Vertex Pharmaceuticals Incorporated

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Jessica Fye Analyst

Hey, good morning, everyone. We're going to get started. My name is Jess Fye. I'm a senior biotech analyst at JPMorgan, continuing the 42nd Annual Healthcare Conference this morning with Vertex. I'm joined by the company's CEO, Reshma Kewalramani.

After the session, you don't have to switch rooms. We're going to go straight into Q&A. You're welcome to ask questions in the room. You can submit them to me on this iPad through the portal or you can listen to me ask questions. So with that, let me turn it over to Reshma for the presentation.

Reshma Kewalramani Executive

Thanks, Jess. Jess, thank you very much. Thank you to JPMorgan. Good morning all. It's great to be here in San Francisco in person to kick off the year.

On behalf of the entire Vertex team, I'm delighted to be here with you to give you an update on the CF business, our diversification into new disease areas with the near-term approval of casgevy and many more near-term commercial opportunities, the continued rapid advancement of our pipeline and the outlook for the company as a whole.

Slide 2, which I will leave on for yet another minute, is our safe harbor statement. I'll give you 1 more minute to review it. The disclosures are in our SEC filings and I encourage you to read those.

With that, let me turn over to the presentation itself. At Vertex we have a unique R&D strategy. It's depicted in the wheel to the left. We invest in scientific innovation to drive serial

innovation and develop transformative medicines for specialty markets, with low SG&A expense. This enables strong operating margins and profitability, which can be reinvested into R&D thus perpetuating a virtuous cycle.

Our R&D approach is a disease-first strategy, causal human biology, validated targets.

That's what we focus on, along with biomarkers that translate from bench to bedside and whatever modality is best to interdict on the target, with regulatory and development pathways that are efficient. This approach was designed to deliver disproportionate R&D success, and it has delivered. We now have approved medicines in cystic fibrosis, in sickle cell disease, in beta thalassemia, and from 2018 through today we put 7 new disease areas into the clinic. 7 have finished their proof-of-concept trials through today, and 6 of the 7 have delivered positive proof-of-concept. Ultimately, this approach enables us to sustain innovation, unlock new disease areas, develop transformative medicines and create value for patients and for shareholders alike.

Let me talk a little bit about our inflection point that I discussed circa 2023 and a little bit before that. And I talked about this R&D inflection point. Today, that inflection point has translated to a new era for the company of commercial diversification. The box to the left has our lineup of commercialized products. The middle box lists the programs in which we are nearing the potential commercialization and launch.

This includes casgevy in TDT, beta-thalassemia in the U.S., sickle cell disease is already approved, and sickle cell disease and beta-thalassemia in additional geographies; the vanzacaftor triple in CF; and the VX-548 acute pain program. The box to the right, that lists some of our programs that are in patients in clinical development. This is really important because these studies, Phase I/II or Phase II studies in patients, allow us to not only evaluate safety but efficacy as well. Each of our programs is a first-in-class or best-in-class program. And each individually is a large opportunity.

Taken together, we have the opportunity to serve millions of patients. By the end of this year, we expect to be in the clinic in 10 disease areas. That's up 2 from this time last year. The 2 newest disease areas are DM1 or myotonic dystrophy type 1, and the second is ADPKD, or autosomal dominant polycystic kidney disease. The DM1 program is a Phase I/II program in patients and the autosomal dominant polycystic kidney disease program, which we expect to enter the clinic later this year, is going to be a Phase I healthy volunteer study.

With the ongoing launches in casgevy, the Phase III readouts through the year, we are well on our way to meeting, if not exceeding, our goal that we described at this meeting last year of 5 launches in 5 years. Given the time today, I'm going to focus the remainder of my comments on our commercialized products, the programs with the nearest-term commercial opportunity and programs that are already past the proof-of-concept stage. And I'll start with CF. We have revised the epidemiology in CF in North America, Europe and Australia from previously 88,000 to 92,000. This comes from 3 sources.

One, there are more patients entering registries. Two, there are better data capture across global registries. And most importantly, number three, CF patients are living longer. And one more thing to mention on CF today. Joe O'Donnell, who is a legend in cystic fibrosis.

Joe is a father to a young boy who lost his life to cystic fibrosis, an entrepreneur, a businessman, and a giant who brought the CF community together and drove the field forward. I want to acknowledge the death of Joe O'Donnell and thank him for all of the contributions he has made to this field. Moving to continued growth from CF. We see continued growth in CF from reaching younger patients and in reaching additional geographies. And in our drive to bring newer and potentially even better medicines to CF patients.

