program. And this is a program that is intended to significantly advance the development of high potential therapies for rare disease. We're excited to be selected for this program. And our first meeting with the FDA is scheduled for October, and we'll start working with the FDA as we have already, but more intensely to make sure that we can accelerate this program and get the treatment to patients as rapidly as possible. Okay, so to summarize, 3705, our early results suggest a significant decline in metabolic decompensation events, as well as declines in our biomarker methylmalonic acid.

These reductions were consistent and occurred in the patients who had doses of 0.4 milligram per kilogram and above. And we have about 17 patient years of treatment data that gives us confidence in the safety and the efficacy of therapy. As I mentioned, the adverse events are quite well-tolerated and manageable. And our next steps we plan to, as I mentioned, assess the patients at 1.2 milligram per kilogram, compare their data with the patients at lower dose levels and define the optimal dose to move on to our pivotal studies. We'll continue to engage with the FDA, particularly via the START program and we hope to be generating our pivotal data by the end of the year.

Okay, that's all I was going to say about our rare disease programs. I'll move on to the oncology program. Dr. Brown is going to talk specifically about INT, but before she does so I just want to emphasize that INT did not happen in a vacuum. INT is a result of a convergence of an amazing amount of research that's been done over the last 20, 30, even 50 years. It starts with some of the data and the research that has been done even from the 1960s on both mRNA and LNP technology, but then continues on to build on the remarkable advances in the immune oncology space.

And it also builds on the advancements in machine learning. This program wouldn't exist without machine learning and prediction of particular neo-antigens. So it's a convergence of both the onset of AI, it's a convergence of the immune oncology and the technology that we've developed from both mRNA and LNP. And last I'll say that we have to sequence every patient. And so sequencing a patient's tumor

was not something that was even available 20 years ago. And now sequencing is fairly routine. So including the sequencing information, both DNA, RNA, as well as all the advancements in the rest of the field have all led to this remarkable program called INT.

And then before I hand over to Michelle, I just want to take a moment to recognize a giant in the field. Dr. Jeff Weber. So Dr. Weber was the principal investigator on our 201 study. He was enormous in the field and led to incredible advancements in immuno-oncology. He was critical for our success at Moderna with 201. Unfortunately last month he passed away. It's a reminder every day of why we are here advancing therapies in oncology. Unfortunately he passed away from pancreatic cancer, and it's one of the cancers that we have our sights on for INT. So hopefully, these stories can change as we advance INT into other tumor types. So I just want to spend a moment thanking Dr. Weber for everything that he did for us on the INT program, and for everything that he's done for all the patients that he treated and those families. Okay. And with that, I'll pass it on to you Michelle.

Michelle Brown:

So hello everyone, can you hear me okay? All right, perfect. So my name's Michelle Brown. I am the portfolio lead for the INT program as Kyle alluded to. And it's my honor to speak to you today about the data we shared earlier this year at ASCO about our three-year update for our phase two INT study. Before we get into the details of that, I do want to build on what Kyle said about Dr. Weber. I believe his legacy will lead on in the pursuit, passion and perseverance towards innovative therapies. And that dovetails very nicely to the principles that we see and showcase with INT. So our INT program, also known as mRNA-4157, or V940, you can pick your preferred adjective on this, is a individualized neoantigen therapy that's novel and mRNA-based. And as Kyle alluded to, sits at the precipice of technological and biological innovation. And we know that this program, as most of you have heard, really builds with the patient and the center.

So we start by sequencing their tumor and their blood to identify their tumor-specific mutations. That information is processed through a bioinformatics algorithm that picks the top mutations that would generate an immune response. Once those mutations are predicted, they're now called neoantigens. Those top selected neoantigens are concatomerized onto an mRNA strand as you see here, and then packaged through a manufacturing process to be administered for the intramuscular injection.

Once they enter into a patient, very similar to most of the portfolio you've heard today, the mRNA is processed, the neoantigens are released, they make their way up to the cell surface of antigen-presenting cells, and then they interact with T cells. And those T cells are then able to expand and become trained and activated to go and search for the cancer cells that are out in a patient. In addition to INT stimulating both sort of the expansion of the T-cell repertoire and starting new de novo responses, we believe that these antitumor effects can be potentiated with the combination of checkpoint inhibitors, which take the breaks off the immune system.

So the entire premise for this program is to stimulate and train the immune system to really go out and target a patient-specific tumor profile. And this hypothesis was tested in our phase two study. We presented our primary analysis last year, which showed a prolongation in distant metastasis-free survival and recurrence-free survival. And the intent of our ASCO presentation this year was to showcase the data from the three-year median followup, to really look at the durability of the treatment effect we observed. So for those of you that don't eat and breathe INT every day, this is the study design.It's a phase 2 study in high-risk stage 3, 4 adjuvant melanoma patients. It is randomized in a two-to-one fashion where patients received either INT plus pembrolizumab versus standard of care pembrolizumab. And then we assessed recurrence-free survival, distant metastasis-free survival, safety, overall survival, some of the exploratory endpoints we've reported from translational biomarker

populations. And importantly, we're continuing to follow these patients for up to five years so we can really see how this treatment effect holds over time.

Now, before we get into the data that we showcased at the three-year mark, I did want to ground ourselves in history. Why did we pick pembrolizumab and what was sort of out there before this trial read out? So, the Checkmate 238 study and the Keynote-054 study are phase 3 trials with nivolumab and pembrolizumab, respectively, that compared PD-1 inhibitors to placebo, because there was no adjuvant treatment available back in 2019 when these studies were reading out.

And what we saw was a profound treatment effect and potential for checkpoint inhibition. And what you see is a meaningful hazard ratio of 0.65 or 0.57 in tiny, tiny print and, basically, a delta between the PD-1 versus placebo of about 10 to 15%. That sort of maintains itself over time. And this was substantial. This was a substantial clinical benefit for patients at the time over nothing. And this resulted in the approval of the nivo and for pembro in the adjuvant disease, metastatic or melanoma setting.

So, if we take our grounding in history and see what that looks like against our current study in P201, I'll walk you through this recurrence-free survival curve. We see pembrolizumab on the bottom. And this again is the standard of care that was at the top line on the previous slide. And we see the INT plus pembrolizumab curve at the top.

Now, there's a couple important features to call out here. The first is this dashed line is what we had reported at the time of the primary analysis. And then what we see is the following of patients over the past year and the evolution of the data.

The second point is that this yellow bar with the pembrolizumab is essentially performing as what you would have recalled from that previous slide on the curve. So, we have a lot of confidence in how the control arm is behaving in this study. And with that increased confidence also increases our confidence in how this treatment effect we see for INT and pembrolizumab is performing. So, I think it's important to note that over time, we see that the green line is stable and that basically three out of four patients at the three-year mark are still not having recurrence events for their cancer returning.

In addition, what we see is a hazard ratio of 0.51, a tightening of our confidence interval and a substantial P-value that's nominal at 0.019 in addition to this delta between the combination arm and the control arm maintaining itself right around that 20% mark. So, everything we see here is very, very similar to the slides we just showed that really established PD-1s.

And this type of dataset had never been seen in any other combination treatment above PD-1. No to combination has been able to generate the type of clinically meaningful activity above what PD-1s could do on their own, which is why we're so excited about this data is because it is just so substantially profound from a clinical perspective for the impact it can have for patients. And this isn't only true for the recurrence-free survival, but this is true also for distant metastasis-free survival.

So, this was the secondary endpoint and a lot of the themes that I just stated hold true for distant metastasis-free survival. So, the combination arm maintains a profound delta over the control arm. The control arm behaves like we would anticipate. Majority of patients close to 90% do not have a distant metastasis-free event.

The hazard ratio here is 0.384, a significant P-value. And this is really important because DMFS is a marker of worse outcomes for patients. If a patient has their cancer come back at a distant site, they're walking the line towards metastatic disease. So, their surgery is bigger, their treatment is more invasive, they require maybe an additional systemic therapy and their chance of death increases. So, being able to impact patients this profoundly saves on morbidity and mortality and is truly impactful for their lives.

And while it's early, we also did showcase overall survival. Now, normally, overall survival is very hard to track in the early disease settings because patients tend to have a number of surgeries or other

treatments before they ultimately succumb to their disease. Or it usually takes a long time to see the washout effect of the metastatic treatment cycles.

So, a lot of studies don't tend to report overall survival for five-plus years. So, we're very early looking at it at three years. But we wanted to see sort of how we were tracking and how RFS and DMFS was truly impacting patient's lives. Are they living longer because of this treatment? And while it's early, we do see a positive trend and we see that almost 100% of patients that were treated with the INT-pembrolizumab combination are alive today because of that therapy.

So, it's early. We need to follow this longer to see how this trend holds, but this again provides confidence that we're not only seeing a clinical benefit for RFS, for DMFS, but we have this positive trend for overall survival and we are truly impacting patients' lives.

In addition to the big clinical profound endpoints, we've also started looking at the data through biomarker subpopulations and other sort of demographic characteristics. And I'm not going to belabor the color code and the complication of the small print of the KM curves, but this is one assessment of our biomarker population which was looking at HLA. And HLA is important because this is a feature that is required for those neoantigens to be presented to the T-cells. So, it's very patient-specific and you need this to work to mount an immune response.

And so, one of the features of our algorithm is to match HLA typing to make sure that the neoantigens we're selecting are appropriate for that patient. And so, what we see in these KM curves is essentially that the INT-pembrolizumab combination was working across the HLA classes. So, what this means is it gives us confidence in our bioinformatics algorithm that it's doing what it's supposed to. But it also means that this is very consistent with how we've been looking at the data across a number of different patient populations as a whole.

