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EDITED TRANSCRIPT

PFE.N - Pfizer Inc Virtual Investor Day: Day 2

EVENT DATE/TIME: SEPTEMBER 15, 2020 / 2:00PM GMT

REFINITIV

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PRESENTATION

Charles E. Triano *- Pfizer Inc. - SVP of IR*

Welcome back, and thank you for joining us this morning for part 2 of Investor Day, where we will cover the remainder of our key R&D programs. Today, we'll hear from our immunology and inflammation, oncology and rare disease teams, and then we'll end with a segment on our COVID vaccine and antiviral programs.

As a reminder, presentations at today's session include forward-looking statements about, among other things, our anticipated future operating and financial performance, business plans and prospects and expectations for our product pipeline, in-line products and product candidates. By their nature, all statements about future events and expectations for our pipeline products are forward-looking. Each forward-looking statement contained in these presentations is subject to risks and uncertainties that could cause actual results to differ materially from those in such statements. Additional information regarding these factors appears in the slide entitled Forward-Looking Statements and Other Notices and under Risk Factors in our 10-K and 10-Qs. Forward-looking statements in these presentations speak only as of the original date of the presentation, and we undertake no obligation to update or revise any of these statements.

As was the case with yesterday's presentations, the slides that will be presented during this call will be posted on pfizer.com/investors after each session. You can also find today's speaker bios and the day's agenda on a separate tab on that site.

As with the format yesterday, there will be time for Q&A via the operator following each business unit's presentation.

So before we dive into our I&I programs, we first like share a video featuring Steve, an atopic dermatitis patient.

(presentation)

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Now I would like to turn it over to our I&I leadership team.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

So that was Steve. I met Steve late last year, and his story reminds us of how inflammatory diseases are so underappreciated. It's so easy to fail to understand the suffering. And we hear things like, "Well, it's just a bit of swelling. It's a digestive issue. It's just a rash." It isn't. It's a life blighted by inflammation affecting self-confidence, relationships, employment prospects and limiting daily activities. And Steve reminds us, too, of the transformative potential of modern medicines because after a life of living by the ocean, when he found a treatment that really worked for him, he went into the sea for the first time in his 50s.

So good morning, everyone. I'm Richard Blackburn, and together with my colleagues, Mike Corbo and Mike Vincent, we lead the Inflammation & Immunology category here at Pfizer. And over the next decade, we will bring breakthroughs, not just for people like Steve with skin conditions, but many others with gastroenterological and rheumatological ones as well.

Now maybe you think of us as tenured in this therapeutic area given our involvement with Enbrel since the 1990s. Maybe you also see us as innovators given our launch of XELJANZ, the first JAK inhibitor for rheumatoid arthritis back in 2012. Well, the time has now come to also see us as leaders in I&I research and development based on the strength and breadth of our pipeline and the exciting range of treatments that we expect to make available in the coming years. We're confident about our potential to change lives with this portfolio, and we want to share some of the reasons why. But I really want to start, though, with 2 simple messages. Firstly, the unmet need in inflammatory disease is enormous and so therefore is the opportunity for innovative new medicines. And secondly, delivering for patients depends on matching the right treatment to the right condition.

So firstly, the unmet need. Let's just consider the U.S. over 2 million people suffer with inflammatory bowel disease, 3 million with rheumatoid arthritis and over 30 million people with atopic dermatitis, and that's just for the U.S. population. Obviously, there are millions more suffering worldwide. Now some of those conditions, such as rheumatoid arthritis and IBD, are widely treated with biologics and other advanced agents. But

today, a huge proportion of patients are still unable to achieve remission. And some other conditions, such as alopecia areata, today have no licensed therapies anywhere. That's another autoimmune disease characterized by hair loss. More than 1 million people live with moderate to severe alopecia areata in the U.S. alone, and it can have a profound impact on people's quality of life and emotional well-being, sometimes even leading to severe depression. So I'm excited that we're on track to potentially bring a first-ever FDA-approved therapy for this condition.

Let's go back to those 30 million U.S. patients with atopic dermatitis. 1 out of 3 of those patients has moderate to severe disease. And today, out of the 6.5 million adults living with moderate to severe AD, only 2.6 million are treated with a systemic therapy and as many as 1.6 million are uncontrolled. Now patients' expectations have rightly been raised in the past couple of years for the introduction of new treatments, but not all patients receiving advanced therapies achieve clear skin. So more alternatives are needed. And there's also an opportunity to focus on the defining symptom of itch, which is a top priority for patients. And you heard from Steve about how everything starts with itch. He's not alone in that. Research has shown that itch is the most bothersome symptom for the majority of patients with AD and the ones that they most like addressed with treatment.

And my second key message is that as more therapies become available, finding solutions for the remaining needs of patients demands us to look at multiple options. There's no such thing as the right medicine for everyone. There is no silver bullet.

Now our aim today is not to take you through the whole pipeline here. But across rheumatology, gastroenterology and dermatology. We're progressing multiple projects. We're studying 5 new immunokinases alone and in combinations in oral and topical formulations across 10 diseases, but our research efforts extend well beyond JAKs with 3 biologics, each with novel mechanisms in Phase 2. And this year alone, we have 4 proof-of-concept readouts, featuring 3 separate molecule.

Now our approach is not one of developing a single molecule for multiple different indications. It's obviously unlikely that any medicine will represent a breakthrough option in, let's say, 6 different diseases. Our approach is to purposefully match the right molecule to the disease where we believe it can make the most difference. But what emerges for patients from our pipeline will only be breakthroughs. We're setting a high bar for what we'll move forward. We're not interested in just another option for RA. We'll only bring to patients a medicine or combination of medicines that will significantly increase the percentage of patients achieving remission compared to current best care. And we'll only launch a medicine in atopic dermatitis if it meets needs that aren't fully addressed by what's available today.

Now in a moment, Mike Vincent will tell you more about our purposeful approach to match the right treatment to the right condition. He'll illustrate it with just 2 examples from our Phase 2 and 3 immunokinase portfolio. And then Mike Corbo will talk in-depth about abrocitinib, our exciting Phase 3 compound that has FDA breakthrough designation for moderate to severe atopic dermatitis.

I'll close my remarks by saying that we are highly optimistic that we are poised to help hundreds of thousands more people like Steve in the years ahead.

Now here's our Chief Scientific Officer for I&I, Dr. Mike Vincent. Mike?

Michael S. Vincent - *Pfizer Inc. - Chief Scientific Officer, Inflammation & Immunology*

Thank you, Richard.

You just heard about the breadth and depth of our pipeline, but let me focus in on our immunokinase portfolio to illustrate our overarching scientific approach. Our strategy is to purposefully match candidates with unique selectivity profiles with the disease or diseases where they hold the greatest potential to release suffering. One point I want to leave you with today is our scientific perspective on differing cytokine inhibitory profiles within the JAK class. As illustrated by the distinctive shapes in each of these spidergrams, we believe these unique selectivity profiles will translate into differing efficacy and safety profiles across diseases. And our scientific view is now supported by a growing body of clinical data, some of which we'll share with you today.

JAK pathways play an important role in inflammatory processes involved in signaling for over 50 cytokines and growth factors, many of which drive immune-mediated diseases. For each of our JAK inhibitors, we have a molecule that's design corresponds, not just a broad immunosuppression, but to the function driven by specific cytokines and corresponding immune cells that drive disease.

For example, in contrast to an agent that inhibits only IL-4 and IL-13, our JAK1 inhibitor, abrocitinib, also targets IL-31, which is a cytokine that's believed to drive itch that torments the AD patients and is generally regarded as the most burdensome aspect of their disease. And our JAK3/TEC inhibitor, ritlecitinib, has a unique activity, shown at 6 o'clock in the spidergram, of blocking CD-8 T-cell killing, which is widely believed to be a key mechanism in the immune system's attack on the hair follicles in alopecia areata.

Our brepocitinib molecule, which I'll share some new data on today, covers some of the same cytokines I mentioned a moment ago that are associated with AD but also inhibits IL-23, which is a key cytokine-driving Th17 inflammation commonly associated with psoriasis. You'll notice the molecule on the right does not have a spidergram, which is because there's 0 overlap with JAK-dependent cytokines. Instead, IRAK4 is downstream of a range of receptors that collectively trigger inflammation in response to danger signals as you might find in an inflamed joint. This was the first IRAK inhibitor to enter the clinic and the first and only to show efficacy in a Phase 2 study in RA, and we have just initiated a Phase 2 trial in RA in combination with tofacitinib or ritlecitinib.

Now to provide some evidence that our strategy is sound, we'll show a few examples of recent data for investigational molecules that, if approved, have the potential to be breakthroughs for patients. I'd first like to turn to our ritlecitinib program for alopecia areata, which has been granted breakthrough designation by the FDA, and it could potentially be the first-ever approved treatment for this disease.

This slide shows the data we first presented at EADV in 2018 and formed part of the data package on which the FDA granted ritlecitinib breakthrough therapy designation. You can see the hairy growth of the patients shown in the study pictures at 12 and 24 weeks of treatment. Positive Phase 2 data showed that the use of ritlecitinib resulted in improved hair regrowth on the scalp relative to baseline at week 24 as measured by the Severity of Alopecia Tool, or SALT, which is scored on a 100-point scale. In addition to meeting the primary efficacy endpoint, ritlecitinib also met all the secondary endpoints in the study and was well tolerated.

Ritlecitinib is currently in a pivotal Phase 3 clinical trial for the treatment of patients with moderate to severe alopecia areata, and we expect top line results in the third quarter of 2021 and a potential filing by early 2022. As a result, we could bring the first-ever approved treatment for alopecia.

I'd now like to transition to another exciting molecule that we're looking to advance to Phase 3, brepocitinib. It's important to emphasize here that matching the right molecule to the right patient includes understanding its formulation properties. We recognize that brepocitinib, our TYK2/JAK1 inhibitor, could be delivered in a convenient daily topical cream formulation, creating a potential novel topical treatment option for patients with a variety of inflammatory skin diseases.

The diagram on the left illustrates a couple of the key activities of brepocitinib. The inhibition of TYK2 blocks the Th17 axis, which is believed to be important in psoriasis and some forms of atopic dermatitis. And the inhibition of JAK1 blocks the Th2 axis, which is believed to be a dominant pathway in atopic dermatitis. Our Phase 2 data for topical brepocitinib in patients with mild to moderate AD indicated a strong dose-dependent efficacy signal with 42% of the patients in the 3% once-daily cohort achieving EASI-90 by week 6, which is really encouraging given that EASI-90 reflects 90% reduction in the score measuring in AD patient's inflamed skin. These data illustrate the concept I described on the spidergram blot a few slides ago, and that this particular selectivity profile shows the potential to provide meaningful benefit to patients with mild to moderate atopic dermatitis.

And I should note that we have an ongoing Phase 2 psoriasis study to explore the full versatility of this agent's diverse cytokine inhibitory profile. That benefit is further illustrated by these images. Here, we see a patient journey over 6 weeks of using topical brepocitinib at the 1% dose, a 20-year-old white male. After 2 weeks, we saw a 50% improvement in the EASI score. And after 6 weeks, we saw an 83% decrease in EASI score from baseline with almost no visible symptoms.

And now I'll hand it over to Dr. Mike Corbo, our Chief Development Officer, to continue our discussion on atopic dermatitis, and he'll walk you through our abrocitinib development program.

Michael Corbo - *Pfizer Inc. - Chief Development Officer, Inflammation & Immunology*

Thanks, Mike, and thank you for sharing some of the new data from our emerging pipeline.

As you may be able to surmise, we are committed to the patients that we serve across our portfolio. In AD alone, we have introduced the first topical PDE4 inhibitor, what we hope to be the first and only dual acting to the JAK1 topical and potentially the first and only dermatology-specific JAK1 inhibitor in atopic dermatitis. This is the right way to address our patients' needs.

While you saw some of the pictures for a mild to moderate AD patients in Mike's presentation, this is what a severe patient looks like. As you've heard today, living with AD is not easy. This is the type of patient we hope to treat with abrocitinib. We have a highly focused development plan for abrocitinib in AD.

The core program consists of 2 placebo-controlled monotherapy studies and 1 placebo-controlled active comparator study. The results from these studies form the core basis of efficacy for our filing. We now have the results from all 3 of the efficacy studies, and we have accumulated the required long-term safety data and have submitted the NDA to the FDA. We have also completed the JADE TEEN, which met all its primary endpoints. Later this year, we will receive top line data from JADE REGIMEN, which should be helpful in understanding dose flexibility in the future.

We will now look at some of the relevant data from JADE MONO-1 and MONO-2 and COMPARE. As you've already seen, the primary endpoints for the 12-week MONO-1 and MONO-2 studies, we're going to focus on raising the bar higher. So first, looking at the EASI-90 over time. Basically, this looks at a 90% improvement in signs and symptoms. Here, we have pooled the data from both monotherapy studies since the trial designs, and results were very similar. You will notice a very rapid onset and substantial portion of patients achieving an EASI-90 by week 12 for both the 200-milligram, once-daily dose in red, and the 100-milligram dose in dark blue. Placebo is in gray. Importantly, in our long-term, open-label, safety extension, using as-observed data, we continue to see improvements in signs and systems through week 24.

As you've heard earlier directly from a patient, the one symptom that is most bothersome and worrisome for patients is pruritus or itch. In that regard, we can look at the improvement in the itch or pruritus score over time, again using MONO-1 and MONO-2 pooled data. Looking over the first 2 weeks, you can see a very rapid onset beginning as early as day 2 after just one dose for both the 200-milligram dose in red and the 100-milligram in dark blue. Again, placebo is in gray. Importantly, these results are sustained throughout the 12-week duration of this study. So beyond just being fast, abrocitinib has an effect on itch that's also durable, which is critically important to our patients.

While the overall safety profile has already been presented, we thought we would focus on some events of special interest for MONO-1 and MONO-2. As you will note, we did see a dose-dependent increase in nausea. The majority of these cases were mild to moderate and occurred shortly after dose initiation and were self-limiting. One thing we have noted is that when abrocitinib is taken with food, the nausea can be mitigated. As expected in this population and with JAK inhibition, we did see herpetic infections, including herpes simplex and herpes zoster, which were dose-dependent. The overall safety profile is well understood in the clinical trial environment to date, and many of these events can be managed with well-established mitigation approaches. Of note, we have not seen an increase in serious infections at this point in time in the development program.

Moving on to COMPARE. As you are aware, we reported top line results from the study earlier this year. This was a 4-arm, randomized, placebo-controlled, double-dummy study. The study allowed for concomitant topical steroid use, consistent with dupilumab labeling. The study met all of its primary endpoints. Also, a key secondary endpoint, abrocitinib at 200 milligrams, was superior to dupilumab at 2 weeks in the improvement of itch.

Again, pruritus is the primary concern that patients have with atopic dermatitis, and we're encouraged to see a rapid and sustained response addressing this key feature of the disease. However, as we have said previously, we always need to strive to do better for patients beyond the standard measures, so we can look at some higher-level responses from the secondary analyses next. Again, we need to always strive to do better.

One way to look at this would be to look at resolution of itch, not just reduction, but resolution, and looking at it just after 2 weeks. Resolution of itch is defined as a score of 0 or 1 in the PNRS score, so essentially complete relief by week 2. Note that the baseline median score for patients in the study was 7, so we're talking about a very substantial improvement. Moving left to right, we can see that the placebo had 4.6% of patients with

resolution of itch. 100-milligram abrocitinib, around 9%. The 200-milligram abrocitinib dose at 15% and 4.6% in dupilumab. If you can think about this, this is resolution of itch in just 2 weeks in moderate to severe patients. This is the goal we need to strive for.

Now let's look at the EASI-90 over time in JADE COMPARE. Again, focusing on 90% improvement, we can see the results from abrocitinib 200 milligram in red with a substantial proportion of patients rapidly reaching an EASI-90. Nearly 50% of patients achieved this level of relief by week 16. 100 milligram in dark blue also has a rapid onset. And dupilumab is in green, which appears similar to the 100 milligram by week 16. Again, placebo is in gray. We are encouraged by these results, and we've used these data to design an additional head-to-head study, which is already initiated.

Turning to safety. We've observed a profile for both doses of abrocitinib that was consistent with our prior monotherapy studies. Qualitatively, the types of events seen in the abrocitinib arm were consistent with the monotherapy studies, and the dupilumab arm was similar to published literature and product label. Now while it's always good to look at data, it's more important to understand what do these numbers actually mean when it comes to a patient.

If you recall the picture of the gentleman that I showed you in the beginning of this section of the presentation, this is a patient with severe AD, but he was a participant in the 200-milligram arm in the MONO-2 study. Well, this is what an EASI-90-plus responder looks like. This is the reason we do what we do and why we're excited about abrocitinib's breakthrough potential.

I hope that we've given you an appreciation for the commitment and the dedication that we have at I&I for our patients. I'll now turn it back to Richard for some closing comments.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

So what Mike just shared is a genuine potential breakthrough for patients with moderate to severe atopic dermatitis. While recent product introductions for these patients have represented real advances, the unmet need in AD remains enormous. Today, only 40% of suitable patients are receiving an advanced treatment. And as new systemic treatment options become available, we expect more usage. Physicians and patients have told us that rapid efficacy against itch, dose flexibility and the convenience of oral administration are highly attractive. And backed by the experience, relationships, geographic reach and resources of Pfizer, we are confident we can make a significant impact. And abrocitinib represents just the first awards to come.

You've seen also why ritlecitinib is a potential breakthrough for alopecia and potentially for vitiligo, too. And even with conservative assumptions about diagnosis and treatment rates and usage of our new medicines, we can model significant potential global peak revenues for both. Beyond that, we intend to bring forward additional breakthroughs with a significant remaining unmet need in a range of other conditions, always with our criterion that nothing comes to patients that doesn't offer an advantage over what is currently available.

So as a reminder, 5 immunokinases, oral and topical, being researched for 10 separate conditions as well as 3 other modes of action in Phase 2. We have the potential to help brush the landscape of inflammatory diseases. Our purpose is to change lives, and this portfolio, we believe, will deliver the power of that purpose.

