Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q3 2023 Earnings Call

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Susie Lisa, Reshma Kewalramani, Stuart Arbuckle, Charles Wagner

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Geoffrey Meacham, Robyn Karnauskas, Salveen Richter, Philip Nadeau, Mohit Bansal, Jessica Fye, David Risinger, Evan Seigerman, Liisa Bayko, Michael Yee, Terence Flynn

Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals Third Quarter 2023 Conference Call. [Operator Instructions] Please note this event is being recorded. I would now like to turn the conference over to Ms. Susie Lisa. Please go ahead, ma'am.

Susie Lisa Executive

Good evening, all. My name is Susie Lisa, and as the Senior Vice President of Investor Relations, it is my pleasure to welcome you to our Third Quarter 2023 Financial Results Conference Call. On tonight's call, making prepared remarks, we have Dr. Reshma Kewalramani, Vertex's CEO and President; Stuart Arbuckle, Chief Operating Officer; and Charlie Wagner, Chief Financial Officer. We recommend that you access the webcast slides as you listen to this call.

The call is being recorded, and a replay will be available on our website. We will make forward-looking statements on this call that are subject to the risks and uncertainties discussed in detail in today's press release and in our filings with the Securities and Exchange Commission. These statements, including, without limitation, those regarding Vertex's marketed cystic fibrosis medicines, our pipeline and Vertex' future financial performance are based on management's current assumptions. Actual outcomes and events could differ materially. I would also note that select financial results and guidance that we will review on the call this evening are presented on a non-GAAP basis.

In addition, the impact of foreign exchange is presented inclusive of our foreign exchange risk management program.

I'll now turn the call over to Reshma.

Reshma Kewalramani Executive

Thanks, Susie. Good evening all, and thank you for joining us on the call today. We've delivered another strong quarter and continue to drive execution across the company. By reaching more CF patients, third quarter global product revenue grew 6% versus the prior year period, and we are raising full year 2023 CF product revenue guidance to approximately $9.85 billion. We are delivering on our marketed medicines in CF while simultaneously preparing for commercial excellence in multiple areas ahead of our potential near-term launches, including exa-cel in both severe sickle cell disease and transfusion-dependent beta thalassemia.

VX-548 for acute pain and longer term in peripheral neuropathic pain and our vanzacaftor triple combination therapy for cystic fibrosis. Most notably, we are tracking towards an exa-cel PDUFA date for sickle cell disease on December 8 of this year and for TDT on March 30 of next year, with global regulatory reviews also underway in Europe and the U.K. Phase III pivotal trial readouts in early 2024, from both our vanzacaftor triple in CF and our VX-548 program in acute pain. A Phase II trial readout by year-end 2023 from our VX-548 trial in diabetic peripheral neuropathy and completion of enrollment in the Phase II portion of the VX-147, Phase II/III program in AMKD later this year. With that overview, let me now turn to a pipeline update.

Starting with cystic fibrosis. For our next-in-class vanzacaftor triple combination therapy, we remain on track to complete all 3 Phase III studies, SKYLINE 102 and 103 in patients ages 12 years and above, and the RIDGELINE study in patients ages 6 to 11 by the end of 2023 and share results from these 3 pivotal studies in early 2024. We have high expectations that the vanzacaftor triple combination can deliver greater improvements in CFTR function than TRIKAFTA based upon the totality of evidence generated to date, including in vitro from our HBE assays and in Phase II studies. The vanzacaftor triple holds the potential for enhanced clinical benefit versus TRIKAFTA for patients and the convenience of once-daily dosing. It also carries a substantially lower royalty burden.

In addition, we continue to make progress with another important program in our CF portfolio, VX-522, and -- our CFTR mRNA therapy in development with our partners at Moderna for the more than 5,000 CF patients who cannot benefit from CFTR modulators. We continue to expect to complete the single ascending dose portion and initiate the multiple ascending dose portion of this study by the end of the year. Turning now to exa-cel. Our CRISPR/Cas9-based gene editing program for sickle cell disease and transfusion-dependent beta thalassemia. This program holds the potential to be a onetime functional cure for these debilitating and life-shortening diseases.

Exa-cel represents an enormous advancement for the estimated 32,000 people living with severe sickle cell disease and transfusion-dependent beta thalassemia across the U.S. and Europe. It is a large commercial opportunity. On the regulatory front, in the U.S., we were very pleased to have had the chance to discuss the exa-cel filing with members of the FDA Advisory Committee last week, and to hear the very compelling stories from patients. The meeting represented a significant milestone for Vertex and the first potential CRISPR/Cas9-

based therapeutic.

We look forward to our upcoming PDUFA dates and to the potential of bringing this precise, durable gene-editing therapy to patients. Internationally, in both the U.K. and the EU, we are also well into the regulatory review process and expect regulatory decisions in these jurisdictions in the coming months. In addition, we recently submitted a marketing authorization application for exa-cel to the Saudi Food and Drug Authority or SFDA. I am pleased to share that exa-cel is the first medicine ever to receive breakthrough designation by the SFDA, reflecting both the high unmet need and the high enthusiasm for exa-cel in the Kingdom of Saudi Arabia.

