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OVERVIEW:

Company Summary

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PRESENTATION

Stephane Bancel *- Moderna Inc - Chief Executive Officer, Director*

Good morning, good afternoon. Welcome to Moderna's headquarters. Thank you so much for taking the time today to be with us in person or to be with us online. So, welcome to Moderna 2025 Analyst Day.

As our mission is really the north star of this company. We want to work together with all stakeholders to deliver the greatest possible impact to people through mRNA medicine. If you think about the near term, our strategy is really set up on two axis. One is to build a large seasonal vaccine franchise for high risk population. And to use the cash generated by this franchise to invest in oncology and in rare disease therapeutic.

If you look about the seasonal vaccine franchise, we're already quite on the way. We now have three approved products. We are positive Phase 3 in Flu, positive Phase 3 Flu plus COVID, and Norovirus is currently enrolling in Phase 3.

And if you look at oncology, 2026 is going to be quite an exciting year with a lot of data in oncology and a lot of new medicine getting into the clinic. PA is now in Phase 3, fully enrolled, and MMA is Phase 3 already.

If you think about the seasonal vaccine franchise, we think there's a lot of positive of that business. One, of course, is the tailwind of a growing older population. If you look at the numbers, there are 250 million people right now in the OCD countries that are qualified as older population, 65 and above, and of course growing with an aging population.

And if you look at Europe and Stephen, we'll talk a lot about Europe in a minute. There's actually 90 million people right now in Europe that are 65 and above. It's a larger population set of countries and so it's an older continent. So I think it's quite an interesting opportunity for us in terms of tailoring.

If you look at the burden of disease, which is why we do what we do, we really think that those products, those medicines are really really important to prevent disease, but even more importantly, to prevent hospitalization and to prevent death.

If you look at the numbers, those are just US numbers. They are very large numbers. It's up to 1 million people hospitalized every year. Think about the impact on those people, the impact on those families. Many of us, being young, do not always appreciate how traumatic a hospitalization can be in terms of how it impacts the quality of your life. When you are older, when you have comorbidity risk.

Sometimes in hospitalization, even if you survive, it might mean a drastic change of your quality of life because of muscle mass that you lose during the hospitalization. And if you look at COVID, the numbers are also very high in terms of what we can do. We didn't even spend time on RSV and so on. So if you look at the burden of diseases, it's really high.

If you look at this franchise, there's some interesting seasonality, which I think is going to be very important for us in the Flu plus COVID combo product. We also think it's important with the mRNA Technology speed, the ability to potentially go very late in strain selection.

And we see from time to time, as we spoke in the past, that you have a mismatch in flu, for example, between the strain pickup by WHO that are in the vaccines and what is circulating around the world, leading to more specialization, more disease and more deaths. And so we think with the mRNA Technology we have shown now several years in a row that we can be informed by the FDA of the regulators in May or June, a news trend and we can very quickly get ready in front of a season, which I think is a huge advantage of the mRNA technology.

And then there's a lot of other benefits. One of our platform is, of course, manufacturing scale up and Jerh in a minute we'll give you a lot of details around that. It's because mRNA is a very flexible manufacturing process. We can literally a week make, a COVID lot, and then a week after make a full product. So as you see over the next few years, as Stephen will describe the product launches, as we get more and more volume, we're going to get an incredible leverage of this manufacturing infrastructure that we have.

The market access and reimbursements are pretty set up because healthcare providers know the burden of disease. If you talk to health ministers, they know that with an aging population and respiratory viruses, they have a massive financial challenge ahead of them.

The life cycle investment is very manageable because those products have a very long tail. Of course you need to update them. Sometimes you need to do seasonal studies, but it is very manageable. And in the US we have a very interesting set up where there's a strong incentive from the channel, especially retail pharmacies, to drive vaccinations every season.

Stephen will discuss in detail why we're excited about the next few years. What you're going to see, we set up a portfolio driving diversification of growth through new product launches. Like you're going to see mNEXSPIKE with a full year next year, launches full year in the US, launches in the rest of the world, potentially flu launches in '27, and then Norovirus, Flu plus COVID, and then also a geographic diversification.

I know sometimes people are worried about the US, but if you think about it, we have now great partnership in the UK, Canada, Australia, with full year impact next year. And then the European contract reopening for us the ability to participate in Europe, which is a very large market in '27. So when you see product growth for launches and also geographic diversification, that's going to drive growth in the next few years. Jamey will walk you through some numbers.

And if you look at that respiratory franchise, you're going to see the next few years, growth. The margins, gross margins are also going to improve because you're going to have additional volume in an existing infrastructure. And as Jerh will share with you, the team has some great productivity improvement and there's more to come. There's a lot of exciting projects that Jerh and his team are leading which will drive improvement in gross margin with those two factors.

And then as we've been talking for a year or two now, the cost of R&D for respiratory disease are going to go down. And they're going to go down because those very large one-time Phase 3 is that you have to invest to build that franchise are basically concluding. They don't conclude the day of launch because you have a tail of investments as you have to finalize those studies, monitor the safety, which is very important.

But when those are over, you have basically a one-time investment, which is very large, which is a great barrier to entry, and then you have many years if not decades, where you can have those products driving revenues. So when you look at this plus commercial in the US, it's mostly a B2B setup.

Where we have direct access to the retailers because we don't go for PBMs in vaccines, we do not need to add teams as we basically grow the portfolio. And actually, as we spoke in the past, a larger portfolio is a strength to our ability to get great contracts and talk about the products with the customers. So if you think about it, growth on the top-line, improvement grows margin, lower R&D cost and very stable for existing infrastructure SG&A, it's very interesting improvement in operating margin that we're going to see over the next few years.

If I now turn to the future, where we're investing the capital that we are generating through the vaccine franchise into oncology and into rare disease. And again, the team will spend a lot of time on the details, so I want to be brief to start at 30,000 feet. You're going to see potentially Intismeran with a launch in '27, as we talk about, the first -- is in '26, and if it's positive, we're working very closely and diligently already with a Mercs colleague to be able to file very quickly, which could lead to a launch in '27.

If you think about PA in rare disease, PA is now fully enrolled for his registration study. And so we could see PA launch in '28. And then for those of you that have not followed at ESMO or were not at the Analyst Day at ESMO, we shared some early but quite exciting data on 4359 in stage 4 melanoma and patients. The team will walk you through some data because of that data, we accelerated the Phase 2 this year to be able to see is that signal real? Can we confirm it with the larger numbers because that could be a very important product for patients and the product that is 100% owned by Moderna products.

So that's really for products that are in that stage. If you look at earlier stage products, as I said, MMA is ready to go into Phase 3. We have a couple more exciting products in oncology, and the team will walk you through it. We have an EBV treatment program that could be very important for patients with Multiple Sclerosis. An EBV vaccine, that's also with interesting data that could be used potentially for mononucleosis infection, Lyme disease as the first bacterial vaccine, and so CMV for transplant.

So those are the two franchises we're really focused on generating cash for a lot of financial discipline, sales growth, respiratory vaccine, investing the cash for innovation for the next wave of products. So we could see sustained sales growth for many years to come thanks to our platform.

As you've seen what we've done in the last couple of years is a lot of financial discipline, and they are so thankful for the teams for what they have done under Jamey's leadership and all my colleagues at the EC to graph cost across the entire enterprise. And the momentum that we have is very exciting, as you saw on the Q3 earning call, which gives us confidence for the ongoing work and projects to come, to be able to get the cost into the right place to drive profitability in 2028. Jamey will walk you through it. There's a lot of productivity, project. There's a lot of digital investment and there's a lot of AI tools also being worked for.

For those of you who are going to stay after lunch, we have set up a bunch of panels to walk you through just vignettes of examples where you have members of a team will come here to use some of the tools we are using every day in the business to drive productivity through AI across the entire enterprise.

So with this, I want to now turn to Stephen to walk you through the more detail of a seasonal vaccine franchise. Then Jerh is going to walk you through manufacturing, before Jamey wraps up everything again at the enterprise level around financials for the next few years.

And then the team will come, we start with seasonal vaccines with Jackie and her team. Then we'll go into early vaccines before we take a break and after we're going to have a lot of exciting things to share in oncology and then rare disease -- before I have a very quick two slide close, and then we'll be very happy with the team to take your questions.

So with this, I'm turn back to Steven.

Stephen Hoge - *Moderna Inc - President*

Thank you, Stéphane, and welcome everyone. Hello, it's good to see you, again.

I want to quickly summarize those drivers of growth that Stéphane just mentioned. There is a diverse portfolio of drivers of growth that we think will contribute to that steady financial performance we're looking for over the next few years as we invest in accelerating our company.

Stéphane already presented this slide, I will just highlight that we do have a mix of geographic and product growth drivers. And really, in the next two years, it is mostly geographic or market expansion into the UK, Canada, Australia, into Europe, and into new regions including Latin America. It's really as you look to the second and third years of the next three years that we'll expect to see a substantial uplift from investments in our portfolio.

And that includes flu, or flu COVID combination product and Norovirus. And I'd like to click through those and just give you a sense of why we are bullish on these opportunities.

So starting in '26, we have multi-year strategic relationships with the United Kingdom, Canada, and Australia that we have been working on for the last few years. And so announced most of them in '23 and this last year in 2025, we have licensed the three facilities that will actually supply those agreements.

As a reminder, these are long-term multi-year contracts. They involve us investing in domestic research and development, and they are part of a national security and biodefense, as well as public health strategy at the core of each of these countries' approaches to protecting against viruses, but also protecting against future pandemic threats. That onshore manufacturing is now licensed and starting to deliver products.

In the UK that covers 69 million lives. And we had already referenced in prior financial statements that we'll see the first approximately $0.2 billion of revenue from that partnership in the first quarter, that was delayed from the fourth quarter of this year into the first quarter of next year. But we'll also be delivering vaccines for their fall campaign, first with COVID, but then eventually with the rest of our respiratory portfolio.

Canada, again, 41 million lives. We do have strong performance this year in Canada, are already delivering made in Canada COVID vaccines, hope to add additional products RSV and next spike to those relationships. And we expect to see a full annualized impact from that agreement starting in 2026.

And then, third Australia, 27 million lives, where again, we've now licensed that facility. We're hoping to make our first deliveries, possibly even this calendar year. And as we look to 2026, see the annual benefit from this strategic partnership. So all of this in place and a major driver of growth for us as we look to 2026.

The other driver for us that I'd highlight is mNEXSPIKE. mNEXSPIKE was our successful launch this year. I will remind you, we've only really launched this product commercially in the United States, and the product was only approved mid-year, really in June, and we had a tremendous amount of work through the summer to get ready for the fall season, not just in manufacturing, but in market access and reimbursement and preparing the market for it.

And so we're incredibly excited to see the market share that we've already grabbed in this first year of launch. 23% of the total retail shots in arms, year-to-date has been from mNEXSPIKE. And actually, if you look in older adults, those 65 and above, that market share is almost a third, a really

strong start. It has become our leading product, in the retail channel as well as in that 65-plus and high-risk market that we really think is the future, for us in COVID.

Now, mNEXSPIKE, we, as we look to 2026, we hope to complete that launch. We've only really had a half year this year, and we look to drive even better performance in the US. And we expect to add many other markets. Europe, we're under review and hope to be approved. We've recently been approved in Canada, although we haven't launched the product yet this year commercially, and Australia, Japan, and Taiwan all have submissions pending for approval. So we are looking forward to continued strong momentum behind this we believe differentiated profile for our next bike going into '26.

So those are the two drivers for '26. As we look at 27, Stéphane already highlighted the role of continued market entry for us. So first in the European Union, we have been excluded from that market largely because of a pandemic era contract that is now falling away in 2026.

If you look at the size of that market in the most recent year for which we have data, so '24. There's about $1.8 billion of respiratory vaccine sales, $700 million from COVID, about $1 billion in flu, and the RSV market that's just starting to grow. It's '24 was that first year launch. We do expect that RSV market will get bigger as it expands.

We have had a very small share there because of that exclusion from the market, only about less than $100 million. And so clearly an opportunity for us as those barriers fall away. So why are we excited about '27? Obviously, the end, the lapse of that COVID contract gives us an opportunity to compete for sure in the COVID market.

We will also have, we think, one of the most diverse portfolios. By '27, that means an RSV vaccine that's approved. We hope also, next spike. A combination flu, COVID and flu. In fact, five different products. And we hope in that combination product, the most differentiated, an opportunity to compete in this very large, very established market, where there's a high burden of disease, particularly in older and high-risk populations. So we're pretty excited about that as a market entry opportunity.

We're not done there. While Europe may be the largest market will be entering, we are also looking to do add additional strategic partnerships. And I'll highlight one here, that we announced, the government of Brazil announced September 5, just this two months ago, which is a productive development partnership which has us transferring and manufacturing with a partner in Brazil, Instituto Butantan, for the delivery of COVID vaccines.

We hope that starts delivering products as soon as 2027. It's the kind of multi-year strategic relationship which allows us to get access to that market, but also grow our share and revenue opportunities. And so that was a recent announcement that we're excited about, and there are several others that we're engaged on across Latin America and Asia Pacific right now that would provide a strategic access and growth of access for our products over multi-year agreements, much like we're doing in the UK, Canada, and Australia for '26.

The other thing we'd highlight in '27 is we'll continue to add product portfolios. And so, flu vaccine, we have filed for, we are in the process of filing for approval across the US, European Union, Canada, and Australia in, by January of next year. So just in the next two months. And some of those filings -- filed as we speak.

Flu is a very large and established market. Approximately $6 billion of sales, growing double-digits, and there's a large enhanced vaccine market, $2.5 billion in the most recent year. We think that will grow to almost $3 billion by 2032. That we believe 1010 is well positioned to compete for.

And so again, a place that is for us a new opportunity. It is competitive. We recognize that. But through our strategic partnerships and the other infrastructure we're building, we believe we can go compete for it. And anything we get out of the flu market is growth for us. And by '27, we do hope that becomes a substantial contributor.

Okay. So those three drivers in '27, mostly market entry and perhaps the beginning of an impact from flu. And then as you look at '28 is when we really expect to have the biggest impact from our pipeline investments. That's not to say that we don't hope these products aren't approved earlier. We do, and we will work to launch them as soon as we can get them approved.

But in most cases, it is how do we prepare to really drive growth, and we think that is more in the 2028 time horizon. So, first among those I would highlight is the flu COVID combination product. We've had very exciting data. We've shared previously, I know the team will walk through some of that now.

We believe flu COVID combination remains a substantial growth opportunity for us, both in the flu space and the COVID space. And some of the data, the reason why is highlighted here, if you look in the most recent season, 2024, 2025 season in the US where we have the best data on this.

I'll draw your attention in the lower right-hand corner. 47% of those over the age of 65 who got a flu vaccine in that channel, also got a COVID vaccine in that same day. It probably won't surprise you to know that when we do market research, people would prefer one shot over two. One arm over two.

And we see that as a real opportunity, both to increase the coverage, if that 47% could be higher, that means there's 53% of people that only got one shot, and some of them because they only want one at a time. There's an opportunity to expand coverage for COVID and grow that market. But there's also an opportunity to provide the convenience and cost savings associated with just that single injection administration. So we really do see this as a growth opportunity for us across our seasonal vaccine franchise.

We have filed for submission in the Europe, and we are on path with that review with the European Medicines Agency. So the first potential approvals could actually be coming in '26. EMA was filed last year, or sorry, in '25. Health Canada has been submitted for approval again, supported by the new flu efficacy data as a part of that, just recently. And so again, in '26, those might be the first markets that we see approval.

We're highlighting this as a '28 growth driver because we'll have work to do on market access and reimbursement and preparing to launch those products. But actually, we think we're in a good direction there in those markets.

And then in the US where we do expect to engage with, we're engaging with the FDA, we're waiting further guidance from them on what they would like to see prior to refiling the 1083 program. But again, by '28, we do hope to have gotten that approved and be driving growth across our regions and markets.

And then the last I'd highlight is Norovirus, which we'll talk a little bit more later today, I'm sure. Norovirus we see is a very big opportunity. There's a high unmet need, currently no products, over 155 million people in this country who either because of risk factors or age or occupational health risks or some lifestyle choices, they will want to be protected against Norovirus.

It is an opportunity for us to add another product into an established channel. We do believe most of the vaccination will be through the retail channel, and it continues to be a seasonal disease, so it really fits into this portfolio that we've been building.

So, as we look forward to those growth drivers, we do think we are incredibly well positioned, both from a market entry perspective and a product growth perspective. Focusing just first on the US, we have established the relationships with all of the key customers we need, our retail pharmacies, our government customers, as well as doctor's offices, hospitals, and integrated delivery networks.

The strength of the mNEXSPIKE launch this year for us really highlights how we've really matured those capabilities and in a good position, and we don't believe we need substantially more capabilities as we add products in the United States market.

UK, Canada, and Australia with those strategic partnerships are well positioned to deliver growth in '26. And as we add additional products, we will be adding value, but not a huge amount more cost. We don't need dramatically more capability. We'll add value to the strategic relationships, but all of those products can be made in the same facility. And as you've seen, and you've heard us talk about, I'm sure Jerh will talk about in a moment, our technology gives us incredible leverage and opportunity to do that.

One place where we'll do some investment and growth over the next couple of years is in the European Union to expand that capacity. Because again, it is a very large, very established market, and we have some capabilities.

As I said, we've been generating some revenue, but it's a place that we do expect to see growth and you'll see us invest in commercial in a disciplined way, as we try to grow our presence in the European market, both with the current products and with new products as we move forward. So we think we're well positioned on the current infrastructure to deliver this plan.

There are places where we will have to expand as we go and make additional investments. Stéphane has referenced these, but just to quickly say, we are incredibly excited by the momentum behind [Antire]. I know the team will come and present that data. We do hope for first potentially pivotal data next year in 2026. And then we must get ready if that is positive, to be launching the product in '27.

Those will be some additional capabilities, but we have the benefit of in just run from a commercial perspective of having a partner in Merck. And so we work together with them to prepare that for 2027.

As you look to 2028, we do expect to be launching our first rare disease program, Propionic Acidemia. That pivotal study or the pivotal Phase 2 portion of that study is fully enrolled, and we're looking forward to that data in '26, as you'll hear about. And by '28, we do hope that is a driver of growth for us as well.

And then our wholly owned 4359 program, where again, Stéphane referenced the Phase 2 data and I'm sure the team will give you a sense of that preview of why we're enthusiastic about it, but something we would need to be ready for in '28.

So what we're really focused on that respiratory and seasonal vaccine franchise, and we do really feel strong. That that sales growth drives us to break-even. We also recognize there are opportunities, perhaps requirements that we invest a little bit above that to drive growth in some of these other areas, particularly oncology and rare diseases.

And then Stéphane referenced the rest of the pipeline. But I would just say as you look to '29 and beyond, there are even more growth drivers, even more important product contributions that we expect. And where we do expect we will get some leverage from a commercial and medical function perspective.

In rare diseases, we'll add MMA. It is a very similar, disease and commercial footprint to Propionic Acidemia. So we believe, as we launch that product, we'll be able to use the existing infrastructure. We have multiple oncology products, oncology therapeutics in early stage, disease, and we'll look to be very efficient as we build out our oncology presence, but Rose and others will walk through those programs and why we're excited about them.

But as we get ready for '29 and beyond, we do believe we'll have the infrastructure launch them. And then the early stage vaccines, these are programs where we are paused in Phase 2 often, waiting for that break-even moment so that we can accelerate some. Of these programs, EBV, Lyme, and CMV for transplant. We'll share some of that data today, some of why we're enthusiastic about those.

All of those we believe will fit really comfortably into our seasonal vaccine franchise and commercial capabilities that we expect to build over the coming years.

So with that, I'm going to turn over to my colleague, Jerh, who will walk you through how we think some of that technical operations really enables that delivery and scale.

Jerh Collins - *Moderna Inc - Chief Technical Operations and Quality Officer*

Thank you, Stephen. Hi, good morning, everybody, welcome. It's really great to have you here and everybody online wishing you a very good day.

Our technology gives us incredible leverage. That's the word that Stephen said. And so I want to take it through. Why and what is about our technology, that's really important. And what is it that allows us to drive great efficiency?

I think efficiency, when I look at manufacturing, is tremendously important. Not only when I think of efficiency that we can deliver speed, speed to market, but that we also have the capability of ensuring highest possible quality and ensuring the highest possible cost efficiency. And that's what we look at when we look at our manufacturing network. So let me take you through a little bit what the network now looks like.

It wasn't that long ago, actually, 2023, when we had over eight CMOs, globally between Asia, between Europe and the United States, manufacturing for us. And part of that manufacturing process was they would manufacture to a demand. And as the demand would change, there would be a take or pay. So it started to get quite expensive.

And it was that that we started to tear down our CMOs to reduce the amount of external CMOs based on quality. CMOs of really high reliable quality, great speed, and great cost efficiency. And at the same time, being able to leverage our own manufacturing.

So here in Massachusetts, we have Norwood, and in Norwood is where we make our drug substance, which is the active ingredient, the mRNA for the medicines that, Stéphane indicated earlier and Stephen indicated.

