Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q2 2024 Earnings Call

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Susie Lisa, Reshma Kewalramani, Stuart Arbuckle, Charles Wagner

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Salveen Richter, David Risinger, Jessica Fye, Evan Seigerman, Christopher Raymond, Terence Flynn, Mohit Bansal, Liisa Bayko, Michael Yee

Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals Second Quarter 2024 Earnings Call. [Operator Instructions] Please note this event is being recorded. I would now like to turn the conference over to Ms. Susie Lisa. Pease go ahead.

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 second quarter 2024 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 be making forward-looking statements on this call that are subject to the risks and uncertainties discussed 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 medicines for cystic fibrosis, sickle cell disease and beta thalassemia our pipeline, including the potential near-term launches of the vanzacaftor triple in CF and suzetrigine in moderate-to-severe acute pain and Vertex's future financial performance are based on management's current assumptions. Actual outcomes and events could differ materially.

I would also note that the select financial results and guidance that we will review on the call this evening are presented on a GAAP basis.

I will 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 continued our momentum from Q1 with another quarter of excellent performance across the board, including outstanding commercial execution in both CF and the early launch of CASGEVY, our preparedness for the potential near-term launches of the vanzacaftor in CF and suzetrigine in acute pain as well as the rapid advancement of our broad and deep pipeline.

In CF, we continue to reach more patients, deliver $2.65 billion in revenue in Q2. And based on this result and our outlook, we are increasing our full year product revenue guidance to $10.65 billion to $10.85 billion, which at point represents 9% growth versus 2023. In sickle cell disease and beta thalassemia, we are pleased with the reception from patients, physicians and payers as we continue the ongoing launch of CASGEVY to bring this potentially transformative medicine to patients across multiple regions. And we are very excited about the multiple near-term opportunities to reach more patients and deliver additional revenue growth from our programs that have completed pivotal development, including the completion and acceptance of 2 significant regulatory submissions. The vanzacaftor triple-in patients with cystic fibrosis 6 years and older, which has been given priority review designation and VX-548 or suzetrigine in moderate to severe acute pain, which has also been granted priority review by the FDA.

Lastly, on the mid- and late-stage pipeline, I am very pleased with our continued rapid progress. I'll call out 3 specific programs. First, the suzetrigine-LSR Phase II study has significantly accelerated, and we now expect Phase II results by the end of this year. Second, in the VX-880 Phase I trial in type 1 diabetes, we have completed enrollment and dosing in the original 17-patient study, and we have secured regulatory endorsement to expand the study to 37 patients in total as we advance towards pivotal development. And third, in the Povetacicept program, having completed successful Phase II regulatory meetings, we will initiate the Phase III pivotal trial in IgA Nephropathy later this month.

With those highlights, let me now turn to an R&D review, limiting my comments this quarter to the programs with the most significant update cystic fibrosis, pain, type 1 diabetes and IgA Nephropathy.

Starting with CF. We are very pleased with the Phase III results on the vanzacaftor triple program we announced in early February as we continue to drive towards our ultimate of bringing all eligible patients to carrier levels, indeed to normal levels of CFTR function as measured by sweat chloride. The vanzacaftor triple demonstrated an even greater reduction in sweat chloride than TRIKAFTA, a very high bar to have crested. And thus sets the stage for the potential to have a new standard in the treatment of CF. The vanzacaftor triple also offers the convenience of once the dosing and a substantially lower royalty burden.

With regard to the Vanza global regulatory submissions, in addition to the U.S. acceptance, our filings have also validated by the EMA in the EU and the MHRA in the U.K. With regard to VX-522, our CFTR mRNA therapy in development with our partners at Moderna, it has

completed the single ascending dose portion of the Phase I/II study and continues in the multiple ascending dose portion. As a reminder, VX-522 seeks to provide me for the more than 5,000 people with, CF who do not make any CFTR protein and therefore, cannot benefit from CFTR modulators. Based on the pace of enrollment and study dynamics, our current expectation is to complete the study and share both efficacy and safety results from the study in the first half of 2025.

Moving now to the Pain program and our portfolio of novel, highly selective NaV1.8 and NAV1.7 pain signal inhibitors. In acute pain, a few points to highlight. First, we are very pleased that the suzetrigine submission has been accepted and granted priority review by the FDA with the PDUFA target action date of January 30, 2025; second, our next class NAV1.8 pain signal inhibitor, VX-993 is in the clinic in a Phase I trial with the IV formulation and is currently enrolling and dosing healthy volunteers; third, VX-993 will soon enter Phase II study with the formulation in acute pain following bunionectomy surgery.

This study is on track to begin later this quarter. And lastly, we continue to make strong progress preclinically on NAV1.7 pain signal inhibitor program that may be used alone or in combination with NAV1.8 inhibitors. Just as an again, we have multiple programs moving rapidly development in peripheral neuropathic pain or PNP, starting with painful lumbosacral radiculopathy or LSR, a condition that impacts more than 4 million Americans. There is a high unmet need in LSR. In the U.S., there are no medicines approved specifically for the treatment of pain from LSR.