We look forward to updating you in the coming months. Moving on to the pain program and VX-548, our novel, highly selective NaV1.8 inhibitor that holds the promise for effective pain relief without the side effects or addictive properties of opioids and, therefore, represents a significant commercial opportunity in both acute and neuropathic pain. The pace of the Phase III program in acute pain has been rapid, which we see as an indication of the high unmet need, and strong patient and physician interest in an efficacious non-opioid acute pain therapy. We have completed the randomized controlled trial in abdominoplasty, the RCT in bunionectomy and a single-arm safety and efficacy study remain on track to complete by the end of this year. As previously discussed, we will unblind, analyze and share results on all 3 studies at the same time, and we expect to do so in early 2024.

This comprehensive Phase III program has been designed to support a broad, moderate-to-severe acute pain label and to enable prescribing and usage across multiple care settings. We're also studying VX-548 in peripheral neuropathic pain or PNP, yet another area of high unmet need. Recall, we previously demonstrated positive proof-of-concept with the predecessor molecule VX-150 in neuropathic pain. In diabetic peripheral neuropathy or DPN, I am pleased to share that we have completed our Phase II 12-week dose-ranging proof-of-concept study. We anticipate sharing the results from this Phase II trial by the end of this year.

As we await the DPN results, we are excited to initiate a second Phase II peripheral neuropathic pain study of VX-548 by the end of the year in lumbosacral radiculopathy or LSR. It's a type of neuropathic pain caused by the impairment of nerve roots in the area of the lumbar spine. Given the limited therapeutic options, the significant opportunity to serve a large number of patients and the promise that the NaV1.8 mechanism holds, we are excited to pursue the potential of VX-548 in each of these neuropathic pain types. Next, on to type 1 diabetes, where we are evaluating stem cell-derived fully differentiated insulin-producing islet cells for people with type 1 diabetes. Our goal is to develop a potential onetime functional cure for the millions of people living with type 1 diabetes, including the more than 2.5 million patients in North America and Europe alone.

The VX-880 or naked cell program, where we have already established proof-of-concept, is foundational to the type 1 diabetes program as a whole. Here, patients take standard immunosuppressants to protect the islet cells from the immune system. At EASD last month, we presented positive updated clinical data from all patients in Parts A and B of the VX-880 study. With regard to study status, Part C of the study, which administers the full target dose with concurrent dosing is now fully enrolled. Our second program, VX-264, or the cells plus

device program encapsulates these same cells in a proprietary immunoprotective device.

And hence, there is no requirement for immunosuppressants. We have begun enrollment in dosing in Part A of the VX-264 study. And finally, our third program, still in the research stage, is our hypoimmune cells, in which we added the same fully differentiated cells so as to obviate the need for immunosuppressants. Transitioning now to inaxaplin or VX-147, the first potential medicine to target the underlying cause of APOL1-mediated kidney disease or AMKD. The inaxaplin pivotal program for patients with AMKD is a single adaptive Phase II/III study with a pathway to accelerated approval in the U.S.

The Phase IIb dose-ranging portion of the study continues to enroll in dose patients, and we expect to complete enrollment by the end of this year. We now expect to select a dose and move to Phase III of the study in Q1 of 2024. Now turning to alpha-1 antitrypsin deficiency or AATD. We have discontinued development of VX-864 due to non-serious rash events in some patients in the Phase II program. Our next-generation molecules VX-634 and VX-668 both have greater potency and better drug-like properties, and are both in Phase I clinical trials.

These trials continue to enroll and dose healthy volunteers. We look forward to sharing more on AATD, including next steps as we learn more in the coming months. With that, I'll turn it over to Stuart.

Stuart Arbuckle Executive

Thanks, Reshma. I will focus my remarks tonight on CF, exa-cel and pain. We delivered strong third quarter commercial results with CF product revenue growing 6% globally versus the prior year as we continue to reach patients in younger age groups as a result of new regulatory approvals and via new reimbursement agreements. Our strategy in CF has always been to develop medicines for all people living with CF and to serially innovate to deliver increased clinical benefit. We will continue to execute near term with a focus on younger age groups.

And then our goal is to drive growth over the medium term with the vanzacaftor triple combination and longer term with our mRNA program, VX-522 that we are developing in partnership with Moderna. Now turning to exa-cel, our next targeted launch and potential multibillion-dollar opportunity. This quarter, I will provide some insights as to launch readiness ahead of potential near-term regulatory approvals and then detail the patient journey. In the U.S. and Europe, we've previously highlighted that there are approximately 32,000 eligible patients with severe disease, 25,000 with sickle cell disease and 7,000 with beta thalassemia.

The majority of sickle cell disease patients are in the U.S., while the majority of TDT patients are in Europe. Within Europe, approximately 75% of all eligible patients live in 4 countries: the U.K., France, Italy and Germany. Italy has by far the highest prevalence of eligible TDT patients, while France and the U.K. represent the majority of eligible patients with sickle cell disease. In the U.S.

and Europe, we are on track with our globally enabled supply network and launch preparations with authorized treatment centers and payers, including our recently completed application for a new technology add-on payment or NTAP, for Medicare patients in the U.S. In addition, Reshma mentioned our exa-cel MAA submission in the Kingdom of Saudi Arabia or

KSA. Our team is engaging with the Saudi health authorities and working on the processes to support ATC activation, access and reimbursement with the aim of bringing exa-cel to the thousands of patients with severe disease in KSA. We look forward to providing you with more information on future calls about this important additional opportunity. As we prepare for approval and launch, it is important to understand the exa-cel patient journey, which can be broken down into 3 key phases, each of which can take several months.