And maybe anecdotally, let me tell you about speed. It was so exciting to hear Stephen talk about the next mNEXSPIKE-1283. It was by us having the ability to manufacture that in Norwood, allowed us to have great speed. The ability that already in June we're identifying what the variant is, and then actually have the drug supplements made and be able to supply it in the United States and have the channels filled already in 2026. Was a huge achievement and not only driven by the fact that we had the manufacturing here in Norwood, but to the amazing people and teams that we have driving that.

And that's one of the big benefits that we have now in relation to having drugs, substance in Norwood. And then using Rovi as our contract manufacturer in Spain. And that's the network that's allowed us to drive the cost efficiency we have, and the supply we have, not just the United States, but the globally.

We have now added, and I'll touch on them a little bit later, three manufacturing sites. Stephen talked about these three sites. Between these three sites, we have Laval in Canada, we have Harwell in the United Kingdom, and we have Clayton in Australia. And as Steven indicated, those three sites serve a population of 137 million people. And these are a long-term partnership and agreements that we have with the United Kingdom that allows us a revenue stream that we can rely on and the supply reliability that these countries can rely on from us.

And then we just announced and you -- a new DP manufacturer in the United States. We are tremendously excited about that, for many reasons. If you just look at the logistics of making drug substance in the United States, then sending that drug substance to Europe with fantastic partners we have in Rovi, and then sending that back again to the United States, operating not only geographically across the Atlantic twice, but also within two different quality management systems.

We also have, as I mentioned earlier, when you work with CMOs, we've exited quite a number of them because we wanted to optimize or take a pay. And that's what drove us to announce, as we did yesterday, a new DP manufacturing facility here in Norwood.

So what this allows us to do is we now can manufacture drug substance in Norwood, and then in the same size, we can manufacture the drug product. So not only are you taking out all of the logistic time, but you're operating under one quality management system, which means you don't have to wait for a release and approval before it leaves your quality management system and then goes into another. Because you're in one quality management system, you can move your product through the system much more efficiently. So from a point of view of lean, you can remove a lot of waste time.

So not only then does this allow us actually even greater speed to market, even greater ability to optimize our channels, but also with Stephen's team from a commercial point of view, to actually fine-tune our manufacturing based on the demands that are there.

It's as close as you can get to real-time manufacturing based on demand. We are super excited by that. The second reason we're super excited by it is the efficiency. So if you look at drug substance manufacturing, we do a lot of that manufacturing already in the earlier months of the year, and then in the mid months of the year, you're doing the drug product manufacturing.

What we'll be able to do in Norwood is optimize our manpower, to be able to work with our drug substance manufacturing operators, be able to train them to do drug product and start moving our people around. Then we have the one quality management system, we have the one quality assurance, the one quality control, the one engineering and facility services.

So the synergies we get from that is absolutely huge. And also we are building out in a facility that already has the infrastructure. So we didn't have to actually break ground to build a new infrastructure because our, we have optimized our footprint, we were able to build this in an existing footprint already.

We had already pre-purchase some of the equipment. So from a cash out point of view, a lot of that cash is paid for this facility. So it's very efficient going forward. Our total CapEx over the next number of years is not going to change.

This also allows us to drive a lower cost per dose. So it allows us to be in a position as volumes increase based on what Stephen presented to continuously drive a gross margin expansion, which is critical for us.

So I'm so excited by this because I think the, I think Honestly, what manufacturing delivers in Moderna is the ability to have top-class speed, the ability of highest possible quality. And at the same time, the greatest possible cost efficiency. That's the magic triangle for manufacturing anywhere. And by us taking control of all of this allows us to optimize. While at the same time, being able to partner with the CMO so that we have the optimized efficiency for Europe, as Stephen already indicated, without having a large number of CMOs.

So we're a very exciting part of the manufacturing journey of Moderna. It wasn't that long ago, not only did we have eight CMOs, but -- we were making a lot of our drug substance and Lonza in Europe. That wasn't that long ago. It wasn't that long ago when we had only one manufacturing site, which was Norwood, trying to do all of this.

Now we got Norwood drug substance and drug products into end to end here in the United States, made in the United States to supply the United States and supply other countries as well. We're tremendously excited by that. And I see Tracy's here with us. We speak a lot about our physical assets. And we speak a lot about our digital assets, and Tracy manages our digital assets, but I don't want to forget our people.

We have top class manufacturing associates that I would class as the best in the world, are definitely up there, who are behind all of this, because it takes great intellect, great design, and great ambition that we have in our Moderna mindsets to be able to make this happen. So this is one of the things we're super excited about.

What's amazing when you look at this slide is not that we have three sites in the United Kingdom, in Canada, and or in Australia. I think what's amazing in this is, two years ago, this was land. It is amazing to be able to be able to build out these sites so fast, and then to be have them licensed already, and to be in a position that they're already supplying the 137 million populations of these three countries.

This is a huge call out to the engineering team and the design philosophy we had, which was State of the class, excellence, the ability to use robotics, automation, to have a learning mindset, so to look at all the experience we had from working with Lonza, look at all of the experience we had from working with CMOs, look at all the experience we had ourselves from working in in Norwood and designed that in, so that these efficiencies are super-efficient in relation to manpower and batches per person, but also super-efficient in how we can use AI robotics and automation already from the start and not having to design it in later.

And what's also unique about these sites, and I would argue you probably won't find any place else in any other manufacturing that have these three sites are exactly the same. So if you were helicoptered into one of the sites, blindfolded, you wouldn't know which site you're in, unless you could look out the window and see which flag is flying. They're designed exactly the same way.

And there was a huge benefit in this because we started off the installation and operation qualification in Canada, then on to the United Kingdom, and then to Australia. So as we started to do installation qualification, operation qualification, and as part of that process, you find issues and you correct those issues, we were already then able to pre-correct them in the United Kingdom and pre-correct them in Australia, so that those facilities were even up and running even faster.

And then we partner in Laval in Canada and we partner in Harwell in the United Kingdom with CMO, so that we have a full integrated vertical supply for those countries. And in Clayton, Australia, we make our own DP because we weren't able to find that capability there.

In relation to operational excellence, we are designing these facilities with optimal cost optimization. So the type of COGS that we're going to deliver out of these facilities will exact will be pretty much exactly the same as what we're delivering here out in Norwood. We have the same one management, one quality management system, one manufacturing system, MS&T quality assurance, engineering right across all of this so that we can drive efficiencies through this.

And so as I speak about efficiencies, let me touch a little bit about -- (technical difficulty) . I think what you might find impressive on this is that despite a 40% reduction in total revenue across those two years, we were able to keep gross marginal improvements pretty much flat.

And why and how fortunately, that was driven by removing taker pays starting to reduce down the amount of CMOs we have. We were able to take a lot of costs out of the system with that.

The second thing we were able to do is drive a real ambition in relation to efficiency, robotics, automation. We were starting in Norwood with, five operators for Sweden. We got, we set ourselves targets for three, we got to 2.2 and then hit 1.9. We drove an amazing efficiency and that type of efficiencies that we have in Norwood is what we have now sent out to the other sites.

We were then able to apply, what I would call lean, but modern lean, the curiosity of understanding the manufacturing process in great details so that you can manage the quality envelope and that you can ensure that you're right first time. Our drug substance manufacturing, for example, this year in Norwood for all of the products that Stephen indicated, the 1273, the 1283, the mNEXSPIKE and the SPIKEVAX. 100% success rate, no batch of the spike.

That is, and not only did we achieve that this year, but also we achieved it last year. In fact, last year, we had one batch of a spike when we pivoted when the FDA wanted to change the variant, and we stopped that manufacturing of that batch overnight, and the next morning we were manufacturing as well.

So this is what gives me the confidence as the, as when we see and Jamie's going to touch on it later. As the volume start to grow, we'll be able to drive an enhancement and gross margin because we've got the system in place. Also, in relation to inventory and inventory management, we've made great progress.

What I would say is a lot done. And what Stefan said earlier in the presentation is a lot more to do. We have a great ambitions ahead and our game is not finished yet. There's a lot more ahead for us. So that's a little bit about that.

So the other element of manufacturing is the personalized manufacturing, which is the Intismeran autogene. This is where we have the ability to manufacture personalized for per patient. And the previous type of technologies that had this was car and what car technologies always had was a challenge in the cogs and the challenge in the manufacturing cogs.

So we built out Marlborough. Again two years ago, Marlborough didn't exist. It was basically a brownfield site. And we built out Marlborough, not with just the ability to supply fast, and in relation to supply fast, we already have clinical supplier from Marlborough in September of this year, two years later. But also the ability to ensure that we're managing the COGS right from the start. Because usually what happens is you focus on getting supply, you focus on regulatory, then you go, we've got that done.

Let's work on the COGS now. We started working on the COGS before the facility was even built. And I think it's that level of just ambition and determination to really keep efficiency at first and center is what allowed us to do that.

So, in relation to Marlborough, what we have is we have an end to end operation that's focused on cost, supply, and, of course, quality. And that's basically is what we're going to look at as we build out Marlborough.

So the second thing, when I say as we build out Marlborough is, we made sure we didn't put all the capacity in there that we need for five or six years' time. We set it up so that we can do line by line. So we have the ability to run out seven lines, and we start with one, and we will maximize that line. And then as that line reaches its full capacity, we will then have line two ready. Line two, we will have a higher standard, and I'll touch on what I mean by that later. And then that the higher standard, we will then go back and retrofit in line one, and then the same later for line three. So not only have we the capability of adding the capacity only as we need it, so we're not carrying a depreciation shadow that's unnecessary. But also that we have the capability to consistently improve our manufacturing capability without having to do a major redesign. And I think that's super-efficient when you're charting out a journey that causes reduction. Again, as I said earlier, we were planning and designing cost efficiency right from the start, not something that we wanted to do later.

Not only are we really proud and again an amazing team there, but not only are we really proud that we've supplying clinical supply out of this facility already in September, but we're very confident that we've got a really great path to a cause reduction here. So this might give you a little, it's a sort of a very simple cartoon example, but it's illustrative just to show you what I mean.

When we started off the manufacturing of INT in Norwood, we had an equipment footprint that was 120 square feet. So if you look at this cartoon, you see a picture of a person, and that was the size of the equipment, roughly to manufacture for a patient. Several pieces of equipment involved a lot of it once only use and then then destroyed. So it had a COGS that was reasonably expensive.

We've already in the current configuration in Marlborough, reduced the size of that down by, driven efficiency in the design. So we're constantly looking at the design, constantly looking at what can be reused, how we put in cleaning validation, how we work with the FDA and that, how we do briefing books with the FDA and that and so we've already made huge progress. So this is what we have already in our Marlborough facility.

And already in our technical development facility in Norwood, we have already the future configuration and we're already, not only have we already designed it, we're already running pilot skill batches on it and testing them. Again, a three-fold reduction site. So not only does that mean then that when line one gets full, but line two is we will build out line two will be based on the future configuration, and then we'll retrofit that.

So that we -- we have not only the ability to drive increased capability for the demand that's ahead for all of the different eight different INT products that are all the way through the different phases of clinical trial, but the ability to drive in COGS. And I think that's something that we've learned also from looking at all the other industries and what happened in the whole CAR technology area. So we're pretty excited by that. And I'll probably finish up with probably three things. Jamie likes three things.

I think the first thing is just a huge call to our people. We have amazing people behind us. That's what gives me confidence that we'll be able to continue this journey. I think the second thing is that we have dependability not only in relation to quality, not only in relation to supply, but also in relation to cost management. And I think lastly is we never finish. We are ambitious. It's never good enough for us. It's a lot done and more to do. That is our attitude.

So we have plans ahead that can continue to drive not only the gross margin expansion improvements that have indicated in the slide, but even better, particularly as we use AI and robotics to drive that in. And you'll see some of our team later we'll take you through some of the AI and robotics that we already use. We already have agentic systems up and running in our manufacturing facilities, and it's quite exciting to see.

And so let me say my last word in relation to quite excited to see. I'd love to bring you all to Marlborough and maybe that's for another day. But let me give you an indication of what the site looks like in a one-minute video.

(video playing)

Yeah. That's real. That's happening right now, and thank you very much for being with us this morning. A real pleasure to hand over to Jamey.

Jamey Mock - *Moderna Inc - Chief Financial Officer*

Thanks, Jerh. All right, so let me also extend a welcome to everybody. It's great to see many of you and thanks for joining live or on our webcast.

So as Jerh said, I do like to cover three things. The first is I will talk through our, where we're headed in 2025. I'll provide a recap from our recent earnings call. Then I'll talk through our financial framework for the coming year. So Stefan laid out the business strategy, Stephen laid out the commercial strategy, Jerh just walked through our manufacturing strategy. So I'll put a financial lens to all that as it pertains to the next three to four years. Then I'll wrap up with capital allocation.

I really take that from an R&D perspective, which is where we are driving most of our capital from an investment perspective. I will then take it to a cash perspective and walk our cash balance over the coming years. And then I'll talk about our exciting announcement this morning, which was the loan that we just, announced, which makes our balance sheet even stronger. So I'll get back to that in a few moments.

So starting with 2025, as a reminder, we narrowed our revenue guidance to $1.6 billion to $2 billion. That's comprised in the US of $1 billion to $1.3 billion and outside the United States, $600 million to $700 million.

So inside the United States, we had provided for -- there's only one large variable left, and that is vaccination rates. And we had provided for within this range in the United States, the vaccination rates would be down 20% to 40%. And at the time of our call, season to date, we were down about 30%. We're now two weeks later and it's down 28%, so it's a little bit better than we at the time of our call. So we feel very confident within the range in the United States as we're in the middle of November now.

Right outside the United States, it really just comes down to two things, delivery timing, whether the deliveries will happen inside the fourth-quarter or shift to next year, and then in a few countries, vaccination rates as well. So, I think the punch line here is after another two weeks, we still feel very confident in our guide of $1.6 billion to $2 billion of revenue.

From a cost perspective, we said we would take our GAAP cost down by another $700 million versus what we had said at the second-quarter. So overall, it's over a billion dollars out this year. We focus a lot on our cash costs, which you can barely see here, but on the bottom of that slide. We started the year believing that we would invest $5.5 billion and now we believe our guidance at the midpoint is $4.6 billion. So from a cash cost perspective, Stefan mentioned it as well, we are taking out nearly a billion dollars of cost versus what we thought outside of the year.

We said we'd make improvements to 2026 and 2027, which I'll get into in a few moments. And all this is really important as we target cash break even by 2028. So that's a quick wrap on the year. From a financial framework perspective, I won't go through this chart again. Stephen and Stefan have covered it.

I, when I step back from it, I see 10 opportunities for growth over the next three years. And we will guide future years at a different time, but right now, in 2026, we believe we will start growing, which is exciting and we believe that growth is up to 10% in the year 2026.

Come our 4Q call, we'll give a greater specifics around that. We want to see where the 2025 lands, and then we'll give a little bit more specifics around what the actual guidance is for next year, but you can expect that we will grow starting in 2026, and we believe every single year thereafter.

So I want to take a minute on cash cost. I said we were going to make improvements. So, our previous estimate for 2025 was $5.1 billion, for 2026 was $4.7 billion and for 2027 $4.2 billion on a cash cost basis. You can see the GAAP cost numbers at the bottom.

Basically, in a year, we're basically advancing one year. So with the previous guidance that I just mentioned of $4.6 billion, we're already beating what we had thought we would do in 2026. And then we're going to do that again. So in 2027, we thought we'd be $4.2 billion. We're actually going to achieve that in 2026. And then finally, we're going to actually take 2027 down to $3.5 billion to $3.9 billion.

So at the midpoint, that's $3.7 billion, which is another half a billion dollars out. That is due to all the tremendous work across all the teams. Basically, if I step back when we laid out this plan a couple of years ago, we thought we were at $9 billion in cash cost. We're going to hit $4.6 billion in two years. And we'll hit $3.7 billion. We knew that we could do this. We didn't know that we would accelerate the timing as much, or that it would be as significant as what the teams have been able to achieve.

There are loads of examples across all the levers we talk about in terms of manufacturing efficiencies, procurement savings, what we can do to make our trials more efficient as well. And so the teams are just doing an exceptional job, and they're actually beating our own expectations. So therefore, we have confidence in being able to take 2027 down to something that starts with a three.

So that's it for the kind of financial framework over the next few years. I want to move to capital allocation. And our primary driver of investing capital is in research and development, which will evolve over the next few years. And I think you can see two things from how it evolved. Number one is that it will go down. That is largely, we've been saying this for a long time, as we complete the Phase 3 trials in infectious disease, those will no longer be there come 2027 and 2028. I'll come back to that in a moment.

And then I think the second observation is you can see the percentage of investment is going to increase in oncology. So we believe as we scale down and have a portfolio of hopefully six products in infectious disease by 2028, that will just require a basic maintenance of life cycle management for infectious disease to maintain that portfolio. And then you can see the large balance will be in oncology.

The last couple of things I'd say on infectious disease is, you can see it remains a little bit elevated in 2026 and 2027 for two reasons. One is our Phase 3 Norovirus trial. We're going to initiate another cohort this this winter. And so therefore, we can see still that'll cover and carry into 2026.

And then our post-marketing commitments as it pertains to COVID. So we do have those in the budget, those will go into 2026, maybe stretch into a little bit of 2027, and then largely that's it. That's it from an infectious disease standpoint, all the Phase 3 trials will be completed, and then we'll get to that life cycle management.

From an oncology perspective, we are super excited to invest behind this. We're obviously super excited to invest behind infectious disease, but that is completing. So everything that you're going to hear today from [Antimaran] or mRNA-4359 or an entire emerging oncology portfolio that Rose will walk you through.

That will increase over the coming years. And we are still investing behind rare disease and autoimmune, but we want to see what those regis how those registrational studies read out before we continue to invest further and either way, it's a relatively smaller investment versus from a patient population perspective as well as dollar perspective, versus what we'll see from oncology and infectious disease. So that's how our R&D is evolving and that's where we're primarily putting our capital.

So I want to talk about the balance sheet. So I had already mentioned at our Q3 call that we will end at $6.5 billion to $7 billion in cash, which is a net cash investment this year of $2.5 billion to $3 billion. So we started the year at $9.5 billion in cash. We are going to have revenue of $1.6 billion to $4 billion or $2 billion and then we will have cash cost of $4.6 billion which is a $2.5 billion to $3 billion net cash investment.

As I walk that forward, we believe we'll having net cash investment of roughly $2 billion in 2026. So that is 10% growth on that revenue line plus an almost $4 billion cash cost. I said $4.2 billion. So that should in the ballpark, basically deploy $2 billion of capital, in which case we would have $4.5 billion to $5 billion by the end of 2026.

Then as we turn to 2027, we're targeting a billion dollars. So we've had a mantra of burning, investing $3 billion in cash in 2025, $2 billion in cash in 2026, and $1 billion in cash in 2027 before we break even. That is still our mantra. That is still what we're targeting. We've provided here for a $1 billion to $1.5 billion because we'll have to see where the revenue line grows.

There are all the opportunities that Stephen's already laid out for you, and we'll see what happens. Maybe it's a billion dollars, but if it's not exactly at that revenue line yet, maybe it's $1.5 of net cash investment come 2027. So therefore, we'll end at $3 billion to $4 billion in cash, which is a very strong balance sheet before the year that we break even. So we're excited by that. We'll see revenue growth as well as cost reduction that will basically leave us with a strong ending cash balance and a strong balance sheet of $3 billion to $4 billion.

So then you might ask why did we then go out and announce an exciting loan this morning. And really, that is a strategic move to maximize flexibility here. So obviously, we're excited about that. We want to make sure that we are in control. And I think if you look at the terms of this loan, we are quite excited about it.

Number one, it's non-diluted financing, from an equity perspective. Number two, it's relatively low cost, and let me explain that for a second. So you can see so far plus $550. So right now, that's about a 10% interest cost. But we will just take the cash proceeds that we get, which the first draw is $600 million and put it in the bank. So the ultimate interest cost is the $550 spread.

So that's what we'll be sitting on for $500 million for $600 million of this. And then the delayed draw component is just pure flexibility over the next two to three years. And that is at a very nominal cost. The average cost of that for three years is 1%. So that gives us significant flexibility, which we're excited about.

We're still able to use it for any general purposes, so we can use it for business development, we can use it for share repurchases, and this is a five year loan. So a lot can happen over five years, and that's what gives us extreme flexibility and a lot of comfortability over the next few years.

So then, just to update our 2025 ending cash balance, so that means we will now end the year with $7.1 billion to $7.6 billion in cash because we'll draw $600 million. And our liquidity will be over $8 billion at the end of this year, which we believe on a year that we are investing $2.5 billion to $3 billion and that investment, net investment will reduce over the coming years. That gives us a lot of flexibility and a lot of comfort as we look at our financial future.

If you fast forward to 2027, that means our liquidity will be roughly $5 billion. So going into a year that we break even, we believe we'll break even in 2028 on a cash basis, we will have $5 billion in flexibility in liquidity, $3 billion to $4 billion from a cash perspective and then this extra $900 million from a delayed draw loan perspective, which we're really confident in. So overall, we really believe in the base plan, but this provides a lot more flexibility to us moving forward as well.

So I want to summarize what I think are the key financial takeaways. I really believe this is a turning point in our financial story. And that turning point starts with growth. So we believe we will grow over the coming years. We've tried to lay that out for you. The first year will be up to 10%, and we believe we will continue to grow thereafter. And I think that's a big change versus the last few years.