The next in-class vanzacaftor triple combination has completed the Phase III trials and I'm pleased to share we're on track to release results early this year. Beyond the vanzacaftor triple, we've already identified and advanced into the clinic additional correctors and potentiators. And finally, there are about 5,000 or so patients who cannot benefit from CFTR modulators but they may be able to benefit from our mRNA program or VX-522. I'm pleased to share that the SAD portion of the Phase I/II program is complete. The MAD initiated late last year.

And now let's transition from CF to casgevy and sickle cell disease and beta-thalassemia. Casgevy is a precise, durable onetime CRISPR-Cas9 gene-editing therapy that holds the promise for a functional cure. The end of 2023 was filled with news about this historic approval because it is the first CRISPR gene-editing therapy to be approved. Significantly, the approval and launch of casgevy also marks a new era for Vertex with diversification in approvals and commercialization outside of CF.

Beyond the landmark approval, Casgevy represents an enormous opportunity to serve patients and has multibillion-dollar market potential. The early days of the launch are underway. In the geographies in which casgevy is approved, our teams have hit the ground running. Our commercial teams, our patient advocacy teams, our teams working in reimbursement and access are out there and are engaging with their customers. In addition to the 35,000 patients we're focusing on in the U.S.

and Europe, there are thousands more patients in Bahrain, where we've also received approval for both beta-thalassemia and sickle cell disease, and in the Kingdom of Saudi Arabia, where we are undergoing final regulatory review and are awaiting regulatory approval.

To share a few more details. As we conduct our market research with physicians, we know that physicians prefer gene-editing therapy to gene therapy. We know that the patients can be served with the approximately 50 authorized treatment centers we're planning in the U.S. and the approximately 25 treatment centers we're planning in the EU. And I'm really happy to share that as I stand here today, 9 authorized treatment centers are already activated in the U.S.

and 3 centers are already activated in the EU. To conclude on casgevy, I want to give you another update with regard to access and reimbursement here in the U.S. We recently signed an agreement for casgevy with Synergy, a network that covers approximately 100 million lives commercially. And while we continue to secure coverage at additional providers above and beyond Synergy, for the here and now people in the U.S. can access casgevy through single agreements and in the EU can access casgevy with the potential of early access programs.

To close on casgevy, the treatment journey is a multi-month process. Patients know that and physicians know that. And they are enthusiastic about this journey because it offers the potential for a lifetime of benefit. And we, at the company, are committed to securing access and reimbursement for patients who have been long underserved and translating the historic approvals into patients benefit in the real world. Let me now move on to pain, an area of enormous interest inside the company, and I know amongst all of you.

This slide lays out the comprehensive view of all of our programs in pain. They include NaV1.8 inhibitors as well as Nav1.7 inhibitors, oral therapies and the potential for IV therapy. Just like in CF and in sickle cell disease and beta thalassemia, our commitment here is the serial innovation and leadership in pain. Let me start with acute pain. The graph to the top left depicts the mechanism of action.

And I want to highlight just a couple of points here. The NaV1.8 access that target is both genetically and pharmacologically validated. Specific inhibition of NaV1.8 channels block the underlying mechanism responsible for pain signaling. Moreover, because NaV1.8 receptors are only expressed in the peripheral nervous system, NaV1.8 inhibitors are not expected to have any of the unwanted CNS side effects, particularly addictive potential.

The right-hand side of the slide demonstrates the unmet need. On the one hand, we have NSAIDs and OTC Tylenol. They have no addictive potential, but the efficacy is limited. On the other side, we have opioids. Opioids provide good pain relief, but they come with side effects, including importantly, addictive potential and abuse potential.

NaV1.8 inhibitors, starting with VX-548, hold a promise to fill this therapeutic gap given the Phase II results showed strong efficacy, a very good-looking benefit-risk profile and by way of its mechanism of action does not hold addictive potential. And our expectations for this program are high. And I say that based on 3 reasons: one, the target is genetically and pharmacologically validated; two, the Phase II results that I just described; and three, the Phase III program is designed very similarly to the Phase II program. It's the same 2 pain conditions. It is the same endpoint, and it is the same high dose from the Phase II program.

Let me move now to another area of pain. This one is diabetic peripheral neuropathy under the broader umbrella of peripheral neuropathic pain. We recently completed our Phase II program and shared the results and they are here again on the slide. The results showed clinically significant, statistically significant improvements in what's called the NPRS score of more than 2 points. And importantly, we also shared a key secondary endpoint, which is the depth of response.