As mentioned in my opening remarks, the pace of enrollment in this study has been rapid and significantly exceeded our projections. Study enrollment is now complete, and we anticipate sharing Phase II LSR results by the end of this year. Also in peripheral neuropathic pain, we are excited to begin the phase III pivotal program for suzetrigine in painful diabetic peripheral neuropathy, or DPN, later this quarter. The DPN pivotal program consists of 2 identical randomized controlled trials of approximately 1,100 patients each, with suzetrigine at a dose of 70 milligrams once daily and evaluating the change from baseline to week 12 in NPRS pain scores relative to placebo.

The RCTs also include an active comparator arm of pregabalin. A key secondary endpoint is changed from baseline at week 12 in NPRS score, for suzetrigine versus pregabalin assessed for noninferiority. And if we meet noninferiority, then we will test for superiority versus pregabalin. Lastly, in PNP, I am pleased to share that we will soon initiate a Phase II study with the oral formulation of VX-993 in diabetic peripheral neuropathy, designed similarly to the suzetrigine Phase II DPN study, this trial is also on track to begin this quarter. Turning now to type 1 diabetes.

VX-880s are stem cell derived fully differentiated islet cell therapy for people with T1D, an impaired hypoglycemic awareness who experience severe hypoglycemic events despite optimal medical care. At the ADA meeting in June, an oral presentation from the ongoing Phase I/II study included updated data with more patients and longer duration of follow-up and continue to demonstrate the potential of VX-880 as a functional cure for patients with T1D. The data reflected 12 patients from Parts B and C of the study who received a full dose of VX-880 as a single infusion and had at least 3 months of follow-up.

The results are remarkable. Specifically, all patients demonstrated islet cell engraftment and glucose responsive insulin production by day 90. All 12 patients achieved hemoglobin A1c levels less than 7% and all 12 patients also had a time in range for glucose levels of 70% or greater. 11 of the 12 patients greatly reduced or completely eliminated exogenous insulin use. And the 3 patients with 12 months of follow-up and therefore, evaluable primary end point, each met the primary endpoint of elimination of severe hypoglycemic events, hemoglobin A1C level below 7 as well as the secondary endpoint of insulin independence.

With these results, we are planning forward towards the next phase of development for VX-880. To that end, we are very pleased to have secured regulatory approval to expand the original 17 patient study, which is fully enrolled and dosed to include an additional 20 participants. We look forward to continuing the work with regulators to finalize the requirements for pivotal development and updating you on those discussions. Beyond VX-880, our cells plus device, or VX-264 program encapsulates the same VX-880 cells in a proprietary device designed to eliminate the need for immunosuppressants. VX-264 is in a Phase I/II multi-part global study.

We have completed Part A of the study at an initial dose with the stagger between patients. We are currently enrolling and dosing patients in Part B, which is at the full target dose, also with the stagger between patients. As a reminder, Part C of the trial is at the full target dose with no stagger between patients. The last major R&D update pertains to Povetacicept, the lead at from our recently closed acquisition of Alpine Immune Sciences, where our enthusiasm for the acquisition and Pove remains high. As a reminder, Pove holds the promise of being a pipeline and a product and has best-in-class potential for the lead indication in IgA nephropathy, given its mechanism of action with dual inhibition of both APRIL and BAF, its preclinical profile and the clinical data through Phase II in proteinuria, hematuria and GFR.

These attributes plus Pove's once-monthly dose frequency and small volume subcutaneous route of administration give us high confidence in its potential to be a transformative medicine for patients with IgAN. I am pleased to share that we are on track to initiate the global Phase III Renier study of Povetacicept in patients with IgA Nephropathy this month. To recap, we had successful end of Phase II meetings with the FDA and global regulatory authorities, and we're very pleased to have reached agreement on the following important elements. The pivotal program is designed as a single, global, randomized, double-blind, placebo-controlled trial of approximately 480 patients with biopsy-proven IgAN and proteinuria. Patients will be randomized to receive either Pove or placebo on top of standard of care.

In the U.S., the Phase III design affords us the opportunity to submit for an accelerated approval. A preplanned interim analysis will take place when a number of patients reaches 36 weeks of treatment to evaluate the change in proteinuria from baseline to week 36.

For full approval, the study will continue through week 104 and an assessment of GFR. Beyond the Phase III study IgA nephropathy, Pove is also being evaluated into 2 Phase II basket trials, 1 in renal diseases, termed RUBY-3 and a second in B-cell-mediated cytopenias termed RUBY-4. We look forward to readout from some cohorts in these studies later this year into next. To close the pipeline review, a brief update on VX-634 and VX-668 in Alpha-1

antitrypsin deficiency or AATD. Safety was demonstrated in the Phase I studies of both VX-634 and VX-668.

However, based on the Phase I Biomarker analysis, we have determined that neither VX-634 nor VX-668 would deliver transformative efficacy for people with AATD. And more, we have decided to discontinue development of both molecules. With these learnings, our research efforts in AATD will continue.

I'll turn it over to Stuart for a commercial update.