The second thing is Jerh laid out a terrific story for gross margin expansion. I would say of this 10%, half of that is volume, and the other half is all the productivity drivers that we are driving. So we feel very confident that with revenue growth and with the outstanding efforts of the entire team and what they're driving from a manufacturing efficiencies perspective, that we will grow 10%-plus from on the gross margin line.

We will evolve our R&D investment from infectious disease, and we will take that down to a life cycle management level by 2028. And then we will significantly invest into oncology and hopefully rare and autoimmune behind that as well. But for the most part, it'll be an oncology story over the coming years.

And then we're reducing our cash cost and investments. So by 2027, we will be $3.5 billion to $3.9 billion. And that really gives us great comfort in seeing cash break even by 2028, great line of sight to that. So we believe in this strong financial framework, we believe that we will have $3 billion to $4 billion in cash absent alone, but this enhanced liquidity gives us a lot of flexibility for both uncertainties or opportunities that present in our future. So with that, those are the financial takeaways that I'd like to wrap up with, and I will turn it over to Jacque.

Jacqueline Miller - *Moderna Inc - Chief Medical Officer*

Right, well, good morning, good afternoon, and good evening. It's a pleasure really always to be with you again, and this year, I again have the happy task of taking you through our scientific data with the team, and I want to say unlike Jamie, we're going to talk about many things, which actually is a super pleasure. So you're going to see a wide variety of the team presenting data with me, and I think that also is a representation of our success. We've really built out a large team of investments who are representing, as Jerh said, an amazing team behind all of these data.

So with that, why don't we get started? So we're first going to talk about our seasonal vaccine pipeline and some of the new data there. This has obviously been a big year for us in seasonal vaccines. So, in the US alone, we've had three FDA approvals, and that's starting with mNEXSPIKE, which as Stephen explained to you has been incredibly important to our US business this year.

That team has also pulled forward to additional supplemental BLA's, first for RSV, so keeping up with our competition, in having data in those high-risk individuals recommended for vaccination 18 to 59. And then in COVID, importantly, the only licensed product currently in the US for pediatric patients. And so you'll see representatives from the entire team who will talk to some of the data that we've generated this year.

I'm going to finish the presentation on Norovirus, which those of you who have followed this story, you'll say, wow, Norovirus changed teams. What happened there? We're now thinking as Norovirus gets closer to being a commercial product, Norovirus more and more seems like it's going to share some characteristics with our seasonal vaccine portfolio. So, like other seasonal vaccines, it has a period of intense transmission, and that's in the winter season.

Like COVID, it also has a small bump in the summer, but we expect that most vaccinations are going to occur in advance of that winter season. And also like COVID and like influenza, it really can vary in terms of epidemiology over time and we're envisioning a world where, maybe not every year, but some years we may want to update that vaccine and so we've gain some expertise obviously in COVID, learning to do that more with influenza this year and ultimately, we'll apply that to Norovirus.

So with that, we're going to start our seasonal journey, and I'm going to hand the podium over to Darin Edwards, who is our program leader on that program.

Darin Edwards - *Moderna Inc - Executive Director*

Thanks, Jacque. So I'm really excited to be here to talk through our data on mRNA-1283 which is mNEXSPIKE as its branded in the US and we've done not only gained the approval but also done the annual strain update and launched the product in the US. So this is data that comes from our pivotal Phase 3 study, and it's data that we were excited to receive, excited to report, and I'm excited to talk about it today.

So a little bit of a description of the trial before I get into the results. So this was a Phase 3 trial designed to assess the immunogenicity, the safety, and the efficacy relative vaccine efficacy of mRNA-1283 versus our commercial product mRNA-1273. Approximately 11,500 participants enrolled in this study above the age of 12 years and older.

A single dose of either mRNA-1283.222 or 1273.222 was administered. And that is the bivalent vaccine composition encoding the ancestral and the BA.4/5 strain. And this was used because that was the licensed product composition at the time the study was enrolled.

So first, a little bit about the participants in this trial. So characterizing the demographics and the baseline characteristics of these groups, they were well balanced between the two arms. That's both in terms of age, with a median age of approximately 56 years, for participants in the trial, breakdown between the different age cohorts, as well as by race and ethnicity, where the demographics were largely representative of the American population. One thing to highlight though is approximately 46% of the participants in this trial also had greater than one or greater comorbidities, as defined by the CDC case definition.

In addition to the demographics, we also controlled for Prior SARS-CoV-2 infection with about 75% of participants that actually had evidence of Prior SARS-CoV-2 infection. Very characteristic of the time during which the trial was enrolled. In addition, most of the participants in this trial had three to four prior vaccine doses, with a median time of about 10 months from the last vaccine dose.

So getting into the results from the trial, first, we look at solicited local adverse reactions, and they were relatively well balanced between the two arms with a trend towards lower local reactions for the mRNA-1273 arm. The highest solicited local adverse reaction was for pain, but for all, they typically had either grade 1 or grade 2 reactions that resolved after about one to two days.

Now looking at the systemic adverse reactions, we see they were well balanced between the two arms of the study 1283 and Spikevax, fatigue, headache, and myalgia were the most commonly reported systemic adverse reactions. Again, grade 1 or grade 2, reactions were most common, and again, they resolved in about one to two days.

So this study was designed to assess relative vaccine efficacy and to do that, we used the CDC COVID-19 Definition for COVID-19 symptomatic disease, and that required a virological confirmation of SARS-CoV-2 infection via PCR, as well as the presence of one or more symptoms consistent with COVID-19 within 14 days of the positive PCR. Active surveillance was conducted in the study in order to capture cases, and that included biweekly symptom surveillance conducted using our e-diary, as well as assessment of participants with symptoms for clinical evaluation and for collection of samples that we then used for PCR.

So starting out with the top-line data from this study, so the pre-specified success criteria was met for relative vaccine efficacy for 1283 versus Spikevax. This is indicated by the data that you see on the screen where a 9.3% positive point estimate was seen for 1283 in relation to Spikevax in terms of prevention of symptomatic COVID disease. The success criteria required at the lower bound of the confidence interval to remain above minus 10%, and that's what we see from these results. But as we know, the people at greatest risk for COVID-19 disease are those older adults.

Here we see a breakdown across three different age ranges, and it was very nice to see that the highest point estimate that we saw from the study when we did an age breakdown was for those at highest risk for symptomatic and severe COVID-19 disease, that being the above 65 year olds. Then we saw a 13.5% positive point estimate in favor of mRNA-1283.

As we look at the younger cohort, that we see relative consistency between the two arms, but the point is the confidence intervals are very wide based on the limited case number, and the limited number of participants at age range. So I think we all know that it's not just age, but it's also the presence of risk factors or comorbidities that put people at higher risk for severe COVID-19.

So we wanted to do a post hoc analysis of the results of the data from this study in order to give us a view on how 1283 is actually performing in prevention of COVID-19 disease in individuals that had these comorbidities. So the top-line in this figure demonstrates or it captures all people in this trial, 12 and older that had one or more comorbidities. And here we see a 17.5% point estimate for prevention of COVID-19 disease.

For those that were above 50 years old, again, increasing the level of risk, increasing, looking at populations that are increasing risk. So above 50 years old and with one or more comorbidities, we see an even higher point estimate that being 23% and above the age of 65 with one or more comorbidities, individuals that have the highest risk for severe outcomes, we see a point estimate of 28.6%. We're very happy to see these results.

So this study was not powered to assess prevention of hospitalizations, but we were in a post hoc analysis able to use the FDA to find guidance as FDA severe disease criteria in order to do a post hoc analysis to give us some view on how 1283 is actually performing in relation to Spikevax in prevention of severe disease.

Now, this is all built on the knowledge that Spikevax has been demonstrated consistently to be very effective in preventing severe COVID-19, not only in our pivotal efficacy trial, but also in real world effectiveness studies that we conduct year-over-year for each vaccine composition that we gain approval for and launch. We were able to identify 55 cases in this study that met the FDA criteria for severe COVID-19. And in this assessment we see a 38.1% positive point estimate in favor of mRNA-1283 versus Spikevax.

So now pivoting to the immunogenicity results from this trial. At the top you can see the view of the neutralizing antibody responses against the two variants that were encoded in this vaccine composition, the original SARS-CoV-2 and BA.4/5.

For those of, for both of those, the non-inferiority criteria was met, that being a lower confidence interval above 0.667. But importantly, you see that the lower bound of the confidence interval is actually above 1. So that indicates that mRNA-1283 is driving a higher immune response.

Same thing looking at zero response rate, the non-inferiority criteria was met, that being above a lower bound of the confidence interval of above minus 10%. But again, the pos -- the lower bound is above zero, again, indicating that 1283 is eliciting a stronger immune reaction than the very strong reaction immune response that we get from have measured consistently from Spikevax.

Again, we wanted to look at those individuals that were at higher risk, so we did an age breakdown and in this assessment, you see that the highest GMR, the ratio between the titers elicited by 1283 versus 1273 was highest in the above 65 year olds, correlates very nicely to the relative vaccine efficacy results that we also measured between in those age ranges.

We also wanted to take a look at durability of this product in relation to the immune, the durability profile that we have consistently measured for Spikevax. So here we're looking at one month, three months, and eight months, or sorry, six months and looking at not only the GMR, but the overall titers that we actually measure for Spikevax and also for mRNA-1283. And we see the GMRs are very consistent at these three different time points. And also, I think it's actually very important to highlight that the overall neutralizing antibody response that we measure for 1283 at six months over 1,000 is actually higher than the neutralizing antibody response that we measure for Spikevax at three months.

So it's been my pleasure to be up here talking through the pivotal Phase 3 results that supported our licensure in the US and are also supporting the reviews of our 1283 applications globally. Just a brief recap. mRNA-1283 was generally well tolerated, had an acceptable safety profile. We met the pre-specified relative vaccine efficacy and non-inferiority endpoints with a point estimate of 9.3% for all participants included in the trial.

We saw a trend for higher rVE point estimates with advancing age and with comorbidities. For all participants above the age of 65, we saw a 13.5% point estimate. And above the age of 65 with at least one comorbidity, we saw a point estimate of 28.6%. We met all pre-specified non-inferiority objectives for immunogenicity. That includes indication that mRNA-1283 elicits a higher immune response than Spikevax and that higher immune response was most evident in individuals that were older.

And we plan, we have plans, and those are actively underway to augment this data with data from clinical studies of our currently approved LP.8.1 vaccine composition, and that data will be published relatively soon and we're also conducting real world evidence studies again, and that data will become available as it accumulates.

So we're approved in the US. Stephen shared that information and that is for the current LP.8.1 composition. We're approved in Canada and we're targeting strain update for next year, and we filed for in our targeting 2026 approvals and strain updates in other markets like Australia, Europe, Japan, and Taiwan. So thank you very much for your time. And I think next, I'll pass it to Raffael to talk about flu.

Raffael Nachbagauer - *Moderna Inc - Executive Director and Portfolio Leader*

Thanks. Morning. I'm really excited to give an update on our influenza program today. A quick reminder, Stephen said, influenza is a major source of morbidity and mortality worldwide. Up to 1 billion cases, occur every year and in the US alone, up to 130,000 deaths every single year. What's also important to highlight is that age and chronic conditions are also playing a role in the increased risk for influenza. And influenza can actually cause downstream events like cardiac as well as pulmonary events like heart attacks, stroke, or COPD.

As you all know, influenza vaccines are licensed. There's also enhanced vaccine market with vaccines that have shown superior efficacy to the standard those vaccines. A quick reminder to mRNA-1010. It encodes for the surface glycoproteins, the major immune response for the influenza vaccines, the hemagglutinin . And there are some inherent advantages of our mRNA platform when it comes to influenza vaccines.

It encodes the exact protein that is being recommended by WHO and other recommending bodies. It has no requirements to propagate the virus in cell lines or eggs where you can sometimes get mutations that can actually change the antigenicity. And what's also important is downstream, we have reduced production times, which gives the potential of having latest string recommendations as well, which could improve the matching of the vaccine strains to what is circulating in nature.

What I'm not going to show today, but we've previously shown that we actually get superior immune responses of our mRNA-1010 vaccine to both standard as well as enhanced vaccines. But today, I'm actually going to talk about the efficacy that we've seen in our P304 study that we conducted last year in the Northern Hemisphere.

It was a large trial of 40, 703 participants. We randomized them to either receive mRNA-1010 or a license comparative vaccine. Last year, as some of you might recall, was when first the change of removing B/Yamagata happened from the vaccines. Not all regions made the change at the same time. So depending on the region, we actually had a trivalent or quadrivalent comparator, mRNA-1010 was trivalent throughout globally.

In terms of the study objectives, the primary objective was to show non-inferiority and superiority of mRNA-1010 versus the standard dose comparator in terms of efficacy, against all influenza strains. We also looked at the safety and retogenicity of mRNA-1010. And then the secondary

objectives, we also looked at specific match to the strains that were circulating, and also the immunogenicity of a subset of participants to confirm the prior findings that we had in our previous studies.

In terms of exploratory objectives, we also wanted to look at the impact of mRNA-1010 against medically attended ILIs, which are more rare events. But they are, as I mentioned, really important as well in terms of the types of disease that you actually want to prevent.

If we look at demographics, you see, again, that it's a well-balanced group because between mRNA-1010 and the licensed vaccine comparator. What I do want to highlight is the last line, which is the baseline high-risk conditions. More than half of the participants had some type of baseline high-risk condition, which included diabetes, asthma, obesity, as well as COPD and atrial fibrillation.

And when we go to first the reactogenicity, it's very much in line with what we previously had presented about mRNA-1010. We do see higher local reactogenicity with the majority being injection site pain, grade 1 and grade 2 in nature and transient.

Similarly, for the systemic reactogenicity, we do see higher rectogenicity for mRNA-1010 compared to the licensed standard dose comparator. However, a low frequency of grade 3 events and most reactions were grade 1 or grade 2 in nature. The most reported systemic reactions were fatigue, headaches, in both of the groups.

This is to me, the most exciting slide of all of it. This is, Darin has shown a very similar slide for COVID, but just to orient you, because we have a couple more slides. We have the geometric mean is the blue diamonds on top which is the 26.6%. But then we have the confidence intervals. And then you have those different lines that actually show the non-inferiority bar, they show the superiority bar, and then the highest superiority bar. And what you can really see is that the lower bound exceeds all of those bars, which really gives us a lot of confidence with those results standing for mRNA-1010 being in fact superior to the standard dose vaccine.

And this also holds true when we then break it down by strains. The confident vitals become a bit wider, because of course you don't have as many cases for every single one of those strains. But you actually see that we get that efficacy for both the influenza A and influenza B strains across, which is really reassuring to say for see for our vaccine.

This, I really like a lot because it really drives home that the waning that has been known for seasonal influenza vaccines for years is not a bigger concern for mRNA vaccines. In fact, actually, we see over the season that the separation of the curse becomes bigger with mRNA-1010 actually showing constant protection throughout the season, which is really reassuring to see where you still see an increase of cases later in the season with the licensed standard vaccine comparator, you see the curve flattening out for mRNA-1010 and then staying separated throughout the season. So that's really exciting for us to see.

A couple more breakdowns, which I think the drive home message is that we see consistency across all those different cross sections that we can make. When we look at the different age groups in this study, from 50 to 75 years and older, you see that we consistently got the relative in vaccine efficacy relative to the standards comparator.

If we go to the high-risk conditions, we again see the same picture. We see that frailty status, we see from the fit to the most frail, the consistent higher relative vaccine efficacy of mRNA-1010. We see with the higher BMI that higher relative vaccine efficacy. So that was really nice and reassuring to see. And then, as I mentioned, we had an exploratory outcome to look at the medically attended ILIs. And if you go from the top down, you effectively see different levels of severity. It goes from urgent care visits all the way to hospitalization. For the hospitalization visits, we didn't have as many cases. They are pretty rare events. But you see that for urgent care visits, outpatient visits, and the overall encounters, we consistently see the superior relative vaccine efficacy.

In terms of the summary, the rate cogency as I mentioned was higher for mRNA-1010. However, most of the solicited reactions were grade 1 and grade 2 in nature and transient. We saw an overall acceptable safety profile for mRNA-1010. We saw higher efficacy across all age groups, influenza strains, including participants at high risk of severe influenza compared to the standard dose vaccine comparator.

The efficacy was maintained throughout the entire season. And what I didn't show here, but I mentioned that subset of immunogenicity, we yet again saw the same, superior immunogenicity as well. And mRNA-1010 prevented more severe and medically attended influenza. And as Stephen alluded to earlier today, we are in the process of submitting filings and we are intending to submit to the US, EU, Canada, and Australia, by January 2026.

And with that, I'm handing over to Christy to talk about the combination vaccines.

Christine Shaw - *Moderna Inc - Vice President, Portfolio Head - Infectious Disease and Rare*

Hello, everyone. So Christine Shaw, I'm the Portfolio Head for Infectious Disease in rare. And today, I'm going to first share an update on our combination vaccine against flu and COVID. And this combination vaccine takes into the two components that you just heard, Darin and Raffael talk about our 1010 vaccine for flu and our mRNA-1283 vaccine for COVID-19.

So despite available vaccines, commercial vaccines for both COVID and flu, there remains a high unmet need and burden of hospitalizations for these diseases. And this visual on the left shows in the US in adults above 75 years, the amount of hospitalizations over the last two seasons for COVID in red and flu in blue.

And one of the reasons for this still significant burden is the low vaccine coverage rate, particularly for COVID-19. And you can see on the right that that coverage rate in the 75 plus population is around 40% in the last two years. As we know, the flu vaccine coverage rate is a bit higher at 75%. And as Steven shared earlier this morning, the individuals getting a flu vaccine, about 30% to 50% depending on the year do in this age group do get a COVID vaccine at the same time.

So we think that a combination vaccine against flu and COVID can do two things. One is it can help to increase the COVID vaccine coverage, because individuals coming in to get their flu shot can now get a combination shot in one arm and one injection that covers both diseases, both pathogens.

And it will help for the convenience of those already getting both vaccines, they can get it in one shot instead of two. So overall, this shouldn't reduce the burden of disease against these two different pathogens.

So our mRNA-1083 vaccine, as I said, is a combination of the 1010 flu and the 1283 COVID vaccine. And we've previously shared that the Phase 3 pivotal study for this vaccine was successful and met the primary endpoints. So I'm going to review that study briefly and also share some of the durability antibody responses in the study.

So it's a randomized, observer blind, active control study in which we assessed safety reactor and immunogenicity. The study is split into two age cohorts. The Cohort A is above 65 years, Cohort B is 50 to 64 years.

And the reason we did this to cohort is that we are able to compare the 1083 vaccine to co-administered license comparator flu and COVID vaccines. And in the 65 plus, we can do that compared to Fluzone HD, which is an enhanced flu product.

In the younger age cohort, the flu comparator is Fluarix, which is a standard dose vaccine. This is the standard of care for flu vaccines in the United States. In both cohorts, the COVID vaccine comparator was Spikevax and there's about 2000 participants in each of these cohorts.

So mRNA-1083 showed an acceptable reactogenicity profile in both of the cohorts. We have a majority of the reactions were grade 2, grade 1 and 2 in severity. There was a somewhat higher reactogenicity profile for mRNA-1083 relative to the code-administered license comparator vaccines, and the reactogenicity was a bit lower in the 65 and older cohort compared to the younger cohort.

So here are the immunogenicity data, and again, we assessed this independently in the two age cohorts. In each cohort, what we did is determined the ratio of the antibody response to mRNA-1083 compared to the antibody response to the license comparator vaccines.

So for flu, each of the four strains in the vaccine, we did this by Hemagglutination inhibition assay, or HAI assay, and those data are shown in blue. And for SARS-CoV-2, we measured neutralizing antibody, and those data are shown in red.

And you can see for all of the strains in the vaccine, the antibody response met the predefined success non-inferiority criteria, and that the lower bound of a confidence interval was above 0.667. But we actually saw a higher response to the vaccine, excuse me, for the flu antigens, H1 -- flu strains H1, H3, and B/Victoria. And these are the clinically relevant strains, as Rafael shared, B/Yamagata is no longer circulating and therefore not recommended to be part of seasonal vaccines going forward.

So in these cases, the response, even above Fluzone HD was higher, and that the lower bound was above 1. We saw similar results and just as importantly, against the COVID antibodies against COVID-19 or against SARS-CoV-2, sorry, in which the responses to mRNA-1083 are higher than the responses to Spikevax. This was true in both age cohorts.

So the new data sharing today is looking at the durability of that antibody response. So we took samples six months after vaccination and measured the antibody response in the same assays. And you can see in the top panel are the older adults and in the bottom panel are those below 65 and the mRNA-1083 groups are in red. And you can see that throughout the time course in the study, the response to mRNA-1083 is higher or equal to that of the comparative vaccine out to the six month time point.

So to conclude this, part of -- sorry, my losing my voice here. The mRNA-1083 showed an acceptable safety and reactogenicity profile and compared to the comparative vaccines. It didn't meet all the co-primary immunogenicity endpoints and elicited a higher immune response against SARS-CoV-2 and the flu strains, the relevant flu strains in both age groups in the study.