Now I'll turn it back to Chuck to facilitate the question-and-answer session.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thanks, Richard. Okay.

Now our I&I leadership team is available to answer your questions about their pipeline. So operator, can we please now pool for questions for the I&I team?

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from the line of Umer Raffat from Evercore.

Bo Chen - *Evercore ISI Institutional Equities, Research Division - Research Analyst*

This is Bo for Umer. Just a quick one on the abrocitinib COMPARE data. I was curious to see that the SAE rate for the 200 mg is higher than 100 mg, but the duration and -- the discontinuation is actually lower than the lower dose. Just curious on the general thoughts on how do you see the duration of treatment on abrocitinib for the atopic derm patients.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Okay. Thanks for the question, Umer (sic) [Bo]. I'm going to hand over to Mike Corbo to address the specific question about from the COMPARE data, and then maybe I'll just make a couple of follow-up comments. So Mike, do you want to address the question about the dosage there?

Michael Corbo - *Pfizer Inc. - Chief Development Officer, Inflammation & Immunology*

Sure. And thank you for the question. Thank you, Richard. The -- in the COMPARE data or the 200-milligram data, there were really not a large difference with SAEs across the board. In general, I think we see a relatively low SAE rate across both the 100 and the 200 milligram. These do not seem to increase over time if you were talking about duration. I think, primarily, what we do see are obviously some initial nausea, vomiting in the beginning, which does fade over time. But as far as SAEs go, we do not see that increasing over the time and shouldn't impact the duration of therapy. Hopefully, that addresses your question. Richard, I can go back to you.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Yes. I mean I think you've covered it, really, Mike. We see abrocitinib as an exciting new option for patients. You've heard in our presentation just how significant the unmet need is and how great the need for new options are. We see abrocitinib as providing physicians exactly what they're looking for, a rapid onset of action, profound and early impact on itch and a sustained efficacy over time. So we see this as an ideal agent for long-term use in patients with moderate to severe disease. I hope that covers the question, and maybe we can go to the next one.

Operator

Your next question comes from Geoff Meacham from Bank of America.

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

Just another one on abrocitinib but more higher level. I just wanted to ask on the commercial positioning. Clearly, the JAK class is pretty crowded. I wanted to ask you how you think the -- what would you say the biggest attribute, the differentiation point is? And then when you look beyond atopic derm, does that same sort risk-benefit profile also hold with respect to differentiation?

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Okay, Geoff. Thanks for the question. So you said that the JAK space is becoming crowded, I guess the first thing that I would say is that the fact that other companies are investigating JAK inhibitors in atopic dermatitis and indeed other conditions rather reinforces our confidence in the value of this mechanism. It's, I think, too early for us to make any comments about potential differentiation between JAK inhibitors in atopic dermatitis. While data is emerging for other compounds, there are no comparative studies available at this point and probably too many differences between development programs to be able to kind of make a definitive statement.

But I will kind of pause here and ask if Mike Corbo would just like to make a couple of comments about potential differences, and then I'll come back and talk about -- a bit more on the commercial position. Mike?

Michael Corbo - *Pfizer Inc. - Chief Development Officer, Inflammation & Immunology*

Okay. Thanks, Richard. And thanks, Geoff.

I think, in general, it's going to be hard to -- as Richard said, to be able to show any kind of an understanding without doing a head-to-head study for differentiation. But I think if you go back to our development philosophy and how we're developing the variety of different JAKs that we have in our portfolio, you can see that we are being very specific.

So for abrocitinib, it is strictly a derm molecule, right? So its next hopeful expansion will be within the derm space. So from a differentiation perspective, abro will be dedicated to dermatology. Again, as we look at our profile, we're lucky that we have so many different varieties of JAK profiling. And it allows us to look at different therapeutic areas, a little bit more focused. And that way, we can direct our benefit-risk to a specific therapeutic area. Richard?

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Yes. So I think the one thing I would want to add is, in your question, you said it's a crowded space between JAK inhibitors. One thing I'd just like you to kind of really remember from our presentation is just how huge the unmet need is, particularly in moderate to severe atopic dermatitis. There are 30 million patients in the U.S. suffering, maybe 27 million that have -- that are aged over 12. Only around half of them are treated with a prescription medicine today, and a small proportion of those get a systemic treatment, less than 20%.

We see an enormous opportunity for a great increase in the systemic treatment of this condition as more new agents become available. And one of the reasons we're confident about that is, of course, that's exactly what we've seen in the psoriasis market, the availability of new, effective systemic agents, leading to a significant increase in the proportion of patients treated. We think that same revolution is coming to atopic dermatitis.

So I guess my point is that this isn't a zero-sum game between new agents competing for a very small number of patients. Actually, the opportunity is to greatly expand the effective treatments, and we're confident that that's going to happen. And we're introducing abrocitinib, we think, exactly at the right time, the right profile coming into the market at the right time.

So I hope that covers the question. Thanks very much.

Operator

Your next question comes from Steve Scala from Cowen.

Stephen Michael Scala - *Cowen and Company, LLC, Research Division - MD & Senior Research Analyst*

I apologize if I missed this. I had some webcast issues, but the topical JAK inhibitor is scheduled for launch in atopic dermatitis in 2025. This is 4 years post the possible launch of topical ruxolitinib by Incyte. So how is Pfizer seeking to differentiate? And will the topical JAK be looked at in vitiligo?

And then a second question, which I was unable to ask yesterday, so allow me to ask it now. The 6%-plus revenue growth for the company overall, yesterday, it was said to be risk-adjusted. When Pfizer has described growth in the past, words risk-adjustment don't seem to have been used. Is this a new disclosure? And if so, what does it imply about Pfizer's confidence in the outlook?

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Okay. Steve, thanks for the 2 questions. The second one, obviously, is not specific to the Inflammation & Immunology portfolio. So I'll just pause and ask if, Chuck, you'd like to kind of take that one first, and then we'll deal with topical ruxolitinib?

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Yes, sure. Thanks, Richard. Yes. So Steve, what we were showing yesterday on an unrisk-adjusted basis was -- we showed 2 numbers. We showed a total value of the pipeline. That was $35 billion to $40 billion, again to caveat that not all of those assets hit peak sales, of course, in the same year, but that's an amalgamation of all the assets and their peak sales in each given year. The unrisk-adjusted number we showed on Angela's slide when we showed what we need to get to achieve the 6% growth, we showed that we had a very large buffer, be it well beyond a 6% CAGR on an unrisk-adjusted basis, and then we risk-adjusted it back down to show you how we hit the 6%.

But I think the main message here is this is not a story about just 1 or 2 assets, either in market or in the pipeline, that need to hit. It's a broad portfolio approach, both on the end-market programs that Angela went through and then within some of the pipeline programs here.

So yes, the disclosure was new on the value on an unrisk-adjusted basis, Steve. We had not put those numbers out up until yesterday. And you're correct. Up to now, we've been saying that 6% is-risk adjusted. So we showed you -- they basically gave you some context around the confident intervals in a sense on the risk-adjustment rate. So -- but I think that's the key takeaway. We have a lot of cushion, and we have multiple programs all contributing, potentially contributing to this growth over that time period.

So I hope that helps, and I'll turn it back to Richard now for the -- for your other questions.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Thank you, Chuck.

So Steve, your other question related to topical ruxolitinib, and I think probably both Mikes will want to comment on that. So Mike Vincent, maybe we can go to you first and just talk about what we see and the question relating to our profile versus that of the Incyte product. And then Mike, you may want to add a little bit. So Mike Vincent.

Michael S. Vincent - *Pfizer Inc. - Chief Scientific Officer, Inflammation & Immunology*

Sure. Thanks Richard, and thanks for the question.

We think there remains an incredible need for other topical formulations for patients with mild to moderate disease, where symptom relief can be achieved via direct action on the skin, minimizing systemic exposure. We're aware of competitor data. We haven't seen all of that yet, but we think that the EASI-90 responses we've seen with topical brepocitinib are very strong in the 40% range with a single-daily application. And the other

feature of brepocitinib that we like and think will add to the differentiation is its ability to hit multiple inflammatory pathways like the Th17 axis, which we think will be useful in psoriasis.

Currently, we have an ongoing study in psoriasis, in addition to the AD program. We haven't yet initiated work in vitiligo, but that's something that we'll certainly consider in the future. And maybe I'll hand it to Mike Corbo to talk a little bit about the differentiation strategy.

Michael Corbo - *Pfizer Inc. - Chief Development Officer, Inflammation & Immunology*

Okay. And thanks, Mike, and thanks for your question, Steve.

In addition to what Mike said, we do think, given its dual activity that we do have the potential to work effectively in the GH17 phenotype that you do see in AD. So that's one differentiator. As Mike mentioned also, QD dosing is also a potential advantage. We also don't anticipate any limitations in body surface area with application of the drug, and we also intend to start our program with children from the beginning, if we can do that from a regulatory perspective.

And the other key feature, I think, of the late-stage development plan that's important is that we will be including long-term dosing data. That's from an efficacy perspective. We'll look at posology out through 1 year from the very beginning. We do think that's going to be an important feature of the development program. And as Mike mentioned also, having the ability to potentially be treating psoriasis will further differentiate us from rux.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Great. Well, thank you to both of you. And Steve, I hope that addresses the question.

Operator

Your next question comes from Navin Jacob from UBS.

Navin Cyriac Jacob - *UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic*

TYK2/JAK1 looks very interesting. Likely we'll show some very good efficacy. But just wondering about the pathway, the TYK2 being -- some investigators that we've talked to, experts have suggested that regulators may view take TYK2 as part of the JAK class. And as such, there's potential for a broad-based class warning. I don't know if you've had those kind of -- I realize it's very early to, perhaps, be having those kind of discussions with regulators. But how do you view that potential for a broad-based class warning, if this was to get to the market?

And then on alopecia areata, very interesting data that you're showing. Wondering if you could give some color on that marketplace, what the dynamics are, what percent of patients are -- fall into managed care versus Medicare as well as what level of pricing power we should think you can achieve there? What are some of the comps that you're looking at?

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Great. Navin, thank you. Thanks. Two questions there, then. I think for the question on ritlecitinib to JAK1, we'll go to Mike Vincent, and then I'll come back and talk about the potential that we see for ritlecitinib in alopecia. So Mike, over to you first.

Michael S. Vincent - *Pfizer Inc. - Chief Scientific Officer, Inflammation & Immunology*

Yes. Thanks for the question.

So I think it's really important to remember that when you're talking about JAK inhibitors, you're talking about 4 distinct enzymes. So unlike the case with TNF inhibitor or IL-6 inhibitors, it's not really a class. And maybe just to follow up on that example, most of the JAK1 inhibitors have pretty profound inhibitory effects on IL-6. Yet if you look at the graph on ritlecitinib, we have no IL-6 coverage at all. So to expect extrapolation of one label for a particular selectivity profile to another molecule that has a different selectivity profile and inhibits a different group of cytokines, we think is probably not the most scientific approach, and we don't think that regulators will take that approach in any kind of a programmatic way.

So we think you really have to look at each individual molecule, the safety and efficacy profile and the population of your study. Then we think that's how regulators will decide on safety labeling. And let me hand it over -- hand it back to Mike, I guess, for the -- or maybe to you, Richard.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Yes. I'll talk a little bit about the marketplace for alopecia, a condition that is not well understood by many people today but a very, very significant autoimmune disease. Maybe it is dismissed as a cosmetic condition, but that's absolutely not the case. As you heard in the presentation, it has a profound impact on patients' well-being. It affects self-esteem. Patients often experience anxiety and depression. So very much a devastating disease that, today, really has no treatment options, licensed treatment options anywhere in the world.

So patients today either really receive no medical care or they receive off-label treatments, which are either ineffective or particularly unpleasant, multiple steroid injections into the scalp, for instance. So we're really excited about the possibility of bringing to market an agent which will be effective and well tolerated and has the potential to really revolutionize treatment for this group of patients.

What may surprise you is how many of them there are. So an estimated 1% to 2% of the population in the U.S. suffers from alopecia, so maybe 3 million people, of which perhaps 1 million have moderate to severe disease. So it's a significant number, and we think that upwards of 35% to 40% of patients may eventually be receiving an advanced treatment, so a significant opportunity.

I think behind your question, there's a question around will payers be willing to reimburse this condition. We think there is a need for education on the burden of disease and the benefits of treatment, and those conversations are already starting. We understand the need to invest in education for a new market area like this. And we have a lot of experience and track record at Pfizer of launching new treatments into new markets. So a little early to speculate on pricing and so on, but I think I can tell you with some confidence that we think we'll be able to bring this to market with good access from payers around the world. So I hope that kind of gives you enough at this point. So thanks for the question, Navin.

Operator

Your next question comes from Andrew Baum from Citi.

Andrew Simon Baum - *Citigroup Inc., Research Division - Global Head of Healthcare Research and MD*

Yes. A couple of questions, please. Firstly, you've highlighted the fragmented, addressing each submarket with its own JAK inhibitor. In the commercial setting, arguably part of the success of Humira delaying the adoption of some of the novel therapies, including your own XELJANZ. There's been the rebate, the sizable rebates having one drug addressing multiple indications has delivered.

So how do you anticipate addressing this going forward? Are you betting that the rebate system will evolve by the time these drugs reach the market? Or it be driven, you believe, by more compelling data, greater familiarity with oral JAKs? That's the first question.

The second question is, obviously, oncology has very successfully adopted precision medicine, identifying subgroup of patients who are more responsive to a particular mechanism within a broader phenotype. To what extent could you think adopt the same approach with autoimmune diseases, i.e. subgroups of patients who may be particularly JAK1 or IRAK or whatever? And is there a role to some type of basket trial in order to try and segment these individual patient groups?

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Okay. Andrew, thanks for those 2 questions. Let me deal with the first one, and then I'll ask Mike Vincent to pick up on the second one.

So yes, I think you hit on the key thesis, really, behind our development strategy, which is that as more new medicines come to market. What's going to really matter for patients, and frankly, for payers as well, therefore, is differentiation. Are we bringing something which offers to patients a benefit that is not currently available? We think the very best way of doing that to develop a broad range of candidates and match purposely the right one to the right disease. We think that that's the best way to bring value to patients, and ultimately, we think that, that will be recognized by payers.

Of course, the rebate system continues to be a challenge with any new product introduction, but I think you've seen our willingness elsewhere in our portfolio to make the appropriate investments to make sure that we secure commercial access for our products. And as our portfolio grows in I&I and the options, obviously, for contracting become wider as well.

So that's a brief answer to the question. I want to give Mike enough time just to cover the second question about precision medicine.

Thanks, Mike.

Michael S. Vincent - *Pfizer Inc. - Chief Scientific Officer, Inflammation & Immunology*

Thanks, Richard, and thanks for the question.

I think it's an astute observation. And indeed, I think we do see the direction of travel in autoimmune diseases reflecting what's been observed in oncology diseases. And maybe just to point out a couple of examples. We know now that diseases where TYK2 might be particularly useful involve the Th17 axis, IL-12 -- I mean, excuse me, IL-23 and IL-17 signaling seem to be important in driving psoriasis, psoriatic arthritis, ankylosing spondylitis as prototypic spondyloarthropathies.

We also think of our JAK3 inhibitor as a molecule, whereby its mechanism inhibiting cell killing of CD8 cells may be particularly valuable for diseases like alopecia, where sensitive stem cells and the hair follicles are killed by immune cells, and vitiligo may be a similar example. So we do see a similar paradigm emerging in autoimmune diseases, and we think our strategy really plays well to that change in the field. So thanks for the question.

Richard Blackburn - *Pfizer Inc. - Global President, Inflammation & Immunology*

Thanks, Mike, and I'm afraid that's all we've got time for. But thanks for the questions, and thanks to everyone for listening. And I'll pass this back to Chuck.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Great. Thanks, Richard. And thanks to the triad for taking the questions.

PRESENTATION

Charles E. Triano - *Pfizer Inc. - SVP of IR*

So now we're going to transition to our Rare Disease programs. And before we dive into the Rare Disease area, we'd first like to share a video featuring Jake Marrazzo, a DMD patient.

(presentation)

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Now I'd like to turn it over to our Rare Disease leadership team.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

There are approximately 7,000 rare diseases in the world, and fewer than 5% have an improved therapy on market. Further, it is important to note that 80% of rare diseases are genetic, and greater than 50% impact children. And although individually rare, with each disease impacting under 200,000 people in the U.S. and less than 1 in every 2,000 people in Europe, rare diseases are collectively common, impacting approximately 400 million patients worldwide.

We are pleased to see that the global community is responding in a robust manner by engaging and investing in an increasing number of clinical trials, which leads to more robust pipelines and potential double-digit growth for the global rare disease market. The high unmet need, coupled with significant investments in this space, have created both a hopeful environment for patients and an attractive one for investors. Pfizer Rare Disease aspires to be the world's leading innovator in rare disease by pioneering breakthroughs that have a profound impact on the lives of underserved patient populations with unmet needs.

Hi. My name is Suneet Varma, and I'm the President of our Global Rare Disease Business Unit. I, along with my R&D partners, am pleased to have the opportunity to share with you our excitement for Pfizer's growing Rare Disease unit anchored by VYNDAQEL and the transformational pipeline we have built, which includes a robust set of gene therapy programs and underlying capabilities.

By way of brief background, I have more than 25 years in the industry, and I've been with Pfizer for more than a decade, having come over from Wyeth in 2009. I lead the Rare Disease business, along with Brenda Cooperstone, our Chief Development Officer; and Seng Cheng, our Chief Scientific Officer. Brenda and Seng will briefly introduce themselves to you during this presentation. However, you also have access to all of our bios.

The Rare Disease unit was formally established in 2015 in order to further pursue our aspiration of leadership in the space after having made key investments internally in tafamidis and externally with Spark in 2014 and Bamboo in 2016, Sangamo in 2017 and Vivet just last year in 2019. We are incredibly proud of the progress we've made to date and for the exciting future ahead.