First, pretreatment. Initially, when a potential exa-cel patient and their hematologist decide the therapy is right for them, the patient is then referred to a transplant physician at an ATC. Once that referral is scheduled, the patient then undergoes a full workup to determine whether they are fit for treatment with exa-cel. Second, cell collection and manufacturing. This phase involves mobilization to move the blood stem cells from the bone marrow into the peripheral blood, where the cells can be collected through apheresis.

The patient cells are then sent to our manufacturing facilities where they are edited and then tested for quality control. Cell collection takes longer for sickle cell disease patients given the need for 2 months of red blood cell transfusions prior to mobilization. And on average, 2 rounds of mobilization in apheresis. In contrast, TDT patients do not require premobilization transfusions and typically only require 1 round of mobilization in apheresis. The final phase is treatment.

Once the edited cells are ready, the patient starts the treatment phase, which includes myeloablative conditioning, infusion of the edited cells at which point we will recognize revenue for the therapy, and then waiting for engraftment and post-infusion care. A critical timing factor in this phase is the patient's preferred timing for treatment as they must choose a time that works best for their lives given that this step involves an approximate 1-month hospital stay. This patient journey is consistent across all geographies. Given the multiple steps and the duration of the journey, we expect 2024 to be a foundational year for exa-cel as the first patients begin this journey, and Vertex works to deliver transformative patient outcomes with the possibility of a lifetime of benefit. Shifting now to VX-548, our highly selective NaV1.8 inhibitor for pain.

Given the program's rapid pace of clinical advancement, we have developed our go-to-market strategies and are actively planning for a potential near-term launch. I'd like to share an outline of some of the work we've done to size each market opportunity. Overall, the pain opportunity is massive. In the U.S. alone, each year, more than 90 million patients are treated for acute or peripheral neuropathic pain.

Both acute and PNP are each multibillion-dollar markets today despite the fact that essentially all prescriptions are generic, and we see additional upside to these opportunities given the challenges of currently approved treatments. The unmet need in pain stems from the suboptimal benefit/risk profiles of existing agents such as the adverse effects and addiction potential of opioids and the lack of consistent efficacy for anticonvulsants like the gabapentinoids prescribed for neuropathic pain. We believe the innovation of VX-548 and its overall profile could provide a transformative option for millions of patients. In acute pain, we estimate approximately 80 million patients are prescribed a medicine for their moderate to severe acute pain every year in the U.S. More than 2/3 of patients receive acute pain

treatment driven by an institution, either during a hospital or ambulatory surgery center visit or at discharge.

As hospital-driven prescribing is concentrated amongst some 2,000 hospitals and 200 IDNs, we can reach a large proportion of the patient opportunity with a specialty sales force. As Reshma mentioned, the peripheral neuropathic pain study in DPN is completed and the LSR study is about to begin. PNP is an exciting commercial opportunity given that approximately 10 million patients are prescribed in medicine for a PNP condition every year in the U.S. with chronic dosing but limited treatment options. PNP fits our Vertex specialty model perfectly.

PNP is a collection of chronic conditions in which nerve impairment causes pain. DPN and LSR are 2 of the largest patient segments. LSR represents over 40% of all PNP patients, while DPN represents approximately 20% of all PNP patients. Specialists play a critical role in treating PNP as patients can be on multiple treatments and are often in search of more effective pain control given the limited therapeutic options. Therefore, we believe the PNP segment is addressable with a specialty sales force and we look forward to bringing innovation to PNP patients.

In conclusion, it's an exciting time at Vertex. We continue to make progress treating more CF patients and are on the verge of bringing a potential functional cure to patients with sickle cell disease or beta thalassemia with exa-cel. We're also preparing for multiple additional near-term launches, including the vanzacaftor triple in CF and VX-548 in acute pain, both of which have the potential to dramatically improve patients' lives and represent significant market opportunities for Vertex. I will now turn the call over to Charlie to review the financials.

Charles Wagner Executive

Thanks, Stuart. Vertex's excellent results in the third quarter of 2023 demonstrate once again our consistent strong performance and attractive growth profile. Third quarter 2023 revenue increased 6% year-over-year to $2.48 billion. U.S. revenue grew 7% year-over-year following the recent FDA approval of TRIKAFTA in patients ages 2 to 5 and outside the U.S., revenue grew 6% year-over-year on continued strong uptake of TRIKAFTA/KAFTRIO in markets with recently achieved reimbursement as well as label extensions in younger age groups.

As anticipated, in Q3, we saw the drawdown of inventory in certain international markets in contrast to the increases in inventory that we experienced in the first half of the year. Year-to-date revenue of $7.35 billion represents 11% growth over the corresponding prior year period, including an approximate 150 basis point headwind from changes in foreign currency. Overall, the primary drivers of revenue growth in 2023 have been in line with our expectations. Third quarter 2023 combined non-GAAP R&D, acquired IPR&D and SG&A expenses were $993 million compared to $758 million in the third quarter of '22. Q3 2023 results include $52 million of acquired IPR&D charges compared to $29 million of such charges in the third quarter of 2022.

Operating expense growth was driven as expected by continued investment in research and our pipeline. Throughout 2023, the most significant areas of increased investment versus prior year included the clinical studies for VX-548 in acute pain, the vanzacaftor triple in CF and for type 1 diabetes as well as build-out of capabilities for our expanding pipeline. In

addition, we continued our pre-commercial activities for exa-cel and other anticipated near-term launches. Third quarter 2023 non-GAAP operating income was $1.17 billion, compared to $1.29 billion in the third quarter of 2022. Third quarter 2023 non-GAAP earnings per share were $4.08, representing 2% growth compared to $4.01 in the third quarter of 2022.