And because antibodies are an established surrogate of protection against both flu and COVID, and because both components of the vaccine have demonstrated efficacy in stand-alone pivotal efficacy studies, we think that the combination vaccine mRNA-1083 should also protect individuals from both COVID and flu.

So as noted earlier in the presentations today, the filing for this mRNA-1083 vaccine is under licensure review by EMA. We also recently submitted applications to Canada, and we are waiting further guidance from FDA before refiling there. Overall, we're very optimistic that this vaccine can help reduce the burden of disease against both flu and COVID in the coming years.

So switching gears to [1080] to RSV mRNA-1345. We are going to share a bit of an update on that vaccine as well. Let me just grab. Thank you, okay. All right, so RSV still causes significant burden of disease in the US, despite there being vaccines.

And in this past year, you can see here, there are millions of inpatient visits, outpatient visits due to RSV. There's hundreds of thousands of hospitalizations and tens of thousands of RSV-related deaths. And we know that vaccination is an effective strategy to reduce this disease burden.

Our mRESVIA mRNA-1345 vaccine was licensed, initially in adults 60 years and above. And at this point, we've achieved licensure in 40 countries across the world, shown on this slide here. Recently, we have achieved expanded indication, licensure in another age group in US and in Europe for individuals 18 to 59 years of age with underlying comorbidities.

Today, what I'm going to share on this program are the revaccination results of both safety and immunogenicity from two studies, one in which we gave a one-year revaccination, and the other which we gave a two-year revaccination.

And so first, the study with the one year revax. So this was a Phase 3 study, 302. And in this study, individuals who had received a mRESVIA vaccine at day one, received a revaccination about one year later with the same commercial dose level. We measured safety, reactogenicity, and non-inferiority of the immune response after the re-vaccination compared to the antibodies levels after the first day one dose.

So here is a visual of the participants in the study. This was a study in 50 years and above, and about 543 participants were enrolled in the study with a having about 60% of them above 60 years of age and a bit more than half of the individuals female.

So this re-vaccination was well tolerated, as you can see in the visual here, with local and systemic reactions, primarily grade 1 or 2, and median onset of one to two days, and a median duration of two days. And now looking at the antibody results from this study, at the 12 month post-initial dose time point, you can see there still are measurable antibodies that are above baseline, about 2-fold above the baseline, day one.

And when these individuals got a re-vaccination at that 12-month time point, the antibodies were restored up to the level seen after the primary injection, where we had demonstrated efficacy previously. So this study also met the predefined non-inferiority success criteria, both against RSV-A, which is shown here, as well as RSV-B, not shown on the slide.

And then moving to the second study in which we now assessed revaccination after a two-year period. And this study was actually part of our pivotal Phase 3 efficacy study. And we took a subset of the individuals and gave them a second injection two years after their first injection. They were randomized to receive either the same commercial dose of MRESVIA or a placebo injection.

And again, it was a safety immunogenicity study and the endpoints were similar to that I just described for the twelve-month booster study. This study was in 60 years and above, and about 1,000 of them received the mRESVIA vaccine about two years after their first dose, as I mentioned. The median age here is 68 years and about 50% female, and here there were about a third of the participants had an underlying comorbidity and a third of the participants were defined as obese.

So I'm sharing the reactogenicity data split across two slides, with this first slide being the local reactogenicity. And most of the events were grade 1, with median onset of two days and duration of 2, and overall showing that this re-vaccination at 24 months was well tolerated. And now the systemic adverse reactions showing a similar picture, where the reactions were mostly grade 1 and 2 with an onset of day 2 and a short duration, again, showing well tolerated revaccination.

So the immunogenicity after this two-year booster is on this visual here showing the RSV-A neutralizing antibody responses. And similar to what I showed you with a 12-month booster here, once you go out to 24 months, you can still see antibodies restored above the or maintained above the baseline after the first injection.

So you can see it's about 4,000 versus 2000, so about a two-fold elevation still, which is actually quite similar to the level we saw in the 12-month post-vaccination in the previous study. And again, after the re-vaccination at this 24-month time point, the antibody triggers were restored and reached a level similar to that after the primary injection. And in this study, we also achieved the pre-defined non-inferiority success criteria, both for RSV-A, the visual here, and for RSV-B, which is not shown.

So summarizing the RSV story shared today, revaccination, either at 12 or 24 months is well tolerated. And we are able to show that durability of the immune response does last up to at least two years. And if you give a re-vaccination at 12 or 24 months, it does restore the immune response and it does meet non-inferiority success criteria.

So we think because of these results, that revaccination at either of these time points would be expected to provide comparable vaccine efficacy to that after a primary dose. And therefore, revaccination has the potential to provide sustained protection against RSV, particularly in individuals with underlying comorbidities in which revaccination might be particularly beneficial.

So we continue to monitor a guidance from recommending bodies on RSV re vaccination approach and timing. Turning back to Jackie for Norovirus.

Jacqueline Miller - *Moderna Inc - Chief Medical Officer*

All right, well thank you, Christy and team. And I think you can see what a pleasure it is to work with this group of people every day. So now I'm going to talk about our newest seasonal vaccine, norovirus, and our progress there. And just as a reminder about why we think norovirus can be such a growth driver for us, so among enteric viruses, this is really the leading cause of diarrheal disease globally. And it results in a substantial healthcare burden. And I'll just say now that rotavirus is a vaccine preventable disease in children. This is a virus that actually can impact both older adults and children.

Unlike rotavirus, norovirus actually has its most severe disease in older adults and immunocompromised patients. So while highest incidence is in kids, greatest impact in terms of severity of disease is in older adults and immunocompromised patients. And that really defines why we've designed our clinical development program the way we have, which I'll talk about in a couple of slides.

The burden amongst older adults is also expected to rise along with societal aging and the increased need for institutionalized care. So this is one of those viruses, just like respiratory viruses that if you have a contained group of individuals -- it's a fecal oral virus, meaning it's passed through inappropriate hand hygiene. You can imagine that where care is being given, it can just rip through one of those institutions. So we think it's going to be important in those settings.

And what you see in the United States, about 20 million infections leading to about 900 deaths, but 100,000 hospitalizations where people will receive supportive care, so rehydration primarily, and then also support for maybe organs that have been impacted by reduced perfusion. That's $2 billion of healthcare costs annually and lost productivity. Same numbers for the global environment, about 685 million infections each year with 200,000 deaths, and about $60 billion lost in terms of healthcare costs and lost productivity.

So I mentioned that norovirus shares some attributes with other seasonal viruses. And really, it's the variability that's one of the key pieces. And I alluded to this a bit earlier, but just to say the reason why you will see us pursuing a multivalent vaccine is because there's actually quite a lot of distribution of geno groups. We've targeted the genotypes that are most prevalent year on year.

So we've really looked across the last couple of decades to design the first version of the vaccine. They're actually both trivalent and pentavalent versions. We're going forward with the trivalent first. If that's successful, the pentavalent in pediatrics where we actually see the greatest distribution of geno groups will be how we move forward next.

And an important piece about the mRNA technology and why we think this is an ideal technology for norovirus, as I mentioned, with the genetic diversity of these viruses, the ability to have a second option in terms of strategies for greater vaccine coverage, meaning, rather than continually adding different strains the way we've done with pneumococcal vaccines, which leads to increased immune interference, also can lead to challenges in terms of how many can you actually put in that syringe.

Every iteration of pneumococcal vaccine gets further away in development because it's harder to both develop and manufacture. With the mRNA technology, as we do surveillance, you can actually swap in and out strains as they become relevant or recede in relevance. And this is actually a discussion we've already started with the FDA, thinking about a diarrheal vaccine maybe differently than people have thought about it before.

So I'm going to share with you our Phase 1 clinical trial. We actually investigated both formulations, the trivalent, which is 1403; and pentavalent, 1405, for obvious reasons. But we observed them in the same clinical trials that we could pick that formulation we were going to take forward into Phase 3 in adults. It was a randomized observer blind placebo-controlled trial. And it actually had 664 healthy volunteers. Pretty big for a Phase 1 study, but that's because of all of the treatment groups, so multiple dose levels in two formulations.

We looked at both one and two doses. Why? In children who are primarily naive to the infection, we think we may need more than one dose to get to protection. But in adults, because all of us have experienced norovirus at some point, one dose is really going to be sufficient. And that's how we've gone forward into Phase 3. And those are the data I'll really be sharing. We've been following participants for 12 months after their last study injection, and that's really to look at the persistence of those antibodies to think about how long could this last. And I'll be sharing some of that with you today. And this was primarily or only a US study.

So before we get into the immunogenicity results, I think, sometimes, it's important to really understand what we're measuring when we do these immunological assays and maybe to also help you understand why we think we have an understanding of how this vaccine might work and what makes us comfortable to make that next stage of investment.

So the assay that we've been primarily looking at is a functional assay, meaning we're not only measuring how much antibody we're making, we're also observing how that antibody interacts with the pathogen or with the human body to understand maybe how it might work. In this case, the histo-blood group antigen-blocking assay -- and from now on, I'm going to say HBGA because it's a lot easier.

HBGA is an antigen that's really important for the virus entry into those epithelial cells in the gut. And what we're looking to do is blockade that virus entry. So this is really a binding antibody, and for the sake of time, I'm not going to go through the details of how the assay works. But just to emphasize, we're looking both at how much antibody we induce and also the quality of that antibody.

So we looked in two cohorts, both older adults and younger adults. So on this slide, you see the older adults. And as I mentioned, I think the target for this population is obvious. It's really because they experience the most severe disease. As we age, we're more susceptible to this kind of disease. And as people age, they're more likely to be in settings that really favor outbreaks of this disease.

So what you see here are the three genotypes that are included in our vaccine. And you see the results from day 1 and day 29. Remember, I told you I'm going to share with you the single-dose data because that's really how we envision this going forward, just like getting your single flu vaccine every year; or in the case of norovirus, perhaps every other year, every third year; remains to be seen with RSV.

What we see is some seropositivity, and it actually really varies across the different genotypes, as you might see at the day 1 level. And why? Interestingly, norovirus, some of these genotypes actually tend to evolve much more quickly than other genotypes where they tend to be more stable. And so where you see lower pre-vaccination titers, that's in the geno group G24 where we see the most variability. So understanding even whether we ultimately may be able to swap out G24 strains might be helpful in the future.

But what we see with all three of our genotypes, regardless of the pre-vaccination titers, is a really robust increase in antibodies and really going from 10 to the 2, to really 10 to the 3, close to 10 to the four. So we're really encouraged by these results, again in this functional assay looking at how the antibodies are able to blockade that key cell surface antigen for viral entry.

And now here you see the data in younger adults, and it's really a similar story. Why younger adults? Well, younger adults, first of all, may be in occupations where they're really at high risk. And so just like this virus can rip through assisted living facilities, it definitely rips through pediatric and adult hospitals every year. And if you are a healthcare provider who's being exposed to that, there's pretty high force of infection.

There are other populations that may choose to be vaccinated as well, like for example, parents of young children, if you've ever taken care of your child and then experienced the infection after your child. I used to be a mom whose kid liked to climb in my lap and throw up, never in the toilet. This is a virus that I would sign up to be vaccinated against, I'll put it that way.

So safety data, again, as we show in all of our slides, dark blue are Grade 1, lighter blue are Grade 2, and the orange are Grade 3. We see our typical pattern in terms of the local reactions. In the different dose levels, we see in younger adults increasing rates with increasing doses. What you'll see is unlike some of our other vaccines. That band of orange is actually really small.

So we're very encouraged actually by the reactogenicity profile. This is something we see. There's generally an increase with increasing doses regardless of the vaccine antigen that's part of the platform, but the different antigens cause different levels of reactogenicity. Older adults, less reactogenic than younger adults. And that's something we've also typically seen.

So as we talk about now, we've moved to Phase 3, and I mentioned to you the reason why we're really going forward with trivalent in adults, but with a longer view towards if this works, moving to pentavalent and starting in the pediatric population. So this is one of our large-scale trials, again, placebo controlled and enrolled about 17,500 per arm.

As Jamey mentioned earlier, we did do an initial northern and southern hemisphere season. We're accruing some cases. The epidemiology was not in our favor, unfortunately, this year. So we're going to need another season to accrue additional vaccine-matched cases, leading to an interim analysis that we're anticipating later in 2026.

So in summary, our single dose was really well tolerated and showed an acceptable safety profile. The functional antibodies really showed robust titer increases against the vaccine-matched strains, and the single similar mRNA-induced titers were observed in both younger and the older adult populations, which is why our Phase 3 is actually evaluating the vaccine in those 18 and over.

We're advancing now into the third cohort and in fact have enrolled our first subjects in the US. And the Phase 3 readout is really going to be subject to those case accruals. But as I mentioned, we are anticipating later in 2026 at least an interim analysis.

Okay, and with that, I'm actually going to announce a pivot. We pivot a lot at Moderna. We're pivoting to have our break a bit early. So unfortunately for you, you're going to hear about latent vaccines after, and then I will introduce my colleagues who will lead into the oncology portfolio. So actually, I should say unfortunately for me, because I have to talk to everyone after the break and the insulin effects that's in, but we'll take how long, Lavina? Ten minutes. Ten-minute break, and I'll see you back then onstage. Thank you so much for your attention.

(break)

Hi, everyone. So thrilled that there are so many great conversations going on, which hopefully we can continue into the lunch and beyond, but if I can ask, I know there are actually a few people still outside. Maybe in the next 60 seconds or so we'll get restarted just to get us back on track.

Right. So I hope you enjoyed your break. I will now take you through a tour of our vaccines that are earlier in development before handing it over to the oncology team. So what you see here are the latent and bacterial vaccines. We're going to talk for a minute about the CMV vaccine followed by our two EBV candidates, the prophylactic candidate and the therapeutic candidate, and then I'll end with a quick talk on Lyme vaccines. And then I'm going to hand it over then to my colleagues who are really leading the charge in oncology.

All right, so CMV and transplant was obviously a huge disappointment to us that we were unable to demonstrate prevention of infection in seronegative subjects. This was obviously our first step to really getting to the indication of prevention and congenital infection. I will say it was always a very high-risk program in the sense that we were studying seronegative patients and hoping to prevent evidence of any infection. And as you may remember from our COVID and RSV Phase 3 trials, we were able to show some prevention of infection, but really at much lower rates than symptomatic infection or severe disease. And that's pretty typical, not just in the vaccine world, but in general. You often see evidence of more severe disease being the first place that you have impact in infectious disease.

So why do we believe in CMV transplant? One, it's a very different population. While there can be CMV-negative transplant recipients, the reality is as you get older you are more likely to have a disease that leads to a failure of some end organ or cancer, and that means transplants are actually weighted more at the older end of the age spectrum. So these people tend to be seropositive and the pathophysiology of their disease, either because they're receiving a solid organ that has CMV-infected cells or because they themselves are already seropositive once they receive their immunosuppression, that really reduces the immune control of latency of that virus and the virus expands, and it can actually cause in immunocompromised people quite symptomatic infection.

So the risks that are associated with CMV disease in solid organ transplants and those with hematopoietic stem cell transplants or HCT, graft rejection. So these CMV can actually cause a degree of inflammation and immune destruction in organs. Since these organs are so very precious, we don't have enough for all the patients that need transplant, that's a huge issue in transplant medicine. Second is it can cause other kinds of end-organ CMV disease. One of the most common in this population is CMV enteritis, causing a lot of diarrhea potentially leading to dehydration. But you can also see rarer forms like CMV retinitis, which is a threat to someone's vision.

So there are currently no approved vaccines. There are antivirals, and they're actually used pretty universally. Different centers use them differently, and we'll talk about that in a minute. But the issue with them is, one, they have a high cost and their own side effects.

They're typically not used forever in people with transplants. And what we often see is when you pull off the antiviral suppression, you do see a rebound in CMV viremia, so the measurement of CMV circulating in the blood, particularly when the medication is first withdrawn. That's not a risk that actually decreases. There's that rebound no matter how long you keep that prophylaxis on board if you then pull it off.

There are 47,000 organ transplants in the US each year and 23,000 bone marrow transplants. So that really leads to about 70,000 transplants in the US each year, so a smaller but still sizable market. Sterilizing immunity, as I mentioned, is really challenging in vaccine development, and that's not what we're aiming for in the transplant population. As I mentioned, these are typically seropositive individuals. Once you're seropositive, you remain seropositive for life. What we are trying to do is prevent that virus from reactivating in the immunosuppressed milieu.

And the way that actually transplant physicians measure whether or not, once we withdraw or even when you're on CMV prophylaxis whether that virus is reactivating is by looking for CMV DNAemia. We actually looked at CMV DNAemia in the Phase 3 trial in healthy women, and we actually did see that initially after infection, we were able to reduce that level of DNAemia. So that actually gives us hope that this may be a place where we can see some effect. And I'm going to show you what T-cell responses look like in transplant patients in just a moment.

So we think it has the possibility to prevent viral replication and reactivation. And so our hope is that we can look in a smaller bone marrow transplant population and then, if that looks positive, so limiting the investment (inaudible) if that looks positive, talk about how we might expand use.

So in summary, CMV is a disease that's associated with substantial morbidity and mortality. It's one of the key issues that transplant physicians across the spectrum have to manage. Letermovir is actually a suppressant that is approved and is currently being used as standard CMV prophylaxis. So it's really considered best in class, and it's a way that you'll see in the next slide we're considering, as we think about how this program could fit in with existing treatment.

Despite its efficacy, it's also been associated with decreased CMV-specific T-cell reconstitution in bone marrow transplant patients. So as I mentioned, these drugs, like all drugs and vaccines, have their own side effects associated to them. And it also can lead to late-onset CMV infections. Again, once you decide to withdraw prophylaxis, we often see a rebound reactivation. So that's why we think the development of a safe and effective vaccine that you might be able to boost year on year might be a way to get on top of this remaining unmet medical need.

So we're studying CMV-positive adults who are over 18 years of age, who received an allogeneic, meaning it's coming from themselves stem cell transplant. We're looking at a slightly different dose level and slightly different schedule than we were in the primary disease. And so this is an accelerated vaccination schedule where we're giving three doses, and that's happening after the initial reconstitution of the immune system. So people are on their letermovir prophylaxis up to day 100. We then start vaccination as they are reconstituting that immune system, and then six months into the trial, we're going to give a booster dose to see what it would look like if you needed to boost this over time. There's an mRNA-1647 group and a placebo group and a randomized 1 to 1.

In terms of the solicited adverse reactions, here you see grade 1 in gray, grade 2 in blue, and grade 3 in orange. As we might expect actually in a transplant immunosuppressed population, we see lower severity for most of the events, and that's really because probably their bodies are not allowing them to have the same reaction to the vaccine that we see in healthy individuals. However, I was actually pleased to see that we do see some reactogenicity, meaning we're causing their immune system to do something in this case.

And now I want to show you actually what the T cell responses look like and why the T cells are incredibly important in suppressing CMV and particularly CD8 T cells are important in controlling that infection and keeping it in latent mode. So what I'm showing you here are the three antigens. GB is the antigen that was on its own, GH and GL and UL. They are part of the combination that makes up pentamer. And we're looking at T cell responses to each of those individual antigens.

We also have the CD4 at the top in the different shades of pink, CD8 in the different shades of blue on the bottom. And also what we see are the placebo versus the mRNA, and this is really looking after multiple doses in the schedule. So as I explained to you, we're studying this in stem cell transplant patients. These are people who need to have their bone marrow and their cancer, importantly, completely ablated before we give them a transplant, and that transplant is actually like a seed that grows into a reconstituted immune system.

So we're talking about people who are immunosuppressed not only because they're on immunosuppressing drugs to prevent graft versus host disease, but because they're in the process of reconstituting that immune system. In the different shades, what you see are the level of polyfunctionality. Polyfunctionality really refers to the different kinds of cytokines and different kinds of activation and cell activity functions that you can see. So darker means better and more functionality.

And so what you see at the top are the CD4 responses. I mean, it's absolutely clear that there's many more in the 1,647 group than we're seeing in that placebo group. And we're seeing about a third, a third, a third in terms of polyfunctionality. So even at this early stage, we're seeing really reconstitution of a diverse CD4 response.

And CD8 similarly, we're seeing polyfunctionality developing. We always see lower CD8s, the fact that we detect them, and at such a different level than in the placebo group is really something that we feel strongly positive about, particularly in the GB space and in the GLUL. And what you're seeing in the placebo group there, as you see, it's kind of even throughout. So people, even as they're reconstituting, have some kind of baseline level. And this probably is because, we're needing some kind of activation, so they're getting a natural boost because they probably are having to control their CMV infection even while on letermovir.

So in summary, the solicited local and systemic adverse reactions were mostly grade 1 and 2. We didn't see any grade 4 adverse reactions reported. And as I said, in a transplant population, I was actually encouraged to see that we can get them to stimulate some of those reactions. For 1647, the most common were injection site pain and headache, fever, and fatigue, similar to the rest of the platform.

Our interim analysis in this population demonstrated that we can induce antigen-specific polyfunctional CD4 and CD8 T cell responses. And as I mentioned, we think that's encouraging for controlling that DNAemia. Of note, our robust cell-mediated immune responses were observed as early as 77 days after transplant. So this is really speaking to the ability of this platform to induce the right kind of immune responses at a moment when someone really is at their worst in terms of immunogenicity, so we're hopeful about that.