Let me share with you our approach to rare disease leadership. First, we are building on a leading in-line portfolio. By extending our current positions in rare hematology and rare endocrine, where we have a 30-year heritage that includes well-known brands, such as BeneFIX and GENOTROPIN, upon which we have now built a pipeline to bolster our presence even further.

Second, we are expanding into 2 new additional therapeutic areas: rare cardiology and rare neurology. In cardiology, VYNDAQEL will continue to drive growth in the U.S., Japan and Germany, and we have many more international launches planned. Further, we have another treatment in Phase 3 today that will augment this franchise. We are also excited to launch new therapies in neurology with our highly anticipated DMD gene therapy program, for which we'll be sharing new details later in this presentation.

Finally, to be a true leader in rare disease, a critical component for us to realize our aspiration is gene therapy. As such, we have made significant investments in end-to-end capabilities that facilitate the discovery, through buying, building and partnering and the development of gene therapies

through our global network of study sites and also to ensure delivery, a full commercial supply at launch, which will be achievable through our state-of-the-art internal manufacturing capabilities.

We are in an unrivaled position to go to market, both commercially and medically around the world, so we can ensure these breakthrough therapies get into the hands of patients.

On this slide, you can see our 4 therapeutic areas horizontally across the top with a reference to our current in-market products, including VYNDAQEL. And along the left-hand side, you can see the development stages of our various clinical programs, which is where we will focus our presentation today. As you can see, we have a robust pipeline with multiple modalities. Let me highlight some key numbers for you. We have 10 products total in clinical development, including 6 new molecular entities in Phase 3, of which 3 are gene therapy programs, all of which will have begun dosing by the end of 2020. We also have 10 preclinical gene therapy programs. Net-net, we have the potential to launch one new medicine every year for the next 5 years.

Today, we will do a deeper dive into the ones highlighted in red. We will start with rare cardiology, and so I will now hand it over to my colleague, Brenda Cooperstone.

Brenda Cooperstone - *Pfizer Inc. - Chief Development Officer, Rare Disease*

Thank you, Suneet.

Hi. I'm Brenda Cooperstone, the Chief Development Officer for Rare Disease, leading our late-stage development. I'm a pediatric nephrologist by training with more than 20 years of industry experience. Throughout my career, my focus and passion has been in rare disease. And recently, it became personal for me as well.

The picture on the right is of me and my father. Just this past year, my dad, Harvey, was diagnosed with transthyretin amyloid cardiomyopathy, or ATTR-CM, at the vigorous age of 83. It was a long and difficult journey to an official diagnosis, even with a daughter who has worked to develop a drug for this condition for the past 7 years. My family is grateful that my father became one of the first patients to be prescribed VYNDAQEL for ATTR-CM, and I'm happy to say that he's doing very well on therapy. At Pfizer Rare Disease, we are all passionate about bringing medicines to patients, like my dad, with the potential to transform their lives.

As Suneet mentioned, we are growing our leadership in rare cardiology, anchored with VYNDAQEL. Our vision is to build a rare cardiac franchise that delivers breakthrough therapies to patients with rare cardiomyopathies, including restrictive, hypertrophic and dilated cardiomyopathy. We have achieved our first milestone for this vision with tafamidis, ensuring patients globally have access to this life-changing medicine with 34 submissions completed or in progress around the world. PF-07265803, formerly known as ARRY 797, and has the potential to be a transformational treatment for patients with a dilated cardiomyopathy caused by an LMNA mutation. Today, I will share with you an update on this investigational therapy and our Phase 3 program, which is currently enrolling.

Additionally, although we will not do a deep dive into this today, I do want to highlight that as part of our overall gene therapy strategy, we have preclinical programs for other genetic rare cardiac disorders. As leaders in transthyretin cardiomyopathy, we remain committed to this patient community and continue to build our knowledge of this disease and its treatment as well as develop innovative solutions to facilitate earlier diagnosis events with ATTR-CM.

First, we have new data that further supports the indicated dose for patients. Given that ATTR-CM is a rare disease with limited numbers of patients available for clinical trial, the pivotal ATTR-ACT study examined both the 80-milligram and 20-milligram doses of tafamidis in a pooled analysis versus placebo.

The combined 80- and 20-milligram treatment group showed a dramatic benefit over placebo in both survival and cardiovascular hospitalizations. However, the study wasn't powered to show whether 80 milligrams was definitively better than 20 milligrams on these important clinical endpoints. We, therefore, randomized patients from the placebo arm who are coming into the long-term extension study to receive either 20 or 80 milligrams

of tafamidis. When these patients were added to the 20- and 80-milligram cohorts from the pivotal trial, we have a robust analysis set of randomized patients with a median of 51 months of follow-up.

As you can see on the left panel of this slide, these data confirm that 80 milligrams of VYNDAQEL, which is equivalent to the 61-milligram dose of VYNDAMAX achieved a 30% reduction in mortality compared to 20 milligrams. This remains significant across adjustments for age and baseline severity of disease. These results reinforce the importance of appropriate dosing for patients with ATTR-CM to allow for the best outcomes.

A second example is our commitment to better understanding the epidemiology of transthyretin cardiomyopathy. We are currently proceeding with 2 large-scale studies, including 3,500 patients to confirm the prevalence of this rare disease. Finally, clinical trial data has demonstrated that earlier diagnosis and treatment are clearly associated with improved outcomes. We have developed an AI machine learning model using medical claims and EMR data sets that can be launched into health care information systems to flag those at risk for wild-type ATTR-CM. We are currently conducting pilot programs with select institutions to further validate its performance and hope to share more later this year upon publication.

PF-07265803 is our next opportunity to potentially transform the lives of patients with rare cardiac disease. This investigational therapy is an oral selective MAPK inhibitor in late-phase development for dilated cardiomyopathy related to mutations in the lamin A/C gene. Patients with this genetic disease present with progressive heart failure with a majority requiring transplantation or experiencing a major cardiac event by the age of 45.

The estimated prevalence is approximately 50,000 in the United States, but this condition is severely underdiagnosed because genetic screening is currently very limited. Today, there are no treatment options beyond supportive care. p38 MAPK activation is seen in this disease, and treatment with this compound improved survival, cardiac function and normalized left ventricular morphology in a LMNA mutation mouse model, as seen in the lower right of this slide.

The Phase 2 trial of this experimental therapy was a single-arm assessment of change from baseline in 6-minute walk distance, which revealed an increase of 69 meters over a baseline of 321. This was sustained for the 48-week period of follow-up. Based on these encouraging data, a Phase 3 randomized, placebo-controlled trial was initiated with a primary endpoint of 6-minute clock distance at 12 weeks and follow-up to 24 weeks to ensure durability of effect.

We anticipate top line results in 2023. We are very excited about the potential of this medicine to be hope to patients with no treatment today, and we believe that we will be able to leverage our expertise, key learnings and synergies with tafamidis to ensure its success.

Now we will leave cardiology, and I will transition to my colleague, Seng Cheng, to discuss our focus on gene therapy.

Seng Cheng - *Pfizer Inc. - Chief Scientific Officer, Rare Disease*

Thank you, Brenda.

Good morning, everybody. My name is Seng Cheng, and I'm the Chief Scientific Officer of the rare disease category at Pfizer. I'm a research scientist by training, and I've worked in translational research and gene therapy of rare diseases for over 30 years, during which I had the opportunity to contribute to the advancement of multiple drug candidates into clinical development. Today, I'm pleased to have the opportunity to share with you our efforts at developing what we believe can be a next wave of breakthrough therapies for rare monogenic diseases, particularly in the context of gene therapy.

And as Suneet mentioned earlier, gene therapy as a therapy modality represents an important component of our growth strategy. And over the past 6 years, we've made significant investments to build a state-of-the-art, end-to-end infrastructure that spans research, development and commercial to enable the delivery of these transformation therapies to patients worldwide. We're proud of our current late-stage pipeline with 3 programs that are expected to gain regulatory approval by 2023, all of which we will discuss in detail today.

Additionally, we have developed a pipeline of 10 preclinical initiatives internally that are at various stages of maturity, and we've built 3 state-of-the-art manufacturing facilities with 30,000 square feet of capacity, which I will also address in this presentation. We are confident that our end-to-end capabilities, combined with our expertise, scale and geographic footprint, are the key ingredients to successfully ensure that these transformational therapies make it in the hands of patients who need them.

Our most advanced gene therapy programs are for patients with hemophilia B, hemophilia A and Duchenne muscular dystrophy. Today, I'm happy to share that our gene therapy program in hemophilia B. We now have data from our Phase 1/2 study using fidanacogene elaparvovec, shown as illustrated on this slide, durable expression of Factor IX in the 20% abnormal range at the 4-year time point when administered a dose of 5E11 vector genomes per kilogram. I want to highlight that this represents longest period of durability data that's been produced by any company to date for a gene therapy for hemophilia B patients. Importantly, the mean annualized bleeding rates and the annualized infusion rates remain significantly reduced in these treated patients.

Given this encouraging safety and efficacy profile, we had initiated a Phase 3 study in 2019, and I'm happy to report that the prospective leading study with 40 patients has now been fully enrolled. Our current plan is to perform an interim analysis and of a pivotal readout with 20 patients in 12 months of ABR in 2021. We're obviously closely monitoring the hemophilia gene therapy development space which continues to be dynamic to ensure that our clinical plans and time lines meet regulatory expectations. However, given the sustained durability of functional factor level and the ABR rates that we've seen over the 4 years in the Phase 1/2 study, we believe that fidanacogene elaparvovec has the potential to be best in class for hemophilia B patients.

Early this summer, we had reported encouraging safety and efficacy data in patients with hemophilia A who were administered giroctocogene fitelparvovec. Today, we're sharing an additional 4 months of expression data in a cohort that have been treated with a dose of 3E13 vector genomes per kilogram of this viral vector.

And as you can see on this slide, we continue to observe expression of Factor VIII activity levels that are sustained at clinically meaningful levels with a dramatic mean of 71% when measured between the weeks of 9 and 52. I should note that we also have additional data for a small subset of patients with up to 85 weeks of additional follow-up, showing consistent Factor VIII levels as well.

Importantly, there had been no bleeds in any of these patients treated in this cohort and that ABRs of these patients remain at 0.

Should we continue to demonstrate sustained Factor VIII levels and reduced ABRs, we believe that this investigational treatment also has the potential to be best in class. We're currently enrolling patients in a 6-month lead-in portion of the Phase 3 study and plan to dose our first patient later this year, which could lead to a pivotal readout of the data in early 2022.

Our third clinical program is for boys with Duchenne muscular dystrophy, a program that we've been working on for over 4 years. And in May, we had reported the results from 9 boys who were treated at 2 different doses. And while we observed clear evidence of expression of mini dystrophin as well as encouraging preliminary signs of efficacy, we had reported the occurrence of 3 serious adverse events in the 6 boys who were treated with a high dose, where we saw evidence of complement activation as well as platelet consumption.

Today, we're sharing new data from an additional 9 boys who were all administered the high dose, so we now, have a total of 15 boys who were treated with a high dose and 18 boys treated overall. And I'm thrilled to share that we have not observed any SAEs using a modified immune modulatory and monitoring regimen in any of these 9 patients. With these boys, we had changed the prophylactic steroid treatment from 1 milligram per kilogram to an intermediate dose of 2 milligrams per kilogram.

I also want to flag that 3 of the last 9 boys were dosed with drug that have been produced using the commercial manufacturing process that have been developed in a facility in Sanford, North Carolina.

As a reminder, we had reported expression of mini dystrophin-in approximately 50% of muscle fibers and at levels that were sustained at 52% of normal levels at the 12-month time point. Associated with these expression levels were encouraging functional results that included improvement of 7.5 points in the North Star Ambulatory assessment rating score when compared with an external placebo group as well as a significant reduction

in fat fraction in the thighs of the treated boys. So based on this positive data, we plan to advance this initiative towards a pivotal study start in the next several weeks with a plan to perform an interim analysis of the clinical data in 2022.

Given the investments in the manufacturing that I mentioned earlier, we believe we'll be prepared to fully supply the global DMD patient demand for drug following approval, and this is particularly important when we engage with non-ambulatory DMD patients who will need higher amounts of the viral vector because of their increased weight.

In addition to these 3 clinical programs, we also have an initiative in Wilson disease which we're developing in partnership with Vivet Therapeutics. Wilson disease is a chronic, life-threatening disease that's caused by aberrant accumulation of copper in the liver as well as other vital organs. And similar to hemophilia and DMD that I just spoke about, this disease is also caused by a loss of function. As such, we are applying the same approach of AAV-mediated gene therapy to restore functional levels of the effective protein which, in this case, is encoded by the gene referred to as ATP7B.

And indeed, as illustrated on the slide, in preclinical studies, we have shown that administration of an AAV vector encoding ATP7B into a mouse model of Wilson disease indeed led to restoration of copper hemostasis in the liver in a dose-dependent manner. This decrease in copper was widespread, as illustrated on the top panel, showing a uniform decrease in copper levels throughout the liver which we can see by the change in color from red for higher copper levels to green for lower levels when measured using laser ablation inductively coupled with plasma spectrometry.

Associated with this decrease in hepatic copper was an increase in fecal copper secretion, the normal route of disposal of copper, as illustrated on the bottom panel. So based on this encouraging preclinical data, we are working to complete the IND-enabling studies and anticipate filing an IND later this year, which could lead to a BLA submission in 2025. We believe that, if successful, this would be a first-in-class therapy for this patient population.

As you're aware, gene therapy development is a complex task, requiring specialized and novel methodologies as well as high levels of expertise. Few companies have complete end-to-end capabilities, expertise and facilities to support the research, development and production of these important new medicines, particularly at scale. In this regard, a critical component and key differentiating feature of gene therapy initiatives is our expanding manufacturing footprint.

In anticipation for the need for large amounts of viral factor, we have proactively invested in manufacturing a sale to support rapid drug development and important the urgent and timely access to these medicines. And over the past few years, we made arguably the largest investment, totaling approximately $800 million to ready 3 manufacturing facilities. Of particular significance is the ongoing expansion of our plant in North Carolina that will house 8 2,000-liter bioreactors, which, when fully operational, will support the production of several thousands of DMD doses per annum. It is our expectation that these facilities will support the production of viral vectors for preclinical and clinical development, and importantly, commercial manufacturing of multiple gene products in parallel by 2022.

And with that, I will hand this back to Suneet.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Thank you, Seng and Brenda.

In addition to updating you on our selected development programs, we also want to share how we are thinking about the go-to-market opportunity. So now I'm going to tie together the information you heard today by sharing insight into our forecasting, which could also be helpful to you for the purposes of modeling. For example, for rare cardiology. In LMNA, we start with prevalence data, then we apply other assumptions which we have simply summarized here and include, but are not limited to, diagnosis rate, eligibility, access considerations and competitive landscape.

As you can see, we show LMNA side-by-side with VYNDAQEL to give insight about the commonalities between VYNDAQEL today and what a future dilated cardiomyopathy therapy could be.

For hemophilia gene therapy, we show both A and B together as there is a synergy and consistency in the assumptions, including our beliefs about patient's intent to seek gene therapy treatment. This assumption on motivation is embedded within the eligibility criteria, along with nab and hepatic impairment. For DMD and Wilson gene therapies, we believe the bolus populations will be drivers of value at launch as existing patients seek treatment quickly given the lack of available therapies.

Beyond that, future value should remain solid for years to come driven by incident populations for DMD with a meaningful number of boys aging in every year and Wilson disease as more patients become destabilized over time.

We aim high in each of our investigational therapies, and they're being developed to be either first or best in class. And in some cases, we expect they will be both. We are excited by the trajectory of our business and the potential of our pipeline. In the first half of this year alone, our Rare Disease Unit grew 36% driven by our first big launch of VYNDAQEL, and we expect to see even more growth with additional launches in many new countries. And VYNDAQEL is just the beginning for Pfizer Rare Disease. You can see here how much substrate we have for the future. Over the next 5 years, we plan to launch at least one new medicine each year with the aim to make a profound impact on patients' lives.

Given our recent success and our robust pipeline, we believe we are poised for significant growth. Our focus, the depth and breadth of our pipeline, our world-leading, end-to-end gene therapy platform and our global footprint, position us to continue to be a leading innovator in Rare Disease.

Thank you, and we will now turn to Q&A.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Now our rare disease leadership team is here to answer your questions about the portfolio and the pipeline. Operator, can we please now poll for questions for Rare Disease. Thanks.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from Geoffrey Porges from SVB Leerink.

Geoffrey Craig Porges - *SVB Leerink LLC, Research Division - Director of Therapeutics Research & Diversified Biopharma and Senior Research Analyst*

And just a couple first. You didn't talk much about somatrogon. I'm just wondering if you could give us a sense of whether that's a meaningful revenue opportunity given the somewhat commoditized market that you're coming into?

Secondly, for this business, a huge amount of capital that you're investing. Could you give us a sense of whether the profitability and the return on capital for the Rare Disease business is going to ultimately or even now be comparable to the rest of the pharmaceutical portfolio? Or should we think about it differently, for example, more like vaccines?

And then lastly, just a development question on the Wilson's disease program. Do you have any sense yet, I mean, with some of the animals but whether you're seeing a reduction in the copper in the CNS that would result in reduction of the CNS liabilities of that disease in humans?

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay. Well, thank you for the -- I'll start off answering the first 2 questions, then I'll ask Seng to comment on Wilson specifically. But let me just say we're very excited about somatrogon. We didn't cover it here today, simply because we had a lot of, let's say, next wave or next stage opportunities in our pipeline that we really wanted to focus on. But that innovation is absolutely on track.

It's a big patient innovation, not just convenience, going from daily to weekly. And -- but it really marks a shift from short-acting to long-acting products, and we are on track to file that this year and launch it next year. And I do believe that, that is not just a patient innovation in terms of daily dose, but in fact, it's an incremental opportunity for that franchise as we build and maintain scale because there are far fewer competitors in the long-acting market than there are in the short-acting.

In terms of profitability and return on invested capital, if I can say, you can think about this the same as the other innovative units within Pfizer. We advise, as you would have heard yesterday in the executive presentations by the same criteria for both internal development and for external business development.

Seng, if I can turn it over to you for Wilson.