So, if we look at ctDNA, PD-L1, TMB status across the board, we see that INT-pembrolizumab does better than pembrolizumab. And what that tells us is that this combination could have a broad impact for a wide variety of patients well beyond what we normally think of as markers of response for immunotherapy. And this helps, again, provide confidence that this treatment is going to be meaningful for not only just their melanoma patients, but across the board for patients with a wide variety of tumors.

Now, as we've heard the theme, we cannot just focus on the clinical efficacy profile. And with INT, we are very focused on that treatment benefit for patients. But we're actually as equally excited about the safety profile we see. Because especially when we're thinking about treatment decisions in early disease curative settings, safety matters.

And what we see with our safety profile is that the INT-pembrolizumab combination is highly manageable, very well tolerated. The majority of adverse events are grade 1, 2 and so they're self-limited. The majority are what we would normally think of for those that have had a COVID vaccine. So, we see the fatigue, some injection site pain, some flu-like symptoms. But importantly, these temper off with subsequent doses.

And what we don't see is the grade 4 or 5 type of clinically meaningful significant adverse events. In addition, what we don't see is a potentiation of immune-related adverse events. And that's a distinction that we have from other types of IO-IO combinations. Because when you start combining checkpoint inhibitors, what we've seen is that you get an increase in severity or frequency of the itises.

And the itises are important. That's colitis, that's pneumonitis, that's myocarditis. You see this really profound potentiation of immune-related adverse events with those types of combinations. And we don't see it with INT. And that tells us that INT is a different mechanism of action. It's not a checkpoint

inhibitor. We're really combining two different novel modalities to get that clinical benefit without increasing a patient's risk.

So, it is very encouraging that we're both seeing what I showed you in the clinical efficacy profile, but we're also seeing a very tolerable safety profile. And that was really the conclusions from the ASCO presentation. And it's not surprising when we think about the 49% reduction in risk of recurrence or death or the 62% reduction in distant recurrence that we've launched and spent our time this year building a clinical trial portfolio around the INT program.

And our first sort of foray that we announced in partnership with Merck was our phase 3 INTerpath-001 study. So, this study launched in July of last year on the heels of the primary analysis data that we had showcased. It has a population or feel that is very similar to what I just walked you through with the P201 study. So, it's in patients with high-risk resected melanoma.

Importantly though, this study actually expands out on the patient population. So, we have the stage 2s included here in addition to the 3s and 4s. We have the same type of randomization between the combination arm and the control arm and we have the same endpoint with recurrence-free survival.

The other major difference with this study is that it is set to enroll about 1,089 patients which is about seven times larger than the P201 study. And as you can read here, it has substantially enrolled in closed screening. And we're anxiously awaiting a profound milestone for this study. And I think I'll take this platform to say that we're very grateful for the level of enthusiasm and engagement we've seen from our sites, investigators and patients in support of this study. And we're very excited to see what the next steps will be.

In addition to the 001 study, we also have launched a series of other clinical trials over the past year. So, this includes the phase 3 adjuvant non-small cell cancer study which is INTerpath-002. It includes the phase 2, 3 perioperative cutaneous squamous cell carcinoma study which is INTerpath-007. It includes the phase 2 adjuvant study in MIBC which is INTerpath-005. And then the phase 2 adjuvant RCC study which is INTerpath-004.

So, as you can tell, we've been very busy building out the clinical development portfolio for INT. And the reason that we've been so bold here is because we have a belief that INT is sitting again at that precipice of technological innovation and biological understanding.

We have a belief in the P201 data that I just walked you through. But we also have a belief that we will be able to deliver INT, a high-quality medicine on demand that's completely individualized in a timely matter for patients. And I think this is best showcased with our current clinical trial footprint where we see that over the past year, we have launched these seven studies across the globe.

And if we really think about this development journey, then we have to zoom back out to what Kyle had on his original slide which was back in 2017, we had one study in one country. In 2019, we had a phase 2 study in two countries. Over the span of four years, we manufactured about 2,000 doses of INT.

Over the past year, we've opened seven clinical studies, manufactured hundreds of doses, and administered those hundreds of doses to patients across the globe. And it's just a testament to not only our belief system of our versatility and adaptability of our mRNA platform, but it's also a testament for the ability to deliver INT on this scale and scope.

So, with that, I put this all together. It means that the mRNA-V940 program is the largest development program for an individualized medicine. With our partnership with Merck, we have two phase 3s, one phase 2, 3, three phase 2s, and one phase 1 that are currently open.

We are dedicated and able to deliver INT in a timely manner to a diverse set of patients across the globe. And what I hope that really shows you is that P201 wasn't just a single study and doesn't

represent just a single step forward for mRNA technology and oncology. What P201 represents is a launch pad. And what we are excited about is continuing our leadership and being able to redefine life-changing transformative medicines for patients. And INT is our leading example.

So, with that, I'll hand it over to Stephen.

Stephen Hoge:

Thank you, Michelle. Okay. I will briefly reprise some of what we've covered this morning before handing it over to Jamey to walk through the financial portion of the presentation. I do want to just take that step back. We have not even done everything on this slide. We have provided you with a bit of an overview of some of our accomplishments over the last year, but in fact many didn't get any attention today. So, we've talked about the approvals. I hope you get a sense of why we are so proud of those four phase 3 results, the red respiratory vaccines on this slide, and why each of them we think really could be a meaningful step forward as a product for us.

We've shared some of the updates on the proof of concepts that continue to become more durable and strengthened. In particular, Kyle covered the rare diseases and Michelle briefly covered where we are in INT with adjuvant melanoma. And we did not get to really cover the early proof of concept studies, phase 1, phase 2 results that we're seeing across the rest of our portfolio in our Latent and Other vaccines. But we are incredibly proud of that as it moves forward. It is by any measure and truly breathtaking body of work. And we're incredibly proud of the productivity of this platform as it continues to build our business.

Now, we did announce some focusing on our programs. And we did announce that we're discontinuing five programs that had previously been in our development pipeline for various reasons, each of them. But mostly as we've gone through and done our semi-annual prioritization process, these didn't meet the bar for carrying forward in our program.

Okay. So, as a final slide before handing it over to Jamey, we really think we're in a great spot in our R&D strategy. In the first few years from '21-'23, we were just a COVID pandemic response company from a commercial perspective. We generated substantial profits and invested that in creating the pipeline you now see.

But if you look at where we are at this pivot point, moving from 2024 into 2025, we now have two products approved. We are submitting three products for approval and we really do think that starts to differentiate our respiratory portfolio commercially very quickly. Those three products could launch next year if ultimately they are approved.

We have five programs that are actually on the launch pad for 2026 including four non-respiratory products, CMV, norovirus, PA and MMA. You saw some of that data today and why we're enthusiastic about it. And then we have in 2027 and beyond, INT full approval with adjuvant melanoma. Thanks to the really accelerated enrollment that we've seen in that phase 3 study. We will continue to talk to regulators about the possibility of accelerating that access around the world. But at this point, we are focused based on initial feedback on that full approval which we do expect to happen one year sooner than we thought a year ago.

It is a remarkable trajectory. We have a lot of work ahead of us, a lot of work. And we need to be humble about that work. Three products to submit, as Jacque said in 24 years of her career, three products to try and submit for approval in this one year is exceptional.

But if you say we're going to try and do five the year after and then try and bring a couple more the year after that, including INT, you get a sense of why we are both daunted by the challenge but fully committed to seeing this through. And that's why we're prioritizing on these 10 product launches. We

do think it is fulfilling our overall R&D strategy and ultimately gives us the commercial footprint and portfolio we need to continue to invest in building our business.

All right, so I will hand this over to Jamey now to start with some of the financial review. Jamey.

Jamey Mock:

Thank you. Well, good morning. Thanks again for joining. And for everybody on the webcast, hope you're doing well and thanks for hanging in there.

So, I want to start by revisiting the operating principles we laid out last year. And for those that are new to these, they basically is how we think about capital allocation. And they're a bit of a sequential walk that I'll kind of walk you through today to think about how are we allocating capital over the next few years. And it's particularly appropriate at R&D Day because the majority of our investment goes into our pipeline. So, I'll walk you through each one.

We first said that at the time, we said our COVID product line is profitable. And that's still true, but why did we say that? It gets back to what Stephen just walked you through in terms of we plan to invest the profits in COVID into this next-generation pipeline, which I'll get to in a second here.

And so, when you look at 2024, we've given these numbers out $ 3-$3.5 billion of sales. This is now the commercial respiratory product which now includes a half a year of RSV. But albeit, that's a smaller portion of the sales line this year. So, the gross profit is about $1.6, almost $2 billion.

When we look at SG&A for the company, we've updated our guidance for 2024 to $1.2 billion in total. And we think about 60% of that goes to the inline products. COVID 1273 specifically, not 1283, which is obviously not yet launched in RSV older adults. So, that gets you to about $700 million of respiratory inline SG&A.

And then obviously, we're spending almost half of our entire R&D budget this year in respiratory. But when you just look at the products for COVID 1273 and 1345, what we're doing, it's about $300 million. So, it tells you once we launch these products, it's quite profitable. So, we generate $0.6 to $1.1 billion this year.

And so, no matter how you think about it, whether you just say, "Okay, well the company's going to invest $16 billion in R&D over the next few years and this amount of SG&A," but we still make $2 billion in gross profit on these product lines. And when you fast forward and we bring more products for approval and launch them over the years, that revenue line's going to grow. So, that will increase this operating cashflow.

And number two, we will pretty much have the same infrastructure. So, both our gross profit will grow, as well as the leverage that we will get on SG&A will be substantial. So, you can expect that operating margin over the coming years to expand quite rapidly and be very significant, ultimately funding what we're doing from an R&D perspective. And then someday when we roll off respiratory, it'll just be a cash cow for years to come.