And our next step is really to plan our Phase 2 data readout. So on the heels of our recent CMV findings, we'll be meeting with the MGH team to really talk about how we build in an interim analysis and look at what's happening in this study in the future.

Okay. So now I'm going to move on to Epstein-Barr virus or EBV and our prophylactic vaccine, 1189, and our therapeutic treatment, 1195. So these two vaccines are really meant to address very different populations, but all of us, just like with CMV, tend to acquire an EBV infection over time. So as you get older, you're more likely to be exposed to this infection and become zero positive.

Unlike CMV, there is a very obvious symptom associated with this -- the severe form of this infection. It's infectious mononucleosis. What you see on the left here are data that we actually generated within our epidemiology team looking at the increase of zero prevalence with age, depending on your location. And so what we know is that in high-income countries, you're a little bit slower to acquire the infection than in medium-income countries.

But what we were kind of surprised to find in the middle is that by the time you're getting to middle school, about 9 to 11, 12 to 14 years of age, you're looking now at more than half of individuals are actually zero positive. And so this really indicated to us, we need to think about this as a vaccine that we would include with some of the other middle school vaccines like meningococcal vaccine and pertussis.

And then finally, I think, really pertinent to the 1195 therapeutic program, EBV accounts for over 90% of cases of infectious mononucleosis. So this is an importantly severe infection we can monitor and manage, and the vast majority are going to be due to EBV. The annual incidence of infectious mononucleosis in the general population is at least 45 per 100,000. So there's a way that we can measure this in Phase 3 with the peak incidence of about 15 to 19 years of age. So again, this is a program where we're really looking to establish ourselves and begin middle school, high school, vaccination programs.

The reason why I say this is important for 1195 comes on the next slide, which is, if you look at the conditions that EBV can be associated with long-term in terms of sequelae, multiple sclerosis tops the list. And it's really when you get to, having infectious mononucleosis, if you had the severe form of the infection, your risk is increased even above getting the infection itself. So this is the interplay between the two programs, and I will say our target indication initially is multiple sclerosis because of what you see in the top bar.

But we know that Epstein bar, which it's latent infection, tends to hide in these cells. It's actually associated with a large number of cancers, particularly B cell lymphomas. And so being able, just like in the CMV program, to prevent that vaccine once infection is established and to stay in its latent phase, prevent the lytic phase where it reactivates and begins to spread, we think it's going to be incredibly important.

Okay, so let's talk for a moment about that ideological link that I just referred to. Nearly a million people in the US have multiple sclerosis, and this is a progressive degenerative neurologic disease. So people really are on all ranges of the spectrum. I think an important piece is when you're born, you have all the neurons you're ever going to have. So as you grow, you continue to myelinate your nerves, they continue to spread. You're born

with the cells you are going to have. And then once those cells die, you don't get to replace them. Every neuron's precious. And so really being able to have an impact early in disease is incredibly important and that will become important as we talk about the Phase 2 study we're currently enrolling.

But there was a landmark study that demonstrated that there was a 32-fold increase of developing MS once you seroconvert to EBV. This is one of the strongest links ever established between a virus and the potential sequelae happening years later. And it was also previously established. We've talked about this in the past, that infectious mononucleosis is a risk factor. And you can see on the bottom that the zero converted have that 32% increased risk.

And then what you see is that, on the right, the risk of EBV plus a history of infectious mononucleosis is really increasing up to 2.3-fold over that history of EBV. So that's really an important population and why we think preventing infectious mononucleosis can be important in the prevention also of sequelae.

All right. So EBV, as we mentioned, associated with several serious medical conditions that we think can be addressed through mRNA therapies. We talked about IM and multiple sclerosis. I mentioned to you that we believe B-cell type lymphomas, of which post-transplant lymphoproliferative disease is one of them, is another place. I think it's important to also emphasize that in addition to prophylactic oncology, autoimmune diseases have a growing body of evidence, and there was a recent paper in Science looking at the link of EBV and SLE or systemic lupus erythematosus. So that is a potential place in the future.

And there actually is a chronic infection with EBV that is quite debilitating for patients. So these are all places where if we can see impact with our vaccine and therapy, we can look forward to further data generation. So I mentioned to you, we have these two programs, and I wanted to go through with you a little bit the difference between them.

1189 is primarily looking at lytic antigens. Lytic antigens are the ones that are responsible for rapid proliferation and cell-to-cell transfer. 1195, or the therapeutic version, also includes those lytic antigens plus two latent antigens. And that's really important because, as I mentioned to you, our goal in these therapies is to not allow that latent virus to get to the lytic phase. The virus actually, in its latency, expresses very different antigens than it expresses in the lytic phase. So only vaccinating against lytic antigens is unlikely to have the impact of keeping that virus suppressed. So that's really why we think we need to look into distinct spaces.

So I'm going to talk about the prophylactic vaccine first. So this was another larger phase trial design. We started in adults 18 to 30 years of age. We then moved down to adolescents 12 to 17 years of age, and that was really based on the epidemiology work we did where we realized we need a younger age group if we are really going to target the majority of infection.

It actually incorporated multiple primary objectives, so looking at safety and reactogenicity, of course, but also looking at binding antibodies, so how much antibody we produce. And then B-cell neutralization antibodies. Remember, I told you that B cells are the bad actors in this infection, and so understanding if we can neutralize EBV-infected B cells is an important endpoint as well.

We are also going to be looking at epithelial cell neutralization and the impact on viral shedding as well as seroconversion. And if we have cases of mononucleosis, we are looking toward those as well. There is also a Phase 2 trial that's ongoing. So in the Phase 1 trial, there was a request from FDA to pause enrollment at one moment and look at safety data.

So we have single-dose and two-dose data in 12- to 17-year-olds, and I think that's going to be helpful as we try to decide how many doses of this vaccine do you need. But again, as data continued to accumulate from the epidemiology study, we actually started again looking at an even younger age group, thinking we want to capture as many infections as possible. At this moment, too, we were able to focus our dose ranging at lower doses, and that's really -- because we are not seeing many differences in immunogenicity, and this is a way, as I mentioned earlier, for us to manage reactogenicity.

So I'm not going to go through the data in the interest of time, so we can move to oncology, and you've seen it before, but the vaccine was generally well tolerated in adults and adolescents. Participants showed an increase in functional binding antibodies as well as they showed baseline EBV

seropositive thresholds, meaning we can induce antibody titers greater in those seronegative by vaccination than people experience through natural infection at baseline.

And then we also reduced measurable viral DNA and the frequency of shedding in EBV seropositive subjects, meaning we can suppress reactivation and shedding in that case in the seropositives. So the data from Part A and B, meaning those 12 to 17-year-olds, are expected later in 2026, and we will have those Phase 2 data in 2026 as well hopefully helping us target how we take this program forward.

Moving quickly to 1195, as I mentioned, our primary indication is going to be multiple sclerosis. That is a disease really characterized by immune dysregulation of EBV-infected B cells, presumably by EBV. And this may be one of the key underlying mechanisms not only of disease initiation but also of progression for EBV control over time. The vaccine mechanism of action is hypothesized to be restoring some robust immune control.

So talking about the Part 1 trial design, this again was in EBV seropositive subjects only. And again, we're targeting people that are already infected. So once you're infected, we can't make you uninfected. But hopefully, what we can do is prevent some of the long-term effects of being infected. We had two formulations and multiple dose levels. Once again, we're really looking at humoral immunogenicity. T cells, also being important here, as I mentioned before, because latency really requires the help of T cells to keep those B cells in check.

Looking at the reactogenicity, here again, you see the dark blue, medium blue, and orange schema. We actually saw relatively comparable reactogenicity across the different dose levels so really are looking to select the optimization between as minimal a dose as possible while seeing the best possible immune responses. Here, you see the binding antibodies. So we have generated binding antibodies to the glycoproteins that are the lytic antigens. Remember, I told you that 1189 and 1195 overlap in this space.

And what we see is that In all of the dose levels even out to day 317. So they finish their dosing schedules, the three-dose schedule, at day 180, so seeing six-month persistence. They're staying above that dotted line, which is the natural infection level. And now, I mentioned to you that neutralization is important, here particularly in B cells, and again, staying above the limit of quantitation of the assay, that's in the gray line, that's true for the B-cell neutralizing antibodies. It's also true for epithelial cells, which can also harbor a latent EBV infection.

And then finally, I wanted to share with you the shedding data. So what you see here at the top, I think, in particular is the placebo group. So these are all EBV-positive subjects. The placebo group is shedding EBV at a certain level over time, and both 1189 and 1195 are reducing that viral shedding over time. So again, hopeful that we can have an impact in that lytic phase of the virus.

And then finally, I mentioned to you that particularly for 1195, we think that these T-cell responses are going to be important. At the top EBNA3A and LMP2B, these are those latent antigens I was referring to where we're going to need to exercise some immune control over those antigens in the latent phase of the virus if we want to prevent that proliferation. So seeing in the pale colors, the median responses being so much higher than median responses which are represented by the dark bar in those that receive the placebo group. Super encouraging to us. And just to say we also see CD8 responses to the glycoprotein GH as well.

And then these are the CD4 responses to the EBNA3A and the GH antigen. And again, including 1189 actually -- no, excuse me, the four dose levels on this slide, we see CD4 responses as well, both to the latent antigen, EBNA3A and the lytic antigen, GH.

So we're so excited that earlier this year, we started enrolling actually now in multiple sclerosis patients. And again, we're repeating the dose-ranging study for two reasons. One, the safety here is going to be important. So these are subjects whose primary disease is neurologic and, as I mentioned, every neuron is precious. So we have an expert DSMB really looking at the progression of those patients over time clinically.

We're complementing that with looking at MRIs over time. So one of the key clinical endpoints in EBV is a loss of myelination in the white matter. This is a way that we can follow very early patients over time. This is known to be a clinical endpoint that actually precedes progression of symptoms. And so we'll see between placebo and those receiving one of three doses if we can reduce the number of lesions over time.

I think I'm going to go to the summary for the sake of time. The interim analysis data demonstrate 1195 is generally well tolerated. EBV seropositive participants show an increase in B-cell neutralizing antibodies. The vaccine is able to boost both CD4 and CD8 cells, and humoral and cell-mediated

immunity persisted out to day 317, so that's six months after the last injection. We reduced measurable viral shedding of saliva with actually both 1195 and 1189.

And then looking this year, we have Phase 1 Part B data coming in younger subjects later this year. We also have the Phase 2 multiple sclerosis study that's coming soon. And with that, we're going to move to Lyme disease. So this is our bacterial vaccine program.

You all have heard of Lyme disease, I know, especially up here in the northeast. Lyme disease is the most common vector-borne disease, meaning an insect is carrying it in the northern hemisphere. Lyme follows a bimodal age distribution. So it typically affects children under 15. They're out in the grass playing in the summer and older adults.

And interestingly, this is also a seasonal infection, but the season is reversed from those viruses we were talking about. It really tends to proliferate in the summer months when everybody is outside enjoying being in the great outdoors.

In the major geographies, there are about 475,000 cases in the US each year and about 200,000 in the EU. The symptomatic infection is actually one of the harder ones I found in pediatric practice to diagnose. It can masquerade as a lot of different things, but subjects typically develop a rash. That rash can take a lot of forms, but the target rash is the classic one. They have some nonspecific symptoms like fever, fatigue, headache, and joint pain. And if it's untreated, it can lead to certain neurologic and particularly cardiac complications that can lead to cardiac arrhythmia. So that's why we're very interested in preventing this infection, and there's currently no human vaccine on the market.

Why are we convinced that this could work through mRNA? Well, the program has actually already been derisked from an antigen perspective, so there was a licensed vaccine, LYMErix, that targeted the same antigen. That vaccine was later withdrawn from the market. It's actually the same antigen that we're targeting. It is a known mechanism of action.

And it actually works a little bit differently than the viral vaccines we have been talking about. We are looking to induce primarily antibodies, and the protein that we target has the very creative name of outer surface protein A. The anti-OspA antibody that we produce, it's not actually protecting the individual person, it's protecting by transferring that antibody to the tick when the tick feeds. So it gets an antibody dose as it gets also your blood. And those antibodies can kill the Borrelia organism, the responsible bacteria for Lyme disease in the midgut. And that prevents transmission from human host. So it's kind of a cool mechanism. And like I said, it's been established in a previously licensed vaccine.

We have two candidates cleverly named after the dates or the years when there were various discoveries made about Lyme disease. The first recognizing Lyme disease in 1975 and then 1982 recognizing the pathogen that's causing it. So 1982 was actually a monovalent, looking at serotype 1 which is basically the only serotype that is prevalent in the US. Europe is a bit more homogeneous in serotypes 1 through -- heterogeneous, excuse me, serotypes 1 through 7 actually proliferate there. And so multivalent vaccine 1975 started.

So we had a Phase 1 study here looking at both the multivalent and the monovalent, so in red and in blue. It was a three-dose study given at 0, month 2, and month 6. And we're looking again at immune responses and safety. And so here, you see the local and systemic solicited adverse events. In this case, I told you we see some differences in antigens. We saw a few more grade 3s, particularly at the higher doses, and this is definitely a case where increased doses led to increased severity. There were no grade 4s that were reported. And most of the reactions are still grade 1 to 2 in severity.

In terms of antibody though, the vaccine really induced robust anti-OspA antibody responses. So you see here on the bottom all of the time points at which we measured. So people are negative at day 1. At day 29, they start to have some immune response, and it's really at that second dose that we start to see some increase day 57 to day 85. And then actually, there's pretty good maintenance of vaccine persistence which we're kind of excited to see with a further boost though that happens about at time 6 months.

So we are seeing the robust antibody titers not only to serotype 1, which you see on the slide, also to serotypes 2 through 7. And they did elicit dose-dependent responses. So there's a bit of a decision to make here as we look at balancing reactogenicity with immunogenicity. Both of the vaccines were generally well tolerated. They had an acceptable safety profile, and they elicited robust dose-dependent anti-OspA responses.

We've actually decided to go to Phase 2 in this program, and we're going to be evaluating not only lower dose levels because we think that even the lower dose levels were really inducing robust responses, but we're also going to be looking. We're a platform company, constantly improving. We're going to look at applying some of those improvements that we've made in other programs to see if we can also improve that reactogenicity event.

And with that, I'm now going to hand over to my colleague, Kyle Holen, who will talk to you about the oncology portfolio.

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

Thank you, Doctor Miller. And thank you all for being here in Cambridge and joining us here at our headquarters building and everyone online. Thank you for taking time out of your day to talk -- to hear about our pipeline updates.

So we're going to have an overview of our oncology portfolio next. But I thought what we do before we talk about our oncology portfolio is just have a reminder of why this work is so important, but not from my words, from someone who's lived this experience. So maybe what we'll do then is quickly move on to a video. Can you show the video, please?

Keith Perrry - - *Lung cancer survivor*

(video starts)

Before my diagnosis, everything seemed to be going pretty well. I was active. I, would go play baseball on the weekends with my friends, and my wife is a big runner, so we would go on a lot of trail runs together. That's the lifestyle that we had as a family when I was diagnosed at that time.

It was a devastating diagnosis. Just about every negative thought you can imagine that went through my life, which is, are you kidding me? I mean, where did this come from? How did this happen? Everything about your life becomes inconsequential. The only thing you can think about, the only thing you can focus on is the fact that this incredibly random, strange thing has happened to you.

Because the treatment options that were available weren't great, the recommendation that I got was surgical removal and chemotherapy. Chemotherapy is a rough road for anyone who ever has to do that. I had the classic issues, which not being able to eat, and suddenly, you turn around and you go, I've lost 20 pounds. And I'm a relatively thin person to begin with, losing 20 pounds is a lot for someone like me.

I realized how much chemotherapy and removing my entire left lung had affected me. I had to stop walking up a stairwell, because I couldn't do it. I would get halfway and I would be done. It raised some really serious questions in my mind about what I was going to be physically able to do. It's really hard on the people around you. I became very tunnel vision about myself and just trying to get better, and unfortunately, it took me away from my family in a way that I wouldn't wish on anyone.

I think future treatments, ideally, are going to be less invasive, less intrusive. Right now, with our treatments, especially with chemotherapy, whether it's the fatigue factor or all of the side effects that go along with that, the ability to reduce that so that you can carry on with more of your regular life so that you can be there for your family and hopefully, you can work at the same time. And so the ability to be able to continue to function in a meaningful way, while in treatment, that would just be huge.

(video ends)

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

So I'm a medical oncologist by training. I spent 10 years taking care of patients with cancer. I can tell you that his experience is not atypical. Nausea, vomiting, severe fatigue, hair loss, diarrhea, infections, hospitalizations. These are all side effects of some of the most brutal therapies that we give people with disease.

And in fact, one of my patients came in and he, unfortunately, was not able to walk on his follow-up visit. He was on sorafenib, which causes very severe hand-foot syndrome. And I said to him, why don't you call me? Why don't you tell me this was happening so I could stop your therapy so you could have walked into the clinic? And he said, Doc, I want to survive.

We have to come up with better therapies for people with cancer. Therapies that honestly can provide the same efficacy, but not ask for the sacrifice on people's lives that they're currently going through with other therapy. And I think we're on to something with our current platform.

So this is a snapshot of 4359 and 4157 or intismeran, of the safety readout from both of these programs. And I think a lot of us appropriately focus on efficacy of these products. But what I'd like to just do is take a minute and show you the safety of these products.

So so far, across our entire portfolio of cancer antigen therapies and intismeran, we have not reached a maximum tolerated dose. The incidence of grade 3 side effects is vanishingly small. I can count on one hand how many times we've seen, from monotherapy treatment, grade 3 side effects from these therapies.

And so I believe that this opens up a whole new window of opportunity for this type of treatment that hasn't been available for other treatments in the field, areas where we can treat patients earlier and pre-cancerous patients, areas where we can combine with other therapies that already have a fairly toxic profile, where other treatments couldn't be added on.

And this leads us to a whole variety of different settings where we can administer these therapies. So you can see here with intismeran and other cancer antigen therapies, we've been able to explore adjuvant settings. We've been able to explore neoadjuvant settings. And for our cancer antigen therapy, we've even looked at early stage and pre-cancerous settings for these types of therapies.

With our T cell engager programs, we're looking at refractory metastatic settings, and with our cell therapy enhancing and in vivo cell therapy, we're also looking at a later stage disease. So this allows us to create a portfolio that can have an effect across all different stages of cancer in multiple different types of cancer.

This is a snapshot of our current oncology portfolio. What I'd like to emphasize is, yes, I'm excited about the number of programs that we have in clinic. But what's more important than the quantity is the quality. We firmly believe that every single one of these treatments can have a dramatic impact on patients' lives.

And as we'll discuss with you today, we'll start out with intismeran, and Dr. Brown will come and talk to you about the latest developments with intismeran. I will then come back and talk to you about our next, most advanced therapy, 4359, which we're all very excited about. And then last but not least, we'll have our fearless leader for our research efforts, Dr. Loughlin, come and talk to us about all the really exciting and amazing products that are coming into clinic, either are in clinic today or will be coming into clinic very soon thereafter.

So with that, I'll hand things over to Dr. Brown, and she'll talk to you about INT.

Michelle Brown - *Moderna Inc - Vice President, Portfolio Head - Oncology*

Hi, everyone. It is nice to be speaking to you again about intismeran, and I'm not really sure how I'm supposed to follow Kyle's performance and then Keith's video, so hopefully what I show today is our resounding belief of why we believe that intismeran can make that type of impact for patients, and a litany of patients at that.

So as Kyle alluded to, we are leveraging the power of the mRNA technology and the platform to develop a precision immunotherapy program overall. And we're anchoring this on four different segments with distinct modalities and distinct potential to impact patients across a wide continuum of cancer care. And the anchor and the lead of our programs is intismeran autogene, which, as you saw on the slide, has a litany of clinical studies. So that is what we'll double down on today.

And if you're not resonating with intismeran, this one is the one that we call mRNA-4157 and V940, INT, it's had a lot of different names and roles, but at its true form, it is a mRNA, lipid-encapsulated, individualized, neoantigen therapy. So it is basically taking and starting with the patient and sequencing their tumor to identify the sort of most immune genetics-specific tumor targets to train the immune system. It is one medicine for one patient, and it is the lead in personalized cancer therapy.

The way this works is, again, what we're doing is taking a concatemerized mRNA, lipid encapsulating them, delivering that concatemer into a patient through an IM administration. Once in the body, the mRNA enters into an antigen-presenting cell. We use host translational machinery to produce those neoantigens. Those neoantigens, which are basically cancer-specific mutations, are presented on the cell surface to stimulate a repertoire of T cells, both CD4s and CD8s that then become activated, but also trained to go out and seek other cancer cells or cancer cells and destroy them. And we think that this mechanism is synergistic with checkpoint inhibitors who just tend to take the brakes off the immune system. So we're essentially targeting cancer cells, activating the T cells to go kill them, and then hyperactivating them to keep them killing these cancer cells.