Seng Cheng - *Pfizer Inc. - Chief Scientific Officer, Rare Disease*

Yes. So thank you, Suneet. So that's a good question. We not had the opportunity to actually measure copper levels in the CNS of the preclinical animals that we tested so far, but we are assuming that if we lower the levels of copper in systemic circulation, that's an opportunity for us to actually lower the levels in the CNS as well. So that's the aspiration that we have right now with the data that we have in hand.

So with that, I'll pass it back to you, Suneet.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay. Thank you.

Operator

Your next question comes from Randall Stanicky from RBC Capital.

Randall S. Stanicky - *RBC Capital Markets, Research Division - MD of Global Equity Research & Lead Analyst*

Great. Just a couple on VYNDAQEL and then a follow-up. But with respect to VYNDAQEL, Alnylam is running Phase 3 studies with an RNA-silencing approach. Can you guys talk about how you're thinking about the opportunity for combinations, any supporting data, any hurdles from the payer stance on that?

Secondly, I was surprised yesterday. I think it was the first time you talked about diagnosis rates in for VYNDAQEL looking to become north of 40%. That's above prior rare disease analogs. What's driving that? What -- we're in the middle of pandemic. Scintigraphy and patient visits are obviously constrained. And now we're talking about the opportunity for higher diagnosis rates.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay, great. I'll start off. I'll take the second one first, and then ask -- I will ask Brenda to comment on VYNDAQEL in terms of the -- your question on RNAi.

But yes, listen, the diagnosis rates have been steadily increasing over time, and we're pretty pleased with that. You might remember that was one of our key areas of focus when we launched the product. Our treatment rate is also increasing as a percentage of our diagnosis rate, so we're very pleased. It's as expected, and that makes us more optimistic for the future, which I think you heard come through before. That's really driven by a concerted effort on our part on the top end to drive diagnosis. We've really been doing a lot of education around our red flag symptoms to educate cardiologists to spot the signs. And then yes, scintigraphy has been the pull-through to make sure the diagnosis is confirmed, and that's worked out very well.

Now in terms of making sure that people get on treatment, access and affordability has been a key focus of ours, and I can say we've also made good progress on that with payers. I think that everyone recognizes the seriousness of this disease and the lack of other available treatments. So that has been a favorable recognition, I would say. And that continues to be the case as we go forward. So net-net, a good outcome for VYNDAQEL.

Yes, we had previously communicated 30% to 50% as the peak diagnosis rate, and you would have heard that we're going to go a little bit in the upper part of the range, and we'll probably achieve that earlier than we expected, so a good outcome.

And to your point about COVID, not an impacting factor given the nature of this disease.

But Brenda, if I can turn it over to you to talk about the other question, please.

Brenda Cooperstone - *Pfizer Inc. - Chief Development Officer, Rare Disease*

Thanks, Suneet. I would say that there is nothing with regard to mechanism that would prevent the combination of tafamidis and RNA silencers. However, since tafamidis was the only approved medication currently for ATTR-CM, we do not have any data looking specifically at that. As competitors run through their pivotal clinical trials, they will likely be coadministration. So there may be data available in the future with respect to the efficacy and safety of that combination.

Thanks, Suneet. Back to you.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay. Thanks, Brenda.

Operator

The next question comes from Terence Flynn.

Terence C. Flynn - *Goldman Sachs Group, Inc., Research Division - MD*

Maybe just 2 for me. On your DMD program, any more details you can share about the design of the Phase 3 program and the interim analysis? And then maybe remind us what the modified immunomodulatory and monitoring regimen actually entails? And how many patients were you with Soliris in the Phase 2 study.

And then the second part of the question, you talked about this at the beginning in your prepared remarks is the acquisition history here in rare diseases where you've built out a pretty broad portfolio. As you think about the forward external opportunities, do you feel like you have more to do here? Or are you pretty full at this point in terms of the opportunity set?

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay. Thanks for the question. I'll start off. I'll answer the second question first, and then I'll ask Brenda to comment on both the DMD Phase 3 and the modified regimen that we discussed.

The short answer is no. We're not done here. Our focus and our approach is -- which has been very successful so far, and you would have seen it from the programs we shared is focused on the 4 rare therapeutic areas that we talked about. We have 3 gene therapies in Phase 3, and we have 10 more in preclinical. It's really a result of our build, buy and partner strategy.

When you look through, let's say, the dozen programs that we showed, it's about 1/3, 1/3, 1/3. 1/3 of them have been internally developed, and that's the build. 1/3 of them are buys, which are sort of more traditional M&A, and about 1/3 are partnering opportunities where we really collaborate with each. We think we've got more head space in this area and building out each of our rare TAs. And we're going to continue to use, let's say, both internal development and external BD as a way to accelerate our development. Remember, BD is not a strategy unto itself. It's really a means and one of the means or levers to achieve the goal that we set for ourselves.

But Brenda, if I could turn it over to you for the DMD Phase 3 interim and modified regimen question.

Brenda Cooperstone - *Pfizer Inc. - Chief Development Officer, Rare Disease*

Thanks, Suneet.

So we are very excited about our DMD Phase 3 program, and we understand how important it is to move this forward as quickly as possible for patients and families that are waiting for it. The Phase 3 trial in ambulatory patients is in boys between the ages of 4 and 7. It's a randomized, placebo-controlled, double-blinded trial. And the endpoint of NSAA is at 12 months.

The interim analysis will occur after a portion of patients have received that 12-month data point and will occur in 2022. We will make decisions with regard to the disposition of the rest of the study and filing based on the data that is generated.

And the immunomodulatory changes were specifically increasing the steroid prophylaxis from 1 milligram per kilogram to 2 milligram per kilogram. No other prophylactic medications were added, and we did increase monitoring. And these are general monitoring diagnostic tests in that critical period of the first 2 weeks post dose.

With regard to your question on the number of patients treated with Soliris, I'll turn that over to Seng to answer.

Seng Cheng - *Pfizer Inc. - Chief Scientific Officer, Rare Disease*

So thank you, Brenda.

So in regard to the amendments that we made recently, we've actually also included guidance on when we might trigger a criteria for use of eculizumab in the event of complement activation with evidence of clinical sequela. But I do want to make the case that with the last-line boys that we've treated, we've not had the need to use this intervention.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay. Thank you, Brenda. And Seng, if I could just say I think if I could capture Seng's words from his talking points, we are really thrilled about where we are on this DMD program. We've made a lot of progress and especially given what we just discussed, the non-new boys that were diagnosed without any SAEs, so very encouraging. And frankly, we're optimistic again about the future here.

Operator

Your next question comes from Vamil Divan from Mizuho.

Vamil Kishore Divan - *Mizuho Securities USA LLC, Research Division - MD*

Great. So a couple maybe bigger-picture questions on Rare Disease, if I could. Appreciate the comments around how you're thinking about the commercial opportunities for these assets. Can you talk a little bit more on the pricing side? We've seen pretty robust pricing power in rare disease so far. I'm just wondering what your expectation is there going forward, and if there's anything you want to share around sort of innovative thoughts you have around how to adapt to our pricing in the U.S. to accommodate these rare diseases.

And then the second one is just you mentioned the -- you areas of focus on things like Wilson, with about a $500 million global market. I'm just trying to get a sense of sort of what size opportunities would you consider meaningful from -- obviously, Pfizer is a large company, and a lot of questions whether these very small targeted rare diseases can move the needle. I'm wondering if your sort of metrics or your threshold or what's considered meaningful is different in rare diseases than, say, in oncology or other areas. Obviously, the commercial infrastructure here is sometimes less as well. So just trying to get a sense of how you think about opportunities on the internal or external that would be meaningful in the future.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Let me take those -- both of those, if I could.

So in terms of Wilson, yes, you look at the 500 milligram. We pulled that -- I mean, the $500 million mark, we pulled that out of a value of pharma. But I want to be clear, we don't think that, that captures the impact of gene therapy. I mean that's based on what current substrate people envision. So obviously, we see that as being a bigger opportunity. You would have seen that we called out Wilson as a $500 million to $1 billion opportunity for us. So right there, our own internal estimates might eclipse what potentially could be as a market size projected or otherwise. So we're pretty pleased about where we're going, I mean, obviously that we believe that will be a first-in-class product, as you would have heard.

Look, when it comes to gene therapies, obviously, we use the same metrics that all, as I mentioned earlier. But it's really an end-to-end platform, where we believe that with the vectors we've chosen, the capacities we've built, the scientific and commercial footprint that we've got that essentially we can create operational leverage on top of what we're building. And so in fact, that is something that might be a little bit different than other parts of Pfizer or maybe any other part of another company. And that's why we have the multiplicity of the programs that we have. Three gene therapy programs in Phase 3 by the end of this year and 10 more in preclinical, so there's a lot for us to benefit from there operationally. But of course, in terms of metrics we use, the same kinds of things that others would use.

In terms of pricing, I mean, obviously, it would be very early to speculate on pricing. But if I could just give a sense of where we are. We price based on value, okay? And that value is based on the profile of the products that we're developing. Those profiles are revealed over time and confirmed, obviously, in Phase 3. So we get to see kind of what comes out of that. And of course, we consider access and affordability to make sure that these would be considered.

Now if I could just add one point. Gene therapy is slightly different than other gene -- other rare disease products because there's the onetime nature of gene therapies and the changes that, that could impact on other chronic treatments that patients might have had that they would no longer need, okay? And so that's maybe an additional variable in gene therapy we might not see in the rest. But in all cases, access and affordability remains important.

Now in the U.S., you would have seen with Medicare Part D, we are a long-time advocate of reforms, specifically capping out of pocket for people on those plans. And frankly, we are also looking internationally at new and creative solutions, such as annuity payments and performance-based payments.

So I think that you're right in pointing out that there's a certain robustness there, but we're being very thoughtful about how we make sure that those innovative therapies get in the hands of patients because that's where the impact is actually going to happen. Thank you.

Operator

Your next question comes from Louise Chen from Cantor.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

First question I had for you is does the FDA's recommendation for BioMarin to show 2 years of ABR data close the commercial gap between you and BioMarin? Or will you also have to show 2-year ABR data?

And then if your hemophilia drug is approved, do you basically think that there's a potential -- where would it fit in the treatment paradigm, basically, with the potential for another therapy to be approved in lentiviral gene therapies potentially in the future?

And then last one here is for hemophilia. What percentage of patients do you think are eligible and would consider a gene therapy treatment?

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Okay, great. Thank you so much. I'll start off answering the portfolio question you asked. And then -- and maybe I'll touch upon the hemophilia numbers, and then I'll ask Brenda to comment on the FDA and our timing with -- versus the BioMarin CRL. So in terms of portfolio, I mean, obviously, we look at our portfolio in a couple of different parts, and you might have seen that we have 3 different hemophilia products coming to market in the next 4 years, 2 of which are gene therapies and one which is a mab, the marstacimab.

We are obviously playing across the full spectrum given that rare hematology is one of our key therapeutic areas. we have -- they will have products for A. We'll have products for B. We'll have with and without inhibitors. We'll have gene therapies and non-gene therapies. So we think there's a place for all of those. And what we've seen recently in the marketplace is that when a new product comes to market, if it has innovation, that innovation is recognized and has the impact that we think it should have. So we're very encouraged by what we've seen, and we see a place for our future innovations in the same way. And so that's very exciting.

In terms of -- when you look at -- how you look -- the second part of your question, which is around hemophilia, and you look at the percentages, we see these markets developing over time. And ultimately, we believe gene therapies and nonfactor treatments will come to represent 40% to 50% of the hemophilia A and B markets. A might be a little bit on the higher end because they've started that earlier with the nonfactors. And B -- so maybe closer to 50%, and B would be on the 40% and maybe on the lower end, but that's kind of where we see those markets coming into play.

Specifically, around gene therapy, just to put it -- to be clear, we know that in this category, people -- which is well developed, some patients may or may not choose to elect for gene therapy, and some may also not be eligible, okay? And we believe that, that number could be in the 30% to 40% range, and we've shown that in our modeling slides in our eligibility, which includes neutralizing antibodies, hepatic impairment inhibitors. And then we filled in the gap with those sort of intent-to-seek treatment metrics. So you'll see that on the slide there.

Brenda, if I could turn it over to you to talk about the timing and the implications of the BioMarin CRL, please.

Brenda Cooperstone - *Pfizer Inc. - Chief Development Officer, Rare Disease*

Thank you, Sumeet. So if for understanding from public commentary that the FDA maintains its same high standards and has not changed the goalpost for approval in gene therapy. We've had robust and collaborative interactions with the agency around our hemophilia A and B programs.

And currently, there are no planned changes to our ongoing development plan. The hemophilia A program will begin dosing in the next few weeks, and we still anticipate data readout in 2022 as planned.

Back to you, Suneet.

Suneet Varma - *Pfizer Inc. - Global President, Rare Disease*

Thank you, Brenda. Thank you so much.

We're nearly at the end of our Q&A time. So we just want to say thank you to everyone for your questions. I think they're very informative, et cetera. I hope you get a sense of our excitement. We're very confident in what we've built here. We are competitive, and we are very focused on what's happening in the market obviously, in the name of patients, et cetera. We've built a lot of capability that we think can really be brought to bear for the benefit of patients and their caregivers, and we ultimately aim to have significant growth and impact from what we've built here. And I think you get a sense of that from our prepared remarks and from our Q&A as well. So thank you so much.

Let me pass it back over to Chuck.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Great. Thanks, Suneet.

Okay, so we will now take a 10-minute break. And when we come back, we will pick up with our Oncology leadership team. So we'll be back in 10. Thanks.

(Break)

PRESENTATION

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Okay, we're back.

Before we dive into our oncology program, we'd first like to share a video featuring Scott Wilson, who was diagnosed with metastatic colorectal cancer.

(presentation)

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Now I'd like to turn it over to our Oncology leadership team.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Hello, and welcome on behalf of the Oncology team.

It's people like Scott who motivate us and why we're here today. My name is Andy Schmeltz, and I'm here with Chris Boshoff, our Chief Development Officer; Jeff Settleman, our Head of Oncology R&D, who oversees our research facility in La Jolla, California; and Nick Saccomano, the Chief Scientific Officer at our Boulder, Colorado research site.

Before we dive deeper into our exciting Oncology pipeline projects, I'd like to briefly touch on what we've been able to achieve over the past decade. I'm very proud of Pfizer's trajectory from a niche player to a bona fide leader in oncology. The portfolio has delivered unparalleled growth with a 32% 5-year revenue CAGR, generating nearly $10 billion in revenue in the last year. Perhaps most importantly, all 6 areas of our portfolio are contributing meaningfully to this growth trend, which bodes well for our future. Each area has multiple growth drivers in place. And as you'll soon hear, we anticipate more potential breakthroughs over the years ahead. Bottom line, we're well positioned to sustain growth over the near, medium and long term.

While most of today's presentation will focus on the next wave of potential cancer medicines at Pfizer, I thought it was also important to address our most significant medicine right now, Ibrance. Ibrance remains an important growth driver for the company and a critical medicine for breast cancer patients. Since its approval in the U.S. in 2015, over 300,000 patients have been treated with Ibrance. As a first-in-class medicine, Ibrance catalyze the use of CDK inhibitors to treat metastatic breast cancer. Today, an estimated 66% of first-line metastatic breast cancer patients in the U.S. are prescribed a CDK inhibitor, and we see continued opportunities for further class growth moving forward. Despite intense competition, Ibrance continues to be the CDK leader. Approximately 7 out of 8 first-line CDK patients are on Ibrance. And as Angela mentioned yesterday, last December, we presented pioneering real-world evidence that showed a compelling 42% overall survival benefit for Ibrance plus letrozole compared to letrozole alone. In short, we expect to maintain our leadership position in metastatic breast cancer due to Ibrance's extensive and sustained positive patient and physician experiences.

As you're likely aware, we also have ongoing late-stage clinical trials for potential new indications for Ibrance on the horizon, including for high-risk early breast cancer that's being evaluated in the PENELOPE-B trial as well as for the PATINA trial, an ER-positive, HER2-positive breast cancer.

Looking at the broader picture, as you can see, the Oncology pipeline is not levered to Ibrance. In fact, our pipeline spans numerous tumor areas. We're advancing a range of targeted therapies as well as medicines that trigger an immune system response to fight cancer, and we expect up to 14 potential approvals by the end of 2025.

When I think about these opportunities, a few themes emerge. First, we're purposely building our leadership in key tumor areas by launching medicines in later lines of therapy or stages of disease and then quickly investigating these agents in earlier settings where typically more patients are treated for a longer period of time. Second, we have world-class capabilities to deliver therapies that can penetrate the blood-brain barrier, which is a particularly difficult area and represents significant unmet need for many cancers. Third, we're focusing our science where we are best, where we are pioneers in areas such as ALK and BRAF as well as CDK inhibition.

For today's discussion, we'll cover the programs outlined in red. Chris will discuss recent positive data for LORBRENA and Braftovi and walk you through our robust life cycle plans for prostate and bladder cancers. And I'm excited that Jeff and Nick will provide a closer look into our early programs, sharing several new disclosures.

With that, I turn the presentation over to Chris to begin our discussion of the pipeline.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Thank you, Andy.

Almost a decade ago, we pioneered the first biomarker-driven medicine for ALK-positive non-small cell lung cancer with XALKORI. Today, we are continuing to make significant advancements for this malignancy with the recent positive top line results from our Phase 3 CROWN study with LORBRENA in the first-line setting for which I will share some data today.

Up to 40% of patients with ALK-positive non-small cell lung cancer present with brain metastases. LORBRENA is a third-generation ALK inhibitor that we specifically developed to be more potent to inhibit the most common mutations that may drive resistance to other first- or second-generation ALK inhibitors and to cross the blood-brain barrier.

A brain scan is shown from a patient participating in the CROWN study, which is in the first-line setting. This patient had a complete intracranial response, which is ongoing after 24 months on LORBRENA. The full data set from CROWN will be presented at a future medical meeting, where the primary endpoint of PFS compared to crizotinib will be detailed.