Stuart Arbuckle Executive

Thanks, Reshma. I'll first discuss CF, then provide some highlights of the ongoing CASGEVY launch and the outlook for suzetrigine in acute pain. As Reshma noted, we once again delivered strong results in CF as we grew the number of eligible patients taking our CFTR modulators, and we continue to expect sustained growth in CF over the near, medium and long term. In the near term, we continue to focus on reaching more eligible patients, including younger age groups as with the ongoing KAFTRIO launches in the 2 to 5 age group in Europe, with anticipated global approvals for additional RARE mutations later this year and through additional geographies such as Brazil, where we now have national reimbursement for TRIKAFTA for patients ages 6 and above. We were also pleased to have announced in June an extended long-term reimbursement agreement with NHS England, which ensures access to our CFTR modulators for all existing and future eligible CF patients in England.

Comparable arrangements have subsequently been entered into in Scotland, Wales and Northern Ireland. The agreements are a result of positive recommendation for NICE and SMC for our CFTR modulators. In the medium, we anticipate growth driven by the launch of our fifth CFTR modulator therapy, the vanzacaftor triple combination. We believe many existing TRIKAFTA patients may seek to achieve even greater levels of CFTR function and the added convenience of once-daily dosing. And there are also more than 6,000 patients who have discontinued one of our current CFTR modulators who at may be interested in a new treatment option.

We continue to execute our Vanza prelaunch activities including pre-approval informational exchange with payers are encouraged by the outlook. And longer term, we expect continued growth in CF from developing medicines to more than 5,000 people with CF who do not respond to CFTR modulators, which is the focus of our mRNA program, VX-522.

Now turning to CASGEVY, our launches in sickle cell disease and beta thalassemia. We continue to make strong progress with ATC activation as well as physician, patient and payer engagement as we work to bring this potentially curative therapy to patients around the globe. CASGEVY represents enormous advancement for the estimated 35,000 people living with severe sickle cell disease and transfusion-dependent beta-thalassemia in the U.S. and Europe, as well as the estimated 23,000 eligible patients in the Kingdom of Saudi Arabia and Bahrain. To update you on the 2 key metrics we are sharing externally as important markers of our early launch progress.

Firstly, ATC activation. We're pleased with our progress as we now have more than 5 activated centers, up from 25 last quarter and 9 at launch. We continue to expect to activate

approximately 75 total ATCs globally. Secondly, patient cell collections. We continue to see a growing number of patients beginning the treatment journey, approximately 20 patients have already had cells collected.

As mentioned last quarter, patients are initiating the treatment journey in every region where CASGEVY is approved, the U.S., Europe and the Middle East. And we are pleased to report growth in patient cell collections across all of these regions this quarter.

We also continue to make strong progress with payers in all regions who recognize the transitive clinical benefits of CASGEVY and are moving quickly rapid and equitable access. Outside the U.S., we are building upon our early successes, such as the early access program in France for TDT, and we now have an early access program approved there for sickle cell disease as well as reimbursement in Austria, Bahrain and KSA. In the U.S., given payer support across all market segments, commercial, Medicaid and Medicare, I'm pleased to report that we do not see coverage as a significant obstacle to patient access.

We have always known that CASGEVY offers an enormous advanced patients. We've also consistently communicated that the patient journey, that is the process to go from patient interest all the way to infusion of edited cells is long and complex. Whilst it's still early in the launch, we have gained many learnings. Interest level is high among patients, physicians, governments and other stakeholders. The value of CASGEVY has been widely recognized, leading to broad access and reimbursement by payers.

The patient opportunity in the Middle East is particularly significant given the high prevalence of these hemoglobinopathies and government's clear focus on elevating the health of their citizens. And lastly, the treatment process does take time, but we are now even more confident in our view that CASGEVY will help large numbers of patients around the world and represents a multibillion-dollar opportunity. Shifting now to suzetrigine. We believe this novel, highly selective NAV1.8 pain signal inhibitor has the potential to provide a transformative treatment option for the 90 million patients suffering from acute and peripheral neuropathic pain in the U.S. This quarter I'll limit my commercial comments to the opportunity in acute pain.

We have continued to make significant progress building out our commercial team now completed hiring of our strategic account leads who will primarily focus on the leadership and formulary decision makers at IDNs, as well our pain territory account managers who post approval, will call on hospitals and other large treatment sites such as ambulatory surgical centers.

Recall that approximately 80 million patients are prescribed to medicine for moderate to severe acute pain each year in the U.S., with approximately 2/3 of patients treated in the institutional setting. As a result, our field force will primarily focus on this institutional setting. We have begun engaging in pre-approval information exchanges in the institutional IDN leadership and formulary decision makers who have responsibility for formularies that enable use in both the inpatient and discharge settings. We've encountered high levels of enthusiasm for a new class of treatment for pain, specifically for an effective and well-tolerated pain medication that does possess addictive properties by way of its mechanism of action. Hospital formulary and payer processes are well defined, and we are engaging

appropriately to encourage and support swift reviews by the relevant bodies like P&T committees, including by providing key clinical and economic information depending on the institution or organization, it can take up to 12 months post approval for hospital formulary and payer decisions to be finalized, but we are working to accelerate these time lines.

We anticipate engaging in contracting discussions in the latter half of 2024 with the goal of building formulary and payer coverage during 2025. We also continue to be engaged with federal and state policymakers, including state governors who have expressed strong interest in a novel, highly effective and well tolerated for pain without the addictive potential of opioids. Federally, in December 2022, Congress passed the No Pain Act, in which non-opioid therapies are eligible for separate payment for Medicare patients in the outpatient in ACS settings beginning in January 2025.