So that mechanism was officially tested in our Phase 2 randomized study in high-risk adjuvant melanoma patients. This data was presented last year at ASCO from our median three-year follow-up. And essentially what we did is we took intismeran in combination with pembrolizumab versus pembrolizumab standard of care in these high-risk melanoma patients who had their tumors completely resected. And we followed them to see if the combination could improve recurrence events, so basically, patients' tumors from coming back after they had their tumors removed.

One thing I want to point out is that this was a November 3, '23 data cut with that median of three years. We know in cancer that five years is usually the big landmark for clinical studies as a whole for durability. We are now in '25, so we add -- we're looking upon our five-year data cut emergently.

Now, the one piece in here is that this data cut-off was on November 3 with the approximately three years. Because five years is such a landmark, we are going to make sure we pass that landmark. And so the data cut here might be a little bit later than this November 3, but we are definitely tracking towards having that, and we're very excited to see the durability, because we are very excited to see the three-year data.

So this is a refresh from that three-year cut, and basically what you saw here is the primary endpoint, which was recurrence-free survival. The green line on top is essentially the combination arm. The yellow line is what happened with pembrolizumab standard of care. And what you're looking at is recurrence events or death. And so from just a global three-year mark, we see a hazard ratio of 0.51, which means that we reduce the risk of recurrence or death globally for these patients by about 49%.

And if we sort of anchor on that 2.5-year landmark, that means that three out of four high-risk adjuvant melanoma patients were disease-free at the time of this cut. And that was 20% higher than what they would have received if they received standard of care pembro. And it's important to note that that delta of almost 20% is essentially what pembro showed against placebo, against nothing. So no other study has been able to showcase this type of effect above pembro standard of care in this type of setting, which was very, very encouraging for us for this type of neoantigen therapy and the impact we could have on patients.

And not only was this seen with recurrence-free survival, but this was also seen with the key secondary endpoint, which is distant metastasis-free survival. And on this one, we see a 0.38 hazard ratio. So in oncology studies, 0.38 is transformative. This is a huge treatment effect. You don't tend to see this, and it translates into almost two-thirds of patients not having distant disease.

And distant disease is important, because what that means is we're preventing patients from having significant surgeries, additional systemic therapies, or death. Their risk is much higher when they have a distant event.

And what you see here, again, at about 2.5 years, is that almost 90% of patients on the study did not have this type of event. And that's compared to 68% that would have had it with just standard of care. So we're really maintaining that spread of 20%, even in this profound endpoint.

And this is actually on point with the mechanism of action that I just showed you, because we believe that intismeran is supposed to train and activate the immune system to go out and clean up all these micro metastases and create long-term disease control. And so having this profound delta on DMFS is actually what we would have anticipated with the mechanism.

And it's not just about the preventing these recurrence events, it's also about preventing death, right? As we heard from Keith's story, when a patient is diagnosed with cancer, it is about survival. And so everyone really cares about survival. And while it's very early, we do not tend to see overall survival in these adjuvant studies, especially at three years. We did see an initial trend of protection for overall survival. Now, the hazard ratio here is 0.42, but if you look at the spread here from 0.11 to 1.5, it's big, and then that's just because there's just so few events. But what's encouraging about this OS trend is just how flat that green line is, and it was flat through that median three-year follow-up, and it's one of the reasons we're so excited for what we're going to see with the five-year data that's coming.

And as Kyle alluded to when he started, we tend to focus on the efficacy picture. But for an adjuvant setting that's curative intent, patients want good quality of life. They want to be able to continue running and traveling and having that same life that they had before they were diagnosed with cancer. And so having a safe profile is amazingly important. And so not only did we see in this three-year follow-up this efficacy benefit, but we also saw that intismeran was generally tolerable, where the majority of patients had low-grade transient adverse events, with fatigue being the most common. So not hair loss, not weight loss, not myalgia where they can't walk, but fatigue.

In addition, we did not see an increase in significant or serious adverse events when combined with chemo, nor did we see potentiation of the immune-mediated adverse events, which is what you see when you have IO-IO combinations. So it really is well tolerated as a whole. And specifically for cancer patients, having a clinical benefit and a well-tolerated safety profile is truly differentiating, which gave us the confidence to move to this broad clinical trial program that we have now with intismeran with our partner, Merck.

So what we have here is not only the Phase 3 adjuvant melanoma, which we'll talk about in a second, but we also have the two other registrational non-small cell lung studies that will hopefully benefit patients like Keith. Then we have studies in renal cell carcinoma, muscle invasive bladder cancer, non-muscle invasive bladder cancer, metastatic melanoma, metastatic non-small cell lung cancer, and then our Phase 1 had expansion cohorts in PDAC and gastric.

And what you see from this picture is that we're hoping to impact and learn across a litany of tumor types and a litany of settings. So we are really spanning with having solid foundations in the adjuvant environment, and then we're beginning to start exploring the bookends to metastatic disease and perioperative.

And one of the reasons that we're actually comfortable looking at the metastatic space and the perioperative space is basically what you heard from Jerh, is we're optimizing our manufacturing, we're building our Marlborough facility, we're getting better at our turnaround times, and we have confidence that we will be able to deliver intismeran to patients that need it most quickly.

In addition, because of the safety profile that I just showed you, it means that we're also able to combine with agents beyond pembrolizumab. So in our metastatic non-small cell study, we're actually combining with pembro and chemo. Within our non-muscle invasive bladder cancer study, we're combining with BCG. In our Phase 1 study, we're combining with different chemotherapies for PDAC and gastric.

So this program as a whole is really going to teach us a litany of things about intismeran, tumor types, patient populations, combinations, and really sets the foundation for us to have a profound impact. And what you can see based off all of this is that we have a series of learnings that are going to come '26 and well beyond.

Now, while everyone can pick their favorite study for a number of different reasons, our team is hyper-obsessing about the -- our adjuvant melanoma Phase 3 study. So this study was launched in 2023, and it looks largely like our Phase 2 study, so it is randomized in adjuvant, high-risk, resected melanoma patients. And it randomizes patients to intismeran plus pembrolizumab versus pembrolizumab standard of care, and has the recurrence-free survival endpoint, which is the appropriate clinical endpoint.

The two major differences from our Phase 2 study is first, we expanded the patient population down to stage 2s, partly because pembrolizumab is indicated there, and we have reason to believe that we can impact that wide range of high-risk adjuvant melanoma patients.

And the other pieces, this is a Stage 3 study, or a Phase 3 study, so there's close to 1,100 patients that got enrolled. It was big, and it enrolled in record time. And I think one of the reasons that I enrolled in record time is that people are very excited for these Phase 2 results that I showed you.

And so at this point, it has been fully enrolled for quite some time, and we are sitting in a very awkward phase right now, where all of us are amazingly excited to see the RFS and to see the endpoint here, but this is an endpoint-driven study, which means that we also don't want these events to be coming in too fast, because we want patients to benefit. So we are in this like, we really want to see it, we want to see this actual output to see how the Phase 3 is going to play out and if it looks like the Phase 2, but we have to be patient because we also want that treatment benefit, we want patients to benefit. So that is the dance we're doing and we're just patiently waiting right now for those events to occur.

So on the clinical summary, what I've basically told you to this point is that we have a manageable safety profile. We have a clinically significant improvement in recurrence-free survival and distant metastasis-free survival. We have encouraging trends in overall survival. We have launched a series of clinical studies, three of which started this year with NMIBC, metastatic melanoma, and metastatic small cell lung cancer. And we have a line of sight for a lot of studies that are going to be coming '26 and beyond, starting with the five-year median follow-up for adjuvant melanoma, but then each of those other studies are going to start reading out.

Now, behind the clinical learnings, we also at Moderna want to lead the science in this space. And so what I like about the intismeran program is that it sits at the precipice of computational, technological, and biological innovation and understanding. And at its heart is our deterministic fixed algorithm, which selects the neoantigens for patients using their specific DNA sequences, and rank orders to the ones that are going to be most immunogenic.

And the thing about [bix] is that it was perfect for the science at the time, but as our clinical understanding evolves, as our understanding of cancer biology evolves, and just as the field overall evolves, we have the opportunity to think or rethink about bix as a whole. But that's going to take more science and more data.

So built into our programs is translational endpoints or collections. So if you reimagine the clinical study schema that I showed you for the clinical side, this is the Phase 2 again, nothing's really changed for how it looks outside of showcasing where we're collecting patients' blood to do some translational work. And so we had patients that gave blood right at baseline before they had any treatment, patients that then they had blood collected after they started pembrolizumab treatment, then they had more blood collected after they started intismeran treatment, and then finally, at the very end of their treatment with pembro a year later, they had another sample collected.

And the data that we presented this year was two things. The first was to address the number 1 question we keep getting from a lot of folks, which is, do you really need an individualized therapy for neoantigens? Why don't you just use off the shelf? Isn't that a lot easier? So that's the first question, and I'll show you that data. And the second was, you've shown us immunogenicity, you've shown us you can mount a T cell response, but do those T cells matter? How does that population look as a whole? So that's the data that we presented this year.

So the first part is addressing the idea about, is a neoantigen therapy have to be individualized? So the first piece is in this Phase 2 study. The majority of patients did have an mRNA that spanned the full 34 neoantigens. So the bix algorithm was working to be able to select the right neoantigens for the majority of these patients because melanoma is a high TMB tumor, they should have a lot of mutations to choose from. But that's not true for every patient, and so we're not forcing neoantigens if they don't have them. And so that's why you have this sort of range.

Now, if we look at the bar graph, this is not patients, right? We don't have 3,401 patients in this study, but we do have 3,401 neoantigens that were completely unique to a patient, which means that 99% of the neoantigens that we are picking, that bix is picking is clearly specific to each individual patient. And what that means is that, no, we can't do an off-the-shelf approach for this. We have to tailor it to the specific person because the specific person's cancer is as unique as they are, and we have to generate a therapy that is going to treat them.

The next part is we started looking at the idea of, what do the T cells look like in these patients? Are they doing anything? Because core to the hypothesis is that we're selecting neoantigens. Those neoantigens are training the T cells, the T cells are going to go and clean up the tumor cells. So we're using TCR sequencing to characterize the T cell milieu of an individual patient and saying, does that change when a patient is treated with intismeran? And we're able to do this because actually, your T cells are also unique, and they each have their own unique fingerprints, so we can sequence them and see how they change over time.

So this first slide is basically showing what the T cell clonal phenotypes of the population looked like at baseline for both the combination arm and the pembro arm, and mapped that against if a patient had a recurrence event or not. And this is basically a negative slide. It basically says, it doesn't matter what your T cells look like to start with, that didn't impact outcome at all. What that means is that the treatment effect matters, because baseline, your T cell and your immune system is intact.

So this is where you're going to squint, but hopefully, you'll take my word for the story, and if you have interest, you can look at the SMR and the AACR picture. But if we're going to look for the waterfall plot first, so what we're doing here is now showing how the T cells change over time with intismeran treatment or pembrolizumab treatment. So the red is the top, and this isn't the combination.

And what you see on the waterfall plot and what you're going to try to read is that 71% of patients that were treated with the combination had an expansion of their T cell population, which means that when they were treated with intismeran, they actually had new T cells grow and adapt, and their population actually shifted, which was different than pembro, which most of the pembro patients did not have that effect.

And actually, if you look at not only the sort of broad population of T cells, but how many were new, which is what we would want with the neoantigen approach, right, how many new T cells are we forming. Those that were treated with intismeran actually had a higher proportion of new T cells, really, which is on point with the mechanism, and that was not true for the pembro arm, which again, doesn't sort of fit pembro's mechanism.

Now, you could say, well, your patients were treated with pembro, isn't it doing something? And the answer is, no, actually, it's not here, based off of the data. Because what you see is that screening, the population, the T cell populations are the same. When pembro starts, it doesn't really change. It's really once intismeran gets on board that we start seeing these novel clones. And not only are we seeing novel clones, but we're seeing clones that are only for those unique neoantigens that I told you about, not the shared ones.

So if you put basically all of this together, it's saying our algorithm is picking neoantigens. Those neoantigens are stimulating T cell responses that are new and that are changing the milieu of the T cells throughout the body to be able to have long-lasting impact.

Now, the question is, what is that impact? Is it meaningful? Great. You showed me that you can expand populations that you want to. And the answer is, yeah, it's actually important. So what we see is these T cells are actually associated with recurrence-free survival. So what that means is it is important for intismeran to have an impact, to have this clonal cell expansion, because that means that these targeted -- tumor-targeted, patient-specific T cells are now going out and cleaning up whatever cancer cells are left in the patient's body to create disease control and prevent recurrence, and that this is true with a statistically meaningful impact.

So all of this basically is to say that mechanistically, we have confidence in what we're doing with bix, and so not only are we seeing clinical impact and a good safety profile, but we're seeing that intismeran is doing what it's supposed to do.

So with that for the translational summary, we're basically showcasing that the mechanism for what we hypothesized is actually playing out in clinic, but not only is it playing out in clinic, it's actually making the clinical data also make sense, and the fact that we are able to have this long-term disease control.

And so the sort of next step here is to sort of tether this one step further and say, are all those T cells that I just showed you that are expanding, do they actually track back to the neoantigens that we've selected? And which ones, and how can we optimize those neoantigen, and how can we optimize bix to create even better ones?

And so that's why when Stephane and Stephen were talking about the excitement we have for the oncology portfolio in '26 and beyond, it's really referencing the amount of scientific and clinical data that we will be coming with over the next couple of years, not only to help our learning, but to actually improve what we're doing as well.

And so on that theme of excitement for '26 and new data and the potential for the oncology portfolio, I'm going to hand this back over to Kyle to talk about our 4359 program. Thank you.

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

So, our most advanced program is, 4359. We also have, other therapies in clinic, that are part of our cancer androgen therapy portfolio, which include 4106 and then our Lynch syndrome, program. So 4359 has two targets, PD-L1 and IDO.

These are targets that are well described and validated in oncology. I don't have to talk to you all much about PD-L1. However, I do want to take second to talk to you a little bit about IDO because we have some questions that we get about IDO and the importance in cancer. What I'll share with you is that we're not targeting IDO to change IDO functioning.

Other, programs that have targeted IDO have done so because they've wanted to, introduce small molecules that change the downstream pathways of IDO. What we're doing instead is we're targeting IDO through a mechanism where we can use it as a flag, where T-cells can be directed towards that, expressed protein.

And use it to both have an effect directly on the cancer cell, as well as have an effect on the overall immune suppression that occurs in cancer. And so we can change the immune environment by targeting IDO and PD-L1, but we can also have a direct effect on the cancer cell.

We presented our safety data at ESMO in 2024. And then, the most recently at ESMO in 2025, we released our first look at some efficacy data in an expansion cohort, that we did in metastatic melanoma. These were patients that were checkpoint inhibitor refractory. So as you all know, checkpoint inhibitors are standard of care for patients with metastatic melanoma. All of these patients had received multiple prior checkpoint inhibitors. All these patients had metastatic melanoma.

And they all received a combination of 4359 with pembrolizumab. So these are some design features of the study design. As well as some demographics of the patients and some baseline characteristics. So we had two different dose levels, that we assessed, a 400 mcg and a 1,000 mcg dose level. As I mentioned, both of these were administered in combination with pembrolizumab, and we had overall 29 patients that were enrolled in the study. However, only 25 patients were eligible for assessing a response to treatment.

I talked to you a little bit already about the safety profile, but what I'm excited to share with you again is that grade three events were very uncommon. Even in combination with Pembrolizumab, we did not see many grade three events. And as Michelle described before, one of the concerns that many people have had when you combine treatment that has immune, the potential to boost the immune system, that you might get an increase in immune-related adverse events.

But fortunately, for both the 4157 program and now consistently with the 4359 program, we have not seen an increase in immune-related adverse events. So this is the first snapshot of the tumor, anti-tumor activity of 4359. When you look at the entire population, both the 400 and the 1,000 mcg patients, we saw approximately 24% of those patients with a complete or partial response to therapy.

The disease control rate was even higher, and patients who had either stable disease or a partial or complete response increased to approximately 60%, and you can see that near the bottom of the slide. And we also have the number of prior therapies listed here. You can see that these patients all had many prior therapies and had progressed through these therapies. So there was a highly refractory population.

What was more encouraging, however, was the data when we separated the patients by those who were PD-L1 positive, by TPS, or those who were PD-L1 negative. So on this waterfall plot, on the bottom of the left slide here, you can see patients who were PD-L1 positive represented in the red bars, versus the ones that were PD-L1 negative in the blue bars.

Every patient that had a partial or complete response was PD-L1 positive. So when you look at the overall population who are PD-L1 positive, you can see now the response rate goes from 24% up to 67%. And these responses were quite durable.

And you can see that from the spider plot. So in the bottom right here, the spider plot has these patients separated similarly to the waterfall plot, where all the patients who are PD-L1 positive are represented in the red lines. And the patients who were PD-L1 negative are represented in the blue lines.

These lines represent changes in the size of their tumor over time. So when the lines come down, that means their tumors have shrunk. And the patients with tumor shrinkage, had continued shrinkage of their tumor out for 200, 300, 400, 500, almost 600 days.

And just as a reminder, this therapy is administered 9 times every 3-weeks. So the majority of these patients stopped therapy much earlier but continued to have a robust and durable response to therapy. We've done some similar analysis that compared to, similar to what Michelle had described around T-cell clonality, as well as T-cell specific responses. I'll walk you through the data on the T-cell specific responses to PD-L1 and IDO.

When you look at these slides, you can see the increase in the number of T-cells with these either IDO directed T-cells or PD-L1 directed T-cells. The patients in purple were the partial response patients. Those patients in purple all had increases in their T-cells specific responses.

Now, what we can tell from this slide is there were other patients that did not respond who had T-cell specific responses. So our takeaway from this is it's probably necessary to have a T-cell specific response, but not sufficient.

And when you look at the novel expanded TCR clones, you can see for the patients that had a CR or a PR there's quite dramatic increases in the novel TCR clones, whereas the patients that had stable disease or progressive disease didn't have the same dramatic increases in the novel T-cell clones.

So this exciting preliminary data has led us to expand into multiple cohorts, this phase one trial. So we now have an Arm 2a. Arm 2a is a trial where we have a combination of 4359 and pembrolizumab in frontline melanoma. Arm 2c is an arm where we are combining 4359 with ipilimumab and nivolumab.

Arm 2D is an arm, in patients who have second line and beyond melanoma, all with PD-L1 positive, disease, and this is a larger cohort to what we had originally described where all these patients will be selected for PD-L1 positive disease.

And then we're also moving into other tumor types. So we have Arm 2b where we're assessing the response in patients who have non-small cell lung cancer and have a TPS score greater than 50%, and this will also be 4359 administered in combination with pembrolizumab.

Okay, so with that, I will move on to the next part of our, presentation on oncology. Dr. Loughlin will talk to us about our early programs.

Rose Loughlin - *Moderna Inc - Executive Vice President – Research*

Thank you so much. All right. So we are going to start by building on what Michelle and Kyle already shared with you. I'm moving into the cancer antigen therapy portion of the pipeline.

Starting with mRNA-4106. Now, similar to 4359, but quite different from our individualized therapies, [1406] is designed to encode for antigens that are shared across many different patients. So this includes many different types of cancer and all of the patients within those types of cancer. So when we think about the design for this cancer antigen therapy, we specifically chose to include Multiple antigens. So if you took a single patient, you would expect their tumor to express multiple antigens within this therapy.

So, 1406 is currently in a phase one study in advanced solid tumors, and we'll be excited to share data once we have those available. But I'm going to spend a little bit more time on the next program, which is Lynch syndrome, because this actually takes our cancer antigen therapies even earlier in disease to the point that we are trying to intercept disease before it truly becomes cancer.

So for those who are not familiar with Lynch syndrome, it's a heritable disease where these patients have mutations, so they have defects and the mechanisms your body naturally has to repair damage to your DNA. So it can be mutations in a couple of different proteins, but basically, as your cells normally divide, occasionally they make errors in your DNA.

And your body has mechanisms that go in and correct that. But if you have Lynch syndrome, that repair mechanism is deficient. So you start accumulating mutations over your entire lifetime. Now, as it turns out, these patients have an incredibly high risk of developing certain types of cancer over their lifetime.

So if you have one of these mutations, you can have about a 50% chance of developing colorectal cancer during your lifetime, and you can have very early onset as well. So these patients go through considerable surveillance, colonoscopy every 1- to 3-years starting at really early ages to try to identify things like polyps in the colon and have those removed before they progress to cancer.

Now, what we've done in collaboration with the University of Oxford, is identify these mutations which happen to be shared between these patients. And so with this therapy, we're actually training those patients immune systems to identify the cells with those mutations before that truly turns into a malignancy. So we're trying to intercept and train that immune system to remove those cells before these patients actually develop cancer. So we're excited with Oxford, we're looking forward to starting this study next year.

Now, I'm going to pivot pretty substantially in terms of the approach that we're taking to treating oncology. So we've talked a lot about cancer antigen therapies and the idea that we were training your immune system to recognize cancer cells and kill them. With T-cell engagers, it's a different approach. So we are actually looking to guide your immune system to those cancer cells.

And we have two different types of T-cell engagers in our portfolio. The first focuses on proteins that are expressed on the surface of cancer cells. So I'm actually just going to start the cartoon on the left-hand side here. So, our lead program in the space is mRNA-2808, and it encodes for T-cell HR that on the one side binds CD3, so it binds to your T-cells. And on the other side, we've actually multiplexed this product. So there are three different targets that are present in multiple myeloma that we are able to go after with a single therapeutic. You can see them here, ECMA, FcRH5, and GPRC5D.