For the first time, I'm sharing the waterfall plot for a subset of patients presenting with measurable brain metastases. The overall response rate is 82% with an unprecedented 71% achieving complete response of brain metastases. The Kaplan-Meier curve, comparing intracranial progressions on LORBRENA versus XALKORI, demonstrates a striking hazard ratio of 0.07. The PFS hazard ratios for the overall population and for those presenting with brain metastases are also compelling. We believe that the CROWN results will position LORBRENA to be highly competitive with second-generation inhibitors in the first-line setting, assuming regulatory approval.

We are rapidly advancing our global regulatory submissions for the first-line indication. In the U.S., the application will be reviewed through the FDA's Real-Time Oncology Review Pilot Program.

I will next update you on our targeted medicines, BRAFTOVI and MEKTOVI, where we're rapidly expanding our presence in BRAF-driven malignancies. BRAF mutations occur up to 15% of patients with colon cancer. These represent a particular poor prognostic subgroup with less than 4% of patients with advanced disease alive at 5 years. Despite challenges presented by the pandemic, the CRC label expansion from the BEACON data has continued to help drive growth for the BRAFTOVI franchise. Since the CRC launch, the BRAFTOVI combination now comprises 36% of the target therapy share of BFAR, and hundreds of new patients have started on this regimen.

This is an early look at a Phase 2 data from ANCHOR, which evaluates the combination of BRAFTOVI, MEKTOVI and cetuximab in first-line BRAF-mutated CRC. The majority of patients benefited from this combination with a high objective response rate of 50% and a disease control rate of 85%. We have also seen encouraging duration of treatment for many patients. These data provide proof of concept to initiate a 3-arm Phase 3 study called BREAKWATER that is planned to start later this year in first-line BRAF-mutated CRC.

We believe that BRAFTOVI is a best-in-class BRAF inhibitor, and we have a comprehensive development plan for BRAFTOVI and MEKTOVI that we are rapidly advancing across BRAF-driven cancers. Across the portfolio, we anticipate up to $2 billion of annual revenue contributions in 2027. In addition to the CRC program, we have an ongoing registration-enabling study in BRAF lung cancer and Phase 2 studies where BRAFTOVI, MEKTOVI are either combined or sequenced with immunotherapies. Note, these studies informed a new first-line melanoma trial called STARBOARD where BRAFTOVI, MEKTOVI are combined with pembrolizumab.

Moving now to our franchise of medicines being developed in urogenital cancer, where we are rapidly expanding in prostate and bladder cancer. Urogenital malignancies represent the first and fourth most common cancers in men. Up to 25% of prostate cancers harbor mutations in DNA damage repair, or DDR, pathway genes, representing potentially a poor prognostic subgroup. For bladder cancer, the majority of patients present with non-muscle invasive bladder cancer. This is an earlier setting of this disease before bladder invasion and before systemic spread. These are the latest results from TALAPRO-1, a Phase 2 study of our PARP inhibitor, talazoparib, in heavily pretreated patients with DDR-mutated metastatic castration-resistant prostate cancer.

At the interim analysis, the objective response rate was 27%. The response rate in those harboring BRCA1 or 2 mutations was 42% with a [complacent] percent response rate of 72%. Note, responses were observed in BRCA1-mutated tumors, potentially differentiating talazoparib from other PARP inhibitors in prostate cancer.

These results also give us confidence in TALAPRO 2, our Phase 3 trial exploring XTANDI in combination with talazoparib in metastatic castration-resistant prostate cancer. TALAPRO 2 has now completed enrollment to the all-comer cohort, and the final analysis is expected in 2021. TALAPRO 2 will be the first study to read out for PARP inhibitor in combination with a next-generation androgen receptor inhibitor. This represents

a significant opportunity as we anticipate that this investigational combination has the potential to become a new standard of care in this setting, if successful.

Moving now to bladder cancer. The waterfall plot is from a Phase 1 study of our subcutaneous anti-PD-1 antibody, sasanlimab, dosed every 4 weeks or every 6 weeks in patients with advanced metastatic urothelial carcinoma. In this study, patients were previously treated with at least 1 prior therapy. These results show activity for sasanlimab comparable to intravenous immune checkpoint blocker data previously reported, and there are ongoing responses in patients coming up to 2 years on treatment.

Earlier this year, we initiated the Phase 3 CREST study combining sasanlimab with BCG or using sasanlimab as a maintenance post-BCG induction. There's significant interest in this study from urologists, and we're seeing rapid recruitment to this trial. This is the only global Phase 3 study, including the U.S., in upfront, non-muscle-invasive bladder cancer. Furthermore, subcutaneous sasanlimab is being developed as a future backbone in various umbrella studies with targeted medicines in our portfolio. And an overview of our GU cancer program shows robust portfolio of Phase 3 studies spanning early to later stages of the disease. Across the bladder and prostate portfolio alone, we anticipate up to $5 billion of annual revenue contributions in 2027. This includes EMBARK in early non-metastatic castration-sensitive prostate cancer.

In summary, we are focused on building our oncology franchises by advancing therapies to earlier lines of therapy. And as you can see, with the shaded boxes, the majority of our late-stage portfolio is following this strategy. Moving into earlier settings allow us to improve outcomes for larger patient populations, which also correlates to longer durations of treatment.

In total, we have 12 ongoing programs that could read out by 2025 with an anticipated $6 billion of incremental revenue contributions in 2027.

I'll now hand it over to Jeff to highlight our next wave of breakthroughs early development, including our BCMA bispecific for which we are initiating a registration-enbaling program.

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Thanks, Chris.

So Chris just described the registration-enabling readouts we're anticipating over the next 4 to 5 years, and now, I'll highlight a few of our earlier-stage oncology programs. Here's an overview of our early-stage NMEs that are currently in the clinic or are expected to enter the clinic within the next year from our research sites in La Jolla and Boulder.

As you can see, there are multiple therapeutic modalities featured in our early pipeline, including small molecule inhibitors, T-cell redirecting bispecific antibodies, an inhibitory antibody, an antibody drug conjugate and a cancer vaccine, targeting cancers in our core indications and more broadly. It's worth noting that there are several potential first-in-class programs listed here that haven't been disclosed previously, and 10 of these NMEs could potentially be approved by 2026.

I'll focus briefly on breast cancer, where there's still a large need for breakthrough medicines that can overcome resistance to CDK inhibitors, including IBRANCE. First, I'll describe our 3 most advanced next-generation CDK inhibitor programs, which enable disruption of each of the critical cell cycle checkpoints. On the left is our CDK2/4/6 inhibitor, which differentiates from our CDK4/6 inhibitor, IBRANCE, with the ability to additionally target CDK2. Since CDK2 activation seems to drive IBRANCE resistance in some breast cancers, this molecule has the potential to overcome such resistance, which would be a major advancement for patients. It also has the potential to deliver benefit beyond ER+ breast cancer, particularly in cancers where CDK2 activation seems to drive tumor genesis. This molecule is currently in Phase 1 clinical development.

In the middle is our CDK4 selective inhibitor, which has been shown preclinically to target CDK4 with more than 10 times the potency of IBRANCE and without the neutropenia, sometimes seen with CDK6 inhibition. That improved TI provides more opportunity for safe combination treatments in other cancer types. And this molecule is expected to be in clinical development later this year.

And on the right is our CDK2 selective inhibitor, which has been shown in preclinical models to combine with IBRANCE to overcome resistance in ER+ breast cancer and has the potential to drive efficacy in a variety of tumors exhibiting CDK2 activation, especially in combination with standard of care therapies. This molecule is also expected to enter the clinical development later this year.

And I should add that these novel CDK2 and CDK4 selective molecules resulted from a real tour de force of protein structure guided medicinal chemistry efforts from Pfizer scientists that yielded candidates with selectivity profiles that many in the industry had predicted would not be possible to achieve.

Now I'll describe another exciting oncology program, our HER2 ADC, for treatment of breast cancer and other HER2-expressing cancers. This molecule is highly differentiated from other HER2 ADCs. With a very stable, site specifically conjugated cell permeable auristatin payload that yields a molecule with the potential for an improved safety and potency profile.

We initiated clinical testing in 2017 and we've seen a very impressive response rate in HER2+ breast and GI cancers in Phase 1, including in many patients who had previously been treated with T-DM1. Notably, we haven't seen any cases of interstitial lung disease to this point, which is expected to enable safer combination treatments and advancement to earlier line treatment settings. We've also seen very encouraging preclinical data in HER2 low, non-small cell lung cancer tumor models with complete regressions observed in T-DM1 refractory xenografts. So when we consider that as many as 40% of non-small cell lung cancers express detectable surface HER2, together with the opportunity in breast cancer, there's a potential for a substantial market for this molecule, and we're now expanding testing in HER2 low breast cancers with plans to expand in HER2+ lung cancer as well.

Now lastly, I'd like to highlight our Phase 1 program that we're very excited about. Our BCMA-targeted bispecific antibody for the treatment of multiple myeloma. While there are several approved myeloma drugs, they aren't curative, and there's still a substantial unmet need for these patients. The antibody format we've used is shown on the left, and it's worth noting that our antibody has been optimized for binding affinity to both BCMA and CD3, enabling more potent T cell-mediated tumor cell toxicity.

We've recently completed dose escalation with more than 50 patients treated, and we're expecting to identify a dose this month to support a registrational study start by year-end. Importantly, we've moved from IV delivery to subcutaneous administration. And as expected, this has significantly reduced the incidence in grade of cytokine release syndrome, which is a dose-limiting toxicity for T cell redirecting bispecific antibodies and for CAR-Ts. So subcu dosing has the potential for better safety and is also more convenient for patients and physicians. And we're very encouraged by the responses we're seeing so far, including stringent complete responses and responses in several patients who had previously experienced other BCMA-targeted agents. So we're now moving aggressively to develop this antibody, both as monotherapy and in combination with other agents.

And with that, I'll hand it off to Nick for some highlights from the Boulder lab.

Nicholas Saccomano - *Pfizer Inc. - Chief Scientific Officer, Boulder R&D Unit*

Thanks, Jeff. I'm excited to join our forces in Boulder with this great team. These forces are the legacy Array BioPharma team that helped build Loxo Oncology and Mirati Therapeutics. But looking forward, our efforts in Colorado will focus exclusively on the Pfizer pipeline.

Boulder's expertise is small molecule drug discovery. And we have a specific track record in drugging the very important RAS, RAF, MEK or signaling pathway, as you saw in Chris Boshoff's portion of the presentation. We have also created 2 novel dendritic cell-targeted I/O therapies. I will touch on one of these today. I'm also going to elaborate on how we're advancing a set of potentially first-in-class tumor-agnostic targeted molecules that we anticipate will have differentiated efficacy profiles. And in particular, have the potential to treat or forestall intracranial progression of disease.

Let me start, though, by telling you a little bit more about our potentially first-in-class AXL/MER tyrosine kinase inhibitor, a dendritic cell targeting I/O agent. This molecule has a unique mechanism of antitumor immunity that not only enhances the function of dendritic cells, but also protects

dendritic cells from the powerful immune suppressing environment of the tumor. Preclinical data support the creation of durable antitumor immunity, both as a single agent and in combination with checkpoint inhibition.

As such, this compound should combine favorably with sasanlimab and other I/O agents.

Our initial clinical development plan is focused on lung and gastric cancers, which represent a potential patient population of 70,000 to 100,000 patients worldwide. But we imagine that this mechanism of action could be active across many other solid tumors, including renal cell carcinoma and melanoma. We'll be exploring these additional opportunities in subsequent studies.

The first-in-human Phase 1 clinical trial is now enrolling, and we are aiming to establish proof of mechanism by the end of this year. A potentially important targeted therapy we'd like to highlight today is a molecule that has the potential to become a first-in-class fully brain-penetrant V600 BRAF inhibitor, which could expand and deepen treatment for patients across multiple BRAF-driven cancers. In melanoma, where we see a significant opportunity, 40% to 60% of patients harbor the Class I V600 BRAF mutation. And of those, approximately 25% will present with brain metastases at first diagnosis.

Preclinical studies have shown that our molecule matches the antitumor activity of encorafenib in treating systemic disease and demonstrate superior activity in eradicating intracranial tumor implants. We're targeting the end of this month for first-in-human clinical trials.

The efficacy of current BRAF inhibitors is limited by poor brain penetrants. Given this, we believe this molecule in combination with binimetinib has the potential, if successful, to represent a significant advance on standard of care regimens in melanoma and other BRAF-driven cancers.

Two other examples of our next-generation targeted oncology programs take aim at HER2 exon 20 and cMET exon 14. In both of these cases, the [cohort] candidate is also engineered to cover the amplified wild-type protein, known drug resistance mutants and to treat or forestall intracranial disease. And as such, together, expand the utility of the molecule. Thus, each of these programs addresses a significant patient need. Our HER2 directed molecule targeting amplified breast cancer and exon 20 mutated lung cancer represents approximately 20,000 and 4,500 patients, respectively.

In non-small cell lung cancer, cMET exon 14 alterations appear in approximately 10,000 to 12,000 patients, or 3% to 4% of lung cancers worldwide, while cMET amplification is recognized as a dominant resistance mechanism in patients progressing on targeted EGFR inhibitor therapy.

Similar to the BRAF program, both of these are designed to improve upon standard of care given their selectivity, ability to target resistance and that they'll treat CNS disease. For both of these programs, we're targeting 2021 for first-in-human clinical studies.

I'll now pass back to Andy for some final remarks.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Nick. So we hope we've given you a clear picture of where we lead the science, how we're prioritizing brain penetrants and moving our medicines from late-stage to earlier settings.

We believe there are several potential breakthroughs in our late, middle and early pipeline. Even with conservative assumptions about diagnosis, treatment rates and duration of therapy, we can model significant commercial opportunities for several of our key late-stage programs, as you can see here.

To summarize, we have a strong and growing in-line portfolio with 23 cancer medicines today. We expect to have 24 new molecular entities in the clinic by the end of 2021. And we anticipate up to 14 potential approvals by 2025. We are determined to change the trajectory of cancer for patients like Scott who are battling this disease every day.

Thank you for your time, attention and interest. I'll now turn the call over to Chuck to facilitate Q&A.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Thanks, Andy. Now our oncology leadership team is here, and we'll be happy to answer your questions about the portfolio and the pipeline. So operator, at this point, can we please poll for questions for oncology.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Our first question comes from Seamus Fernandez from Guggenheim.

Seamus Christopher Fernandez - *Guggenheim Securities, LLC, Research Division - Senior Analyst of Global Pharmaceuticals*

So just a couple here. On the HER2-targeted ADC, can you guys talk about the importance of efficacy and the kind of -- and -- versus tolerability. I know with your ADC at ASCO, the data were quite impressive on response rates, but we also saw some neutropenia. And just wondering how that might compare to the kind of efficacy that we see with trastuzumab [direction] and the safety issues that we see there or the lung safety issues that we see there.

And then separately, can you just help us understand how you think about the size of the HER2 low market opportunity and the path to development there?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Seamus, for your questions. I think I'll hand it over to Jeff first to speak to our HER2 ADC program, specifically on the data. And then I think Chris can chime in, in terms of forward development options. Jeff?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Yes. Thanks for the question. So yes, let me start by saying we certainly understand that we're not first with our HER2 ADC. We do see some unique attributes of our molecule that we believe give it the potential to be a best-in-class treatment in the right indications. As I mentioned, our ADC was developed using a proprietary linker payload technology and a site-specific conjugation strategy as well as a very potent, so permeable cytotoxic payload.

That's produced a molecule, which so far has shown a very favorable safety and efficacy profile. And importantly, without any signs of interstitial lung disease, which we think could be a real advantage, especially as we move into earlier lines of treatment.

So we'll need to see how we fare against competitors as we initially expand in HER2 low breast and lung cancer, as I mentioned. We're being very purposeful about where to pursue further clinical development, but we're prepared to move opportunistically and aggressively as we learn about the strengths and liabilities of the various HER2 ADCs across this landscape.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Jeff. Chris, do you want to pick up?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Perhaps just to add, I mean you're absolutely correct that the HER2 low is a much bigger space in both breast cancer, but also an opportunity in lung cancer. So we are planning to start an expansion cohort specifically in HER2 low, including lung cancer.

In the HER2 low breast cancer space, as you know, a lot of those tumors do overlap with hormone receptor positivity. So there's an opportunity to combine with either palbo or preferentially for us in the future with one of our next-gen CDK inhibitors, for example, CDK4, which Jeff described.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Chris. And maybe just to wrap it together. Well, we're mindful with our HER2 ADC program, we are not first-in-class. We're going to leverage that opportunity to use the totality of information available, not only about where we can differentiate with our program, but where there might be gaps in the profile of other programs that are ahead, gaps either in the inherent profile of the molecule, perhaps on the safety side, or gaps in populations where they're not studying, and we'll capitalize on that information to differentiate because to be a best-in-class breakthrough HER2 ADC, we're certainly going to need to have a differentiated profile. That's front and center to us. Thanks. Operator, next question, please.

Operator

Your next question comes from Andrew Baum from Citi.

Andrew Simon Baum - *Citigroup Inc., Research Division - Global Head of Healthcare Research and MD*

A couple of questions. Firstly, in light of PALLAS, and while noting your real-world data, you do not have a randomized controlled trial, which has shown survival benefit, unlike your competitors. What is your confidence in being able to preserve that market leading position? It would seem a challenge despite the fact that penetration of the class may go up.

And then second, on the pipeline, two questions. Number one, for your ZYTIGA talazoparib combination, there is a significant co-pay contribution given the Medicare-centric nature of the patient population compared to abiraterone LYNPARZA. How are you thinking about that? And then same vein on your subcutaneous PD-1, again, given fairly substantial Medicare representation. The out-of-pocket contribution is going to be much greater than under Medicare Part B, given Medigap. Again, how do you think about that?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Andrew, for your questions. I think all 3 are right on my alley. So I'll take a shot first. So first, in terms of IBRANCE and kind of our prospects, given the intense competition, especially in metastatic breast cancer. IBRANCE is the undisputed leader in metastatic breast cancer, even over the past year with the accumulation of competitive data, 7 out of 8, first-line metastatic breast cancer patients are on IBRANCE relative to other CDK. That being said, because it's competitive, one would expect when you start as the only CDK inhibitor and now you're one of three that share will be challenged over time, although I must say we've held share very nicely. We do expect growth to come from continued CDK expansion. In the U.S., it's about 66% first-line CDK penetration. In Europe, it's a little bit below 50%. And in Japan, it's around 30%. And we see continued opportunity for CDK penetration that will enable growth. And I've got to say that we've had lots of discussions with thought leaders. We've done lots of market research since the PALLAS result's been out and some of the competitive announcements in early breast cancer have been out. And it is clear that oncologists treat early breast cancer very differently, patients, than they do metastatic breast cancer.