It is promising to see CMS continuing the process of implementation as the annual outpatient prospective payment system or OPPS, proposed rule was released for public comment last month. Because suzetrigine is still investigational, it is not currently included in the list of 7 drugs in the proposed rule, but we fully expect suzetrigine will be eligible for separate payment once it is FDA approved. We view the No Pain Act as an important indication of the broad range of supportive policy initiatives, both at the federal and state level that can provide a meaningful tailwind to suzetrigine adoption. We are also encouraged by the progress of the alternatives to Pain Act, which aims to level the playing field for access to non-opioids for Medicare Part D patients.

In the discharge or outpatient pharmacy setting, it's important to understand that patients who receive a prescription, must be able to access their acute pain medication immediately. Unlike patients with asymptomatic or chronic conditions, patients in acute pain cannot wait for another day or another week to have their prescription filled.

We are, therefore, working with key pharmacy retail organizations to ensure broad availability of suzetrigine nationally. In addition, we are planning a range of initiatives for the first year of launch, including co-pay assistance and other financial assistance programs to enable patients at the pharmacy to access their prescribed suzetrigine to payer coverage decisions. We are very enthusiastic about the potential launch of suzetrigine for patients with moderate to severe acute pain and the impact we believe it will have on society.

We recognize that even in the case of significant unmet need, it can take time some components of our health care system to adopt new technologies, and we are working to accelerate these processes. Ultimately, our goal is to fundamentally and forever change the way pain is treated, and we look forward to delivering on the first of this vision for patients with moderate to severe acute pain in early 2025. In conclusion, it's an exciting time to be at Vertex. We continue to treat more CF patients around the world and are well advanced in planning for the launch of the Vanzacaftor triple combination. We are entering a new era of commercial diversification with the launch of CASGEVY in the U.S., Europe and the Middle East, and our launch preparations for suzetrigine in acute pain are well underway.

As we seek to redefine the treatment of pain and drive further diversified revenue growth. I will now turn the call over to Charlie to review the financials.

Charles Wagner Executive

Thanks, Stuart. Vertex's excellent Q2 results demonstrate once again our consistent strong performance and attractive growth profile. Second quarter 2024 revenue increased 6% year-over-year to $2.65 billion with solid growth of 7% in the U.S. and 5% outside the U.S. The drivers of this strong quarter were in line with our expectations, including an anticipated reduction in channel inventories in select international markets.

Second quarter U.S. growth was driven by continued strong patient demand for TRIKAFTA. Outside the U.S., growth was also driven by strong demand with continued uptake from the KAFTRIO launches in children's ages 2 to 5, partially offset by the reversal of the first quarter channel inventory. On the expense front, Q2 '24 combined non-GAAP R&D acquired IP R&D and SG&A expenses were $5.43 billion compared to $1.04 billion in the second quarter of 2023.

Q2 '24 operating expenses include over $4.4 billion in AIP R&D charges, primarily as a result of the Alpine acquisition, which we previously disclosed is being accounted for as an asset acquisition. This compares to just $111 million of AIP R&D charges in Q2 of '23. Q2 '24 our non-GAAP R&D expenses of $697 million were roughly flat year-over-year, reflecting ongoing investment in the advancement of our broad R&D portfolio, offset by reduced costs from the recently completed clinical trials as well as the associated transition of certain costs from R&D to COGS and inventory.

Q2 '24 non-GAAP SG&A expenses of $280 million increased 28% versus prior year primarily as a result of investments in the commercial organization, including launch activities for CASGEVY and prelaunch activities for suzetrigine acute pain. We anticipate that quarterly non-GAAP R&D and SG&A expenses will increase over the remainder of 2024 within our guidance as we advance multiple studies, including suzetrigine, Pove and inaxaplin in Phase III programs VX-993 in acute and peripheral neuropathic pain studies and the expansion of the VX-880 trial in T1D. In addition, we continue to invest in preparation for upcoming potential new launches, including the further build-out of our commercial capabilities in acute pain. Q2 '24 results reflected strong revenue and underlying operating results, though due to the $4.4 billion AIP R&D charge from Alpine transaction accounting, we reported a second quarter 2024 non-GAAP operating loss of $3.1 billion. In the second quarter of 2023, we reported $1.15 billion in non-GAAP operating income.

Our tax rate for the quarter was also impacted by the onetime nondeductible Alpine AIP R&D charge leading to a reported non-GAAP tax rate for the second quarter of 2024 of negative 10% compared to a tax rate of 21% in Q2 of '23. Aside from the effects of the nondeductible Alpine charge, there were no material changes in Vertex's non-GAAP tax rate for the quarter, which would have been approximately 21%. The $4.4 billion AIP R&D charge for the Alpine acquisition equates to an impact of approximately $17 per share on Q2 GAAP and non-GAAP results, and drove a non-GAAP loss per share of $12.83 in Q2 '24 compared to non-GAAP earnings per share of $3.89 in the second quarter of 2023. We ended the quarter with $10.2 billion in cash and investments after paying approximately $5 billion to fund the acquisition of Alpine Immune Sciences.