We ended the quarter with $13.6 billion in cash and investments. Our priorities for cash deployment remain unchanged as we continue to prioritize investment in innovation, including external innovation via business development. Year-to-date, we have completed nearly 10 transactions with total consideration of over $500 million. We've also continued to allocate cash to share repurchases and year-to-date, we have spent approximately $285 million to repurchase approximately 900,000 shares. Now switching to guidance.

Given our strong year-to-date results and our consistent execution, we are increasing our 2023 revenue guidance as detailed on Slide 17. For the full year 2023, we now expect CF net product revenue of approximately $9.85 billion versus our prior range of $9.7 billion to $9.8 billion. Note that this revenue guidance continues to include an expected approximate 150 basis point headwind to our revenue growth rate from changes in foreign currency. We are maintaining our 2023 guidance for combined non-GAAP R&D, acquired IPR&D and SG&A expenses in the range of $4.1 billion to $4.2 billion. We continue to invest the majority of our operating expenses into R&D given the momentum in our multiple mid- and late-stage clinical development programs.

We are also funding the expansion of our commercial capabilities in anticipation of the multibillion-dollar opportunities represented by our programs with near-term launch potential while continuing to leverage an attractive business model afforded by our focus in specialty markets. Due to an increase in our current year U.S. R&D tax credit estimate, we are lowering guidance for our projected full year 2023 non-GAAP effective tax rate by 100 basis points to a range of 20% to 21% versus the prior range of 21% to 22%.

In closing, Vertex delivered excellent results yet again in Q3 '23, achieving strong revenue growth, important regulatory milestones, continued clinical trial progress and ongoing investments, both internally and externally. As we continue to advance our programs to close out 2023 and head into 2024, we anticipate further important milestones as highlighted on Slide 18 to mark our continued progress in multiple disease areas. We look forward to updating you on our progress on future calls, and I'll ask Susie to begin the Q&A period.

Operator Operator

[Operator Instructions] And the first question will come from Geoff Meacham with Bank of America. [Technical Difficulty]

Susie Lisa Executive

Geoff, sorry, you were garbled. We can't understand you.

Geoffrey Meacham Analyst

I am sorry. Is it better?

Susie Lisa Executive

Yes, that's better. Thanks.

Geoffrey Meacham Analyst

So first question on AAT. It seems like a much more difficult indication than initially thought. At a high level, what would you characterize that as? Is it just a mechanism? Is it the bar for risk/benefit?

Or is it the molecules itself? And the second question is when you look to vanzacaftor in the data, maybe help us with how rapidly you think you could roll reimbursement out across Europe and OUS indications? I know -- I wasn't sure if this was part of your portfolio agreements or if you had to renegotiate that.

Reshma Kewalramani Executive

Yes. Sure thing. This is Reshma. Let me break that into 2 questions. I'll take the first part on AAT, and I'll ask Stuart to comment on the vanzacaftor and our plans for launching globally.

Geoff, the particular issue with the VX-864 molecule in AATD is a nonserious rash. That's it. That's what it is. And when you see this, it's almost always molecule-specific. So no, it's not the mechanism of action.

This is where the portfolio strategy is really important and comes into play. VX-634 and VX-668, which are the next 2 molecules, they remain in Phase I development. And we're looking forward to getting those results and the data event will be a '24 data event when we get to see those results and select a molecule or molecules and settle on next steps. Let me turn it over to Stuart to talk about Vanza. And to clarify, the study is a global study, and the intent is for global regulatory submissions and for a global launch.

Stuart?

Stuart Arbuckle Executive

Yes, Geoff. So on expectations for access and reimbursement outside of the U.S., as Reshma said, importantly, this study is a head-to-head comparison with TRIKAFTA. To your specific question, was vanzacaftor imagined when we embark on some of our portfolio agreements? It was. Some of them do include clauses to include increasingly better and better medicines, which is our anticipation of what vanzacaftor will prove to be.

It isn't in all of our reimbursement agreements, just to be clear. But if the product can deliver the kind of profile that we expect, I would expect like we did with TRIKAFTA, that we will beat the kind of industry benchmarks for getting to access patients across ex-U.S. markets.

Operator Operator

The next question will come from Robyn Karnauskas with Truist Securities.

Robyn Karnauskas Analyst

It sounds like '24, '25 is going to be a breakout year for Vertex, transformative in many ways. 2

questions for me. One on pain, Reshma, thanks for clarifying you're unblinding at the same time. But we get all these investor question, saying, are you having concerns about the [abdomectomy] trial? Maybe help us understand the strategy for why doing that at the same time and if you -- if there's any risks.

My second question is on PNP. So you said you'll have a specialty sales force. How do you market it in the context that Lyrica exists even though it's now a scheduled drug? Maybe some expectations for what you're looking for, for that data.

Reshma Kewalramani Executive

Yes. Robyn, 2 questions on VX-548, one on the acute pain side and one on the neuropathic pain side. Let me tackle acute pain and I'll ask Stuart to comment on our commercialization approach on the neuropathic side. So to ground everyone, the acute pain program is, in its entirety, 3 pivotal trials. One is the abdominoplasty RCT, the second is the bunionectomy RCT, and the third is a single-arm safety and effectiveness trial.