We've not seen to date an impact in our metastatic business, and we don't anticipate one going forward. Based on the strength of IBRANCE's benefit risk profile, the perception of efficacy across all 3 CDK inhibitors is generally the same, but on the safety tolerability side, IBRANCE continues to stand out.

Your second question in terms of -- really, talazoparib, you said ZYTIGA, but I know you meant XTANDI in TALAPRO-2. And then also with our sasanlimab in non muscle-invasive bladder cancer. Clearly, these are going to be not infusion, so not Part B, although I think, still to be determined for (inaudible). We have lots of experience in Pfizer oncology with oral oncolytics, that's the majority of our portfolio. We understand the considerations now of pocket costs and the importance of patients being able to get the medicine that they are prescribed regardless of their situation.

With XTANDI already, lots of experience in an older male population that's Medicare. And so while we anticipate continued considerations and thoughtfulness that need to be put there, we don't anticipate any downside or concerns.

Obviously, we'll have an opportunity with these medicines to be thoughtful in how we price, certainly with sasanlimab and in terms of how we contract as well. Thanks for the question. Operator, the next question?

Operator

The next question comes from Chris Schott from JPMorgan.

Christopher Thomas Schott - *JPMorgan Chase & Co, Research Division - Senior Analyst*

Great. Maybe first on the CDK2/4/6, can you just talk about what type of incremental benefit you're looking at here relative to IBRANCE to move that asset ahead? Or does this asset play more of a role in IBRANCE failures. And maybe as part of that, can you just talk about the selectivity of that asset to CDK2 versus 4 and 6?

And then the second question is just coming back to IBRANCE and the metastatic breast cancer market. Certainly, hear your argument in terms of IBRANCE remaining a leader in that setting. But can you just elaborate a little bit more just on the size of that market? I think you've talked in the past about you expect that there could be some CDK retreatment postadjuvant therapy. But just talk a little bit, is that something you expect that we need to see more data for that to occur? Or can we think about maybe some of these markets contracting a bit as adjuvant comes on the market and maybe slows the progression of some of those patients to metastatic?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Chris, for your questions. Jeff, I'll hand it to you on the CDK2/4/6 program. And then Chris, maybe you can speak to some of the clinical trials that are underway in terms of CDK. It's in early breast cancer and subsequently CDK-based regimens in metastatic breast cancer as well. Jeff?

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

Sure. Yes, thanks for the question. So first, just to reinforce the point, Andy, that you made. It's worth noting that Pfizer has been leading the way in the CDK space. And by doubling down in this area with our next-generation CDK inhibitors, we now have really 3 different kinds of opportunities to further improve on IBRANCE and to expand the utility of cell cycle inhibition to tumor types beyond ER+ breast cancer. Your question was focused on CDK2/4/6 with that program, where we're close to identifying a safe Phase 2 dose, and we'll be exploring its ability to overcome resistance to IBRANCE in the setting of combination treatment with endocrine therapy, where, as I mentioned, accumulating evidence implicates CDK2. And you would ask about how hard we're hitting CDK2 versus 4 and 6 when we compare to IBRANCE, we're pretty potent on and almost equal potent on all three: 2, 4 and 6, with this molecule. So we're optimistic about its profile in terms of target coverage. We anticipate a pivotal start for that combination potentially in 2022.

Now as I described, we expect to be in the clinic in the next few months with our CDK2 and 4 selective programs, which you asked about as well. With our CDK4 selective inhibitor, we anticipate being able to cover that really important cell cycle regulator with unprecedented potency and without the neutropenia that we can sometimes see with IBRANCE.

When we consider the critical role of CDK4 and cell cycle checkpoint control in cancer cells from breast and other tissues, we see several additional opportunities for this molecule and depending on what we experienced in terms of safety and efficacy, the CDK4 inhibitor could potentially be combined with our CDK2 selective inhibitor. Or in other indications, that could be combined with other targeted agents as well as I/O agents where preclinical data support a rationale.

With our CDK2 selective inhibitor, there are 3 different kinds of ways that could deliver value. As I just mentioned, it could be combined with our CDK4 selective inhibitor to cover both CDK2 and 4 while avoiding CDK6 mediated neutropenia, and it could also be combined with IBRANCE to overcome CDK2 driven resistance. It could also be used in tumors that are CDK2 driven primarily, such as those that have lost RB or those with increased cyclin E, which is seen, for example, in many ovarian and triple-negative breast cancers. And because neither of these selective inhibitors is expected to cause significant neutropenia, we also expect them to be combined safely with other agents, including cytotoxic chemotherapies that can cause neutropenia.

So we see a variety of development opportunities in indications in both breast cancer and beyond where CDK activation seems to be playing an important role. Chris, do you want to add to that?

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Yes. I think just to state in endocrine or hormone receptor positive breast cancer, we really see the cell cycle as foundational because as [Jonathan] said, down the progressor in the sector pathways work by way of the cell cycle. So blocking CDK2/4/6, we see it as a foundational therapy that should be used in different lines. We already have some evidence for palbo after palbo, but there's ongoing at least 6 studies that we're aware of, of testing a CDK4/6 after CDK4/6. So we suspect it's going to be just like endocrine therapy that's used after endocrine therapy. Also from a Phase 2 study, one of our in-house PI3K inhibitors, which we combined with palbociclib post palbociclib, we did see significant responses.

We also have to remember in terms of adjuvant versus metastatic treatment, there's often a difference in the time of progression. So for tumors that progress during adjuvant treatment or within 6 months of adjuvant treatment, that's very different from a cancer or malignancy that progressed 6 to 12 months post stopping adjuvant therapy. And in this case, in hormone receptor positive breast and the majority of the tumors will progress much later.

So I suspect there will not be any erosion into using a CDK4/6 in first-line metastatic setting post use in the adjuvant setting.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Jeff and Chris. Operator, another question, please?

Operator

Your next question comes from Steve Scala from Cowen.

Stephen Michael Scala - *Cowen and Company, LLC, Research Division - MD & Senior Research Analyst*

I have a few. First, now that you have seen the full PALLAS data, perhaps stratified by risk, are you more or less confident in the outcome of PENELOPE-B? The second question is, would you think about the prospects for success of immuno-oncology in prostate cancer generally? And then third is, what is Pfizer's interest in KRAS and specifically combination of KRAS with CDK4/6 and BRAF/MEK?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Steve. Good questions. PALLAS and PENELOPE prospects, I/O and prostate cancer and then KRAS and KRAS combination. So Chris, maybe to you for the first two, and then you can comment on KRAS, but Nick probably will take that one.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Okay. Thank you. Very good question. So obviously, we were very disappointing -- disappointed in the result of PALLAS. Reminder that this study was not -- Pfizer is not the sponsor. This study was conducted by external sponsors. So we are working very closely with them to understand the subanalysis better, to understand the subgroup analysis better. And some of those data will be presented later this week at ESMO when monarchE will also be presented.

Just a reminder that between monarchE, [Natalie], PENELOPE and PALLAS, the baseline patient characteristics, the inclusion criteria and the trial designs are very different. So it's going to be very difficult to just compare between the different studies, very different studies. PENELOPE-B will read out, as you know, later this year in Q4. It's designed specifically for the highest risk population. So it's a subgroup of that -- of the stage 2 and stage 3 disease population, specifically those patients with residual disease after new adjuvant chemotherapy with a high clinical pathological stage to CPS scoring is a standard scoring use by oncologists and pathologists and for risk stratification. So it's the high-risk group, specifically. So we -- I'm looking forward to the readout later this year.

In terms of prostate cancer, we do have, I think, the next question of [Procentra] immunotherapy. There's 2 ongoing studies that we are collaborating with Merck and Merck are conducting these studies with pembrolizumab in combination with XTANDI enzalutamide. One study is in metastatic castration-resistant prostate cancer, and one is in metastatic castration-sensitive prostate cancer. These are ongoing studies that haven't read up yet.

I think in general, we think of prostate cancer certainly like you as a tumor that's more cold, low tumor mutational burden and also a low PD-L1. So certainly a higher bar in prostate cancer. We do have a program, though, that's ongoing in terms of bispecifics that we're developing in early development, that's potential -- that could potentially be -- T cell redirected therapy is potential one way to get T cells into prostate cancer and have activity there.

I don't know if you want to add anything to prostate cancer and the immune landscape, Jeff, and then over to Nick.

Jeff Settleman - *Pfizer Inc. - Chief Scientific Officer, Oncology*

No. I think you covered it well, Chris.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Nick, KRAS?

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Okay. Nick, to KRAS question?

Nicholas Saccomano - *Pfizer Inc. - Chief Scientific Officer, Boulder R&D Unit*

So picking up on KRAS. We're clearly aware of the attributes of the Mirati compound as well as the [other carriers]. As well as the preclinical data supporting beneficial combination with CDK inhibitors as well. I know the Boulder side was very involved in drugging [GTPases] over the last several

years. And we clearly maintain an interest in this area as well. And I think you should look to some of those who are in the clinic right now to capitalize on the preclinical data in configuring studies and combination.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Nick. Operator, I think we have time for 1 more question.

Operator

The next question comes from Umer Raffat from Evercore.

Umer Raffat - *Evercore ISI Institutional Equities, Research Division - Senior MD & Senior Analyst of Equity Research*

I had a couple, if I may. First, I noticed on your slide deck yesterday that PENELOPE readout timing has now been -- is now indicated for 2021, and it was previously expected second half 2020, broadly speaking. I just wanted to understand what drove that. And also, is there any possibility that the PENELOPE data, which is in higher risk patients, CPS, [EG 3 plus] could be combined with the higher risk subgroup of PALLAS to form the basis of some sort of adjuvant indication for IBRANCE. Does that possibility exist? That would be really helpful.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Umer. Chris, to you, for this.

Chris Boshoff - *Pfizer Inc. - Chief Development Officer, Global Product Development, Oncology*

Okay. So the -- Umer, as you know, PENELOPE is obviously like all these studies' event base. And we are now confident that the readout will occur in Q4 2020. So it's not 2021, Q4 2020. And we have to wait for the results. If PENELOPE, as we hope, is a positive study, then we'll have to look at that opportunity and whether there's an opportunity to use some of the data from pilots. We don't want to -- I don't want to speculate about that yet until we have a positive study or a positive readout for PENELOPE-B.

Andy Schmeltz - *Pfizer Inc. - Global President, Oncology*

Thanks, Chris. Well, it looks like we're just about out of time. So on behalf of the 4 of us, I want to thank you for your questions. We're very excited about our future prospects on oncology. And we look forward to bringing breakthroughs to help serve the cancer patients. Chuck, back to you.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

So we'll now have a short break, 5 minutes, and then we'll return to hear from 3 of our leaders regarding our COVID-19 antiviral and vaccine programs. So we'll be back in 5 minutes.

(Break)

PRESENTATION

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Okay. We're back. We'll move into the COVID program. And I just want to make one quick comment just so there's no confusion. The question on the PENELOPE-B study readout in 2021. What Mikael Dolsten's slide showed yesterday was a potential launch in 2021 for that potential indication. So the readout is, as Chris and Andy still reiterated, is still expected in the fourth quarter of this year.

So before we jump into our COVID-19 program, we'd first like to share a video. Roll the video, please?

(presentation)

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Now I'd like to welcome back live, Mikael Dolsten, our Chief Scientific Officer and President Worldwide Research, Development and Medical; Angela Hwang, Group President, Biopharmaceuticals group; and Kathrin Jansen, Senior Vice President and Head of Vaccines R&D. I'll now turn it over to Mikael to start the COVID presentation.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Thank you, Chuck. Today, we will focus on Pfizer's robust response to COVID-19, discussing the development of a potential mRNA vaccine and our efforts advancing a potential novel antiviral. I want to talk first about our potential first-in-class antiviral.

As COVID-19 began to emerge, we screened some of the compounds from our legacy source protease lead collection for activity against SARS-CoV-2 3CL main protease and against other coronaviruses.

From the compound screen, we identified PF-231 as a potential drug candidate. On the top left, we can see the effect of PF-231 against 2 key lineages of SARS-CoV-2, the one that originally emerged in the pandemic in yellow and a strain that emerged later in the pandemic in blue. As you can see from the table on the bottom left, our compound has strong antiviral activity against both SARS-CoV-2 lineages in a human lung carcinoma cell line.

On the right-hand side of the slide, you can note that our drug candidate displayed potent activity against a series of different coronaviruses. This suggests that we have a pan coronavirus protease inhibitor as it is effective in vitro against many existing coronaviruses and thus may possibly also be active against new coronaviruses.

In the next chart, you can see lower numbers reflect better potency. The Pfizer 231 drug candidate displays hundredfold selectivity for coronavirus 3CL proteases over human proteases. We have in vivo antiviral studies ongoing with academic labs, and we are encouraged by the interim results we are seeing.

Given that remdesivir and our compound have distinct antiviral mechanism of action and antiviral treatments have historically benefited from combination therapy, we explore the antiviral in vitro activity of this combination. The figure shows different concentration levels of remdesivir, represented by different line colors in a dose response with our 231 drug candidate. Our compound has a potent single agent EC90 in this SARS-CoV-2 to antiviral assay, a level where there's precedence for clinical efficacy with viral protease inhibitors.

We recorded that there was a 2 to 3 fold more potent EC90 value with both agents combined. This in vitro data suggests that you may be able to get the same control of the virus with lower concentration of each compound when used in combination. Collectively, this in vitro data suggest our compound has the potential to be effective as a single and combination agents against SARS-CoV-2.

To develop 231 into a drug candidate for intravenous infusion, we prepared a phosphate pro-drug, which has high solubility. The pro-drug candidate is efficiently converted in vivo models to the active 231 drug candidate. Intravenous fusion of the pro-drug candidate is expected to deliver high concentration of the active compound to efficiently inhibit the viral protease.

Well tolerated and safe in rodent preclinical safety thus far, which has brought the IND filing, is being further studied in ongoing multi-dose GLP rodent and nonrodent studies for up to 4 days. Collectively, the preclinical data suggests that we should be able to test several multiples of the antiviral EC90 clinical trials. We believe these potential first-in-class protease inhibitor may give us the best opportunity to show meaningful antiviral activity to help treat COVID-19 patients.

We initiated a Phase 1b study early in September and recently began dosing. We are planning a pivotal Phase 2/3 study start in late 2020 or early '21 with a projected approval in the second half of '21.

Moving on to our mRNA COVID-19 vaccine candidate in collaboration with BioNTech. The mRNA platform is well suited for a pandemic response on many levels. First, safety. Unlike some conventional vaccines, mRNA vaccines are non infectious and there is no need for virus to deliver the mRNA vaccine. These are potential favorable safety properties. Second, mRNA vaccines post minimal risk of anti-vector neutralizing antibody response, thereby permitting repeated boosting, which may be important if additional vaccinations are needed to control the virus in the future. Third, speed. mRNA technology enables rapid development if the vaccine needs to quickly adapt to potential mutation of SARS-CoV-2. mRNA vaccines have an efficient, fast production process without the need for complex mammalian cell systems.

Now let's discuss more about the design feature of our COVID-19 lipid nanoparticle. In the middle, we see the depiction of a lipid nanoparticle based on prior EM data and informed by our hypothesis on how we expect lipids and RNA to behave. The lipid nanoparticle or short, LNP, has 2 components: the encapsulated mRNA and the lipids. On the left is the encapsulated modified mRNA, which is codon optimized and encodes the viral spike protein.

Our encapsulated mRNA vaccine candidate elicited a broad immune response in the Phase 1/2 trial and we have seen mostly mild to moderate vaccine reaction in our trials today.

Now let's look at the lipids, which, together with the RNA form chemically defined lipid nanoparticles with no ability to infect or spread. The lipid nanoparticles do not include foreign viral proteins or vector protein with autoimmune potential. In our Phase 1/2 trials, LNP formulated vaccine candidates have elicited robust antibody CD4 and CD8 T cell response against the virus at low doses with favorable tolerability.

Now I want to share our thinking on the long-term opportunity to expand on the mRNA platform across 3 possible ways. We are in the first wave with a BNT162b COVID-19 vaccine [day] that has the cutting-edge design of a lipid nanoparticle and modified mRNA. We are currently working on wave 2, which we anticipate in 2021 to have a defined lyophilized formulation candidate that would be stored at refrigerator temperature. We will also explore new mRNA technology with a potentially lower dose and augmented immune response. These innovations could help us deliver next-generation SARS-CoV-2 vaccine potentially suitable for different variants of SARS-CoV-2.

In Wave 3, possibly around 2022, we see the emergence of a potential self-amplifying multi-valent flu mRNA vaccine. This may substantially improve flu vaccine efficacy. We see the opportunity to extend the use of this technology beyond flu and into other infectious diseases.

Now it's my pleasure to turn it over to Kathrin.

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

Thank you, Mikael. It is a pleasure to speak with everyone. My name is Kathrin Jansen. I'm Senior Vice President and Head of Vaccine Research and Development at Pfizer. Today, I will share data with you on our quest to develop a COVID-19 RNA vaccine with our partner BioNTech, to curb this devastating global pandemic.

To briefly orient you again to our program, unlike other companies, we have made a conscious decision to evaluate multiple RNA-based candidates to position ourselves and select the one with the best safety and tolerability profile and

(technical difficulty)

From day 1, we knew that the selection would be data-driven with an emphasis on clinical data. Based on the totality of data obtained at the end of July, we announced that our BNT162b2 candidate, or b2 as we call it, based on a modified RNA platform expressing the full spike protein and at the 30-microgram dose level would advance in our Phase 3 efficacy study using a two-dose regimen.