Additionally, we deployed over $300 million of cash in the second quarter to repurchase more

than 700,000 shares. Now switching to guidance. We are raising our 2024 total product revenue guidance to a range of $10.65 billion to $10.85 billion, representing 9% revenue growth at the midpoint at current exchange rates. We continue to have high visibility revenue outlook as we expect continued growth in CF as we reach more patients, including younger ones in core markets and select other countries. Guidance also continues to include a contribution in the second half of the year from the commercial launch of CASGEVY.

For Vertex operating expenses, our non-GAAP guidance continues to include a $4.2 billion to $4.3 billion in combined R&D and SG&A expenses, which is unchanged from the guidance provided on our last earnings call. As previously communicated, we are absorbing Alpine's projected non-GAAP operating expenses for the remainder of 2024 within our guidance range for R&D and SG&A. For acquired [AIP] R&D, we now expect approximately $4.6 billion for the year, including the Alpine asset acquisition charge recorded in the second quarter.

Given that the Alpine AIP R&D charge is not deductible for tax purposes, we expect a non-GAAP full year 2024 tax rate of approximately 100%. Note that, the anticipated percentage tax rate is highly sensitive to projected pretax income. Aside from the impact of the nondeductible Alpine AIP R&D charge, our underlying full year 2024 non-GAAP effective tax rate would have remained in the range of 20% to 21%. In closing, Vertex posted excellent results yet again as we delivered strong revenue growth, advanced our CASGEVY launch and secured important regulatory approvals. We also strengthened our capabilities in preparation for additional near-term launches progressed our pipeline and made rapid progress closing and integrating Alpine.

A compelling fit with Vertex's R&D strategy with significant potential as a pipeline in a product.

We are already leveraging Vertex's clinical, regulatory and commercial capabilities to accelerate development in IgAN with Phase III set to begin this month. we are targeting U.S. accelerated approval in IgAN in late 2027 and a contribution to Vertex's revenue growth and diversification beginning in 2028. In addition, as we move through 2024, we anticipate further important achievements, including multiple milestones in our pain portfolio, such as a Phase II data readout with suzetrigine in LSR Phase II initiation of VX-993 studies in acute pain and in diabetic peripheral neuropathy as well as progress towards pivotal development in T1D. These and other anticipated milestones of continued progress in multiple disease areas are detailed on Slide 17.

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 Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

Noting that around 6,000 patients continued CFTR modulators as we think about uptake for vanzacaftor triple, can you help us understand what the early launch dynamics could look like and whether they could be a significant bolus of early adopters? And then just a second

question, if I may. What is the relative contribution of CASGEVY to the updated product revenue guidance?

Reshma Kewalramani Executive

Thanks, Salveen. We will be breaking down the revenue for the CF franchise versus CASGEVY. And I'll turn it over to Stuart to tell you a little bit more about the vanzacaftor launch dynamics.

Stuart Arbuckle Executive

Yes, Salveen, thanks for the question. I don't think there's going to be a single bolus of patients based on our research with physicians that they are considering for the vanzacaftor triple combination. I'd say that they are excited about the prospects for vanzacaftor both for their existing patients who are honestly, CFTR modulator, many of whom I think are going to be very interested in a treatment option, which promises the potential for increased CFTR function. And also being the fact that it's once a day. And then as you say, there are also patients who are not currently on a CFTR modulator, who I think are going to welcome the opportunity for a new treatment option.

So I don't think it's going to be one or the other. I think there's going to be broad interest in the vanzacaftor triple across both patients who are persistent today and those who've discontinued previously.

Operator Operator

Next question will come from David Risinger with Leerink Partners.

David Risinger Analyst

Congrats on the strong execution. I have 2 questions. First, could you just discuss the potential to develop VX-548 ex-US for neuropathic pain? And second, could you provide latest on your preclinical development efforts for NaV1.7 inhibitors?

Reshma Kewalramani Executive

Sure thing. Hey Dave, this is Reshma. Let me break that into 2 parts, and let me take the preclinical NaV1.7 first, turn it over to Stuart to talk about our goals ex-U.S. So we are making really strong progress on the NaV1.7 inhibitors. They are still in preclinical development.

But I would characterize it, Dave, as it's in late preclinical development. And to contextualize this a little bit more for everybody else, we expect that the NaV1.7s could be used alone in acute pain or neuropathic pain or they could be used in combination with our NaV1.8 inhibitors, be it 548 or 993 or any in our portfolio. With that, I'll turn it over to Stuart for a little bit on ex-U.S. ambitions.

Stuart Arbuckle Executive

Yes. Hi David, thanks for the question. So I would say that the clinical landscape and by that, I mean the kind of the treatment options and the way that they're used is very similar outside the U.S. as it is here in the U.S. with things like ANCA to acetaminophen in neuropathic pain, things like pregabalin, gabapentin, and then obviously opioids.

And that's true in both acute pain and neuropathic pain.

And I know you're asking specifically about neuropathic there are differences. I think it's fair to say that the level of abuse and misuse of opioids is less. It's not zero, but it's less outside of the U.S. But in addition, the pricing dynamics and the value recognition of health care and innovation by health care systems outside the U.S. is very different.

And as such, our focus at this time is very much on the unmet need and opportunity to serve patients here in the U.S. first. And ex-U.S. is something that we will consider later on.