And the reason we are planning to unblind, analyze and share the results all at the same time is because our goal is to secure a broad moderate-to-severe acute pain label. And in order to do that, we need the results from all of these trials. So that's the reason for sharing the results all at the same time. With regard to PNP, I'll just frame it up with what we are looking to do and how you may want to think about the profile, and then I'll turn it over to Stuart for commercialization. The Phase II study, that's the study we have completed and expect to share the results before the end of this year, it is a study that has a Lyrica reference arm.

So it's not a comparison but it's there so that we can assess the magnitude of the treatment effect. And our goal here really is to have a medicine that can compete effectively and bring a better benefit/risk profile than Lyrica for this patient population. And just so that it's not missed, one of the comments I made in my prepared remarks is we're now expanding our progress into the peripheral neuropathic pain area with a study that we will initiate before end of year in what's called LSR or lumbosacral radiculopathy, another kind of neuropathic pain. Stuart?

Stuart Arbuckle Executive

Yes. Just to expand on that, Robyn, very briefly. So PNP is kind of an umbrella term, which is used to describe a collection of conditions all of which have as their cause nerve impairment, which causes pain. DPN, which, as you know, is the study, which is ongoing with 548, obviously, there, the standard of care has been the gabapentinoids, and as Reshma said, what we're looking to do there because there are approved therapies there, which are generic, is demonstrate an improved benefit risk profile to be able to compete successfully in that market segment. And the Phase II study is obviously going to be very revealing in that regard.

LSR is very different -- and DPN I should say, accounts for about 20% of all patients in the U.S. with PNP. That's 20% of approximately 10 million people. LSR accounts for over 40% of patients with PNP. There, there are no products which are specifically approved for LSR.

So we see that as a very significant opportunity as well. There, obviously, with no approved therapies, it's likely that the comparator is going to be, can we demonstrate effective pain

relief versus placebo.

Robyn Karnauskas Analyst

And one follow-up, if I can. Do you have to look better? I know Lyrica has just a sidearm but I know a lot of doctors want it looking better for reimbursement. Do you have to look better or just safer? We obviously know the issues with safety with Lyrica.

Reshma Kewalramani Executive

Yes, yes, yes. The point you make about the safety tolerability issues with Lyrica are real. The -- what we're looking for in the Phase II program is change from baseline at the various doses with Lyrica as a reference arm, not a comparator. But our goal here, to be clear, is to have a product, VX-548 that is a better benefit/risk profile than Lyrica.

Operator Operator

The next question will come from Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

One here on the pain side with the LSR trial. Can you help us understand why start this trial now versus waiting for the DPN trial to read out and get a better understanding of the profile there? And then a second question on the cells and device program here. That seems to be a partial dose with staggered enrollment. Again, and I'm just wondering why in the context of maybe the derisking that you saw on the naked cell approach?

Reshma Kewalramani Executive

Sure thing. Let me start with the VX-264 question, and I'll go back to pain. The reason that we are at a partial dose with staggered dosing in the Part A part of the 264 program is because the cells plus device is a first-in-man program. And we are doing that to go slowly and ensure that we have sufficient time between patients to be able to assess safety and it is the way that the protocol is designed in consultation with global regulators. So that's the reason.

It's because cells plus device is a first-in-man trial. Let me go back now to VX-548 and LSR, and why now? It's really a very good question. The reason we started with DPN is because DPN or diabetic peripheral neuropathy has and has had an established regulatory pathway as well as an established commercial marketplace. So that's why we started with DPN.

We started with it actually when we did the 150 program, and that's the first PNP or peripheral neuropathic pain indication, we pursued when we started with VX-548. As the VX-548 study has gotten started and frankly, as we near that completion, we've turned our attention to LSR. It was always our intention to pursue a broad peripheral neuropathic pain label for VX-548, just like we're pursuing a broad label in the acute pain setting. We recently completed our regulatory discussions on the LSR pain type and gained confirmation that LSR from a regulatory perspective is a PNP pain type. As Stuart said, medically, scientifically falls under that umbrella of a peripheral neuropathic pain type.

And we completed our discussions with the regulators and confirmed that it is indeed, from a regulatory standpoint, also a PNP type. That's why we're starting the LSR Phase II study now.

And I got to tell you, I'm terribly excited about that.

Operator Operator

Your next question will come from Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

A couple of follow-ups from us. First, on pain, investors saw The New England Journal of Medicine editorial over the summer that was somewhat skeptical of 548, and it's a topic of debate. Could you respond to that editorial? What do you think the author got wrong? Or where do you disagree with the author?

And then, second, a follow-up on Vanza. In the prepared remarks, you mentioned that Vanza was going to drive intermediate growth of the franchise. Can you elaborate on those comments a bit more, what new patient populations or opportunities could Vanza explore that TRIKAFTA currently can't?

Reshma Kewalramani Executive

Yes, sure thing. Phil, when I think about the distillation of the editorial, I think it comes down to this is the holy grail of pain in terms of targets. There looks to be very promising results. It's a Phase II study, how should we think about the magnitude of the treatment effect, how should we think about it in terms of the effect and the potential not only versus placebo, but versus opioids and then maybe a desire to learn a little bit more about the secondary endpoints. And what I would say is we're going to have a far bigger study, 2,000 people in all.

There's 1,000 people in the abdominoplasty study, another 1,000 people in the bunionectomy study and another 250 people in the safety and effectiveness study. And we'll have all the data we need to make a full assessment in this Phase III trial. So I think the best answer is let's look towards the Phase III trial. And I agree the Phase II results are very promising.

Let me turn it over to Stuart to talk about Vanza.