So why did we choose b2? We chose the b2 vaccine candidate because our early work showed beneficial protective effects in the primate SARS-CoV-2 challenge model, a safe tolerability profile in younger and older adults, a robust SARS-CoV-2 neutralizing antibody response across all ages and strong CD4 and CD8 T cell responses.

First, I'm excited to share our preclinical challenge data that are now available on a preprint server. 6 rhesus macaques were immunized with 2 doses of our b2 clinical candidate. The immunized rhesus and 3 unimmunized controls were challenged with 1 million live SARS-CoV-2 virus units split equally between the trachea and nose. As you can see in the control rhesus in the gray bars, viral RNA was detected in the bronchoalveolar lavage, or BAL, indicating infection in the controls. In b2 immunized rhesus, shown in the teal bars, infection was completely prevented in the bronchoalveolar lavage of the lung, while RNA positivity was still observed on day 6 in the control group. The difference in viral RNA detection in BAL between b2 immunized and control rhesus macaques after challenge is highly statistically significant.

Here, I share with you the clinical safety and tolerability profile from our Phase 1 U.S. clinical study that evaluated multiple b2 dose levels. Shown on this graph are post dose 1 tolerability data after administration of 30 micrograms of the b2 candidate in 12 subjects 18 to 55 years of age and 12 subjects 65 to 85 years of age. Also shown are the 9 subjects in each age group that received placebo. We see a mostly mild and moderate tolerability profile.

On this graph, we see the post dose 2 data. As expected, we saw a somewhat higher systemic event rate after dose 2. The 30-microgram b2 candidate continued to be well tolerated in both younger adults on the top and older adults on the bottom, with only mild to moderate events and low incidence of fever and chills in older adults. There were no Grade 4 events or SAEs reported. In general, tolerability was similar to the rates we see in some licensed vaccines.

I'm delighted to share with you now our clinical SARS-CoV-2-neutralizing antibody responses. Note that the data were generated in a real virus neutralization assay. The vaccine candidate at the 30-microgram dose level has elicited modest neutralizing antibody responses after a single dose that were boosted to higher and very robust levels after a second vaccine dose shown here for day 28 and 35 in young and older adults. We were pleased to see that neutralizing titers in older adults, the right panel, while somewhat lower than the younger adults, still increased between day 28 and day 35. For 18- to 55-year-old participants, only 11 serum specimens were available per protocol on day 28 and only 10 were available on day 35, which makes an interpretation of the day 28 to day 35 responses difficult in this cohort.

Note, however, the generally very tight neutralizing antibody responses in young and older adults compared to naturally [infected] individuals in the HCS panel. For all post dose 2 time points, neutralizing titers in immunized individuals were higher than those in the convalescent serum panel. As Mikael mentioned, the ability of RNA vaccines to boost without the vulnerability of antivector immunity is a strong plus for the RNA platform should we see the need to give more frequent boosters.

Now I'm pleased to share with you an example of the T cell responses we see with our vaccine candidate, b2. Why are T cells important? We are learning now that people can contract COVID-19 more than once and antibody levels to prevent infection may wane over time. CD4 and CD8 T cells are first responders and help our adaptive immune system. CD8 T cells particularly are important to identify and destroy virally infected cells to contribute to prevent disease.

Shown here are representative T cell data from a single trial participant who received 10-microgram of b2 to exemplify the T cell response. On the left, note the CD4 T cell response elicited by b2 that is comparable to recall responses to common pathogens. That's the CEFT role. Very importantly,

note the strong CD8 T cell response on the right elicited by b2. As with the CD4 responses, we see higher overall T cell responses to the full spike protein, that's S1 and S2 peptide pools combined, than to the small RBD domain. And these responses are as strong as recall responses to pathogens such as influenza and CMV. Additional T cell responses elicited by b2 will be provided in a scientific manuscript in the near future. This strong CD8 response was another important selection criterion for b2 and we believe differentiates our b2 vaccine candidate from some other late-stage clinical development programs.

Based on the totality of data that I just described to you, we decided to advance b2 at the 30-microgram dose level into our Phase 3 efficacy study. As a reminder, Phase 3 is a 1:1 vaccine to placebo randomized, observer blinded study to collect safety and efficacy data needed for future licensure. It is an event-driven trial. The primary end points are the prevention of COVID-19 in those who have not been infected by SARS-CoV-2 before immunization and prevention of COVID-19 regardless of whether participants had previously been infected with SARS-CoV-2. We are also exploring protection against asymptomatic disease. Enrollment in the study has progressed very well. It's closed to 30,000 subjects enrolled in 3 countries and sites planned in an additional 3 countries. As of yesterday morning, over 12,000 subjects have received a second dose.

We are also very proud of the diversity in our study population, as shown here, reflective of populations that are in particular need of a vaccine. I'm pleased to announce that we plan to increase enrollment in our Phase 3 trial to approximately 44,000 participants. This allows us to further increase the trial population diversity and include adolescents as young as 16 years of age and individuals with chronic, stable, HIV, hepatitis B or hepatitis C as well as provide us with additional safety and efficacy data.

So what about our time [map]? The pivotal trial is event based, and there are many variables that will ultimately impact timing. But as stated previously, based on current infection rates and our assumptions, we continue to expect that a conclusive efficacy readout is likely by the end of October. It is clear from FDA's June 30 guidance on COVID-19 vaccine development that the agency is continuing to apply its high standards for an EUA and BLA, an approach that we support. A rigorous approach to the development of a safe and efficacious COVID-19 vaccine is critical to help fight this pandemic.

Our trial design allows for interim analyses and unblinded reviews by an independent external data monitoring team for ongoing data and safety monitoring. We are in the process of preparing our regulatory packages and providing information on an ongoing basis to regulators. In order to preserve the integrity of the study, we will provide information about interim analysis or numbers of events only if and when the DMC notifies us that there is a conclusive readout of efficacy or futility.

Given the importance of safety, I wanted to share a few words about safety evaluation in our trial. As for all our vaccine studies, we utilize rigorous and continuous safety monitoring. Safety monitoring is performed by blinded, Pfizer-qualified personnel and by an independent external safety monitoring committee composed of vaccine and safety experts that reviews unblinded safety data on a weekly basis. As expected with a trial of this size, SAEs have been reported to regulatory agencies as well as to the DMC, which has access to unblinded data. The DMC has not raised any concerns to date, and we continue to recruit and enroll as planned.

Lastly, I would like to share with you blinded emerging tolerability data from our Phase 3 study with the data cutoff of August 27. This first graph shows post dose 1 data from over 5,000 18- to 64-year-olds and nearly 2,000 65- to 85-year-olds. When you look at this data, it is important to understand 2 things. First, since these are pooled blinded data, about 50% of subjects have received b2 and about 50% of subjects have received placebo. Second, we are collecting the tolerability data only from a subset of the trial participants up to around 6,000 in the U.S. and then around 500 subjects from each country participating in the study. This is designed to give us a reliable impression of the frequency of local and systemic reactions. That is why the number of participants reflected is fewer in number than the nearly 30,000 enrolled that I mentioned earlier. Note, they're mostly mild and moderate tolerability profile.

This second graph shows Phase 3 post dose 2 data also blinded in over 1,200 participants 18 to 64 and nearly 500 participants aged 65 to 85. We are pleased that this blinded tolerability data from our Phase 3 study after both dose 1 and dose 2 show a mostly mild to moderate overall tolerability consistent with what was observed in Phase 1 studies. Again, we see this data only on a blinded basis so we do not know if the subjects experience the event have received vaccine or placebo. The DMC has access to unblinded the data, so they would notify us if they have any safety concerns and have not done so to date.

With that, I'd like to hand over to Angela. Thank you.

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Thank you, Kathrin. Well, you've heard about the exciting R&D activities behind our potential COVID vaccine program from Mikael and Kathrin. So let me take you through our commercialization plans now.

What differentiates the Pfizer-BioNTech collaboration is that our vaccine capabilities are end-to-end and all in-house. Our clinical capabilities are our strength. It is not easy to conduct a 30,000 patient vaccine study, but we've done this before. We successfully ran an 80,000-patient vaccine efficacy trial, the CAPiTA study for Prevnar 13 in adults. And Pfizer has had a strong track record of vaccine development and commercial distribution that has led to the successful registration and launch of multiple vaccines over the years.

For our potential COVID vaccine, I see a pandemic phase first that could last until the end of 2021 into 2022, where we will need high volumes of doses to be provided to governments for large-scale vaccinations. For this pandemic period, we're pricing the vaccine for broad access rather than using the typical value-based pricing framework and supplying it mainly through government contracts. We expect to supply up to 100 million doses globally in 2020, 1.3 billion doses in 2021 and we expect to have agreements covering all of these doses. To date, we have already gained commitments for over 450 million doses with options for 600 million more.

We're in active negotiations over term sheets with 22 countries right now, and we're at various stages of discussions with 30 more countries, including the COVAX facility where we have issued an expression of interest. The COVAX facility is a mechanism established by Gavi, the Vaccine Alliance, the Coalition for Epidemic Preparedness Innovations as well as the World Health Organization that aims to provide governments, including those in the emerging markets, with early access to a large portfolio of COVID-19 vaccine candidates.

The in-country dose allocation will be the responsibility of the health authorities of each country, and we will work with them to provide input. We also know how important it will be to increase the public's confidence in vaccines. And so we're activating multiple channels, including DTC, to educate the public on the importance of vaccinations as well as providing education around the safety standards of the COVID vaccine.

Pfizer is also supporting industry education campaigns, such as the Stronger campaign launched by BIO, which aims to build a movement of pro-vaccine supporters and to counter the vaccine misinformation that you see online. Our global supply team has worked so hard to develop a practical and reliable [logistics] scale, cold chain logistics plan built off a supply chain plan that we're using for our Phase 3 trials currently. We believe governments will be able to effectively dose patients.

Our distribution centers will be equipped with ultralow temperature storage capabilities. The vaccines will be shipped directly to vaccination centers in a thermal shipper that can maintain the ultralow temperatures. These shippers can hold anywhere between 200 and 1,000 vials. Each thermal shipper also contains a reusable GPS-enabled temperature monitoring device to ensure that the vaccines are maintained within required temperatures.

At the point of use, there are going to be 3 options for storage. One, the [ultralow] temperature freezers are commercially available now, and the freezer can extend shelf life for up to 6 months. Alternatively, the thermal shipper can be used by recharging it with dry ice. This can provide 15 days of storage. Or the vaccine can be stored for 5 days at refrigerated 2 to 8 degree conditions. And we're continuing our stability studies to generate additional data. Given the pandemic though, we don't expect that the doses will be stored for long. On the contrary, we anticipate doses will be administered shortly after they are received at the sites.

To prepare the vaccine for administration, each vial will be diluted with saline, and this will enable 5 doses per vial. The diluted vial is stable at room temperature for 6 hours. Remember, the vaccine distribution, storage and administration processes that we just described are routinely and effectively done now as part of our clinical trials, and it works. This is why we're confident about our ability to distribute these doses and for the vaccine to be stored appropriately until administration.

Now let's shift to the potential vaccination scenarios that we're preparing for. The durability of the vaccine efficacy will inform what vaccinations will look like in the pandemic and post-pandemic phases. If immunity is short-lived, then you may expect annual vaccinations to take place. If immunity is prolonged, then there's potential for a scenario where you have to boost after several years, much like tetanus today. If immunity is very prolonged, then we may not need boosting, similar to what you see in some childhood vaccinations today that are given just once like hep B, measles. However, the possibility of the virus changing exists and/or the emergence of other closely related viruses is possible. And therefore, the need to make will always be present.

We specifically chose to collaborate with BioNTech because of the unique benefits of the mRNA technology and the advantages that this would offer to cover the entire range of vaccination possibilities. The 3 key advantages to the mRNA technology are as follows: the ability to quickly modify and to develop a new vaccine if the virus strain changes; the ability to boost if we need; and the ability to also elicit both B-cell, which is the antibody, as well as T cell immunity. The good news is this technology will allow our vaccine to have a role in any potential post-pandemic scenario, and this is why we will have a sustainable business.

So thank you. And now I'll hand it back over to you, Chuck, for Q&A.

Charles E. Triano - *Pfizer Inc. - SVP of IR*

Great. Thanks, Angela. So what we'll do now is we will bring Albert in, and we'll have a Q&A session with Albert, Angela, Mikael and Kathrin. So you can address COVID questions or any questions from the presentations yesterday by Albert, Angela and Mikael. So I'll now turn it over to Albert to kick off the Q&A session here. And operator, if we can poll for questions.

QUESTIONS AND ANSWERS

Operator

(Operator Instructions) Your first question comes from Vamil Divan from Mizuho.

Vamil Kishore Divan - *Mizuho Securities USA LLC, Research Division - MD*

Thanks also for all the info and all the work you're doing on the COVID-19 side. So maybe one question for Albert, more general from yesterday's presentation and one on COVID-19. Albert, a question we receive from some investors just around, I guess, sort of you mentioned the current pipeline, you seem -- you've been replacing all the revenues that are going to be lost on the upcoming LOEs. Question is -- we know those revenues will be going away in the second half of the decade and sort of the pace at which you think those can be replaced. So if you think about the second half of the decade, are you comfortable giving any sort of hints on the sort of annual basis or over the 5 years, will there be a sharp decline in revenues? And then we see a strong recovery as the pipeline sort of matures and plays out over time? Or do you think potentially we may not see any decline in revenue at all as we go in 2026, 2027, 2028?

And then my question on the COVID vaccine, I know you said you're not going to speak much in terms of timing around interims and things like that. I'm just wondering if you could comment at all in terms of the DMC and what they're looking at in terms of especially the follow-up, how much duration of response will they have as they're sort of making their decisions around the conclusive efficacy for the vaccine. Obviously, people are kind of wondering what the long-term efficacy is useful. Any comment on there would be helpful.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Vamil. We do feel confident that post '26, our pipeline will at least replace, which means that we do feel comfortable that we will be at -- not decline. We will be at growth. Our ambition is to have sustainable growth. Our ambition, it is to move it to almost 6%, and this is what we

strive to do. Data will come from the pipeline, also from additional enhancements of the pipeline with early to mid year assets so that they will be able to replace this streamline of the growth. And with that, I will take it to Kathrin to reply to you about the DMC.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Okay. Then maybe, Mikael, you take the question until we fix the technical issues with Kathrin.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Happy to do that. We have a DMC with renowned experts in medicine, infectious diseases, vaccine and pediatrics. They review on a weekly basis serious adverse events and any adverse events and on an unblinded fashion, in addition, of course, Pfizer's expert review on a blinded basis. And at certain case counts, and I think we have revealed that the first round would be 32 cases, they will review efficacy distribution between the vaccine groups followed by several other interim analyses that may allow them to stop the study because of efficacy, continue the study or declare futility. So far, we have -- there has been no safety signal reported, and you have seen also from Kathrin blinded data on tolerability and reactogenicity, which confirms the mild to moderate favorable profile in the Phase 1/2.

Operator

Your next question comes from Navin Jacob from UBS.

Navin Cyriac Jacob - *UBS Investment Bank, Research Division - Equity Research Analyst of Specialty Pharmaceuticals and Large Cap Pharmaceutic*

A couple, if I may. Number one, I think you had suggested that the enrollment in the Phase 3 was in part due to a desire to enroll a more diverse set of subpopulation, which is understandable. But also, I believe I missed -- please correct me if I'm wrong, but it seemed -- there seems to be perhaps a slowing of also the event rate or slowing of infections. If that's true, is that also part of why there was an increase in the trial size?

And then with regards to the elderly cohort and the neutralizing antibodies increasing through day 35, certainly encouraging. But when we cut the data for the convalescent plasma patients, the neutralizing antibody titers that is, for patients above 55 years old, that -- the [ND50] was 142 versus the roughly 200. And apologies, I'm just seeing that data very quickly. You had -- you put up about 200 or so, which is about maybe 1.5x convalescent plasma for the patients that were above 55. Is that level of fold enough in your mind to provide enough of a event reduction in those patients that are most at risk, i.e., the patients that are over 55 years old?

And then my last question is how are you thinking about durability of efficacy? What are the -- what gives you confidence about how long the efficacy could be -- could last for?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Yes. As we said already, the enrollment is -- the increase of the number of the subject in the enrollment is coming mainly from the fact that we have already 30,000 people. We feel much more comfortable with the profile, the safety profile of the vaccine. So we are going to much more vulnerable populations, 16 years old, people that have HIV or hepatitis C or hepatitis B. The events, indeed, in the U.S. are slowed down. Just to make clear, though, that we are taking this current events when we speak about we expect the conclusive readout by the end of October. We are not using previous assumptions, but we were a little bit more optimistic. So based on the current level of events, that we are speaking that it's going to be by the end of October.

Now I will turn it to Mikael to speak a little bit about how comfortable we feel with the immunogenicity in elderly population and what about the durability. And I can see also Kathrin is on the panel, so maybe the technical problem has been resolved. So Mikael, you start then Kathrin will end.

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

Yes. Thank you. As you could note in the presentation from Kathrin, we do have a very nice response in older adult, continue to rise at day 35 and being above the seen convalescent plasma. I want to point out that our vaccine, as you noted, induce also potent CD4 and the CD8 cells that Kathrin pointed out. The CD8 cells, in particular, are great producers of an antiviral substance called interferon. And indeed, interferon determines susceptibility in studies for coronaviruses. Some of these data are coming from SARS-CoV-2 where patients that were protected from infections had CD8 cell activity for a very long time. And particularly, as antibodies decline to intermediate level over time, the CD8 cells will be a very important additional tool. So you have to look at the totality of strong immune response induced by our mRNA vaccines, including robust antiviral antibodies and CD8 cells.