So, then we said, "Okay, well, we're putting all of most of our capital behind the R&D engine that we have and this incredible organic growth engine that we have." And so, as you heard today, we've prioritized these 10 products and you've heard a lot about them today. The team's done a great job. But I'll just tell you the next couple pages are to say why did we prioritize those products and how do we think about that?

So first, you can see that there's a large addressable market across all the products on this page. And then if I dive into respiratory, we look for strong efficacy, ease of use in terms of pre-filled syringe ultimately leading up to. And our strategy is basically to have a standalone vaccine for each one, but

then ultimately lead up to a combination vaccine that we really think can change the market. So, we think it can change the market in terms of compliance and better economic outcomes for the entire healthcare system.

And if you look at respiratory as a whole, Stephen said it earlier, we think we will have one of the broadest and strongest respiratory portfolios on the market by 2026. Then if you look at the next three, they all meet large unmet medical needs. There's limited to no competition. And in the case of INT with Merck, we have a strong commercial partner. So, we are diversifying and expanding our revenue base away from respiratory, at the same time growing respiratory. And we're quite excited about it.

So, if I double click in a norovirus which you heard today is our next candidate for a phase 3 trial that will start imminently, I want to just give you our logic as to why we selected this one because it helps shape, again, further detail around how we prioritize our portfolio.

So, first is near-term launch potential. So, we recognize that we were a COVID company, we want to launch new products, we want to expand and diversify out, but we also need it in the near-term, not just in 2035 or 2040. So, we think norovirus has a chance to launch by 2027. So again, bringing near-term revenue. Obviously, it diversifies away into the Latent and Other category. And I already talked about how it's a high unmet need with limited competition.

But then double click into the US opportunity. It addresses a large patient population, number one. And then, what we're particularly excited about is the channel. We believe that this will be mostly sold through retail pharmacies. And then, you can bundle that with the entire respiratory portfolio that we will have. So, it brings another tool for us to be able to compete competitively out there. And so, we're quite excited and we believe it brings a pretty high ROI in the relatively near-term.

So then, Stéphane mentioned this and Stephen mentioned the highlights. You've heard a lot of highlights today, the platform's working extremely well. And so, we have a ton of confidence to continue to invest behind it. And so, you heard all the highlights in terms of respiratory and all the news on Latent and Other and rare disease. But then just to dive into this, I'll take a little bit more time on this than Stéphane did earlier. This probability of success versus the industry, albeit relatively small sample sizes is still quite impressive. So, if you look at phase 3 with 23 candidates, our success rate is 65% versus the industry average of 35%. So almost 2x.

In phase 2, there's 10 candidates here. We had an 80% success rate, almost 3x the industry average. And then if you look at phase 3, still 14% above the industry average with six candidates. And cumulatively, that's where it gets really impressive. So, if you multiply 65% times 80, times 83 and you compare that to the industry average, it is a quite substantial difference. And this is what gives us the confidence to continue to invest our capital in R&D in this pipeline.

But we did say last year that based upon our commercial performance, we will adjust our investment both in R&D and SG&A. And that's what we're doing today. So, it is what we've lived by and that's what we've said when we're doing what we said we would do. So, if you look at it, this is another way to looking at what Stephen had laid out, but I look at it on a cumulative basis.

So yes, we gave the point estimate of taking R&D from $4.8 billion to $3.6 to $3.8 billion by 2027. But if you remember, for those of you that have been following us, we said that we were going to invest $25 billion in R&D over the next five years. So, in the four-year period, that's $20 billion and we're taking that to a cumulative investment of $16 billion.

And again, this all is guided by how much investment and how much capital we're willing to put behind it based upon the revenue line and the gross profit that we are generating. And by 2026, we expect to complete the majority of our respiratory investment. And I think it's another way of showing the diversity and how it's going to change in our pipeline.

So, if you look from '24 and '25, respiratory makes up nearly half the entire investment. If you look at '26 through '28, it makes up maybe a third. If you look at the dark blue oncology today, maybe makes up 10% to 20% of our investment. It'll make up a third from '26 through 2028. So, it's very much changing.

Latent and Other is actually pretty similar. And that's where we're pacing some of the investments. That's what Stephen's walked you through. And that's a conscious choice because we are just trying to be mindful of the capital that we allocate behind R&D, but it's not due to any less excitement that we have in those products.

So then we said, by 2026, we were going to break even. And that's not the case anymore. So, what we now believe is that for our planning assumptions in 2028 at $6 billion of revenue, we will break even on a cash cost basis which I'll define in a moment. It's not the same as GAAP, cash cost basis. But we run this company for cash. And all these principles are about capital allocation.

So, that's how we've thought about it and that's how we continue to think about it. And we think about what is the cash burn year over year. And we believe by 2028, we will break even on a cash cost basis. So, what is a cash cost basis? So, on the left, you see what is our 2024 operating expenses. And on a GAAP basis, you'll recognize some of these numbers. It adds up to $7.4 billion, $4.8 billion in R&D which we increased today versus our prior guidance of $4.5, largely due to the priority review vouchers that we purchase to advance those three submissions.

Cost of sales, $1.4 billion and SG&A of 1.2 billion. But if you take out stock-based compensation and depreciation and amortization which are all non-cash expenses, we are spending actually $6.8 billion on a cash cost basis. And as we project out to 2028, $6 billion of cost, the cash cost, and $6 billion of revenue, that's what would break even. And you can see cost to sales actually goes up because today, we're only $3 to $3.5 billion of sales.

So, when we're $6 billion of sales, we'll actually have to spend more because there's more variable costs. Same thing with SG&A. As we grow and launch products, we're going to have to invest behind that to do it well. So, we're taking on the cash cost basis SG&A from $1 to $1.2 billion.

And then what that leaves you with is this notion that we're reducing R&D at least by 2028 by $1.2 billion in cash costs. It's a curve. It doesn't happen overnight. It'll go down in 2025. It'll go down in 2026. It'll go down further. We've already given the number for 2027. And then this is the cash cost.

And just to reconcile to make this clear, the same $400 million difference that you see on the left in R&D which is stock-based compensation and depreciation amortization, if you add that to the $3.2, that's the $3.6 to $3.8 that we're talking about. So, that's how we think about breaking even. And it's all about cash because all of our guiding principles are about capital allocation.

So then the last thing we said is that we have the balance sheet, the capital today, this year we walked in with $13 billion. At the end of the second quarter, we have $11 billion. And combined with that gross profit that we are earning from the current portfolio today, our plans are sufficient to fund this plan without raising equity. So, I kind of want to wrap it all together and extend and revise our financial framework for you to make it clear, so I'll go line by line here.

From a revenue perspective, we're being a bit more cautious for 2025 and we now have expanded the range to $2.5 to $3.5 billion due to the uncertainty that's in the marketplace. And then thereafter, we are growing about 25% a year which at the midpoint, $3 billion going to $6 billion by 2028. It's pretty straight math.

We're also assuming that though we might launch products next year, for instance, we said we're going to submit three products for 2025, we are not expecting meaningful revenue contribution until the year after. And that is the same with all 10 products. So, no matter the year they launch, we're assuming in

our base plan and planning our capital behind the fact that the revenue will be meaningful though a year after approval.

Cost of sales for 2025 would be 35% to 45%. In general, cost of sales is exactly what we laid out literally almost a year ago today. So, we said at $6 billion in revenue, we could be 30% cost of sales which you see on the right. At $4 billion in revenue, we'd be 35%. So, as you go down that curve, we could have a higher cost of sales rate because we have an infrastructure and we don't get as much volume leverage.

R&D for 2025, we're expecting $4.2 to $4.5 billion based upon that same sales range. So, if the sales range is higher, we will invest more. If the sales range is lower, we will try to invest less. And then moving forward, that's the $11.5 billion. So, the $3.8 billion number that I had a couple pages ago times three, $11.5 billion plus the $4.5 billion, that's the $16 billion of R&D that we're going to allocate over the next four years and which is down from the $20 billion that we've once thought a year ago.

SG&A, similar to R&D, we think will be $1 to $1.2 billion based upon our sales performance. And that's really with flat G&A. The teams have done an excellent job building out our own capabilities. We've talked about it in the past. We're using AI all over the place. And then really, this growth is for selling investment. If we launch 10 products, we're going to have to go spend behind that and educate the market.

Some are different. Respiratory, we already have a substantial commercial team. We might need more education. In other areas like CMB, we might have to build a small team to actually both educate the market and then sell it as well. Taxes will be negligible. Capital expenditures will come down dramatically. And I really want to tie this together for everyone.

So, this year, we started at $13 billion. We're going to $9 billion in cash. That's a $4 billion burn, but we're spending $900 million in capital expenditures in the year 2024. In 2025, we're spending $300 million. So that's a $600 million reduction. So, when I get asked, how are you thinking about capital going from $4 billion of use, the $3 billion of use year over year with basically the same sales range, if not lower, that's one of the big drivers.

The other driver is R&D and there's other drivers in terms of some of our recent deferred payments that we collected. But we feel very good about ending next year at $6 billion in cash, which would be another $3 billion that we are burning. And as you look out, we think that that burn will reduce. It'll reduce by number one, the top line growing. And number two, the R&D line that I just walked you through, that'll come down every single year. The cash burn will be reduced, and we feel very comfortable with the capital that we have moving forward.

I hope you take away five things from this financial framework. Number one, two different statistics. One is that we are reducing our R&D both through cost efficiencies, not just program prioritization, there's a lot to do from an efficiency perspective from 4.8 billion to 3.6 to 3.8. And reducing the total cumulative capital in R&D of the next four years from 20 billion to 16 billion. That's number one.