Stuart Arbuckle Executive

Phil, on Vanza, I would really think about the opportunity for patients to be initiated on Vanza to be threefold. One is people who are currently on an existing CFTR modulator. But if we deliver the sort of profile with Vanza that we're hoping to versus TRIKAFTA, they may want to be switched onto vanzacaftor. Then you've got patients who have not yet been initiated on a CFTR modulator, that's a relatively small number of patients. But really, the big opportunity for growth is there's about 6,000 -- just over 6,000 patients globally now who've actually discontinued a CFTR modulator.

So they wanted to be on a CFTR modulator but for a variety of reasons have had to discontinue. As I say, that's over 6,000 patients now around the world. We don't often talk about discontinuations from our CFTR modulators because it's actually a relatively small percentage compared to any other sort of chronic medication, but it's still a sizable number of patients. We know they would like to be on a CFTR modulator because they previously

tried. And so we think they could be patients who are very interested in Vanza if we deliver the kind of profile that we're expecting.

Operator Operator

Next question will come from Mohit Bansal with Wells Fargo.

Mohit Bansal Analyst

Congrats on all the progress. One question, again, staying on DPN study. So could you remind us how prevalent is the opioid use in this setting? Because from our reading, it seems like it is more a third-line agent. And is the thought to replace Lyrica in that setting?

Or is it more like to replace opioids in that setting? I mean how do you think about the profile of the drugs?

Reshma Kewalramani Executive

Sure thing. I'll have Stuart talk about the -- what is being used in DPN today.

Stuart Arbuckle Executive

Yes. Mohit, there is a lot of polypharmacy going on in DPN right now, largely because the efficacy of the various classes of pain medicines, which are available today is pretty variable. So you do see patients who are on nonsteroidals. You see a lot of people who are on the gabapentinoids, which have been studied and approved there. And you also do see parents -- patients on opioids as well.

So it really is a disease characterized by sort of polypharmacy largely due to either variable efficacy and/or the adverse events of the currently available therapies. That's why we're so excited about the prospect of 548 being able to establish a new standard of care for these patients.

Operator Operator

The next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

The press release makes mention of Vertex's portfolio approach to R&D and additional NaV1.8 and 1.7 inhibitors you're working on. How far along in development is the next most advanced 1.8 inhibitor behind VX-548? And do you have any dual 1.8 and 1.7 inhibitors?

Reshma Kewalramani Executive

Yes. Welcome back, Jess. Really terrific question. The portfolio strategy, as you've seen it play out in CF is authentically and reproducibly extended across our R&D pipeline. So as it pertains to pain, the next NaV1.8 inhibitors are already in the clinic in Phase I trials.

And we have more after that, making their way through the research part of our organization.

In terms of NaV1.7, they are in the research stage and making very good progress. And we see the NaV1.7s as potentially for use as a single agent, and we also see the real opportunity

for combining NaV1.7s and 1.8s. And just for all of the others who are following along, the reason I say that and the reason I think it's an excellent question, is that the way that the action potential works in the periphery in transducing the pain signal is that there is a stimulation of the action potential and then the propagation, and NaV1.7 works on that stimulation of the action potential and NaV1.8 works on that propagation. So, we see a lot of opportunity in the combination but we also see opportunity of NaV1.7 in and of itself.

Operator Operator

The next question will come from David Risinger with Leerink Partners.

David Risinger Analyst

Yes. I have 2 questions, please. First, if the VX-548 succeeds in Phase II in DPN in coming months, how do you plan to conduct Phase III? Do you plan to go it alone? And could you complete Phase III in '25 or likely not until '26?

And then regarding VX-548 acute pain Phase III studies, how should we expect rescue medicine used to potentially benefit patients in the placebo arms? And how will rescue medicine use be disclosed?

Reshma Kewalramani Executive

Okay. David, let me start the answer to both of these questions. But the PNP question has a component of can we go at it alone. And so I want to make sure that Stuart touches on it.

Let me cut to the punchline, for acute pain and for neuropathic pain, both in terms of diabetic neuropathy and in terms of LSR, this lumbosacral radiculopathy, we are going to do the development by ourselves and we are going to commercialize by ourselves. Both of these, acute pain and neuropathic pain, are absolutely Vertexian diseases, if I can call it that, in terms of commercialization.

I'll ask Stuart to comment a little bit more in commercializing neuropathic pain, and I'll come back to tell you about acute pain, rescue meds, et cetera.

Stuart Arbuckle Executive

David, so kind of building on what I said about this being a disease state, which unfortunately for patients is characterized by polypharmacy. And so patients are often seeking superior pain relief to what they are getting. It is heavily influenced and/or treated by specialists for DPN and indeed, for LSR as well. And so for both of those pain states within PNP overall, we believe we can achieve success commercially with a specialty sales force. As a result, of wanting to go it alone commercially, we're going to be doing the studies in DPN and hopefully, in LSR, Phase III studies are successful and Phase II ourselves as well.

Reshma Kewalramani Executive

And David, to round it out with your questions on acute pain. The -- we have thought through very carefully as we did in the Phase II portion of the study, the same in the Phase III portion of the acute pain studies, about the use of rescue medicines and how to consider the statistical analysis plan in that light, and there are -- it's been very well considered in there.

So I don't have much more to say other than the use of rescue medicines, of course, will be disclosed in the publications and when we share the results, but how to think about it has been deeply considered and well accounted for just as it was in Phase II. I think there was a question in there about Phase III and the peripheral neuropathic pain structure. I'll focus my comments on DPN. That one will be designed with the FDA. We haven't yet had our end of Phase II meeting and therefore, I can't give you specifics on what that program will look like, but that's exactly what will be the next step once we have the Phase II DPN results, assuming they are positive.