The VX-548 mid- and high-dose groups showed high levels of 30%, 50% and 70% reductions in pain. Shown here on the slide is also the pregabalin group, which was in the study for the purposes of providing context. We can't make direct comparisons because the study wasn't designed as such. But I shared it with you here today also to give you context for what the pain reduction that VX-548 achieved can be evaluated for. A final point on this slide.

This was the first dosing of VX-548 in the chronic setting. And hence, it's the first demonstration of safety with VX-548 with chronic dosing.

Let me roll forward to the next steps in the program. They are laid out on this slide for acute

pain. It's sharing VX-548 data in the near term. It's about the VX-993, the next in our molecules in the portfolio of serial innovation. The oral formulation is going to come forward in a Phase II study this year and the IV formulation of 993 is going to come forward into a healthy volunteer study.

And in peripheral neuropathic pain, we look forward to our end of Phase II meeting with regulators and starting our pivotal development program thereafter. It's about continuing to dose and enroll in what's called lumbosacral radiculopathy. It's another kind of peripheral neuropathic pain. This one actually with 6 million patients in the U.S. and for which there is no approved therapy in the United States.

With that, I'm going to move on now to Inaxaplin and the AMKD program. This is another disease with high unmet need. About 100,000 people in Europe and the United States. It's an aggressive disease that progresses rapidly to end-stage renal disease. There are no approved therapies for this.

I'm happy to share that the Phase IIb portion of the Phase II/III study has completed, and we are on track to pick the dose for the Phase III portion and initiate the Phase III portion later this quarter. Let me now move to type 1 diabetes. This slide shows the trio of programs in our type 1 diabetes portfolio. Each of these programs uses the same cells, allogeneic, fully differentiated insulin-producing cells that have already demonstrated proof of concept. I'm going to start with VX-880 at the very bottom.

The VX-880 trial, let's call it the naked cells program, uses immunosuppression to evade the immune system. This multi-part Phase I/II study is fully enrolled. We have dosed 14 patients in the study, and the results continue to look unprecedented. The efficacy for the patients dosed to date in Parts A and Parts B minus the 1 patient who withdrew consent show that patients have achieved hemoglobin A1C levels of less than 7%, which is the ADA target. And these patients are all no longer taking exogenous insulin.

We are also looking at the Part C patients. And what I'll share for now, these patients are earlier in their course of disease is that their trajectories look like Part A and Part B. Moving then to the safety profile. For the safety profile, it looks consistent with immunosuppressives, the past medical history of diabetes and the postoperative period. 2 patients have died in our study, and those 2 deaths are unrelated to VX-880.

We, Vertex, have placed the study on a protocol specified pause, pending review of the data by the DSMB, the Data Safety Monitoring Committee and global regulators, and I look forward to resuming the study when appropriate. Moving to the middle column, or I should say, middle row. This is the VX-264 study. Here, we take those same cells that have already demonstrated proof of concept, and we put them into a proprietary device designed to evade the immune system, hence obviating the need for immunosuppressives. Here, I'm pleased to share that the Part A has been initiated, enrolled, and we have dosed multiple patients and we are preparing for Part B of the study.

At the very top is the program that takes those same cells where we gene-edit them to evade the immune system. That is in the preclinical phase of the program. Let me look with you with this slide now and just share a broad view of our portfolio. Compared to this time last year, the

programs are even more advanced than what I shared. There continues to be a balance between internal and external innovation represented on the slide and the next wave of innovation.

Those programs that are in discovery and development stage in terms of preclinical development continue to make rapid progress.

I'm going to turn here to the penultimate slide, and our financial profile and performance, which remains exceedingly strong. Our revenue guidance for 2023 was $9.85 billion, which represents yet another year of double-digit growth. Our profitable revenue growth and our specialty model allows us to deliver strong operating margins while also continuing to invest in innovation, both internal and external. And on external innovation, we continue to be active in business development, and we closed about 10 deals in 2023 that complement, supplement or accelerate our internal efforts in disease areas that fit our corporate and R&D strategy. Let me move on then to the last slide.

As is tradition, let me share with you a slide that you can use to mark our priorities and forward progress. First, in CF, we seek to expand our leadership in this area. Next, we are entering a period of portfolio diversification with multiple new commercial opportunities. Third, our differentiated R&D strategy is delivering. We are well on our way to meeting or exceeding our 2023 aspiration of launching products into 5 disease areas in the next 5 years.