Number two, I just walked through our revenue assumption for next year, but thereafter, we really believe in this organic growth engine as we launch products. And even if we have product approvals next year, we're assuming the meaningful revenue comes starting in 2026, not 2025. Cost of sales, the team is doing a fantastic job. There's more to do. There's always more to do. They're looking at it, and we will continue to try to improve upon that, but we are very proud of the efforts that we've made. And still, the framework we laid out is still intact. And then we talk about break even on a cash cost basis. Again, not the same as GAP. And we're running the company on a cash basis, and we believe that we will break even in 2028.

Of course, there are things that could either advance that date or, frankly, move that date behind. There's lots of assumptions out there, but this is how we're planning the company right now. And if all

this happens, then we believe that the balance sheet is more than substantial combined with some of the future profits. But what I hope you take away is we're basically doing what we said we would do. And the same principles that were there last year are guiding our decision-making today. With that all, I'll turn it over to Stéphane.

Stéphane Bancel:

Thank you, Jamey. And before closing, I would like to thank the team for the great presentation, and for Lavinia's team for preparing this event. Just a few slides before we move into Q&A. As you can see, we're quite excited about what the next three years will bring for patients we bring to the company. If you just look at what we presented today, we're going to have quite a number of approvals in respiratory, and we expect to have a broadest respiratory portfolio of the industry. Which will be really important commercially, especially in the US where we have a retail market. With CMV and Norovirus, we have potential to bring two new vaccines where there is no vaccine available today for patients. And again, as the team said, the Norovirus product will be an interesting combination to our portfolio with a retail channel.

Michelle and Kyle talked about the INT, and we believe that we have an extremely unique opportunity to have a very profound impact on patients with cancer thanks to this product. And as you saw from Kyle's presentation, in MMA and PA, we can help a lot of families. I know the numbers of course in rare genetic disease are not what they are for vaccines or for cancer, but all those families are having a child at home that is sick where there is no hope today. And through our science and through our products we can bring hope to those families, and that's the heart of the mission of the company. The product launch will of course drive revenue growth in the next few years, and it's going to be quite an exciting journey.

Let me say a couple words about COVID, because the season just got started. We're very excited and very pleased and thankful to the CDC and the FDA for having the product available earlier this year in season. As you know, the product was available 19 days earlier than last year, which we think is really important. The CDC estimate, as we spoke in some of our calls, that around two to 3 million people last year got a flu shot before the COVID shot was available, and never came back to get the COVID vaccine. And as you saw the numbers from Jacqui and myself in term of hospitalization in the 65 and above, people at high risk and the long COVID, we think it's really important that people get their vaccination. Just in the last week, I think I already heard two or three people who got COVID in this wave that could have been prevented because the vaccines are available. And I'm happy to get both my flu and COVID shot two weeks ago.

As you know, last year the vaccines were launched later. And as you recall, there were quite a number of operational challenge in the first few weeks at the wholesale level, making some of you and some of your friends not able to get the vaccines when it was scheduled. And those are the volume of what we shipped at vaccination sites. This is not sales from the company or shipping out of our warehouse. This is at vaccination site. What is interesting to see is what we've done this year so far in the first 12 days, including weekends, because we've been shipping on weekends as well, we've shipped much more product than we shipped last year based on the day of approval on those two years. That's more than 3 million dose in the first 12 days at vaccination sites. The CVS, the Walgreens and so on. A lot of hospital network have started this Monday on the 9th of September, the vaccination campaign with flu and COVID, which we didn't really do last year. So great start in the retail channel. Much better start and earlier start than last year in the IDN hospital network.

In term of RSV, the RSV uptake in the US we expect now will be slower than we anticipated earlier. We expect to have a good increase in market share next year for two reasons. One is a labor expansion that

the team work you on the new data, the 18 plus, which going to be important in terms of being at parity of recommendation by CDC, which we got in June, and the ability to have the customers able to provide to any of our patients walking in the products. And of course, the other piece is going to have the ability to compete in the world season. Having the products available only past the June ACIP meeting where a lot of contracting already happening in the market of course impacted us negatively. The other piece, as you heard, we got approval in Europe. We're going to get more and more approval in the months to come, and of course that will be helpful as we look into 2025.

As you saw in my introduction, our priorities for the company are very clear. The first priority is to drive revenues of existing products that are on the market. As you heard from the team, we are very focused in our R&D teams and manufacturing teams to provide the 10 product launches over the next three years. And that's really, really important for us to drive, of course, sales growth and product diversification away from COVID. And as you heard from all of us, we want to make sure that we drive financial discipline across the entire business in term of our cost, but also driving efficiencies. As you know, we've talked about it a lot, we've embarked into quite an extensive program around AI and GPT. There's more than 1,500 GPTs that have been written by the teams across the business in each other function that will help us launch all those products with the use of technology.

We are very pleased where we are in term of delivering on our mission. As you know, we are building this company believing mRNA as an information molecule can impact the lives of millions and millions of people. As you saw from the team's data today in respiratory vaccine, in latent vaccine, in cancer, and in rare disease across four modalities already, we are having patients impact. Those products are getting very, very close to launch. Some are launch in '25, some in '26, and some in '27. But also, the team back in Boston is still working on the next gen of products in research. As you know, we have partner program like the H5 program with BARDA that was launched in the spring. C6 fibrosis, we've inhaled the money, we were colleagues at Vertex. So still a lot of things, but the focus of a company is right now on launching those 10 products. With this, I like to close. Thank you for your attention, and get my colleagues to join me on stage so we can take your questions. Thank you.

Moderator:

Okay, thank you very much. We will start taking questions from in the room, and then I will take questions over the webcast as well. Before you ask your question, please state your name and affiliation. And we'll start with our first question.

Jessica Fye:

Great, thank you. Thanks for the presentation today. Jessica Fye, J.P. Morgan. On the financial updates, can you talk a little bit about what top line inputs changed the most since you originally provided that '26 break even guidance? Was there an expectation for INT revenue in '26, something like that? And then turning to the new long-term guidance, can you help us think about the relative contribution of your key franchises to a $6 billion top line in '28? For example, how much of that is the near term respiratory vaccines, COVID, RSV, flu, versus INT or the other vaccines like Norovirus and CMV, even just broadly? Thank you.

Jamey Mock:

Yeah. Thanks, Jess. Maybe I'll start, you're free to chime in there. I think in general what you're seeing in our guidance is part mostly uncertainty, and that we're trying to frame in both our 2025 guidance, but also some areas within Moderna specific. Let me talk about uncertainty. When we look at next year, of course everything that we can control we believe we are very happy with and we believe that we have

the chance to drive growth. If you look at an overall market though, just to step back, the COVID market has gone from $50 billion in sales a couple of years ago, to what might be $8 billion this year. And we've tried to understand that. And we're reflecting, well, what happens if vaccination rates continue to go down a little? It's also a more competitive market with three players as well. And so when you step that up, that is a little bit of what we are trying to put into all the years.

You asked also about 2026. I think we're trying to be more realistic, but we also believe in our ability to execute as well. As an example in terms of realism, our product approvals, while they come out in a year, we're really going to assume that the majority of the revenue is next year. That's another example of trying to be more realistic. Of course we'll do everything in our power to try to make it as much revenue the year before, but we're going to put it into the next year. Versus last year's 2026, yeah, I think we thought the market would be larger both in COVID and our ability to execute on RSV as well. That's the other thing, maybe we were overly optimistic about our ability to compete in the first year of RSV. We still believe in our product profile, but we go up against two large competitors.

And as we look at 2026, I think we're being more realistic about what is our share and what is the size of that market. And then the same is true with combination. While we believe it has the chance to truly change the game in terms of both a market size, compliance, better outcomes for patients, better outcomes for economics, I think we want to be patient about that. How much can it really penetrate the market in 2026? There's a wide range on that. Of course it could be more, but we're going to put in what we believe is an appropriate step-up every single year, and that is all the way through 2028 as well.

And then the last part of your question was the non-respiratory products contribution to 2028, I think. I won't give an exact number, but I think you can assume the same assumptions we're making right now with what everything I just said year by year. All the approvals that happen in '26, maybe '27, we're not going to assume they start until 2028, and we're going to be very cautious about how big they will be in the first year out of the gates. It's a contributor, but clearly not the largest contributor. [inaudible 02:32:01].

Gena Wang:

Gena Wang, I'm from Barclays. Maybe two questions. One is regarding the R&T accelerate approval pass. What is the FDA initial pushback based on the initial discussion? And then second one is a flu-COVID combo accelerate approval pass. Now you decided to push the 1083 forward, but not the mono standalone one. Was that based on the FDA feedback? And any concern when we look at the phase three reactogenicity, we did see a little bit higher in the combo one. Any concern that FDA will raise some questions there?

Kyle Holen:

Maybe I'll start with the INT questions. We're very confident in our data with INT. And it's not just us that are confident, but you can tell by the way the studies have accrued, the phase three study has accrued, that investigators are confident patients, even regulators are confident in the data. Every time we've looked at a subgroup or an endpoint in that study, it's been positive. The part of the discussion with regulators is really about, what type of approval paths exist today around accelerated approval? And accelerated approval was originally designed in the metastatic setting where you have a surrogate endpoint that can lead to then a confirmatory study that would then predict for impact on a clinical endpoint.

And it wasn't designed, unfortunately, for us to use in an adjuvant setting. But we'll continue to have these conversations with regulators, we'll continue to look at our data to see how well we can advance the program into patients. Because patients need access to INT. And so, it's something that we will

continue to have discussions around, but it's something that I think deserves a hard look at the policy to see whether a policy needs to change around accelerated approval.

Jacqueline Miller:

And maybe I'll talk then to accelerated approval on flu. And I'm going to build on maybe what Kyle said, and then also bring in some other considerations. Accelerated approval, as Kyle was saying, really relies on two things. You need a biomarker broadly that's predictive of efficacy. You also need to demonstrate large unmet medical need. And the reality is, both of them will have the correlative protection work that we will submit as part of our file, but the unmet medical need that can be met is just greater with the combination vaccine because there are two components in that vaccine.