Operator Operator

The next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

I wanted to ask about your type 1 diabetes effort. How do you envision the regulatory path for VX-880? And for VX-264, the encapsulated cells product, I believe you've completed Part A with the low-dose patients. Is there anything you can share with respect to kind of what you're seeing so far with that one?

Reshma Kewalramani Executive

Yes. Jess, it's Reshma. Let me take those 2 questions. Maybe we'll go with 264 first, and then we'll go to VX-880. So on VX-264, this is the calls plus device program.

You're exactly right about the stage of the program. We're in Part B, which is the full dose. It's a full dose with the stagger period between patients. I would say that results are a 2025 time frame. We're making progress, and I'm really happy to be in the clinic with both 264 and 880.

On VX-880, this is the naked cell program, so cells alone. This is the one that has now completed, which is obviously a big milestone enrollment and dosing in the original 17 patient study. We are in the phase of development where we're in full dose with patients who don't have a stagger. I'm really happy with the regulatory discussions to date and their endorsement for us to expand the study to a total of 37 patients, so an additional 20 patients. And with regard to your direct question on how should we think about the path forward with regard to regulatory expectations.

I don't have an answer for you today because that's exactly the conversations that we're going to compete in the coming months. But I would think about the type 1 diabetes program more like a CASGEVY program than a small model program. You'll remember that CASGEVY program in either TDT or in a sickle cell was a very efficient sample size. And what we did in the case of CASGEVY is converted from a Phase I/II to a Phase I/II/III trial. Exactly look like for VX-880.

I look forward to keeping you updated as we complete the discussions with regulators.

Operator Operator

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

Evan Seigerman Analyst

I think, Stuart, in your prepared remarks, you suggested that the launch of suzetrigine might be more gradual than some other launches -- maybe once approved, can you walk me through some of the gating factors to really get to the hands of patients to have a maximum impact on the health care system, kind of what you have to do once approved to really get it to these patients.

Stuart Arbuckle Executive

Sure, Evan. Thanks for the question. And just to be absolutely crystal clear, our enthusiasm for suzetrigine is growing as we get closer to the launch, not diminishing. And that's due to the benefit we've got from market research and also our interactions and discussions with physicians post the Phase III data and the filing. But there are practical realities that we are going to have to face and they are things like.

Obviously, the majority of patients with acute pain are treated in the institutional setting.

That means we're going to have to go through formulary and P&T processes with those institutions. We're going to have to work with payers and work through their formulary and other policy adoption processes. And so whilst those policies are very well defined, they do take time. And obviously, work everything we can to accelerate those timelines. And that's why we're already engaging for instance, with GPOs and IDN leadership to support institutional use.

We're talking with payers and PBMs to support rapid policy adoption. In addition, we are going to want suzetrigine to be broadly available at retail pharmacies across America. And so we're also reaching with the major retail the organizations as well. And lastly, because we know that these processes can take time despite the fact we're going to do everything we can to accelerate them. We are also looking at deploying a range of initiatives, including things like co-pay assistance and financial assistance program so that if a physician and patient decide that suzetrigine is right for them, that patient can access the product without delay and isn't forced to kind of abandon the prescription because their particular plan or payer has not finalized their medical policy yet.

So those are some of the challenges we're going to be facing. They're not unique to Vertex. They are relatively well defined, and we're going to do everything we can to accelerate them to suzetrigine, can become the multibillion-dollar drug. We know it's going to become.

Operator Operator

Your next question will come from Chris Raymond with Piper Sandler.

Christopher Raymond Analyst

Just maybe 2 questions. First, maybe on pove. Just a competitive question as IgAN seems to be getting a little bit more crowded. Biogen just got access to [indiscernible], which I think had a pretty interesting Phase II data. Just maybe talk a little bit about how you view the sort of match up to that?

And maybe how does anti-CD38 compared to BAF APRIL inhibition? And then maybe a CASGEVY commercial question. Just on the HHS suit around fertility treatments for patients getting CASGEVY. Can you maybe talk about the overall timelines there with that case? And maybe also talk about how much of an impact it is to not have this reimbursement for fertility in place during the early stage of the launch.

Reshma Kewalramani Executive

Sure. This is Reshma. Let me take the first question first, and then I'll turn it over to Stuart to talk about CASGEVY and how that's going. So important things to know about IgA nephropathy. It is a rare disease, but it is one of the more common rare disease.

There's more than 130,000 with IgA nephropathy in the U.S. alone. It's actually the most common primary glomerulonephritis. So there are lots of patients that are waiting to be served. To date, there is no specific therapy that treats the underlying cause of this disease.

And the reason for our enthusiasm and after a IgA nephropathy has been in our sandbox as it were a disease area of interest for a long time. And after there has been some activity in this space and a full analysis by us of everything available out there our enthusiasm for Alpine and their povetacicept, which is a dual-APRIL BAF inhibitor comes from the fact that it is the agent that works directly on the underlying cause of the disease to put it in a short way, the disease is caused by B cells. It is the activation of these B cells.