Operator Operator

The next question will come from Evan Seigerman with BMO Capital Markets.

Evan Seigerman Analyst

Congrats on the progress as always. I wanted to talk about the implications of the recently released U.K. NICE appraisal of TRIKAFTA essentially indicating that was not cost-effective for the U.K. system. Because I was under the impression that this was settled in 2019.

Could you maybe expand on the impact to your U.K. franchise and steps to resolve to ensure access in the U.K.?

Stuart Arbuckle Executive

Yes, Evan. So the first thing I'll say about the ongoing NICE review is that this was an expected part of the contract that we negotiated with the NHS in 2019. So this isn't a surprise that NICE is reviewing our medicines after 4 years on the market. So that's the first thing to say. As a part of the original contract, we agreed with the NHSE and with NICE that we would collect and submit data after a period of being on the market.

And we have done just that. We submitted clinical trial data, open-label extension data and real-world data from the U.K. And I think -- it's unusual, I think, to see a medicine, which is what I think we've seen with TRIKAFTA, that performs perhaps even better in the real world than you expected having seen the Phase III results because the results we've seen in the real world, as you well know, are absolutely extraordinary, including things like reductions in exacerbations, increases in life expectancy, reductions in hospitalizations, a virtual elimination of lung transplants.

So we're pretty disappointed, it's fair to say, with the draft guidance from NICE. It is just that, though, it's draft guidance. There was a period of consultation. There's going to be a second NICE Committee Meeting, and I certainly feel confident that the full value of our medicines will be reflected at the end of this process.

Operator Operator

The next question will come from Liisa Bayko with Evercore ISI.

Liisa Bayko Analyst

I wanted to circle back to pain and just 2 questions from me. First of all, the article -- so the editorial in The New England Journal of Medicine did focus in on overwhelmingly more

females in the 2 acute pain indications that you're using as examples. So maybe you can just speak to that and addressing sort of the underrepresentation of males. And then finally, just if you could comment on any capabilities that you've been working on developing. This is obviously a much different market to commercialize into than CF with a lot of generic competition and the need to get on hospital formulary, et cetera.

And how are you building sort of those capabilities as you're waiting for data?

Reshma Kewalramani Executive

Sure thing. Liisa, this is Reshma. Let me start, and then I'll pass it over to Stuart. Most companies, including our own want to ensure that we have more people of color in our trials, more women in our trials and I guess we have succeeded. So I see the fact that 548 has many women as a positive.

Perhaps one point to make underneath -- just underlying that comment is, remember, in the acute pain study, one was an abdominoplasty study, and abdominoplasty is a procedure involving fat in the belly kind of surgery. It's -- some people call it a tummy tuck. And that is a surgical procedure that more women undergo. With regard to the commercialization of pain, I'll turn it over to Stuart, but I want to frame up the following concept. In the acute pain setting one of the most important elements that VX-548 could address is effective pain relief without the addiction potential of opioids.

And that part of it, this addiction potential of opioids is something that is not only of interest to Vertex but it's of interest to the community, the policymakers, to physicians, and we see a lot of tailwinds. And so as I turn it over to Stuart, I'll ask him to comment on our commercialization efforts but also the tailwinds we see. Stuart?

Stuart Arbuckle Executive

Yes. So to your question about capabilities, I think we're trying to get the best of both worlds. We are trying to leverage the capabilities that have made us be successful to date, and much of that is based around our ability to get reimbursement and access for our medicines and also work with policymakers, with guideline institutions, et cetera, to support the appropriate use of effective medicines like ours. And as Reshma said, we're already seeing tailwinds if we can call them that, in the pain market with people looking to kind of move away from the sort of restrictions that they've previously put in place for things like opioids in terms of who can prescribe them, for how long, for which patients in which settings, to people looking at policy changes like the NOPAIN Act, which we highlighted a couple of quarters ago now where people are looking to make sure that there are no financial barriers or disincentives to people doing the right thing and using a non-opioid effective pain medicine just because there are generic medicines available. So that's something that we're going to be looking to build on some of the capabilities that we've used to help us be successful.

Having said that, we are going to be selling into a different segment of the market. This is obviously going to be a very hospital institution-driven sale. And so we are looking to bring in and have brought in new capabilities as we brought on our pain business unit, people who are experienced in that kind of institutional setting. So I would say we are trying to get the best of both worlds, leverage what we've been good at in the past, while bringing in people who bring

new knowledge, skills and experience to the company as well.

Operator Operator

The next question will come from Michael Yee with Jefferies.

Michael Yee Analyst

Congrats on a great quarter. We had a follow-up question on pain and then a question on Vanza.

On the acute and chronic pain, can you just remind me since you've never disclosed doses, should we expect that it's the same doses used in the Phase II and also the Lyrica and Vicodin doses as a control or basically the doses from the label? And is that pretty well understood? And then from a safety tolerability standpoint, I think there was a QT study that had completed. So was there anything to disclose there? That would be great to hear if that was the case, that would be a positive.

And then on Vanza, I know that there was questions around noninferiority and superiority. And I know it's powered potentially for superiority. But can you just remind us, is there a magnitude of clinical meaningfulness on FEV, et cetera, that you would deem to be meaningful? Or is it more the totality of everything as well, like sweat chloride and the benefits that, that may provide?