As Stéphane started to explain, and maybe I built upon a bit, the unmet medical need with COVID is actually the largest amongst the big three respiratory vaccines. Flu vaccination rates, like Christy told you though, are much higher than COVID vaccination rates. So if you could bring that COVID vaccination rate to the same level of flu, it's not only the improvement that we see with the 1283 component in terms of relative vaccine efficacy. We would actually, from modeling, get a larger boost just from getting people vaccinated against the disease. We think that the pace for public need is just more compelling with a combination vaccine.

But the other point is a theme that we've touched upon a few times, which is my team is actually trying to bring forward three of these files this year. And at a certain moment the COVID flu files... We have a COVID file that's going forward, and we have a flu team also working on two different files. We also think that we needed to prioritize in order to get through the first three files.

Yeah, reactogenicity. Thank you. The reactogenicity always is a part of the overall benefit risk. From our perspective, we think that the benefit risk is really strongly favorable. We've been quite transparent about the observed reactogenicity with the product, but we think that the benefit that's going to come not only from having components that have what we think will be improved effectiveness long-term, but also from the convenience and improvement in vaccination rates that totality will be strongly favorable for the combination vaccine.

Ted Tenthoff:

Great. Thank you so much for all of the detail today. This is Ted Tenthoff from Piper Sandler. I have a lot of questions but I'll just ask two, and maybe hopefully get back to it later. You guys mentioned a profound milestone for INT with the melanoma data. With that substantively enrolled, how soon could we actually get that data appreciating that it's a event-driven? Is that something that could happen this year? Should we be thinking more next year?

And my second question has to do with the... Actually kind of similar, but for the rare disease programs. What do you mean in more detail by generating registrational data? Just maybe characterize that a little bit more and what we should expect, how you'll be communicating that. Thank you very much.

Stephen Hoge:

Great. Well, I'll take a first stab at the timing of INT. Obviously, it's a event-driven trial, and so now it's essentially fully enrolled, we will start to accrue events like we did in our phase two study. We don't ultimately control the pace of that, but we did say today that we do think that is possible that we be achieving full approval by 2027. And so, that's essentially a year sooner than we were saying a year ago. That gives you a sense if you back up some enrollment timing and what we think is likely to happen. But again, it's beyond our control, we just need to execute that study. The most important milestone in that

was getting that fully enrolled so that we would have a large population and those events would ultimately, we think, accrue more quickly. Kyle, do you want to take any for the rare?

Kyle Holen:

Yeah, sure. Let's talk a little bit about rare. And before we move on to rare, we don't have enough events unfortunately with the 001 study, the phase three randomized study for us to even start predicting when that event-driven trial will mature. So, more to come as we start capturing some events, and then we start modeling out when those events will occur. And then I think we'll have a really much better sense of when we'll have our first data cut. But back onto the rare disease portfolio, we've had discussions with regulators about what it would take for us to capture data that would allow us to move forward for registration. And we believe we have a pretty good understanding of what that will be. And we hope that our patients will start enrolling into those cohorts by the end of the year, so that's what I mean by generating registrational data.

Michael Yee:

Michael Yee from Jefferies. Maybe just to take a step back for Stéphane, and maybe for Jamey. If you look back at the last 12 to '24 months, there were consistent reductions in '23 guidance. '24 guidance, you guys were super bullish on RSV, and there were some disappointment there. And so I think that the street is struggling with some credibility questions on guidance, and I think that's reflected in what's going on with stock today. Thinking about '24 and '25 guidance, what is imputed in that for COVID and for RSV? For RSV presumably you're going to pick up, but I think the revenue guidance for next year's down. So maybe just talk a little about '24 and '25 is a risk to that, or do you think it's kitchen sink? And then on expenses, are you committed to further taking a look at that, given that the expense cuts are really '27? And I think, again, to hit profitability there's a lot of expenses in there.

Stéphane Bancel:

Good. Thank you, Michael. Let me start on the sales. As we said on the COVID sales, I think there was some risk and unknown around the BCR. The other piece as we discussed on the Q3 call is there's been a lot of competitive pressure happening in the US market this year, which were not as anticipated to be as drastic as there have been that have impacted the top line. Again, we'll have to see what the season is going to look like. Because, as you know, the vaccination rate has come down over the last few years. So the question is, are we going to be flat? Are we going to be down? Are we going to be able collectively to turn the wave and to have it going back up? So that's the big unknown for COVID.

The other piece, as we discussed on Q3 call, is there's a few geographies where the timing of the deliveries on some of the APAs outside the US is the peak. That we got surprised in term we were expecting the deliveries to all happen in 2024, and some are going to be pushed out at the request of governments into Q1 2025. So of course it's not a good thing. It will have no cash impact for the company, because those are countries that have been good customers of Moderna, happy with the service and the product. And have been good payers of product over the years. So we don't think there's a cash risk, but there's clearly a timing of sales risk in terms of Q4 to Q1.

And for RSV, we were maybe naive or maybe too optimistic about the start of the launch of RSV. And I take full responsibility for it as a CEO in terms of our ability to contract with competitors that have portfolio offerings to offer, which we didn't have. As you know, the inability to contract with customers until product approval, getting the AC recommendation late, and then having a lot of products in inventory at wholesaler from competitors and in the pharmacies. And so I think we'll have a slower uptake than we anticipated.

I'm already getting signal from the supply chain that we have customers. We've already tried and we are now reordering MRSV. As we are talking to customers, I think customers are getting interested mostly about next year in terms of big retailers. Because as you know, when you have 8,000 pharmacies, you have a lot of people to train. Very different from an independent pharmacy set up where your local owner, entrepreneur who can make decision and didn't really participate in the market last year. So this part of the learning that we are integrating into the numbers and the guidance that we're putting forward.

Jamey Mock:

And maybe just to address the second part of the question in terms of expenses, and whether we would adjust again. That's one of our principles, and I hope that's what everybody's taken away from today. We said this last year, that based upon sales performance we would adjust. And if the sales performance is not in the ranges that we have identified, then we'll have to adjust again. We run the company from a capital perspective, we're going to be monitoring it, and we feel comfortable with this plan. We think we put in both uncertainty and realism into these numbers and into this framework to manage this cash burn. And we're excited about what will come out on the other end, but we will adjust if need be.

Salveen Richter:

Salveen Richter, Goldman Sachs. Just following up on Mike's question, when you look at the guidance for this year, maybe help us understand what proportion of that is covered by existing orders versus at risk based on vaccine rates for the year. And then a second question here on the CMV vaccine. You've talked about 60 to 65% being the proper clinical bar for efficacy, maybe help us understand how to put that in context in terms of meaningfulness and when you look at some of the other maybe higher rates that you've seen with other vaccines like a Gardasil, for instance.

Jamey Mock:

I'll take the first one. It's a little bit of a difficult question to answer in terms of what percent is locked in. All of our contracting is done. Let me start there. And we had at once said that about a billion dollars was APAs. Those are locked in unless there are deferrals and revenue recognition timing. We believe we will have a good share in the United States, which is the vast majority of the remaining sales for the year, but that'll come down to vaccination rates. And so we've been clear that we're assuming flat vaccination rates year over year. The contracts are there to be successful, but we need vaccination rates to ensure that sales, if that makes sense. Which is a similar approach, a little bit different for next year. I think next year into that wide range we are starting to say, well, what if vaccination rates drop a little bit? And we're putting some of that in there as well.

Stephen Hoge:

I'll take CMV. We'll do CMV between us. In terms of CMV, first of all, it's important to recognize that there isn't a standard of care right now, there's a really high unmet need. And also, that the endpoint for the study that Jacqui described earlier is prevention of infection. So this is serial conversion. The real endpoint we're trying to prevent though is the vertical transmission in the case of let's say congenital CMV, which can lead to the birth defects Jacqui was describing.

And so, we're using an endpoint that is further upstream, if you will. Prevention infection might actually even be harder than what you see with other traditional vaccines, like take our respiratory vaccines or you referenced other latents. Where you might be talking about the disease, a symptomatic disease, not prevention of infection. I would say it's an apple and an orange in terms of a comparison. We do believe,

I think it's quite logical, that if we can prevent infections, we will prevent the downtime between SQUALA. But we might even do better at preventing those downstream SQUALA. Think of it as the analog of, if we can prevent you from getting a respiratory disease, we're going to probably do even better at preventing you from being hospitalized from it, which is the more severe outcome that you're really worried about.

Jacqueline Miller:

And I guess to build on that, I would say I think I've done a disservice. Maybe every year I do a disservice when I explain the statistics there. What I was quoting with the 60, 65%, because it's a very obvious place on that graph, it is an example of one place where your probability is much lower to meet the interim analysis than a higher true vaccine efficacy. That doesn't mean that the vaccine efficacy will be 60%. And the reason for that is, there actually was a previous CMV vaccine, it contained only the gB antigen. That vaccine had a 50% vaccine efficacy. Now we've included the pentamer on top of it. We know that the pentamer actually is important for cell entry into multiple cell types, not just one cell type. And we also know it's the most immunodominant antigen in the CMV virus. So when you have a natural infection, pentamer is actually what your body makes its best antibody too.

It's been very difficult up until now to really get a pentamer antigen with the right confirmation. And the mRNA technology with the sequences, five of them that then naturally reassort into this protein, actually, I think is a big advance with this product. All of that by way to say, I was using 60% as an example, not necessarily as where I think the ultimate vaccine efficacy will land. And I guess everything Stephen has said is also true, but I think we have to wait to see that vaccine efficacy point estimate to really know. And I don't think you should take away that we were targeting 60%.