And lastly, we seek to sustain strong financial performance. We continue to see significant growth from CF, including from the potential of the vanzacaftor triple with its promise for even better efficacy for patients and an improved royalty structure. And we will begin to diversify our revenues in 2024 with the launch of casgevy. With the progress in 2023, including the approval of casgevy and the expected milestone-rich period ahead, Vertex is very well positioned to deliver value for patients and shareholders alike. With that, I'll say thank you and turn it back to Jessica.

Jessica Fye Analyst

Great. Thanks. So again, if anyone has a question in the audience, if you raise your hand, I think someone will bring you a mic, but I will start off. So with pain, obviously a lot of excitement about that asset. But I do hear some investors sort of cautious on the commercial opportunity, specifically in acute, more so than chronic.

So what are the points that you would make to investors who are maybe cautious about going into a generic marketplace or facility incentives or whatever else?

Reshma Kewalramani Executive

Yes. As we think about the commercial opportunity in acute pain, let's just start with some basics to ground ourselves. The number of patients who seek treatment for acute pain in the United States is enormous. It's 80 million. And it's an almost entirely generic market, yet it's a multibillion-dollar opportunity.

With generics, it's multibillion. So you can only imagine what it would be with a branded product. Those are just some grounding facts. With regard to how we would approach it, the

truth of the matter is there is a gaping hole in the treatment landscape between acetaminophen and NSAIDs and opioids. And there is simply no medicine to fill that gap.

You can see it with patients being reluctant to take opioids, you can see it with patients not wanting to take these medicines. And you can see it with policymakers who are working, for example, with policies like NOPAIN, which was passed in December of 2022, where they are putting additional funding into the system in order to support medicines that are non-opioids that provide effective pain relief. So our approach fits our specialty model.

And here's what we intend to do. There are about 80% of patients with acute pain, are in about 2,000 hospitals that ladder up to about 200 IDNs. We aim to pursue patients in those systems. Second, we look forward to even more policies that support non-opioid pain medicines. And third, we do have an expectation that the limitations on opioids that have been there for the last 5, 7 years will continue.

Actually, every state in the union has a limitation for who can prescribe, for whom and for how long, which makes it very difficult for patients who are experiencing pain to get good relief. And I expect 548 to fill exactly that niche.

Jessica Fye Analyst

And then thinking about DPN where you just had those positive Phase II results and have been talking about going into Phase III. I guess when we think about the most likely trial design there, should we think of something akin to acute in the sense of maybe stats are against placebo but there could be a Lyrica arm in there? And why would you or wouldn't you kind of do it that way?

Reshma Kewalramani Executive

Yes. So great question about what is the Phase III design for DPN, diabetic peripheral neuropathy, going to look like. The answer really is cannot share that just yet because we simply haven't gone through our end of Phase II meeting. This is obviously going to be a topic of discussion there. What I can tell you is what our goal is.

Our goal is to have a broad PNP, peripheral neuropathic pain, label. It's actually not to have a label solely directed at diabetic peripheral neuropathy. I expect that we're going to be able to get there by doing studies in both DPN and LSR, lumbosacral radiculopathy. And more to come on the exact designs after we go through our end of Phase II meeting, which will happen later this quarter.

Jessica Fye Analyst

Maybe switching to casgevy. You mentioned in the presentation that physicians prefer a gene-edited therapy versus other gene therapy mechanisms. They tell you why?

Reshma Kewalramani Executive

We have not specifically questioned on why. But as we look qualitatively at the data, there is awareness of the difference between gene editing and gene therapy. There is awareness that by mechanism of action there is the possibility for random insertional mutagenesis with a

gene therapy approach that uses a viral delivery mechanism. And there is awareness of the safety and efficacy data before the approval based on the New England Journal of Medicine papers and presentations at ASH, et cetera, for what the benefit-risk and the efficacy is. And I expect that that is the reason there is this preference for gene editing.

Jessica Fye Analyst

And I guess maybe just another maybe multipart question on casgevy. So when do you expect to get to kind of full reimbursement versus the kind of one-off coverage that's available now. And I think you've talked about '24 being a foundational year for the product, but it's still ultimately being a multibillion-dollar opportunity. So what needs to happen for you to get from kind of the foundational year to the multibillion year?

Reshma Kewalramani Executive

Yes. So let's take the last part first. What do we need to do to go from a foundational year to realize the multibillion-dollar opportunity? As Stuart, our Chief Commercial and Chief Operating Officer, always says, the destination for casgevy is the same as we see for cystic fibrosis. There are many patients to treat, and it is an enormous opportunity.