It is about auto antibodies. And this drug APRIL BAF directly inhibits B-cell proliferation, maturation and proliferation. And what we have seen by way of mechanism of action, this dual-APRIL BAF inhibition all of the preclinical data potency affinity as well as the clinical data, it is through its Phase II development. So we're talking about proteinuria, hematuria, GFR and also the biomarker of what's called GVA IgA, that's the Advertently glycosylated IgA, which is the underlying problem.

Not to mention 2 monthly dosing, it's subcutaneous and small volume. You put that all together, pove has the most transformational profile and holds the potential to be best-in-class for IgAN, but also holds the potential to have effect -- transformative effect in a whole host of other cell-mediated kidney diseases like lupus nephritis, membranous, ANCA associated and a host of B-cell-mediated heme diseases like ITP, cold agglutinin disease, warm hemolytic anemia. So I couldn't be more excited about this molecule getting to its first Phase III program, which is IgA Nephropathy.

Stuart Arbuckle Executive

Yes, let me just take a step back before I talk specifically about fertility preservation. So because of the treatment early to get CASGEVY, which requires multiple trips to the activated and authorized treatment centers. And because there's only a certain number of sites in the United States, and in addition, because of the b-cell fan conditioning regimens is where the fertility risk comes in, we have sought to try and provide support to patients in 2 particular areas.

One, travel and lodging and the other one is in fertility preservation, and we want to provide those support services to patients equitably no matter what the payer. We are able to buy

both of those services to commercially insured patients. And we are able to provide travel and lodging support to government-insured patients because that has previously been ruled on by the OIG. What they have not met decision on is on fertility preservation, and that's why we've launched our suit to try and get fertility preservation approved for government-insured patients as well.

It's impossible that exactly on the timing of when that suit will be heard and resolved. In the short term, I don't see it as being rate-limiting to a successful launch of CASGEVY, and I think we're already seeing that in the number of patients who are beginning the treatment journey and in the number of collections. Having said that, we are completely committed to the sickle cell and TET communities, and we are going to fight for their rights to cable access, whatever their payer.

Operator Operator

And the next question will come from Terence Flynn with Morgan Stanley.

Terence Flynn Analyst

Maybe 2 for me. Stuart, you discussed at a high level your confidence in vanzacaftor pricing. Maybe just -- I know you're not going to comment directly on the price, but just what are some of the inputs you're considering as you think about making that decision on next year? And then any update on where we might see the full Phase III data for VX-548 this fall?

Reshma Kewalramani Executive

Terence, let me take the second question first. I think it's now been released. The VX-548 suzetrigine data have been accepted at the ASA fall conference, and it has been accepted in the best abstract category. So you can expect to see it there. I'm sure the teams are also going to be working on full manuscripts probably in the fall/winter time frame, but the Congress acceptance of suzetrigine as best-in-class abstracts has already been announced.

Stuart, over to you.

Stuart Arbuckle Executive

Yes. Terence, on vanzacaftor, we're going to approach the pricing of vanzacaftor as we have with all of our medicines, which is we're going to base it on the clinical benefits and the value it provides to patients. And as you know, we're very positive about the vanzacaftor profile. It performed brilliantly in the Phase III program, noninferior as anticipated to TRIKAFTA on FEV1, but demonstrated superior restoration of CFTR function as measured by sweat chloride. And of course, it has the convenience of being once daily.

So we're going to take all of those factors into consideration when thinking of the pricing, which is obviously a decision we'll make much closer to the launch.

Operator Operator

Your next question will come from Mohit Bansal with Wells Fargo.

Mohit Bansal Analyst

Maybe one question on LSR trial. If you could help set some expectations there. It's a placebo-controlled trial. So -- should we think a 2-point improvement just like a DPN trial would be good enough here? The other one is that, are you expecting any AdCom for the acute pain program at this point?

Reshma Kewalramani Executive

Mohit, let me take the second question first. As I said in my prepared remarks, we are thrilled that suzetrigine, the submission was not only accepted but granted priority review. The agency has let us know that they do not plan to hold an Adcom as it stands today. But also, as you know, the agency can let us know that they wish to have one at any time between the acceptance of the filing and the actual approval.

On the LSR, so that's also a VX-548 trial. That has significantly honestly, far significantly exceeded our projections in terms of enrollment and study, and we're now expecting that study this year and for us to be able to share results this year. So with regard to this study and how you can think about it, it uses the high dose. So the 69 milligrams from the Phase II study of DPN. The big difference between DPN and LSR is that LSR has no specific therapy approved for the treatment of this kind of radiculopathy pain.

And so our Phase II trial in LSR is a within group. So it's within arm change of the NPRS for the LSR -- sorry, for the VX-548 group. And equally, we'll have the placebo group change. And the goal for the LSR study, which frankly was goal as the DPN study to get a magnitude of the treatment effect so that we can appropriately power the Phase III study. And the reason the DPN study had a pregabalin arm was because pregabalin is an available therapy for the treatment of DPN.

This study, LSR, as a placebo arm because there is no specifically approved therapy for the treatment of LSR. I hope that helps.

Susie Lisa Executive

Chuck, we'll take 2 more questions, please.

Operator Operator

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

Liisa Bayko Analyst

Just a follow-up on vanzacaftor. Maybe you can talk about how you're expecting the rollout there in terms of patient uptake. It's not quite as much as at least as some of your other therapies are, but nevertheless, like the value there is obvious. Do you expect like quite quick conversion? Will it happen solely over time?