Tyler Van Buren:

Great. I'll add my thanks as well for the presentations. Tyler Van Buren from TD Cowen. I have a couple for you. First for RSV 18 plus, just curious how you guys think the ACIP recommendation for that will play out, given that at the June meeting for 65 plus it was obviously a limited recommendation for high risk individuals. And then, the second question is on flu. You guys plan to file the flu-COVID combo by year-end, but you have the 1010 phase three vaccine efficacy study that's ongoing. And I think there was a comment that data would be used to support the combo. Will you augment that review or filing with vaccine efficacy, or is that a later timeline?

Jacqueline Miller:

Yeah, let's start with RSV. Look, I think it's really difficult to predict how that discussion will work out. The way that we enrolled our trial actually was really to target populations of people who are at higher risk for RSV disease. So people who have COPD, people who have cardiopulmonary disease. There's also separately an immunocompromised cohort that we'll look at. And I think 18 to 59 actually covers a wide range of individuals. And so, while maybe not all 18 year olds will get RSV this year, or maybe even ever, it's different in terms of general risk factors if you're 50 to 59 years of age. We wanted to be as prepared as possible so that anyone who walks into the pharmacy and wants to get mRESVIA has the opportunity to do that. Hopefully the submission will allow that to happen in time for the season in '25/'26.

Stéphane Bancel:

Maybe if I can add, Jacqui. There's an important commercial point building on Jacqui's comment. Which is, if you are retailers, because some private insurance reimbursed now that it's approved by the FDA, but not recommended by ACIP, reimbursed the product from 18 plus for people with high risk. And so,

for us not having that label is a liability in term of some pharmacies not wanting to have two or three products for the same use RSV vaccination. We think it's really important because, as Jacqui said, it's tough to know exactly what ACIP will decide or not. It's important to realize that there are some private payers in the US right now that are reimbursing people with comorbidity risk in the 18 to 59 range. So it's really important for us, which is why we're using the voucher and we brought the voucher for that.

Jacqueline Miller:

And then the next question was about flu efficacy trial that we are getting ready to start imminently. This goes back to that accelerated approval question. While accelerated approval can allow you to utilize a biomarker that is predictive of effectiveness in part of your initial filing, we know that for the combo vaccine and for the flu vaccine, we're going to need to demonstrate flu efficacy with our product. This is a way for us to also get ahead of that, get started with the flu efficacy program. Which has also been outside funded, so clearly there are other believers in that as well. And the plan would be, if we should have data, of course that will definitely be helpful in terms of telling the story of our combo vaccine and then our flu vaccine. But if we don't have data, we will then continue to have the conversation based on the data that are available at the time.

Stephen Hoge:

If I could just add from an R&D overall portfolio strategy perspective. There was a pragmatic consideration too, very much in our choice here, which is we don't believe we could get four products launched in the next year. And we made our own determination that the highest impact of the two that we were ultimately making the final choice between was the flu-COVID combination product, for all the reasons that Jacqui just covered. We think public health officials agree that's the one that deserves acceleration. And then you run into the pragmatic reality that we were already going to be running a confirmatory efficacy study that's starting right now, and that data will be coming. And so as we look to the flu program, it just makes sense that we would probably file on net efficacy data that will be coming in the next year or two. That was a big factor in our decision to prioritize 1083 first.

Alec Stranahan:

Hey, Alec Stranahan from Bank of America. Two questions from me. First on COVID, would be interested to hear your thoughts around KP.2 versus JN.1. And specificity vis-a-vis casting a broad net in regards to vaccine efficacy this fall. And then secondly, AI machine learning was mentioned a few times throughout the various presentations. Curious as to how you're investing in these capabilities, given mRNA is an information molecule, as Stéphane likes to say. And how you see these feeding into your success to date, and maybe hit rate moving forward.

Stephen Hoge:

Maybe I'll take the first one, and then I don't know, Stéphane, you're going to take the second part of it. On the question of KP.2 and JN.1, I would say actually nobody knows. We're going to play that forward over the coming fall season and see where the virus evolves. What's pretty clear is this virus continues to change its stripes every three to six months, and so nobody really is going to be able to predict what we're facing in December or January. We'll have to see where that evolution goes. The benefit of being an mRNA platformer, is we could do both. And so it's important to defer to public health officials the hard choice of which strain to select in this year as it was three years ago.

Different decisions were made, for instance, in this country or outside of this country. The great thing about mRNA is we can support both, and we will ultimately have to follow the epidemiology to

understand if there was a benefit. But at the end of the day, we will always partner with public health to make sure that they have the product they think they need for their population. Thanks.

Jacqueline Miller:

Just build one thing on that, which is, I didn't actually dive into this during the presentation, but I feel like it's worth saying it now. The vaccine that we put into the efficacy trial I mentioned was the Bivalent vaccine. So 25 micrograms of Wuhan, 25 micrograms of VA45. We actually followed those patients through an XBD.1.5 season. So the relative vaccine efficacy that you're seeing, both of them were protective, one more protective against a strain that actually wasn't really matched with anything that was in the vaccine. And it speaks to in the Omicron family, all of these daughter strains have maybe some additional mutations, but they're really similar to the original Omicron. In terms of reducing your risk for COVID-19, it's less important if you get KP.2 Or JN.1, it's most important that you just get your booster. I didn't want to pass up an opportunity for that PSA.

Stéphane Bancel:

Thank you, Doctor. Thank you, Doctor.

Jacqueline Miller:

Opportunity for that PSA.

Stéphane Bancel:

Thank you. Thank you, Doctor. And on the AI question, as you know, we've always used technology since the company's beginning, whether it's 3D printers, whether it's robotics, whether it's being in the cloud from the get-go to try to help us and help our team discover new drugs or run the company better. We started doing machine learning before OpenAI. The teams had quite an interesting couple of use case of machine learning, actually pre-COVID including using a new enzyme that we use in our manufacturing processes.

And so, the teams now with the tools available are really working toward both what can we use in term of all the data we have to figure out patterns and so on, on large data sets on more the research side of the house. And then, on running the business, whether it's development, whether it's manufacturing, whether it's commercial or SG&A, Jamey has GPT in its finance team. There's some in HR, there's some in legal. We're just trying to use just technology to help us improve quality of things we do across the business, improve scalability and, of course, improve efficiency. So if you want to talk more about it, we have actually a lot of opportunities and Lavina has a lot of examples we are very happy to share. Thank you.

Ellie Merle:

Hey guys. Ellie Merle from UBS. Thanks for taking the question. Maybe just a first quick one on norovirus. How should we think about the time length in terms of the time to data from the study and when we could potentially see that in terms of the trial design, like when you'll be taking the analyses. And then a second just on CMV, can you walk us through how you're thinking about the potential for approval and use in both the seropositive and seronegative population and specifically speak to any feedback that you got from the FDA when you discussed the design with them. And just in terms of the seropositive patients in the Phase 3, any secondaries or other types of markers that you might be looking for that would be supportive of use in those patients? Thanks.

Jacqueline Miller:

So norovirus first. So, like the respiratory viruses, norovirus also is a seasonal virus. Its season actually occurs a little bit later typically than respiratory viruses. So, we're anticipating the bulk of the cases being captured in the first quarter of this year. Like all of these efficacy studies in infectious diseases, it all depends on collection of endpoints. So, we have a certain minimum number of cases that we need to capture in order to assess the trial. If all goes well... Well, if all goes well and we capture enough data, it obviously didn't go as well for the placebo group who got sick. We should capture sufficient cases this year and be able to report later in the year. It will probably be later than what you're used to from a respiratory perspective just because the season is a bit shifted.

Then, in terms of CMV and in terms of how we're thinking about seronegative, seropositive, so there are actually seronegative and seropositive women that are enrolled in the trial together. The design of the study actually was discussed not only in the U.S. but in Europe. It's actually been quite a while. It's one of the first things I did upon joining Moderna back in 2020 was to really talk to regulatory agencies about what we were going to do. So, we have incorporated their feedback into the design.

The study is really powered, and the end point is based on seronegative women and that's because it's easy to define. They were negative before and it's very clear when you've seroconverted to CMV later. Seropositive women though are also, we think, an important group of women to investigate, and I mentioned that we would be looking at the impact in babies in a post-licensure space. That's probably where we're also going to be able to demonstrate the benefit to the babies of seropositive women in that post-licensure space. But we are continuing to the end of the trial now in... Like I say, both regulatory agencies had the opportunity to contribute and certainly impacted the design of the study.

Courtney Breen:

Hi, there. Courtney Breen from Bernstein. Thanks for the presentations today. Stepping back a little bit, you spoke about today what you've chosen to cut and what you've chosen to prioritize and there seems to be a little bit of pushback on the depth of the '25 and '26 cuts. And obviously, there are elements that are fixed in '25 and '26 and already locked in particularly as we think about Phase 3 spend in respiratory and some of the other programs. But can you talk a little bit more about those margins of choices that you've chosen to make, some of those areas where there's '25 and '26 spend that's not truly fixed right now and that you've decided to make those choices and continue to initiate that spend? And what were some of the reasons why today it's still the right choice to make those decisions?

Stéphane Hoge:

So, maybe I'll take the first bit of this, which is the overall portfolio strategy and those choices and then hand off to Jamey to fill in a little bit on capital allocation, how we think about maybe the other part of the question. From our perspective, we have a semiannual process where we look and prioritize across the pipeline and this year we added extra energy to it because we recognized that there was changes happening in the broader business that we need to reflect. When we looked to say which programs do we prioritize moving forward, as you can see in the list today, they were ones that we believed could launch or ultimately could get approved in the next three years through 2027. We got through 10 programs very quickly there, many of which we'll hope for submit for approval this year and next year and a couple in '26.