And we think this is really important in disease because if you have the ability to multiplex, you can really avoid antigen escape, which is a clear mechanism in cancer, and you can account for the fact that not all tumor cells will express every single antigen. There is some heterogeneity in cancer, and we can go after multiple targets at once. And this is actually played out in the field. So there are recombinant protein, T-cell engagers already in use in multiple myeloma.

If you take two of those and clinically combine them, it's already been demonstrated that you can improve response rates and that depth of response. In our lead therapeutic, we are able to multiplex three targets. Now, I'm using the word multiplex intentionally, not the word combination, because for us, this is one drug product from a regulatory perspective. We're advancing one product that can target three proteins.

Additionally, as you move further into our T-cell engager pipeline, we can encode other signals that can help the T-cell engagers be even more efficacious. So we can include, for example, co-stimulatory signals that really help those T-cells be more activated and add another layer of specificity to that activation.

Now what we're showing here on the right-hand side is data from non-human primates, where we were looking to see, with 2808, depletion of a cell population that actually doesn't even express those targets very highly. These are healthy non-human primates, but really demonstrated to us that we could truly deplete those populations, and that we're seeing a nice durable effect until those populations are able to come back. And we're able to do this with both IV infusion, as well as subcutaneous injection, which you can see here in the blue line.

Now, the second approach that I described for our T-cell ingators, oh, I apologize. So 2808 is actually already dosing patients in our phase one study. And for that, of course, our primary end point will be safety, but given the patient population, we should have a pretty good read on pharmacodynamics, so the impact on those pathogenic cell populations and the proteins that we secrete. And we, again, will be excited to share those data as soon as they're available.

So the second approach that we're taking, rather than going after proteins that are on the surface of cancer cells, is actually focused on intracellular antigens, so proteins that are within the cancer cell. Now, we're excited about being able to target those because it really opens up the target

landscape for us. Proteins that are on the cell surface tend to be shared between cancer cells and healthy cells. There may be more on the cancer cells, and that's why we target them.

If we're able to go after intracellular proteins, it actually opens up a much larger pool of targets that we can pursue, and these targets tend to be very specific to tumor cells. So as Kyle and Michelle talked about, that safety and tolerability profile is really important for patients, and we think this will improve that as well. We are still able to multiplex and go after multiple targets with this approach, or to encode some of those supporting proteins like co-stimulatory factors. And so we're pursuing this in partnership with thematics.

Okay, we're going to transition to another part of our pipeline. We're going to talk about our approaches in cell therapy. And I'm actually going to start by describing something that Moderna does not do, which is ex vivo cell therapy.

So our first approach in the cell therapy space is actually looking to enhance the performance of a partner's ex vivo cell therapy. So for those who are familiar with ex vivo cell therapy, you might have heard about CAR-T, and in certain blood cancers, CAR-T therapy can be absolutely transformative. Now, in solid tumors, these exal cell therapies haven't delivered quite that same level of impact. And so we're looking to truly improve those outcomes with a focus in that space.

So how do we do that? You first start with your typical ex vivo cell therapy. So you need to take the immune cells out of your patient. You need to engineer those immune cells. You need to try to remove the remaining immune cells in the patient to try to conceptually make more space for those engineered T-cells to engraft as you infuse them back into the patient.

Now, after the engineered cells are back in the patient, we administer mRNA 4203. It's an intramuscular injection, and we have designed it specifically to encode for the antigen that is recognized by that engineered T-cell therapy. So MRA 4203 is specifically designed for AZN cell, but it is not specifically designed for any individual patient. It will work for all of those patients. And you're actually Taking those engineered T-cells after they're in the body and boosting them.

So you're showing them the antigen that they're engineered to recognize. So they will get activated, they can proliferate. And we think this has the ability to enhance the performance of those engineered T-cells, because it has been shown clinically that when you have these T-cells that are in a good immune state, and that they are able to persist for longer in the body, that those tend to be correlated with better clinical outcomes.

Now, we are in an active phase one study in collaboration with thematics for this combination, and this is a true combination of mRNA 4203 and AZN cell. So our second approach in the cell therapy space is quite distinct from ex uvo CAR-T. It's actually in vivo CAR-T. So as I said, we do not do ex vivo cell therapy. Our approach here is to actually engineer those T-cells inside the body in the first place. So for this approach, we actually use a lipid nanoparticle that is specifically targeted to T-cells. So it's specifically going to T-cells and it encodes for that same car that you might have engineered outside of the body, but we can do all of this inside of the body.

And importantly, this means you do not need to take the cells out of the patient. They do not need to have these tough conditioning regimens that take out the rest of their immune cells. You don't have this large individualized manufacturing component. All you do is infuse LNPs.

So we see this is having substantial advantages there. We can also rely on some of the differentiation that I described for T-cell engagers. So for example, we can multiplex. If you wanted to encode a car for multiple targets, you could do that with this platform. If you wanted to encode other proteins that would help these T-cells stay activated and go into that tumor microenvironment and be very efficacious, you can also do that. And we see two application spaces for the in vivo CAR-T style approaches.

The first is actually an autoimmune disease. So there's been quite a bit of really promising clinical data of late. That if you go into autoimmune diseases like lupus, and you actually use CAR-T to eliminate and deplete those B cells, you can actually help those patients reset their immune system, so they can go into remission for a remarkably long time.

So we think that's certainly an application for in vivo CAR-T. Where the in vivo profile as well from a safety perspective will be really important to those autoimmune patients. We also think in vivo CAR-T will be highly relevant as you go into oncology. As I mentioned, CAR-T in general has been incredibly transformative in the blood cancers, and we believe this will help us go into solid tumors as well.

And our third approach in cell therapy actually focuses on a different cell type. So where CAR-T is very focused on T-cells, CAR-T is actually much more focused on a different cell type, myeloid cells. But the approach is still similar. So we infuse patients and using LNPs, we transfect different types of myeloid cells and we're encoding a car. Now those cells will move around the body in traffic, and when they get to the tumor, that car will recognize the antigen.

Those myeloid cells can then actually ingest some of the tumor cells, so they're killing some of the tumor cells. They will secrete other proteins that will help other cells in that tumor microenvironment to be able to kill cancer cells. And then having actually engulfed and ingested a tumor cell already, The cells can present multiple antigens from that tumor cell.

So Michelle talked about how you get that broad T-cell response, even with INT. This is a similar concept, where even though we only encoded a car that recognizes one antigen, by the time you get to this part in your mechanism of action, you're able to really expand that response to lots of different antigens that are present within the cancer.

So, I know we moved quickly, but we did want to have a chance to share this part of the oncology portfolio with you and give you a sense of the diverse set of therapeutic approaches that we are able to take because we can leverage so many different aspects of our platform technology.

So with that, I believe I'm handing it to Dr. Rita Das. Oh, no, we're going to take a break. Lavina said we're going to take a break and bring lunch in.

Lavina Talukdar - *Moderna Inc - Head - Investor Relations*

Yeah, so if I can invite everyone to please grab a plate of lunch and a beverage of their choice and bring it back in here, and we will resume the rest of the meeting.

Thank you.

Rita Das - *Moderna Inc - Clinical Development Head for Respiratory and Rare Disease*

All right. Hi, everyone. My name is, I'm going to bring us back from break. My name is Rita Das and I'm the Clinical Development Head for Respiratory and Rare Diseases.

And it really gives me great pleasure to focus on our rare disease portfolio today because as a pediatrician, I've taken care of these children with inborn errors of metabolism and seen the impact on their lives and. Also, the underlying pro progression, neurologic and otherwise. And I'm really excited by Moderna's commitment in this space, and I'm very excited that we're getting closer and closer to bringing these therapies forward.

So first, I'll talk about propionic asidedemia, which is where we're the most advanced. And propionic acidemia is a rare metabolic disorder, primarily diagnosed in infancy that causes a huge amount of morbidity and mortality. It's very rare, ranging from 0.29 to 4.24 per 100,000 newborns. So it's actually formally in the ultra rare category, and it's And it's caused by pathogenic variants in the PCC enzyme. There's two subunits, PCCA and PCCB, that

That stand in the way of the enzyme. In the metabolism of proteins. And so when that metabolism is not going properly, you build up these toxic metabolites. And so, because this is so pervasive, PA is a multi-systemic disease with not only these metabolic decompensation events which can be life-threatening, but there's underlying neurologic cardiac endocrine and immunologic manifestations.

Now, there are no approved therapies for propionic asidedemia. And so the management involves severe dietary protein restriction, and as the disease progresses, the patients often progress to needing liver transplantation. Now, here's a bit more on the PA biology, which really shows why mRNA therapy is particularly well suited to succeed in this space.

And so, as I mentioned before, there's two components of that enzyme, PCCA and PCCB, that come together and allow people to metabolize particularly proteins. And when that enzyme is not functioning, you build up these toxic metabolites that are that are damaging to the brain and other organs.

And for mRNA 3927, what we're able to do is encode the functioning both PCCA and PCCB, package it in a lipid nanoparticle and deliver it IV but target it towards the liver where then the patients are able to make these enzymes and correct their inborn error of metabolism.

And so, first, I'll talk about our op our Phase 1 study, which is called Paramount. It's a global study that enrolled in multiple countries. And the analysis from this study was presented in the [ICIEM] conference in Kyoto, Japan earlier this year. The primary endpoints for this study were safety and tolerability. And the key exploratory endpoint was the Was the reduction in metabolic decompensation events, and I'll tell you a little bit more about that after.

The study design was a dose escalation design. So we started from a dose of 0.3 mg per kilogram delivered every 3-weeks, and we progressively increased that dose to 0.9 mg per kilogram delivered every 2-weeks. Now, the key inclusion criteria for this study were, participants had to be greater than one year and had to have a confirmation of the PA genetic defect.

The key exclusion criteria were if the if the patients were in grade three or four heart failure, which unfortunately happens in PA or either had a plan or a history of liver transplantation. So now, here are the demographics and baseline characteristics of the patients. So 20 participants were enrolled in this study, 18 completed treatment, and 17 participants entered the Open label extension study, and 10 are continuing to receive treatment even today.

The mean age was 11 years, and the range in age was from 1- to 26-years. Now, mRNA 3927 was well tolerated and had a manageable safety profile. In this study, we've administered almost 1,000 doses of mRNA 3927.

And we've seen no drug dose limiting toxicities. We've seen some serious treatment emerging adverse events, as would be expected in this population of chronically ill, children and young adults, but the adverse events that are related to treatment have been much fewer.

Here's a little more detail on the adverse, events that are, that have been emergent. And these are fairly expected in this age group, and those that are related are mild to moderate. We also saw very few infusion reactions, and those were managed with conservative therapy.

So just an overall summary for our PA program to date is that we've enrolled, sorry, 20 participants in part 1. 13 participants have been dosed for over a year. There's been 43.6-years of cumulative patient experience of the study drug. The longest treatment was 3.1-years, and the median duration of treatment was 1.45-years.

Here's a little bit more on these metabolic decompensation events. These metabolic decompensation events have occurred in both PA and MMA which I'll talk about next. And they're, usually how these patients present first to medical care. They're either screened at, they, they're either identified on their newborn screen or they present with this, these metabolic decompensation events. And they're a major contributor to both morbidity and mortality, and also to these long-term irreversible sequelae such as brain and cardiac damage.

Now, we had to discuss with the agency and agree upon a definition for these metabolic decompensation events, which we've done now. And so the definition that we've come up with is that the signs and symptoms include vomiting, anorexia, lethargy, and seizures. There's also these observations of metabolic acidosis, which is a buildup of Acid in the blood or high ammonia. Also, there's often a need for acute medical care, emergency room visits, or hospitalizations. And so this is the scope of the definition that we've agreed upon with regulators.

And this is what's really exciting about the data to date. The red dots represent the spectrum of metabolic decompensation events in the study. And on the on the Y-axis, you see the different doses and on the X-axis, it's over time. So, pre-treatment is before that black vertical line and post-treatment is after that black vertical line. And it's individual within patient comparisons.

And you can see pre-treatment, you see a lot of these red dots. So these patients are having multiple metabolic decompensation events every year. And as you get past the vertical line, you see these events really decrease in frequency. And as you go higher in dose, the 0.6 mg per kilogram and the 0.9 mg per kilogram, you see these events virtually go away.

And so when you do the statistical analysis of this, you see that across all doses, the mRNA 3927 is related, it is associated with a 76% relative risk reduction in metabolic decompensation events. And when you look at just the doses above 0.6 mg per kilogram, that comes up to an 83% relative risk reduction. That's statistically significant.

And so this is what makes us really excited about our pivotal study, which has completed enrollment. So, in summary, mRNA 3927 is well tolerated at all the doses administered with no dose limiting toxicity. All the IRR's were grade three or lower and resolved with conservative management. mRNA 3927 treatment continued to demonstrate sustained reductions in these metabolic decompensation events, with the highest benefits seen in those patients dosed at 0.6 mg per kilogram and higher.

And the fir and these findings support the clinical development of mRNA 3927 at that dose, 0.6 mg per kilogram for the first treatment for patients with propionic aidemia. The registration. The study is ongoing. This is part two of the study that's that I already presented.

Target enrollment has been reached, and we're really looking forward to seeing the results next year. Also, since PA often That since some of the neurologic decompensation happens in infants, we're also doing a dose finding study in infants to bring the greatest benefit of mRNA 3927 across the spectrum of age in these patients.

So now moving on to MMA, which is a related organic asidedemia. Like PA, MMA onset occurs very early in life, and it's associated with these MDEs and then this underlying chronic toxicity. The MMA defect occurs a little bit farther down the pathway than PA, but the enzyme that's responsible is the mutt enzyme. And this enzyme.

And the downstream sequelae are very similar. It results in an in a buildup of these toxic metabolites from proteins and fatty acids because of an for because of an inability to metabolize them. Again, protein restriction is the mainstay of therapy because there's really nothing else curative available. Some patients have levocarnitine supplementation, and many of these patients progress to liver or kidney transplantation.

So the MMA, the three, the mRNA, the MMA therapy, 3705 encodes the mutt enzyme. So it replaces the mutt enzyme. It's packaged in the LNP just like the PA and the LNP is specifically trafficked to the liver where replacement of the enzyme restores the metabolism and the buildup of these toxic metabolites.

So, I'm going to present to you the Phase 1, 2 study. That's the dose finding study for MMA. This was a first in human study, and that was, it was enrolled, globally as well. And it was also a dose escalation study. So we started with a dose of 0.1 mg per kilogram administered every two weeks. Every 3-weeks, sorry, and then we progressed to 1.2 mg per kilogram administered every 2-weeks.

The key inclusion criteria were again, MMA that was genetically confirmed to be due to a mutt deficiency, greater, the age was greater than one. And then the key exclusion criteria were very similar. Children with the background chronic disease that was too advanced were excluded, and children who had a history of organ transplantation also were excluded.

And so here are the demographics of the cohort. 18 participants were enrolled across 6 countries worldwide. The mean age was 7, and the age ranged from 2 to 39. Now, there's two different phenotypes of the, major phenotypes of the mutt enzyme, mutt zero, where the enzyme is completely absent, and mut minus where the enzyme is not completely absent, but has a decreased function.

And so here's the safety profile. The median duration of treatment was 99.6 weeks, so just above 2-years. All 18 participants con finished their dosing in that base dose finding study and continued into the extension study.

Just above 860 doses were administered. The total patient years of exposure was 3617. The safety profile was overall well tolerated. The infusion, reactions also were easily managed, and there was no dose limiting toxicity.

So again, 18 participants have been dosed. The longest treatment duration is 2.3 years, the median duration is about 2-years. It was well tolerated, and all the participants are continuing in the extension study.

Now, here, so for MMA there is a plasma biomarker that we are hoping to use for our Phase 3 study. And we see that, and that's the plasma methyl melonic acid level. And we see here, That there is a greater than 50% decrease from baseline for participants who were treated at with the mRNA 3705 at doses greater than 0.4 mg per kilogram every two weeks.

And the plasma biomarker is more evident on this slide. And you can see here, the greatest evidence of the plasma biomarker decrease is seen in those M zero participants who are on the bottom. And as you can see, almost all of the mt zero participants, all the different doses are in the different colors on the right-hand side.

The plasma biomarker, as you go up in dose, you see a very consistent decrease in the plasma MMA biomarker. And So it's just the lowest doses that have the higher residual. This is a little bit less clear in the minus phenotype.

Now, again, we're, the thing that we're most excited about in MMA as well, is this reduction in these MDE events. This chart is set up the same way as the PA chart. The doses are increasing on the left-hand side. Time is on the X-axis, and you can see pre-treatment and post-treatment.

And pre-treatment is in the red circles, or the are in the red circles. And as you can see, pre-treatment, these children are having these children and young adults are having quite a few metabolic decompensation events. And as you go to post-treatment, you see a 91% relative reduction in the MDE events and a 75% relative reduction in MMA related hospitalizations.

And so, we're very excited about our MMA preliminary dose finding results. And so in summary for MMA mRNA 3705 was well tolerated in participants with the mutt deficient MMA in this study. There were no dose limiting toxicities and no treatment emergent adverse events that led the patients to discontinue the study.

We saw, reductions in disease-related biomarkers, that was the plasma MMA levels, that that indicated improved metabolism. And we also saw the reduction in the MDE events as well the as well as the MMA related hospitalizations at all doses greater than 0.4 mg per kilogram. MMA is ready for phase for the pivotal Phase 3, and we aim to begin that in 2026.

So with that, I'm going to hand it back to Stephan.

Stephen Hoge - *Moderna Inc - President*

Thank you, Rita, and thank you to everybody who presented this morning. As I said this morning, I'm going to be quick, 2 slides. The first one is, as you heard me this morning. Our near term strategy is clear, is drive sales growth through the respiratory seasonal vaccine franchise, drive profitability, drive cash to invest in oncology and rare.

You've seen sometations that the oncology portfolio is very exciting and extremely differentiated from what you can see from other companies. So we're very eager to see what this does for patients and how we can help patients.

And as Jamie closed, if you think about what we are trying to do is drive a top-line, drive a cross marginal improvement, evolve our investment to diversify further away into oncology, reduction of project cash cost through every year in the process, and really drive a company back into profitability in the 28 and from there deliver a lot of patients impacts.

So with this, I'm going to ask my colleagues to please join me, and we'll be delighted to take your questions.

QUESTIONS AND ANSWERS

Lavina Talukdar - *Moderna Inc - Head - Investor Relations*

We will take questions in the room and as well as online. By yourself and tell us your question.

Unidentified Participant

Great. Thank you very much for taking the day and for lunch. Yeah, I have to say I never thought I'd have so many questions about manufacturing, but in the interest of time, I'm going to kind of skip to some of the other stuff that I jotted down throughout the morning. So, if I may start just with respect to the 1083 combo vaccine. What is the FDA waiting on? What do you need to hear from them? And is there a potential risk that you might have to do another study?

Unidentified Company Representative

Yeah, so, you look, our efficacy data are relatively new. The FDA has not had the opportunity to review that data in the very in-depth way, that they do as part of their review. So I think what they really want is that we submit this flu file and really get to check under the hood, and then we certainly will have additional discussions.

Jarwei Fang - *Citi - Analyst*

Hi guys. Yeah, thanks for hosting us today. This is Jar Wei, here for Jeff Meacham at Citi. So with the new debt facility, you guys mentioned that it's going to, further bolster the balance sheet and open up optionalities. And so with that, what future opportunities could that provide and how might that share your shape your view on which pipeline programs you might bring back online and or partner out.

Jamey Mock - *Moderna Inc - Chief Financial Officer*

Yeah, thanks for the question. So I would say we don't know right now. We're prepared for both upside and downside. I think that's what this does for us. Right now we plan to park the cash on our balance sheet and therefore bear a small spread from an interest rate perspective. And then we'll see how the next few years unfold, whether that's pipeline increase on the opportunity side, whether that's pipeline increase. Whether that's share buyback or BD, we'll see how that goes on the opportunity side.

We'll also understand what's happening with our revenue line. We need to execute our base plan first. So our base plan is to break even by 2028, and that is what we are going to monitor to to make sure that we do that. And so this, facility provides flexibility both for the opportunity side, but if there is something that happens, we're not pointing to anything, we believe in our base plan. But should something happen to the downside, it also provides flexibility on that side as well.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Yeah, I mean, if I could just add, I think as you asked the question about where we'd focus in the pipeline, we do have a large number of products to launch in that vaccine space as we talked about, but I think as Jackie and Rose and the team highlighted, there are some exciting programs either in the mid-stage development in vaccines, or EB vaccine, Lyme, and others.

And our early oncology pipeline that we're equally excited by. We're going to wait until we're ahead of plan on cost, which we've been lately and showing we can grow that top-line. But having the flexibility of the facility to be able to invest when we have very high confidence that we're ahead on that break even target is going to give us an opportunity to accelerate that mid-stage pipeline.