Concerning the durability. So Angela spoke a bit to that, but we don't know yet. There are conflicting reports in durability after patients contracting disease and how long they retain protective antibody levels. We expect after a number of months from those patients that the antibody levels may settle at a lower amount and then additional immune parameters may be additive. However, the advantage of vaccination is that you do that during a healthy immune status rather than when the immune status is perturb by the virus. So I do think we should have some cautious optimism that when you activate antibody CD4 and CD8 cells, there can be a reasonable long-lasting immune response. We will monitor this up to 2 years and if required, longer. That will guide us when a possible additional boost should be given. Thank you very much.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Kathrin, anything to add to what Mikael said?

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

No, I think he covered it. Thank you very much.

Operator

Your next question comes from David Risinger from Morgan Stanley.

David Reed Risinger - *Morgan Stanley, Research Division - MD in Equity Research and United States Pharmaceuticals Analyst*

Yes. This is extremely helpful. So I have 3 questions. First, certain political figures and news media have been challenging the legitimacy of science and judgment of the nation's top scientific leaders. How is Pfizer addressing these challenges? Second, Slide 12 indicates an opportunity for a next-gen vaccine in 2021 that generates augmented immune response. What are you seeking to improve upon with respect to BNT162? And then third, what is your understanding about the purpose of the FDA's planned COVID vaccine panel meeting on October 22?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Kathrin, why don't you take the question about the next generation in '21? What type of improvements do we anticipate to bring?

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

Yes. Thank you for the question. What we are thinking about is, as Angela noted earlier, our current vaccine candidate is a frozen candidate. So one of the improvements that we are going to think about is can we produce a vaccine candidate that would have a, let's say, a refrigerator, a stability profile. That's one. Another way of thinking about an improved COVID-19 vaccine is as you know and what I presented earlier, it is a 2-dose vaccine.

So one of the ways to improve this vaccine would be to find a way to make it a 1-dose vaccine. So those are 2 major things that we are thinking about in the context of a, what I would call, a second-generation COVID-19 vaccine. Thank you.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Kathrin. And then as regards to the political environment, yes, it's very disappointing. Right now, unfortunately, the COVID crisis and particularly the vaccines development has been intensively politicized. And we have politicians or journalists speaking about efficacy or safety about medicines, which, of course, is not appropriate. The scientists should be having these discussions. The pledge that we did together with other 9 vaccine makers was [to address this], was our promise that no matter what other thing, we would not ourselves provide -- submit either for authorization or for full approval data without having a conclusive readout of a Phase 3 result. And this is coming together with the reputation of our companies, as I said multiple times. Ourselves, who are developing medicines for 171 years, we plan to honor this tradition, and we are not planning to stain it.

You asked for my comments about what I think the advisory committee that the FDA has called. I don't think it's appropriate for me to comment about what this committee will do. But what I would say is that I'm very happy to see that the FDA sends a very clear signal that they will use, in addition to their own staff experts, that they have seen it all basically, they know exactly what to look when they are looking for safety or efficacy in a vaccine, in addition to that, they will use also the opinion of experts that will be in addition to that.

Operator

Your next question comes from Terence Flynn from Goldman Sachs.

Terence C. Flynn - *Goldman Sachs Group, Inc., Research Division - MD*

Thank you for all your work during the pandemic. I had 2. Maybe Albert, just what do you see as the most underappreciated aspect of the Pfizer investment case right now? Obviously, we've listened to all the division heads over the last 2 days give us a pretty detailed overview, but would just be curious to kind of get your thoughts there. And then on the COVID vaccine front, probably a question for Kathrin, but was wondering if you're capturing follow-up data on antibody levels from participants in the Phase 1 trial. And if so, are you able to share any details there about durability? Or maybe you have access to blinded Phase 2/3 data on the antibody levels? So just be curious kind of what you're seeing longer term on this front.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Yes. Thank you very much. The investment thesis of Pfizer, I think I articulated very well in my opening comments yesterday, we have a very robust line of strong, growing products. Last year, 8%. This year first half, 9%. And we have a pipeline that is very diversified. It's not dependent on events -- binary events. It is a pipeline that has mild assets. So when you apply risk adjustments, it's meaningful because if you have, for example, 5 or 6 assets, maybe [luck can weigh in different] than what you think. But when you have 20, statistics should work.

In addition to that, it's very clear that we have the gift of no major LOEs all the way to '25, '26, basically to '26. With that, if you add the financial robustness of our company, all the cultural changes that we have done, the way that we are running the company, the proven record, for example, you see now how we jumped into developing a vaccine like COVID within -- in a time line that nobody would believe that Pfizer could have done this in the past and, of course, the fact that we have a very nice dividend that is going to grow and also we have the financial flexibility to be able to enhance our pipeline with Phase 2/Phase 3 assets, it is very clear top line organic growth sustainable for the long term and at least 6% in the mid-term all the way to 2026. This is the investment [is suffice]. But let me turn to Kathrin now to speak a little bit about the COVID-19 question.

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

Yes. Thank you very much for the question. And like in all of our studies, we do actually evaluate persistence data. And those data will come primarily from our Phase 1 studies because there, of course, we started ahead of our pivotal Phase 3 study. So we're planning to look for persistence of antibody. We will also evaluate memory T cell responses, which I think particularly on the COVID-19 situation, as we described before, is very important to demonstrate that we have a good memory T cell response. That will help us to address particular neutralizing antibodies intervening with a strong memory T cell response. We have an opportunity to -- or potential to provide persistent protection. We cannot, because we are blinded -- you asked are there any data coming out of the pivotal Phase 3 study. Unfortunately, before -- because we are blinded, we cannot access any data from our Phase 3 study. But once the study is concluded, we will be able to publish the persistence data from Phase 3.

Operator

Your next question comes from Geoffrey Porges from SVB Leerink.

Geoffrey Craig Porges - *SVB Leerink LLC, Research Division - Director of Therapeutics Research & Diversified Biopharma and Senior Research Analyst*

Congratulations on all the remarkable progress [and the speed]. A few questions on the pivotal trial. First, could you talk about the consent form that patients have signed and what obligation the patient -- you have to the patients if you do get a positive efficacy readout? How will you manage the demand from the part of patients to get the active intervention? Because of course, they have significant risk then if they are blinded, that they might go out in the community and expose themselves to COVID. But on the other hand, you have the societal obligation to get the full safety data and to look at the durability of efficacy. So how are you going to balance those 2 to get that information?

Secondly, could you talk a little bit about the statistical plan for the Phase 3? What sort of p-value and reduction in events do you need to see to unblind the study? And then lastly, Angela, are you thinking about multiple vaccines being successful? Or are you operating on the assumption that yours will be the only one?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you very much. Let's start with Kathrin, the statistical plan and also about the consent form, what -- how are we going to manage the situation when we have a conclusive readout.

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

Yes. Thank you for the question, very important question. So let me start with the consent form. So as part of the patient consent, we have made it clear, since we are not a diagnostic laboratory, that we would not provide on a real-time basis any data that pertain to the PCR positivity status of SARS-CoV-2. However, after starting the baseline studies, and we saw that actually we have individuals enrolling in the study that were already positive for SARS-CoV-2 at baseline. We made the decision that as soon as we have evidence that a participant is positive, we're talking baseline data here, that we would notify the investigator to work with the participant in the appropriate manner.

So the second part of your question was the statistical analysis plan and how we -- what the plan is to define whether or not our vaccine is successful. So first of all, I need to say that we follow the very stringent guidelines of the FDA. And the FDA has made it very clear that a vaccine has to be at least 50% effective with an observed 50% effectiveness, but the lower bound has to be more than 30%. And so those are very stringent criteria. Our study is powered to be successful if we see at least 60% efficacy. Now this is just to say that it is powered and successful for at least 60%. That's not to say the vaccine will only be 60% efficacious, but it could be much more efficacious. I just wanted to make this clear. But in any case, whether at the final analysis or at the interim analysis, the intent is, of course, to analyze the data under those stringent conditions and make sure that whatever the efficacy is, that we can demonstrate that there's a lower bound above 30%. And that's part of our statistical analysis plan.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Kathrin. Mikael, anything to add here?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

I think Kathrin described it great. Of course, everything that you alluded to was with the original 30,000 participants. Now as we even expand the trial, as we focus on additional groups that can be protected, of course, our power will, over time, be even stronger and overlap completely with the FDA minimal criteria. But we do believe given the very robust immune profile and also the preclinical profile protecting from infection that vaccine efficacy is likely to be 60% or more.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Angela?

Angela Hwang - *Pfizer Inc. - Group President of Biopharmaceuticals Group*

Thanks for the question. Well, I think you've heard today the very positive progress of our program as well as potential of the scientific profile that we expect to see from our program. But I think that the science is just one aspect. One has to remember that the ability to manufacture at scale and the ability to distribute and to bring the supply chain is equally as important once we have the vaccine in our hands. And so this is where I think Pfizer brings its best to bear. We have the science. We have the supply chain. We have a track record of having done this over and over and over again. And so while I acknowledge that there are going to be multiple competitors out there, we are in a pandemic, a global pandemic. What my assumption also is, is that we will have a strong leadership position in this field.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

All right. So let's get now our final question because we are a little bit over time.

Louise Alesandra Chen - *Cantor Fitzgerald & Co., Research Division - Senior Research Analyst & MD*

Can it be final questions? So first one I wanted to ask you is how long do you think it will take to achieve herd immunity with viable vaccines? And then outside of a clinical trial, how many percent of patients do you think will come back for that second dose? And then last question is how representative are the convalescent serum data used as controls in the trials?

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Mikael, what do you think? How long it will take for herd immunity?

Mikael Dolsten - *Pfizer Inc. - Chief Scientific Officer and President of Worldwide Research, Development & Medical*

It's too early to know about that. And right now, it's still a relatively small fraction of the population that have contracted the disease, even with a larger estimate. So the majority of the population across the globe has not contracted the disease. And we do hope, of course, assuming that we could conclude positively the trial pending outcome and the regulatory aspect in October, that starting a vaccination across the globe to ensure herd immunity is what you would like to accomplish, but that will take time. And we need to understand how long-lasting the immunity is because

in general, coronavirus immunity in natural infection have not been that long-lasting. And that's why Angela spoke about that it may even require annual or every few years' boost, which is, of course, a great advantage of this platform.

So in summary, I think it's too early to know. We think this vaccine has potential to give reasonable and good protection, but we need to monitor. And it's reasonable also to assume that you need maybe in the future to boost because this is a real pandemic, and there's going to be a lot of virus circulating even after global campaigns.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Kathrin, you want to take the other 2 questions about the trial?

Kathrin U. Jansen - *Pfizer Inc. - SVP & Head of Vaccine Research & Development*

Yes, I'm happy to. Thank you for the question. So the question was of how many individuals and participants in the study come back for the second dose. As we said earlier, our vaccines is very well tolerated. And so we see actually very good compliance of trial participants to come back for the second shot. Then you asked about the relevance of our human convalescent serum panel. We have collected this panel. It's about a panel of 38 individuals. They were collected very early on as [we start to put] our program, and they reflect what we see. They reflect individuals that are asymptomatic. They affect individuals that showed symptomatic disease, and there was also 1 of the 38 individuals was hospitalized.

So we see the -- what we see now after generating more information, we see everyone, everything from individuals that have very low neutralizing antibodies to very high neutralizing antibody responses. So the whole degree of what you would expect and what we do see right now in the real world. So we believe that this panel is an appropriate panel to compare our vaccine-induced immune responses to.

Albert Bourla - *Pfizer Inc. - Chairman of the Board & CEO*

Thank you, Kathrin. So with that, I think we have reached the end of this 2-day event. But before I share some closing thoughts, I want to thank my colleagues who served as presenter over the past 2 days. They are the ones that are driving Pfizer transformation. And the greatest strategies in the world are worth nothing unless they are executed well, and it is their ability to execute with excellence that had led to advent to our new Pfizer.

So as I said yesterday, building upon a dramatic R&D turnaround gives us one of the best biopharma organizations in the world as we presented data yesterday with improved success rates, reductions in cycle times. We have also taken the steps necessary to create the focus and culture that is needed to drive our success over the next decade. We have clearly defined that the new Pfizer will be a highly focused, science-driven biopharmaceutical company. We put in place the people, the processes, the incentives, the operating model that enable us to deliver breakthrough science. And of course, we are playing to our strengths in 6 targeted therapeutic areas where the intersection of new science, significant unmet medical need and Pfizer's strong platforms and people give us a competitive advantage. We believe that this construct represents the greatest opportunity to deliver value for patients, our shareholders and all stakeholders in both the near and the long term.

Over the past 2 days, hopefully, you have come to appreciate our deep passion in science and come to understand why we believe so strongly that science will win the battle against disease. I'm thrilled that we're able to showcase some of Pfizer's top scientific and commercial leaders to have an open dialogue with all of you and to provide you with a better sense of depth and breadth of what we believe to be an industry-leading pipeline. When combined with our highly successful in-market portfolio, this pipeline, including what we believe are some undervalued programs, it is what makes us believe that we expect -- will allow us to sustain a revenue CAGR of at least 6% over the next 5 years and beyond.

Thank you for your continued interest in Pfizer, our people and our purpose. I hope you and your loved ones continue to stay safe and well, and I look forward to speaking with you all soon. Take care.

Project Matrix
Post-EGM Legends

Forward-Looking Statements

This communication contains "forward-looking statements". Such forward-looking statements may include, without limitation, statements about the proposed combination of Upjohn Inc. ("Newco") and Mylan, which will immediately follow the proposed separation of the Upjohn business (the "Upjohn Business") from Pfizer Inc. ("Pfizer") (the "proposed transaction"), the expected timetable for completing the proposed transaction, the benefits and synergies of the proposed transaction, future opportunities for the combined company and products and any other statements regarding Pfizer's, Mylan's, the Upjohn Business's or the combined company's future operations, financial or operating results, capital allocation, dividend policy, debt ratio, anticipated business levels, future earnings, planned activities, anticipated growth, market opportunities, strategies, competitions, and other expectations and targets for future periods. Forward looking statements may often be identified by the use of words such as "will", "may", "could", "should", "would", "project", "believe", "anticipate", "expect", "plan", "estimate", "forecast", "potential", "pipeline", "intend", "continue", "target", "seek" and variations of these words or comparable words. Because forward-looking statements inherently involve risks and uncertainties, actual future results may differ materially from those expressed or implied by such forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to: ongoing challenges and uncertainties posed by the COVID-19 pandemic for businesses and governments around the world; the parties' ability to meet expectations regarding the timing, completion and accounting and tax treatments of the proposed transaction; changes in relevant tax and other laws; the parties' ability to consummate the proposed transaction; the conditions to the completion of the proposed transaction not being satisfied or waived on the anticipated timeframe or at all; the regulatory approvals required for the proposed transaction not being obtained on the terms expected or on the anticipated schedule or at all; inherent uncertainties involved in the estimates and judgments used in the preparation of financial statements and the providing of estimates of financial measures, in accordance with U.S. GAAP and related standards or on an adjusted basis; the integration of Mylan and the Upjohn Business being more difficult, time consuming or costly than expected; Mylan's, the Upjohn Business's and the combined company's failure to achieve expected or targeted future financial and operating performance and results; the possibility that the combined company may be unable to achieve expected benefits, synergies and operating efficiencies in connection with the proposed transaction within the expected time frames or at all or to successfully integrate Mylan and the Upjohn Business; customer loss and business disruption being greater than expected following the proposed transaction; the retention of key employees being more difficult following the proposed transaction; Mylan's, the Upjohn Business's or the combined company's liquidity, capital resources and ability to obtain financing; any regulatory, legal or other impediments to Mylan's, the Upjohn Business's or the combined company's ability to bring new products to market, including but not limited to where Mylan, the Upjohn Business or the combined company uses its business judgment and decides to

manufacture, market and/or sell products, directly or through third parties, notwithstanding the fact that allegations of patent infringement(s) have not been finally resolved by the courts (i.e., an "at-risk launch"); success of clinical trials and Mylan's, the Upjohn Business's or the combined company's ability to execute on new product opportunities; any changes in or difficulties with Mylan's, the Upjohn Business's or the combined company's manufacturing facilities, including with respect to remediation and restructuring activities, supply chain or inventory or the ability to meet anticipated demand; the scope, timing and outcome of any ongoing legal proceedings, including government investigations, and the impact of any such proceedings on Mylan's, the Upjohn Business's or the combined company's consolidated financial condition, results of operations and/or cash flows; Mylan's, the Upjohn Business's and the combined company's ability to protect their respective intellectual property and preserve their respective intellectual property rights; the effect of any changes in customer and supplier relationships and customer purchasing patterns; the ability to attract and retain key personnel; changes in third-party relationships; actions and decisions of healthcare and pharmaceutical regulators; the impacts of competition; changes in the economic and financial conditions of the Upjohn Business or the business of Mylan or the combined company; the impact of outbreaks, epidemics or pandemics, such as the COVID-19 pandemic; uncertainties regarding future demand, pricing and reimbursement for Mylan's, the Upjohn Business's or the combined company's products; and uncertainties and matters beyond the control of management and other factors described under "Risk Factors" in each of Pfizer's, Newco's and Mylan's Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q and other filings with the Securities and Exchange Commission ("SEC"). These risks, as well as other risks associated with Mylan, the Upjohn Business, the combined company and the proposed transaction are also more fully discussed in the Registration Statement on Form S-4, as amended, which includes a proxy statement/prospectus (as amended, the "Form S-4"), which was filed by Newco with the SEC on October 25, 2019 and declared effective by the SEC on February 13, 2020, the Registration Statement on Form 10, which includes an information statement (the "Form 10"), which was filed by Newco with the SEC on June 12, 2020 and declared effective by the SEC on June 30, 2020, a definitive proxy statement, which was filed by Mylan with the SEC on February 13, 2020 (the "Proxy Statement"), and a prospectus, which was filed by Newco with the SEC on February 13, 2020 (the "Prospectus"). You can access Pfizer's, Mylan's and Newco's filings with the SEC through the SEC website at www.sec.gov or through Pfizer's or Mylan's website, as applicable, and Pfizer and Mylan strongly encourage you to do so. Except as required by applicable law, Pfizer, Mylan and Newco undertake no obligation to update any statements herein for revisions or changes after this communication is made.