We think it's essential that we look in that short term because those products, they're the drivers of our revenue growth and our ability to continue to reinvest back in. I would've loved to have keep going down that list. I think we all would. The science is really working and our R&D really is remarkably productive, but we kind of hit a limit in terms of the number of products we could even advance with

the resources we have. And so, we said, " Let's focus on those 10, let's grow the business on the top line with those 10 products and anything that might take a little bit longer, that might be a '28, '29, '30 launch, let's tap the brakes on that and wait until we show more progress on the front things." Now, we still are committed to this platform and maybe, as I hand it off to Jamey, I would say we are still investing our profit in this platform.

We made incredible contributions obviously in growing the business, but ultimately the public health, '21, '22, '23 and the capital that we were able to generate from that, we think the single best use for that capital is organic growth. And we have invested in creating this pipeline of these 10 product launches. We're not willing to say that that's not there still. We still believe that organic growth and investing in a platform that has proven to be this productive in the last three years is the correct thing. We just need to do it in a paced way, in a measured way and grow the rest of the business to match what we think we've grown and shown we are able to do in R&D.

Jamey Mock:

Obviously, we all fully support investing in the pipeline and I think I already made that clear. My additional perspective is, as we look at the future, answering some of the prior questions, we've tried to put in both uncertainty and realism into our forecast, and what that results in at the end is sufficient capital. So take norovirus, which is probably the biggest decision we've recently made, so whether that's, I won't pick a number, but let's say it's a half a billion to whatever, $750 million, we believe we're going to end with a good amount of capital and with norovirus launching or being approved in 2027. Would we rather have that extra capital and not norovirus with what we think we have is a good projection on revenue and gross profit? I think we've come back and said, "No, we think that we've got sufficient capital, we like that product. It brings near term revenue." Which goes back to our overall strategy, which is, we need to expand and diversify our company. And with these projections, we believe we're doing so and still have capital left over in the end.

Stephen Hoge:

I think the alternative is leaving that capital on the balance sheet, is investing in treasuries or something. We do believe norovirus, as an investment, beats that quite substantially. But I think to Jamey's point, you asked the marginal choices, we try to get very conservative in planning what the next three, four years looks like to make sure that we can confidently say that, across a range of outcomes, including a wider range of sales for next year, that we actually are doing the right thing by investing capital rather than leaving it in some other short-term investment.

Adirath Sikand:

Hi, this is Adirath Sikand for Cory Kasimov from Evercore. Couple of questions on your upcoming submission. For 1283, you did see the relative vaccine efficacy for younger patients is negative and grade three four events are high. So do you expect to go after this population in the approval as well and how competitive it would be? And then pricing for 1283 and combo, any latest thoughts on that?

Stephen Hoge:

You want to take the first part?

Jacqueline Miller:

So, I think I'll talk about the trial and I'll leave it to others to answer the second part of your question. So for 1283, we've conducted our trial in those greater than 12 and that would be our intent in terms of

seeking licensure. If you go back to the slides, which, of course, will be posted, what you'll see is that there was an order of magnitude fewer cases in the adolescents than there were in the other age populations, and there are two reasons for that. We enrolled fewer of them, but also they just don't get infected at the same rate that you get infected as you age. So, that result is expected and the imprecision around the point estimate, so there's a very wide confidence interval, and I'll invite you to take a look at the upper limit which is up to 25%. The lower limit goes much lower as well.

I think that that is maybe something that we will be discussing with regulators and answering questions about, but I think it's also largely what we expected based on the immunogenicity data that I also showed you. So, what we have seen is that the immunogenicity is actually improved with this product in adults over 18, but in particular over 65 years of age. So, the immunogenicity was at parity with the 1273 product and that's basically what we observe from an efficacy perspective as well if you look at the 95% confidence intervals. I have a teenager, it would be fine to give the teenager 1283 in my view, but I think the best benefit is going to be in those who are older adults.

Stéphane Bancel:

And maybe to tie this with the next question on pricing, obviously, we're not going to share pricing strategy right now for obvious competitive reason. As you know, we price our vaccines, we're looking at the pharmacoeconomics as Jacqui showed you, in the elderly, which the highest medical need because of the hospitalization rate, there is a lot of value in this product in terms of driving benefits. So we'll translate that into the right pharmacoeconomic model and we'll have a right discussion once we have approval, and we'll communicate the pricing at that time. But again, the efficacy is what drives the pharmacoeconomic value.

Lisa Walter:

Oh, great. Thanks for taking our questions. This is Lisa Walter on for Luca Issi at RBC Capital Markets. And thanks so much for the presentation and all the updates today. Maybe first one for Jacqui. For the COVID and flu combo, I think you mentioned that you are going to submit for approval later this year in some regions, if we captured that correctly. Can you clarify whether this means you're filing directly in the U.S.? I guess what we're trying to ask is, should we assume that the flu-COVID combo will be commercially available in the U.S. for the fall of 2025 or will this be more of a fall 2026 launch? And maybe just one on CMB. How should we think about the uptake of the CMB vaccine in the context of getting approved without evidence that the vaccine can actually prevent clinical sequelae for infants? Thanks so much.

Stephen Hoge:

So, maybe I'll take the launch timing question because it relates to... So, we did indicate that we're using a priority review voucher, that's in the U.S. market. So, we are submitting in the United States for the 1083 program. The assumption about when it gets approved, that's ultimately beyond our control because that will depend upon the review process and FDA's decision around that. But by using a priority review voucher, it's a possibility. It's a possibility that we will have 1083 approved in the United States next year that would make it available. But as Jamey said, we're going to be conservative about the assumptions about what that means, because, if we've learned from the last year, launching a seasonal product in the middle of the season can be difficult and challenging. And so, we're not assuming meaningful revenue from the product right now in the guidance that we gave, but we do intend to try and get the product approved and possibly available, and I guess that could represent an upside. On CMV-

Jacqueline Miller:

Oh, go ahead.

Stephen Hoge:

I was going to go on. Well, I'll keep going on CMV.

Stéphane Bancel:

You're on a roll.

Stephen Hoge:

I'm on a roll. On CMV, so I apologize if I confused now in any way, but obviously, the prevention of infection, we think, is an important endpoint in and of itself because it also shows the inability to do vertical transmission. And so, there is a direct link we believe between those. Ultimately, when you go do health economic modeling and argue for the value of the product and ultimately, hopefully when we're in front of the... If the results are positive and the product is approved and we're in front of the CDC, ACIP, it will fall to them to determine how they want to translate that data into a recommendation on the value of the product. So, we'll have a lot of uncertainty that will resolve first with the data and then the approval and then those conversations. From our perspective, we do believe that it's a pretty clear link that if we're able to prevent infections, it's quite reasonable to assume that we're not going to get vertical transmission, which will quite reasonably not lead to birth defects.

Jacqueline Miller:

Maybe I'll just add that this isn't actually the first time that we've prevented a congenital infection with vaccinations. So, this is building on the pattern that was established with rubella or German measles, part of the MMR vaccine. So congenital rubella is an equally awful congenital syndrome. And actually, while rubella does cause a symptomatic infection in children, I don't think there ever would've been a vaccine simply to protect against rubella. It really was to protect against this congenital syndrome. So, pre-licensure, obviously, knowing that things have changed since the time that vaccine was approved, but pre-licensure, there was no demonstration that this vaccine was going to impact congenital rubella syndrome. We vaccinate young toddlers, they had to age up and then eventually have children that didn't have congenital rubella syndrome. So, I guess what I'm trying to say is, there is a precedent for licensing on a predecessor or antecedent event and then seeing the larger event later down the line. Maybe another example would be HPV vaccination and the demonstration on CIN 2, which ultimately prevents cancer because you don't get to cancer without going through CIN 2. Sorry to wade into your territory there.

Kyle Holen:

No, it's great.

Chris Yu:

Chris Yu here on behalf of Terrence Flynn, Morgan Stanley. Previously, you mentioned that for INT melanoma, it's possible for full approval in 2027. Are you assuming an interim analysis or a final analysis based on the timing?

Stephen Hoge:

So, if you want to take that or you want me to?

Kyle Holen:

Yeah, I can take that. So, we do have interim analysis planned as well as a final analysis planned. And the timing of the interim and the final analysis as we mentioned, is going to be completely driven on the events that we observe. Our first estimate of when we might be able to take a look at the data, obviously would be at the first interim. So, that's how the study is designed and that's when we expect that we'll be able to then package the data for a potential BLA. Anything you want to add?

Stephen Hoge:

Kyle said this a moment ago, the study is now enrolled and so we'll start seeing cases.

Kyle Holen:

Almost.

Stephen Hoge:

Oh, sorry.

Kyle Holen:

This close.

Stephen Hoge:

Really, really, really close. The only data we have to really predict what's going to happen in the future is the 201 study that we've published and showed, and that's where you look forward. We really start to see those benefits, 18 months, two years, it started to became quite profound and that's the best intelligence we have of when we might start to see really substantial benefits. But, at the end of the day, we'll need to let this study enroll. It's a slightly different population, it's done in a different year, and we'll start to get a better sense. Our view is, standing here in 2024, fully enrolled, looking three years into the future feels reasonable, but we'll learn more as the study progresses.

Kyle Holen:

And as Stephen mentioned around the different populations, so we are including Stage 2 patients into the randomized Phase 3. Stage 2 patients have a lower risk of recurrence and it takes longer for that recurrence to happen. So, the event tracking maybe is slightly different than what we've observed with 201. And I just want to highlight that because I don't want it to be a surprise to anyone if it takes a little bit longer for us to observe those events.

Evan Wang:

Hi, Evan Wang from Guggenheim. Two for me on the respiratory franchise. First with the combo, just wondering if your current assumptions assumes a parity preferential recommendation in older adults for flu at launch or is that dependent on the new 1010 P 304 trial or future study? And is that assuming that that's expanding the goalpost by 2028? Second on RSV, just with some of the RSV guidance laid out, I know you highlighted some of the competitive pressures there. Are you still assuming that one third or

reaching one third share longer term, is that achievable by 2028 or do you need a broader vaccines portfolio to achieve that? Thanks.