Tyler Van Buren - *Cowen and Company LLC - Analyst*

Great. Tyler Van Buren, TD Cowen, thank you very much for the presentations. I wanted to start on the financial side. So can you elaborate on the assumptions behind the 10% revenue growth year over year in '26? I think that's a little bit above consensus. The slide says it doesn't include flu, even though I think consensus does. So just curious to know if that growth is coming primarily from the partnerships piece with the UK, Canada, and Australia.

And do you have confidence in that because you're already deep in those discussions and is that assuming stable COVID revenues or decline? And then the follow-up to that would just be with respect to your year-end cash balance exercise through '28, that clearly has some sort of revenue assumptions through '28 or '27, ['20] and '28. So how are you? Thinking about revenue in those years as well in that exercise.

Jamey Mock - *Moderna Inc - Chief Financial Officer*

Yeah, I'll start and then feel free to add Stephen. So, as it pertains up to 10% growth in 2026, there's a couple of questions in there, but the short answer is yes, it primarily is driven by those three facilities, which is what Steven tried to lay out today.

We're not only in advanced discussions, we actually have it contracted and built. So these facilities are built. The contracts are already in place, so, and we're already executing on the contract for all three of them, but there is some revenue as it pertains to Canada in our assumption this year and a little bit in Australia.

If you remember from the UK earlier in the year, we pushed out over $200 million in revenue, so that will take place next year. So if you just think about 10% growth by itself, if we're $1.6 billion to $2 billion or $1.8 billion at the midpoint, $200 million is 10% growth. So that alone is sufficient. Now, we will have a fully annualized impact for all three contracts. So therefore it will be a primary driver of growth next year. So that's number one.

Next spike share, as Steven laid out earlier as well, is the other primary driver. You asked if COVID is flat. I think as it pertains to the US. We can basically offset further decline actually. So with the what we believe will happen outside the United States with the three contracts I just talked about and other countries, but these are three primary contracts, we actually believe we can offset and still grow up to 10% with the US decline.

Now, we're hoping it doesn't. We're hoping the next spike will, increase our share and value, but nonetheless, we still feel confident even with a little bit of decline. As it pertains to walking forward the cash balance. Yes, obviously that has some revenue assumptions in there. So, I said that we would invest $2 billion in the year 2026 and I said $4.2 billion of the cash cost target.

We're $1.6 billion to $2 billion on a revenue side. So it's a $1.8 billion and if you're at the midpoint. And if we grow up to 10%, that's $2 billion. So that's technically a $2.2 billion net cash investment, but I'm kind of rounding here. And we'll see where this year lands. So if this year lands on the high side, then certainly $2.2 billion could be in play if we're at $2 billion plus 10%. If we're on the low end, then we'll have to re-look it and understand what will happen. But I still feel good about the overall $2 billion.

As you look out a year, we said that we would invest net $1 billion to $1.5 billion with a cash cost of $3.5 billion to $3.9 billion. So on the low end, a $1 billion cash burn would imply $2.5 billion of revenue. So if we had $3.5 billion in cash cost and $2.5 billion of revenue, that's obviously a billion dollars of cash burn.

But we're not trying to be specific about that. We're not guiding that number. We will continue to ebb and flow two years from now is a long ways away. In 2-years we took out $4.5 billion of cost. So what can happen in two years? There's a, it's a lot that could happen in the next 2-years, which

is why we're not guiding a revenue line, but it gives you some semblance of understanding. We do expect revenue growth, not only in '26, but also in '27 and '28, and Steven laid out the drivers earlier.

Tyler Van Buren - *Cowen and Company LLC - Analyst*

That's great, remarkably detailed as always, Jamie, I appreciate it. I have to ask about INT before I pass the mic. Watching the Marlborough facility video and having Jeff walk us through the optimization, it's clear that, you all, are not only very excited but have invested significantly in the future of -- in INT in general. So, can you just elaborate on one, your confidence in the face that we read out next year and the powering of the primary endpoint.

Two, if you need to show an OS trend for approval. And three, how confident you are that it will come next year based upon what you're seeing with the events and where you're at with the events.

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

Yeah, maybe I'll take a first stab at this and please ask my colleagues to chime in. So this is probably one of the most de-risk Phase 3, programs that happens in oncology because we have a randomized Phase 2 trial that showed an incredible hazard ratio of 0.51 in RFS at our 3-year data point. So, given that de-risking, I'm very confident in the Phase 3 program being successful.

But this is a blinded study. So, I can't tell you what the results are until we finally get to, our first interim and then can, I'm blind and check. In terms of the powering, so we've made some fairly conservative assumptions on powering that study and those conservative assumptions are much higher than a hazard ratio of 0.51, and I think that gives us even more confidence that we'll hit the target that we're hoping to achieve.

Lastly, we currently are on track with our events to what we had discussed in previous guidance, which is the third quarter of next year is when we hope this matures and we can do our first analysis. However, event rates, are sometimes unpredictable, and we really need to wait until all those events can happen before we do our first analysis. And so depending on the continued trend on those events, we'll have a better idea of when that first analysis will take place. But right now, we expect it to be in that third quarter next year time frame.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

I would just add a couple of things. So, it could come sooner than that. In fact, we're, we really don't know, it's an event-driven trial. And so, throughout 2026, we'll be looking for it, but we do expect it to happen in 2026. I would highlight that there are a couple of other, either fully enrolled or largely enrolled studies. We highlighted some of them today, Phase 2 studies to be randomized studies that actually also could read out in 2026.

And provide strong confirmation of what, what's possible with INT. And so the way we look at 2026 is there will be multiple readouts of mid to late stage studies, obviously the first being the face, well, not the first necessarily chronologically, but the one most anticipated being INT, for, melanoma. But, a lot of data coming in very short order. And so we're looking forward to 2026. All of them event-driven, so we'll wait and see.

Stephen Hoge - *Moderna Inc - President*

Yeah, maybe where the last piece is also, it's not only all investments, it's investments with Merck as well. As you remember, Merck is investing, half of all the investments in manufacturing. Marlborough, we are running it, but Merck is financing half of it. And of course, for the studies and all the medical commercial readiness and so on. So it's actually a huge commitment from a company who I think does a few things about immuno.

Unidentified Participant

Hi, this is [Addie] for Korey from Evercore. Just on the topic of [indisimmerin] in adjuvant melanoma, how do you view it in the context of the emerging data and potential use of Pembro in an earlier neoadjuvant setting?

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

Yeah, it's a great question. So we've looked very closely at how much neoadjuvant use is happening, both for pembrolizumab and for Nivvo and IPI. And right now we haven't seen a dramatic trend in those neoadjuvant rates. So we don't believe that this is going to be a major factor. Those are also not approved uses of Pembro or Nivvo or IPA.

They're not labeled, and there's no plan from these companies that I'm aware of that they're planning on changing the label. So if intimoran is a positive study, it will be labeled as such, and it'll be something that we can discuss with prescribers about the impact that this can have on their patients. So I'm confident that we'll be able to make sure that this is changing the treatment landscape based on positive Phase 3, data and based on a label that explains that.

Unidentified Participant

Yeah, this is [Kong Wang] on behalf of Gina Wang from Barclay. We have three questions. First one, regarding the ongoing ITU litigation with [RB2s], does it apply to the next generation spike and for section 1498, defense, what's your strategy to to defense the for the government rather than for the American people?

Second question, it is very exciting to see this new discovery assets. Given the cash guidance of the breakeven in 2028, what's the priority list for all those assets? So the questions for anti assets, since we need individualized and new antigen, what's the process time now and, which steps could be improved?

Thank you.

Stephen Hoge - *Moderna Inc - President*

Let me start with the first question. As I said during the Q3 call, because we got the similar questions. We believe in our IP and we're going to be defending it actively. I won't comment further given there's a litigation coming soon.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Yeah, I'll take some of the pipeline question. Look, I think we'll be data directed. We are very excited, to, move forward with the mid-stage on, vaccines, with the early stage oncology programs as we get clinical data over the next year or two.

It'll ultimately depend upon where do we see the most compelling opportunities and the data from those ongoing clinical trials. Hard to speculate, but a large number of opportunities to invest as we start to continue to grow, in 27 and beyond.

And there was a a a turnaround time. It was a question was sort of, how are we doing on delivery and turnaround time for INT, and any opportunities to further improve that as we go forward from manufacturing.

Unidentified Company Representative

From a manufacturing point of view, we're we're doing really well. I mean, compared to where we were 12-months ago versus now, we've improved our manufacturing turnaround time by 50%, and we have plans to even continue to do that more. So I'm looking at the whole needle to needle, we have plans to continue to drive that forward as well. So not only will that give us further capability to be there for the patients and their need, -- but allows us also simultaneously to drive efficiency.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Just to give you a sense, across our clinical trials, there's 1,000 plus patients, you saw some of that data. And we are already ahead of our target turnaround time for commercial launch. And so we're quite confident that we're already performing at the level that we need to. We'll always look to do better, but it's actually even better than we saw in the study. And so we're pretty confident we can achieve our target product profile.

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

And this is across multiple countries around the world. So over 40 countries, we've been able to continue to achieve these really robust turnaround times.

Myles Minter - *William Blair & Company - Analyst*

Thanks, Miles Minter from William Blair. Jamie, I think we were here last year, and you put a $6 billion cash cost basis number up on 2028. Obviously, I haven't seen the 2028 number yet, but I assume that's going to be closer to 3 than it is to 6.

What's changed in 12-months that gives you the confidence there, and how much of it is just efficiency versus a need to get that low because revenues are maybe not projected to grow as much as you thought 12-months ago.

Jamey Mock - *Moderna Inc - Chief Financial Officer*

It's a good memory, yeah, so we did say that that that we would break even in 2028 by $6 billion. That's $6 billion. I think it's probably a bit of both, frankly. We continue to say that it is both prioritizing the pipeline, as well as driving efficiency, to which our teams have done it faster and to a much greater level than what we could have ever anticipated. So I think it's a little bit of both, frankly, that instead of being at $6 billion I don't know if we'll be at $3 billion but we'll certainly be at least $3.5 billion to $3.9 billion.

So we have been able to take it down and it is a mix of both, but I've been super encouraged by the entire team, how everybody has done it across every single or function inside the company. And we continue to see greater opportunity. Like I said earlier, more than we thought we could do and faster than what we thought we could do. So that's a big driver of it, but we definitely had to prioritize the pipeline as well. But everything that you've seen across all the products, you've heard our story.

The candidates that we think we'll read out over the coming years that are we believe will be launched in those respective years, '26, '27, '28 have always been prioritized and will continue to be prioritized. We made a decision on a lot of the Phase 3 trials, which is what Stephen was just referring to and the answer to the question, that we will not be able to take those to phase three until we actually see that we can break even and can afford those Phase 3 trials. So that was some of the prioritization that we had to do as well.

Elizabeth Webster - *Goldman Sachs Group Inc - Analyst*

Hi, this is Elizabeth Webster, from [Salvi Richter's] team at Goldman Sachs, and we wanted to ask about the opportunity for RSV to come into play, in the growth story in a bigger way, and could that be an upside lever and then, framing what you would like to see at the interim for the norovirus Phase 3 next year.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Okay I'll take the first step. We do hope RSV becomes a growth driver as well. It is built in to some of those strategic partnerships. And so when we highlight UK, Canada, and Australia, I'll remind you those are across our entire respiratory portfolio. So not just COVID and RSV and flu and the combination, all of those are built in. And so it is an important driver internationally to expand. And as I highlighted, as we move into Europe, we do expect it to be a contributor as well.

In the United States, it has been, there was a very rapid launch in that first year, and there has been a bit of a waiting game for the re-vaccination year for our opportunity to present itself. We did show up a year after that first wave of vaccination. We have had some wins. We want a VA contract. We're slowly and steadily adding to our share, and we're getting ready for that re-vaccination, but that determination will be made by public health, not by us. So, as we expand internationally, we do expect RSV to be a contributor.

Unidentified Company Representative

And then in terms of norovirus and what we're hoping to see at the interim analysis, I think it's pretty typical of what we want to see. We want enough cases to be adequately powered to give us a potential shot on goal in terms of vaccine efficacy.

We also want to conduct a futility analysis. So we're investing in a cohort here to capture a certain number of cases and we want to understand from our DSMB without unblinding data but just are we in the right direction or not. So we anticipate that later next year.

Unidentified Participant

Hi, I'm [Luinsongo] from Learing Partners on behalf of [Money forarar]. I wanted to touch on, the projection in terms of cost reduction, specifically as it relates to R&D. Regarding the vaccine franchise specifically. So you'd mentioned that you expect a reduction given the completion of the Phase 3 studies. I wanted to understand, can you give us a little color in terms of, what type of post-marketing studies are baked into your assumptions as it relates to the two COVID programs as well as the flu program and the vaccine.

Unidentified Company Representative

Yeah, so, thanks for the question. So we actually did bake into those assumptions that need to do, some post-marketing work. So our assumption is that we will be starting actually imminently, the post-marketing commitments that we have in COVID. One of them is actually already well underway. The second one is starting soon.

And then, we have plans that in flu, we may need to do some post-marketing work, certainly on the safety side, potentially on the effectiveness side, as well, but, I think the flu efficacy data is really what we were, waiting for. It is controlled against flu vaccine that's licensed in the US, so we're really confident in the strength of those data.

Unidentified Participant

Maybe just a follow-up for the COVID component does it include post-marketing studies for the below 65H.

Unidentified Company Representative

It does, actually. So we have, taken FDA guidance, had some back and forth on what they need to see from that study design, and like I say, one of them, the immunogenicity one is ongoing and we're looking to start the effectiveness one soon.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

And I think Jamie alluded to that, there is a little bit of an artificial elevation of that number compared to what we expect the maintenance to be in '26, and a little bit into '27, related to the new postmarketing commitments that the US FDA asked for. Outside of the US and the rest of the world, we've already really transitioned to that more standard postmarketing number.

Unidentified Participant

Great, thanks. I'll try to squeeze in two, if I may. So, I, first, I really enjoyed the redosing data on mRESV. I found that really compelling. Where are the regulators currently in terms of considering, recommending redosing for adults or the currently approved population? And then I have another quick kinda high-level question if I may.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Yeah, I think, maybe I'd say it's probably not a regulatory decision on when re-vaccination happens, right? Again, this is re-vaccination. And so the decision on when we see waning of efficacy from a respiratory vaccine and when that public health benefit is sufficient to justify paying for an additional dose, in most countries it will be made by NItags, not by regulators.

Ultimately, in the US that's the CDCACIP. What you're starting to see in some of the real world effectiveness data is, and this has come out for all three vaccines, is there's pretty substantial weaning, by year-2, and by year-3, we'll look to more data, but we do expect it to be down. If you have high risk factors, immune compromise of some form, it's actually happening even really after 1-year.

And there's a ration. Now to be made, to put forward for protecting those at higher risk even more frequently than let's say every 3-years to 5-years. So I'd look for that to be the first place you'll see movement, and probably you'll see it through the recommending bodies first, not regulators.

Unidentified Participant

Yeah, that makes a lot of sense. And then kind of a high-level question. So as we think about, individualized neo-antigen therapies versus shared antigen, therapies. What do you really see as the future playing out? Like, the, immunogenicity data that you shared was pretty compelling. I mean, why would you ever not go with an individualized therapy if you're getting that kind of unique response to the INT?

So, how do you guys kind of see the this developing obviously near term it'll be whatever it's approved for, but longer-term when you have multiple, approvals, where do you think INT might be appropriate versus shared antigen?

Thank you.

Kyle Holen - *Moderna Inc - Senior Vice President, Head of Development - Oncology*

That's a great question. So, couple of comments I'd like to make about that question. One, we need to learn more about the populations that really would benefit from a personalized approach versus a shared approach. And we're learning more about that, and we'll learn more when we have our Phase 3 data and when we have more data on 4359.

I think there could be some populations that might benefit from one versus the other. But of course, the obvious challenge with INT, as amazing as [JAR] is on getting that turnaround time to happen, there are patients with bulky metastatic disease who are diagnosed who need therapy immediately. They can't wait even 6-weeks to receive INT. And I think for those patients, it's really important that we have some off the shelf options that we can deliver to those patients and they can get the benefit of that therapy immediately.

There's also a world where you can combine these therapies. You can say, hey, let's get the benefit of both to these patients. Let's give them access to an individualized treatment as well as start them off on a off the shelf product, and that way they could have a better chance of efficacy from these programs. So, I think there's a series of potential scenarios that could play out. And we'll have to make decisions based on the ongoing data that come in. Anything you'd like to add Rose on that? Okay, or Jackie?

Stephen Hoge - *Moderna Inc - President*

Right, thank you.

Alex Hammond - *Wolf Research - Analyst*

Alex Hammond, Wolf Research. Just one quick follow-up on RSV. Do we now have a correlate of protection? And then on the Lyme disease vaccine, I'm very excited about that. Would you expect this to be a vaccine you're going to be getting in like every couple of years, every year, how should we think about that re-vaccination?

Unidentified Company Representative

Yeah, thanks so much for the question. So starting with RSV and the correlative protection, so I think at one of these previous meetings, we actually talked about the work that we did to establish the correlative protection, which we had previously presented at ACIP and it's actually been pretty well received by the regulatory authorities.

It's how, for example, we were able to expand the indication to 18- to 59-year olds. So we actually are utilizing that work a fair bit and as you saw, the immunogenicity data is really the booster data that we've generated in order to unlock that potential indication. Second question on Lyme disease and how we're thinking about dosing.

So, I'll say it's always dangerous to compare assay to assay. We know that assays can be different when in different hands, but we're seeing incredibly robust, antibody titers relative to some of the competitive data that are out there with all of those caveats in mind. And so, Our thinking is actually, we want to explore in Phase 2, about how we can reduce that dosing, particularly in the primary series as much as possible because in that first offseason three is a lot of doses to get into place and there's not a lot of wiggle room for people to miss doses.

Subsequent to that, I think it's a similar story to RSV or NORRO as I've been describing, it's going to depend a lot on observing what happens in the real world, but we would imagine that The booster actually could be administered as a single dose, just like with other boosters, and that could be done in advance of the season, obviously at a different pre-season time than currently, but it's the way that we're thinking about it as a seasonal vaccine that may actually be able to go a few years in between needing re-vaccination.

Unidentified Participant

Great, thank you. [Woody Pogla] from Bernstein on behalf of [Courtney Breen]. Just wondering if you could talk about the program discontinuations announced this morning. Aside from CMV, what was the rationale and what was the framework you used to make the decision? Was the data not sufficient, or are there still options for partnering?

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Maybe I'll start and ask you guys to fill anything I missed. For the most part, it's, product by product will have different answers, but the broad strokes are as we look to prioritize and drive towards break even, and we look at the next step investment often in those programs, a large several $100 million Phase 3, we have a specific bar for the return on that investment.

It has to really contribute meaningfully to our growth trajectory, and we have to view it as more valuable for the long-term than other programs we have in our late stage pipeline across all of the pipeline, including oncology, rare diseases, and what we're doing in the vaccine space right now.

The ones that we discontinued, in different ways for different reasons didn't meet that bar. They didn't feel like the commercial opportunity justified the level of investment necessary for us to do it. Even if we viewed it as value creating, we have a very tight, we have a very high bar as we drive towards break even as Jamie has reiterated again today.

Unidentified Company Representative

And maybe I can just add, I've been actually asking for some of this clarity on some of these programs for a bit because as Jamie mentioned, If we have to cut an R&D once we go into human clinical trials, there's actually a burden of work regardless of whether you're actively vaccinating or not.

And so, somewhere where we're winding down and it's not clear that that's a program we would prioritize, actually, it really helps me manage the workload and the staff if we can just stop. So I think that was another piece of it, is to prioritize within latent, what we would go and do next, which I think you heard from Steven is very much EBB in one.

Lavina Talukdar - *Moderna Inc - Head - Investor Relations*

Okay, we'll take our last question from Myles.

Myles Minter - *William Blair & Company - Analyst*

Thanks, sneak in there. Just on the 1010 vaccine efficacy data, looked pretty compelling, quite provocative versus standard of care there. So, there are some safety considerations, obviously, but just wondering how you see that as a commercial opportunity if you did have a claim to superior efficacy to what we're taking today, especially in such a large market.

Stephane Bancel - *Moderna Inc - Chief Executive Officer, Director*

Yeah, we, that's why we highlight that as a really '27 growth driver. Now, we hope, we're filing now. We hope to have that product approved. If everything goes well, in a year, but we'll probably miss the '26 season, but we really want to step into 2027. We think it's an enhanced profile, ultimately, regulators will get a chance to review that and offer their perspectives.

And we want to launch it globally. And so you'll see us in the United States, which is a, obviously is an enhanced market, but actually across Europe, as I tried to highlight as well, we see this as a big opportunity. And then as I alluded to, it is built in to our contracts, our strategic partnerships with the UK, Canada, and Australia, and beyond.

So, It is a, we tried to do two major growth drivers in each of the years, and the one place we allowed ourselves a third is in 2027 because it is between Europe, between expanding in Latin America through that partnership with Brazil and flu. We think there are multiple shots that get us there.

Stephen Hoge - *Moderna Inc - President*

Thank you, Stephen. So this concludes the formal part of our annual analysis. So thank you so much for coming. I suggest we take a 10 minute break to grab a coffee outside, and then for those of you who can stay, we have a team that does some interesting AI demos for you. Stay tuned, speak soon. Thanks.