How we get there is going to be different. With cystic fibrosis, it's a pill, there's a prescription, you go to the pharmacy, and it is immediate. That is simply not the case with casgevy. For casgevy there is a multi-month process involved from patient identification through the process of plasmapheresis, through the process of editing the cells and then the reinfusion. But no doubt about it, the destination is exactly the same.

With regard to access and reimbursement, I want to make sure that we talk about the fact that patients have access in the United States, and I am not concerned that a patient who may want to be treated in the near term before there are contracts in place is denied. There are single agreements in the government payer world and there are pathways to approval in the private payer world. And as I discussed in my prepared remarks, we've already secured an agreement with Synergy that covers 100 million commercial lives. So this is the year that we're going to be working on reimbursement and access and having policies in place because that makes it easier for patients in the U.S. And obviously the time span to securing reimbursements are a little bit longer in the EU, but that's exactly what we're going to do after we have EU approval.

Right now, we have CHMP positive opinion.

Jessica Fye Analyst

Okay. Question in the audience.

Unknown Analyst Analyst

Can you maybe just talk a bit about -- although I know that there's maybe reimbursement for casgevy but a lot of the families can't afford to just in terms of travel and actually have the housing and things of that nature for months on. Can you just maybe talk about possibilities in terms of solving that issue?

Reshma Kewalramani Executive

Absolutely. So as in the clinical trials program, there are supports that Vertex provides for our patients in terms of travel and lodging. And there's also support that Vertex provides for fertility preservation. Importantly, that is allowed in the private pay system. Unfortunately, we have received a ruling that we are not able to provide fertility preservation in the government payer setting.

We're working very hard to find alternative means for doing so. But for lodging, for travel, we're able to provide support, and we do so.

Unknown Analyst Analyst

Real fast, my son's longtime girlfriend is a cystic fibrosis patient. So thank you Vertex for giving these young adults a future together. I am also on the board of team type 1. So I'm very interested in the type 1 therapies. Can you give us any more color on that runway and what you see the market looking like?

Reshma Kewalramani Executive

For type 1 diabetes? So type 1 diabetes is over 9 million patients globally, about 3.5 million in the United States, Canada and in Europe. And what we're looking to do with our first program is target the about 120,000 people with very brittle type 1 diabetes and/or patients who are type 1 diabetics and have already received a kidney transplant, because in those patients they already take immunosuppressives and in the about 120,000 people with brittle type 1 diabetics, the benefit-risk for taking immunosuppression we see to be positive. So in that program, we are done with the enrollment, as I described, in the Phase I/II study and we next need to have our end of Phase II meetings, move on to Phase III and then we can get to the market. So a little bit early to predict how far from now, but we're certainly making rapid progress.

Jessica Fye Analyst

Another question on type 1. I mean you're closing really interesting efficacy with 880 with all those patients coming off of insulin and getting their A1C under 7%. I wanted to ask about safety, where you mentioned the safety profile was consistent with immunosuppression, the procedure and type 1 diabetes in general, but the 2 deaths you saw were unrelated. Can you elaborate on what they were? Like, were they related to the immunosuppression or are they just car accidents or something totally unrelated, anything else you can offer there?

Reshma Kewalramani Executive

Yes. Sure thing. Let me tell you 3 things about the safety, and then I'll get to your direct question. The first is the overall safety profile is consistent with exactly what you said, immunosuppressants, the past medical history of diabetes and the postoperative period. The 2 deaths are unrelated to VX-880.

And the third thing to say is we're going to release all of the data at upcoming meetings. But I'm going to refrain from going into the details of patient information and such until all of the data are reviewed by the DSMB, and we have the opportunity to share it at a medical

congress.

Unknown Analyst Analyst

So with 264, you're moving that into Part B. Are you happy with the performance of the device you've seen in Part A in terms of whether it's met the expectations the company had?

Reshma Kewalramani Executive

We haven't done a review of the totality of the data. That's what's being prepared and as we prepare for Part B.

Jessica Fye Analyst

Maybe last one from the portal here. Can you talk about the expected impact on the royalty structure and your margins for the new vanza triple versus TRIKAFTA?

Reshma Kewalramani Executive

Yes. So the way that the royalty structure works for our portfolio of CF medicines is it's per molecule per component of the regimen. And there's a time-date stamp between our agreement with the CF Foundation for the revenues -- for the royalties on those revenues. The vanzacaftor triple regimen will have substantially lower royalty burden than the TRIKAFTA royalty structure. And that obviously means on a big base of business that there will be substantial improvement on the bottom line as well.

Jessica Fye Analyst

Okay. Great. We'll wrap it up there. Thank you.

Reshma Kewalramani Executive

Thank you so much, Jess.