Stephen Hoge:

Maybe I'll take the ACIP question and then hand to Jamey on some of the others. So, we do believe the product profile, that's why we ran the clinical trials against an enhanced or high dose vaccine, and ultimately, we demonstrate immunogenicity. There is precedent, by the way, for products being approved in that enhanced category and being successfully taken up and recommended based on immunogenicity. And so, at this point, it's not our expectation that there's going to be a requirement for the efficacy data for that kind of a parity recommendation. But again, the recommendation is not ours to make and it'll ultimately fall to the CDC working group ACIP to decide whether that's the case again for this.

Jamey Mock:

And as it pertains to RSV market share, we do believe over time we could get to 33%, but certainly not in 2025 as evidenced by the range we put out there. So again, it's just another one of the assumptions that, over the long term, we believe in our product profile and our ability to compete. But in the short term, I think a little bit more realistic in how we achieve more market share versus today.

Lili Nsongo:

Hi, Lili Nsongo from the [inaudible 03:15:13] team at Leerkink. So I had two questions. So the first one regarding the revision of the revenue guidance. So, you had mentioned specifically as it related to COVID that it was including variability in vaccination rates. But I was wondering, do the revised guidance also include pricing pressure? So, you'd mentioned that this is something that has been played in or do you model the price to kind of stay flat? Does it also include competitive pressure from new entrants with different modalities that may be differentiated, namely Novavax as well as CSL Arcturus in Japan, subsequently in Europe? And thirdly, how much of that hinges on the EU tender? And if you could also give us an update on how the tender is evolving. And then, the second question will be more of a general question. So, as the cash guidance is revised down and as cash is likely to continue to erode between now and 2028, so it's been management position that you would not do an equity raise, but what's the view on debt issuance to potentially bolster liquidity?

Jamey Mock:

Good questions. So, let me [inaudible 03:16:33], so competitive pressures both price and market share or new entrants, yes, embedded into our guidance into 2025. And I think that not only to 2025, 2026, 2027 and 2028 as well. We recognize that. I forget the second part of the...

Stephen Hoge:

All three. Right? So you mentioned pricing-

Jamey Mock:

Pricing, yeah.

Stephen Hoge:

You mentioned [inaudible 03:16:56] markets and Japan, all of that's built in.

Jamey Mock:

All of that's built in. And what was the last part of the first question?

Moderator:

EU tender.

Jamey Mock:

Oh, EU tender, sorry. Right, so not much at all. So, not much revenue expected from EU both in 2025 and also 2026. 2027, we hope to break back in but not much. And in terms of the progress on the tender, we continue to go back and forth with [inaudible 03:17:23] on revised drafts and discussion, and we'll see, but at this point, it's already September 12th, so I, again, do not believe it would have any impact in the year, should we sign in and should we come to a conclusion, if anything. And maybe it has a little bit of impact to 2025, but it's not much. And I would say it's immaterial in the range that we are given.

And then, the last part was on debt, so I think at some point we're going to have to turn over our capital stack. So, once we approach break even, and let's say we're sitting on a certain amount of capital, we're not going to hold a bunch of cash and we're going to want to reconvert it into some amount of debt. So, when that exact time period is, we're not sure, but certainly, to have traditional debt, we're going to have to have positive EBITDA. And so, we basically laid out that that's not possible until 2028, 2029 today. So that's really, we're not assuming that we need debt in the interim. Could we do an asset backed loan in the interim to bolster the balance sheet? Of course, if we think that makes sense, then maybe we go do that. But in terms of traditional debt, I think that capital change will happen towards the end of this time period that we're talking about right now. Thanks.

Jake Batchelder:

Hi, this is Jake Batchelder for Myles Minter at William Blair. Two questions for you. The first one on mRESVIA. I was wondering if you could dig into the molecular mechanism of why you're not seeing any GBS compared to your protein-based vaccine competitors. And then, for the INT program, as you continue to iterate or potentially develop your algorithm for how to make new neoantigens or generate them for each patient, will that require new trials or can you make slight changes to the algorithm specifically within a trial?

Jacqueline Miller:

So GBS and RSV. So look, the antigens are actually really similar. They're presented maybe, and the difference with mRNA is that you're making your own antigen as opposed to injecting something extraneously. I think it's actually very, very early days to tell. We're thrilled that the people that have received mRESVIA have not reported GBS, but we're obviously going to be following this safety finding in the future because our competitors are following that safety finding and we're interested in making sure that we are ensuring the safety of our population. So, I would really hesitate to speculate because it's quite early days in our launch of our product. And I wish I could give you a better answer than that because that would mean I really understood GBS a lot better than I do. But unfortunately, I think we'll just continue to see the data, but we're very encouraged by what we've seen so far.

Kyle Holen:

All right, and around the algorithm. So, it's a fascinating topic and I just love to talk about it. We've had some discussions with the FDA about what constitutes a mild change, a moderate change, and a major change. And certainly, with mild changes, we should be able to make those slight fixes to the algorithm to ensure that it's operating efficiently and correctly over time without any significant impact to a clinical trial. But if we pile up a ton of major changes, it changes the algorithm significantly where I think then we'd be in a space where this is a new product and we'd have to run a new clinical trial.

So, trust me when I tell you that all of our Phase 3 trials are not having significant major changes to the algorithm. And we do that because we want to lock it down and have it safe and secure for the entirety of the trial, and then that's the product that then we'll deliver successfully to patients and be commercialized. But there is a future when perhaps we would want to make major changes. And at that point, we might be coming forward with a different product.

Ted Tenthoff:

Great. Thanks. Ted Tenthoff, Piper. Two quick follow-ups, if I may. So, you guys talked about flu-COVID combo. Are you still advancing the triple with RSV-COVID-flu? And does that still make sense in terms of the vaccination rates you discussed? And I guess, a companion piece on that, how would you over time envision layering flu vaccines beyond 1010, i.e., the other multivariants that you're working on? How do you assess how that flu component fits into combo vaccines going forward?

Stephen Hoge:

I'll take the second. You want me to do [inaudible 03:22:11]?

Jacqueline Miller:

No, no, I got this. I got this. So first, with the triple combo, I think you've hit the nail on the head. There's a question around whether RSV boosters will be annual updates in the same way that COVID and flu are annual updates. And there's a big difference in the biology of these viruses. The biggest difference is that RSV isn't really changing. There are two antigens A and B, and they flip-flop year-on-year. It's not like COVID and flu where we're constantly updating. So, I think we have to really see what's going to happen there in terms of will people need boosters and if boosters do end up being licensed and recommended at what cadence are they licensed and recommended? So there are probably other better places where we could address more on medical need. And then, the second piece of your question, please remind me.

Stephen Hoge:

Updated COVID.

Jacqueline Miller:

Updated COVID.

Stephen Hoge:

No flu. I'm sorry, 1020.

Ted Tenthoff:

Update flu.

Jacqueline Miller:

Yes, yes. Yes, of course. Of course. So, I think, for the time being, you heard that the flu team really has a huge focus on the very late development stages of 1083 and 1010. I think, though, the news this week of the unfortunate man in Missouri keeps pandemic flu really top of mind. So, that's actually where we're focusing right now. We have a contract with BARDA and we're working towards accelerating that program. Once we get through this bolus of work, as Jamey showed you, there's continual investment, and I think at one moment we're going to pull forward the 1011, 1012 as a follow-on and improvement to the 1010 product just like we're doing with 1283, for example, over 1273. So it's part of a longer term life cycle, and obviously, we're keeping a very close eye on what's happening epidemiologically with respect to novel flu strains to make those decisions.

Ted Tenthoff:

And just a quick one for Jamey too. Thank you for that. So, with the cash guidance and the burn projections that you've laid out, is the stock buyback still active and are you considering opportunistically employing that on days like today?

Jamey Mock:

No. So, it is not still active. I think we shut it off early part of last year, first quarter or the second quarter of last year. And so, our primary capital allocation priority is to invest in this pipeline and to expand and diversify the company, and that's where we're going to put all our capital. So, to the question of whether we should have cut more, we believe it's the appropriate amount of capital at the end with all the uncertainty and the cautious approach that we have here. And so, I don't think we would risk it with additional share buybacks right now.

Moderator:

So one last question before lunch. Jamey, can you please state the assumptions that go into your 2025 guidance of two and a half billion to three and a half billion in revenue?

Jamey Mock:

Yeah, sure. Without too much detail. So look, let's start with 2024 and it's three to three and a half billion dollars, and I think we've been pretty transparent that what we're assuming for RSV in there is quite small from a revenue perspective. So, as we fast-forward to next year, let me first clear that there are certain APA's that are going away. Or, going down, not going away, but going down year-over-year. And then, in '26, our resilience contracts will kick in actually quite substantially. But for the year-over-year of '24 to '25, we actually have a reduction in our APA's. So that brings COVID down a little bit.

On the high end, so I'll talk through the high end first. You would assume maybe there's RSV growth to offset that as well. So, that's how I would broadly characterize the high end. The low end would have to say, not only is there not much RSV growth, which already is very minimal in 2024, but it remains to be minimal in 2025. But something had to happen to COVID above and beyond what I just talked about, whether that's vaccination rates, whether that's competition, something else is happening to actually drive that COVID range down. Because RSV, already in the current range, is not very much, so that it would have to be something happens to COVID. But we do have some unique one-offs, the APAs that will be down year over year and then up. So, there will be some reduction in COVID.

Moderator:

Okay, great. With that, we invite everyone live here to please join us and management for lunch.