Do you think the vast majority of patients will switch over? Just curious about what the feedback has been there?

Reshma Kewalramani Executive

Stuart, any additional comments to make?

Stuart Arbuckle Executive

Yes, just that we're as excited about the vanzacaftor launches of any of our other CFTR modulators for the reasons I think it's got a great benefit risk profile. And I think it is going to -- as I said earlier, I think it's going to be equally of interest to patients who are on a CFTR modulator today, but would like increased CFTR function as demonstrated by sweat chloride because these patients know that, that is important for their kind of health and well-being, but I think it's also going to be of value to those who continued.

So as I said earlier on, I really don't think there's kind of 1 group or another who are going to be more interested than others. I do think it's something that's going to be broadly of appeal to people. And as I also mentioned, not to forget the fact that it has the benefit of being once daily, which again, is an attractive part of a chronic medication. So as I said, we're as excited about the launch of vanza as we have been about any of our other CFTR modulators.

Liisa Bayko Analyst

I was just trying to get a sense of the -- like how quickly people might convert over your thinking? Do you think it will be kind of slow and steady or pretty rapid.

Stuart Arbuckle Executive

Yes. I mean certainly, the reaction with physicians and patients, the profile has been very enthusiastic. I'm not going to speculate exactly on how much -- how rapidly we're going to get the transitions and people restarted, Liisa.

Reshma Kewalramani Executive

Liisa, maybe I'll just add 1 thing if you want to think through it. Patients with CF usually visit their doctors once a quarter. As Stuart said, the patients are very aware of drug development and vanzacaftor, in particular, as are their physicians and patients have consistently expressed interest in thinking about medicines that may bring them the potential for higher efficacy. I think that's as far as we can go with regard to timing. But maybe those are pieces of information that are helpful to you.

Operator Operator

The next question will come from Michael Yee with Jefferies.

Michael Yee Analyst

Two questions. On the Alpine product, can you just remind me, I know you guys think it's best-in-class, but how to think about greater reduction in proteinuria versus, say, a [beta] program that will have data in first half '25? And is it your idea that you have greater reductions and therefore, better stabilization of 3GFR or that it also will just be shining through in lupus and other autoimmune diseases for which we will have to wait for RUBY-3 data.

So just maybe talk about and remind us how you think the benefits will be seen on that product? And then really quickly on the Acute Pain launch, can you just remind me on the comments on the No Pain Act, you believe you'll eventually get reimbursement there, but that's more of a CMS exposure population to take that in considering. And for commercial, that's more about blocking and tackling on formularies and commercial plans?

Reshma Kewalramani Executive

Yes. Mike, I'm going to ask Stuart to comment on no pain first. I think it was a little hard to hear you might. But I think Stuart Mike's question is there's the No Pain Act pertain to government-paid patients and how are you thinking about commercial? And then I'll come back for pove.

Stuart Arbuckle Executive

Yes. So No Pain, Mike, is looking at the add-on payment to patients who are treated in the out-patient ambulatory surgical center setting. As you said, we were not listed as 1 of the products, but that is because we're not approved. And so yes, we do anticipate being added to that list -- suzetrigine is approved.

In terms of in the Medicare area, maybe you're also thinking of the alternatives to No Pain Act, which is looking at the level the playing field in terms of things like step therapy and not allowing things like that and utilization management in Part D and also making sure that there is parity in terms of the co-pay for patients between opioids and non-opioids. In terms of commercial, as you said, these are less relevant to that. This is really the sort of, as you said, blocking and tackling is what we'll be doing in talking to commercial plans

Reshma Kewalramani Executive

And Mike, on the question on pove, I think the question was how should we think about pove in IgA nephropathy? And then how should we think about it in the other studies all about proteinuria. So the way I would think about it is underlying cause of disease and B-cell diseases. We have 2 Phase II studies going on. It was a very clever design by Alpine scientists.

There's a RUBY-3, which is a basket of B-cell mediated renal diseases, IgA nephropathy, which is now going to Phase III this month. It has lupus nephritis in there, ANCA-associated nephritis as well as membranes.

All of these diseases are B-cell-mediated diseases. In many of these diseases, proteinuria is important. But I'll tell you, for example, in membranes, PLA2R is a very important biomarker. And in some of the Nephritis, as you may know, hematuria is very, very important. So I think protein is -- proteinuria is clearly very important in IgA nephropathy and its prominence is elevated because of the FDA's acceptance of proteinuria in IgA nephropathy as an accelerated approval endpoint.

But hematuria is important in some looking at biomarkers like PLA2R is important in others.

And in the RUBY-4 basket, these are B-cell-mediated heme diseases, it's really not about proteinuria. It's about other markers of interest like it could be something like hemoglobin or in the case of ITP, it would be platelets. But the way I would look at it and my enthusiasm for

Povetacicept is because it is such a good B-cell -- such a good medicine to tamp down the B cells because it's dual inhibition and impacts maturation, proliferation and differentiation of B cells. And that's where my optimism for B-cell mediated diseases comes from.

Operator Operator

This concludes our question-and-answer session as well as our conference call for today. Thank you for presentation. 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 replay access code 10186971. Thank you for your participation, and you may now disconnect.