Reshma Kewalramani Executive

Sure thing. Mike, let me start, and then I will ask Stuart [indiscernible] the market research that Stuart and the team have done on Vanza and what is valued vis-a-vis sweat chloride, et cetera. But I'll go back to 548 to start and then I'll set up the clinical trial structure for Vanza. So to confirm, on the VX-548 acute pain Phase III trials, it is exceptionally similar to the VX-548 Phase II trials. Same pain conditions, abdominoplasty and bunionectomy.

We selected the high dose, the dose that showed the benefit in the Phase II trial for the Phase III trial. And you are correct, standard labeled doses for the opioid.

And on the Phase II diabetic peripheral neuropathy trial, correct, the Lyrica is standard doses from the label. The doses in the peripheral neuropathy Phase II study are different than the acute pain doses, obviously, because one has chronic dosing and one has acute, and we need to make the appropriate adjustments so that we have the exposure we seek. But with regard to the reference arm, correct, it is the standard dosing from the label.

Lastly, on vanzacaftor, this is -- remember, this is a study that is head-to-head versus TRIKAFTA. The primary endpoint is ppFEV1 because that's the regulatory enabling endpoint. And recall, we have a key secondary endpoint that is on sweat chloride and this is very important because sweat chloride is the direct -- it's the most direct readout of CFTR function. You know that there have been great debates about whether or not there is a ceiling on ppFEV1, we can't have better than normal lung function, right? But in terms of sweat chloride, that is how patients are diagnosed with the disease, and it is very well understood that if we provide better CFTR function benefit that would show up in terms of sweat chloride, that is a secondary endpoint in the Phase III trial, and that's what we've already studied and

reported out in a variety of Phase II trials, and it does indeed look to be the case that the Vanza triple is even better than -- I know that's a tall order, but it's even better than TRIKAFTA.

Over to you, Stuart, on the marketplace with that in mind.

Stuart Arbuckle Executive

Yes. So Mike, just as Reshma said on the study, the primary endpoint is noninferiority versus TRIKAFTA on FEV1, which, as we know, is an incredibly high bar but we will be able to see how vanzacaftor does versus TRIKAFTA in the study. So that's the first thing, just to remind you. As Reshma said, we're also looking at measures of superior CFTR function in patients. And when we've done research with physicians, even if the FEV1 benefit is the same with vanzacaftor.

If we can demonstrate improved CFTR function, which, as Reshma said, the pharmacodynamic measure of that is sweat chloride. There is a lot of enthusiasm from physicians for a product which has that profile.

In addition, just to remind you, vanzacaftor is also going to be a once-a-day regimen as well, which is also considered to be a benefit, particularly for those patients who have compliance challenges as well. So we're very much looking forward to the Phase III results and think there's going to be -- if the results come out as we expect them to, a high level of enthusiasm for vanzacaftor.

Michael Yee Analyst

Super helpful. Could you clarify on the QT, that was a study that's out. Is that -- can you say that, that was completed and offset?

Reshma Kewalramani Executive

Yes. Nothing new to report there. This is -- the QT is a study we do for cardiac function. It's one of our standard studies that we do in the clinical pharmacology around.

Susie Lisa Executive

Last question please, Jack.

Operator Operator

The last question will come from Terence Flynn with Morgan Stanley.

Terence Flynn Analyst

I was just wondering if, let's say, the theoretical situation where one of the randomized controlled Phase III acute trials is positive and the other is not. Can you still file for approval on that data set? Or do you need 2 positive trials? And then, Stuart, I just wondered if you could clarify your comments on 2024 being a foundational year for exa-cel, what that means. Is that -- does that mean you're comfortable with consensus where it stands?

Or you think it's going to be somewhat more measured launch? Just want to clarify what foundational means.

Reshma Kewalramani Executive

Yes. Terence, this is Reshma. Let me comment on the acute pain, and then I'll turn it over to Stuart. We are very close to having the results from the acute pain program and I'll just leave it at our goal is to have a positive set of 3 studies. And our goal is to file for a broad moderate-to-severe acute pain label.

Stuart?

Stuart Arbuckle Executive

Yes. And on exa-cel and the comment we made about it being a foundational year, that has nothing to do with consensus. I actually couldn't tell you what consensus is for 2024 for exa-cel to be perfectly honest with you, Terence. It was really a response. We've been asked a lot of questions about what the launch dynamics will look like for exa-cel.

And so we thought it was important to remind people of what the patient journey is, and that's obviously going to begin, hopefully, later this year when we get regulatory approval, and it was really to try and provide some context around that multistage journey that patients need to go through to get exa-cel.

So that was really the reason for the comment. I was responding to questions we've had about launch dynamics. I do want to reiterate something which I said in my prepared remarks as well, whatever the journey to get there, we see this as being a very large commercial opportunity. There are tens of thousands of patients with severe sickle cell disease and beta thalassemia who could benefit and despite the journey being relatively long, this is a journey that, at the end of it, that has the potential for a lifetime of benefit. So we feel very optimistic about the exa-cel opportunity and we're looking forward to launching.

Susie Lisa Executive

Thanks, Jack. If you could give the details, please, for callbacks.

Operator Operator

Yes, ma'am. A replay of today's event will be available shortly after the call concludes by dialing 1 (877) 344-7529 or 1 (412) 317-0088 using the replay access code 2047491. The conference has now concluded. Thank you for attending today's presentation. You may now disconnect.