Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q1 2024 Earnings Call

Monday, May 6, 2024 4:30 PM

Event Participants

Executives 4

Susie Lisa, Reshma Kewalramani, Stuart Arbuckle, Charles Wagner

Analysts 10

Geoffrey Meacham, Jessica Fye, Salveen Richter, Evan Seigerman, Colin Bristow, Terence Flynn, Philip Nadeau, Olivia Brayer, Debjit Chattopadhyay, Liisa Bayko

Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals First Quarter 2024 Earnings Conference Call. [Operator Instructions] I would now like to turn the conference over to Ms. Susie Lisa. Please 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 first quarter 2024 financial results conference call. On tonight's call making prepared remarks, we have Dr. Reshma Kewalramani, Vertex' 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' marketed medicines for cystic fibrosis, sickle cell disease and beta thalassemia, our pipeline, Vertex' anticipated acquisition of Alpine Immune Sciences 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 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. Continuing our strong momentum from 2023, we've kicked off '24 with another quarter of excellent performance across the board. Vertex continued to reach more CF patients, delivering $2.7 billion in revenue in Q1, representing 13% growth versus the prior year period. We also began our journey of revenue diversification with the launch of CASGEVY in both sickle cell disease and beta thalassemia in multiple regions.

In our late stage pipeline, we continue to drive programs into Phase III and towards regulatory approval, creating multiple opportunities for both revenue growth and diversification, including: one, completing our regulatory submissions for the vanzacaftor triple in patients with cystic fibrosis 6 years and older in both the U.S. and the EU; initiating the rolling NDA submission for VX-548 or suzetrigine in moderate-to-severe acute pain; three, advancing inaxaplin into the Phase III portion of its pivotal trial in APOL1-mediated kidney disease and expanding the eligible patient population down to age 10; and four, following the successful completion of the end of Phase II regulatory meeting with the FDA, we are on track to initiate the Phase III trials of suzetrigine in painful diabetic peripheral neuropathy in the second half of this year. And milestones in our early and mid-stage pipeline matched this pace of progress as we resumed the VX-880 trial in type 1 diabetes; initiated clinical development of VX-407 in polycystic kidney disease; and three, achieve regulatory clearances in multiple regions, including the U.S., and initiated the Phase I/II clinical trial of VX-670 in patients with myotonic dystrophy type 1. And of course, we are very excited to expand the Vertex portfolio and team with our definitive agreement to acquire Alpine Immune Sciences announced on April 10. Alpine's lead asset, povetacicept or pove, is a potential best-in-class Phase III-ready molecule for IgA nephropathy or IgAN, a disease with high unmet need.

Pove is also a molecule that holds a pipeline in a product potential in a number of other serious autoimmune renal diseases and cytopenias in Phase II development. We see the acquisition as just the right fit with just the right assets at just the right phase of development, where Vertex' capabilities can accelerate pove's development in IgAN and other indications. And lastly, Alpine will add protein engineering and immunotherapy expertise to Vertex' capabilities, with particular relevance for our development programs in gentler conditioning for CASGEVY and immune evasion for type 1 diabetes cell therapies. We are excited to begin working with the Alpine team and together, advance pove into Phase III in IgAN later this year. With that overview, let me now turn to a more detailed pipeline review.

This quarter, I'll limit my comments to the programs with the most significant recent updates: cystic fibrosis, pain, type 1 diabetes and the pending Alpine acquisition. Starting with CF. We are very pleased with the Phase III results of the vanza triple we announced in early February as we continue to advance towards our ultimate goal of bringing all eligible patients to carrier levels of sweat chloride. Results from the vanza pivotal program met our high expectations, and were an important milestone in our progress towards this aspiration. Results from the 2 randomized studies in patients 12 and above demonstrated vanza was non-inferior to TRIKAFTA on lung function and superior to TRIKAFTA on sweat chloride, including as measured by the proportion of patients achieving sweat chloride levels below the diagnostic threshold of 60 millimoles per liter and below the carrier level or normal levels of sweat

chloride of less than 30 millimoles per liter.

Included in the pivotal program was the RIDGELINE study in patients 6 to 11 years of age. To underscore the potential impact of vanzacaftor, consider 95% of patients age 6 to 11 in this study achieved sweat chloride levels below the level of diagnosis for cystic fibrosis, and more than half reached sweat chloride levels considered to be in the normal or carrier level range of sweat chloride. We believe these results indicate that vanza could set a new standard in the treatment of CF. To round out the profile of the vanzacaftor triple, it's important to note that the therapy also offers the convenience of once-daily dosing and a substantially lower royalty burden. With these results in hand, we've been working rapidly to compile the regulatory marketing applications, and I am pleased to share that we have completed submissions in the U.S.

and EU for patients ages 6 years and older ahead of our midyear goal. In the U.S., we use one of our priority review vouchers, which, if the filing is accepted, provides an expedited 6-month review versus the standard 10-month review time line. We're also on track to complete submission in the U.K., Canada, Australia, New Zealand and Switzerland by midyear. I'll close on CF with VX-522, our CFTR mRNA therapy in development with our partners at Moderna for the treatment of the more than 5,000 people with CF who do not make any CFTR protein, and therefore cannot benefit from CFTR modulators. We continue to enroll in the multiple ascending dose portion of the study and expect data late in 2024 or early 2025.

Moving to the pain program and suzetrigine, our novel, highly selective NaV1.8 pain signal inhibitor. Suzetrigine offers the compelling combination of both strong safety and strong efficacy with the potential to treat moderate to severe pain across multiple settings of care. In acute pain, suzetrigine has secured Fast Track and Breakthrough Therapy designations, and we were very pleased that the FDA granted us a rolling NDA submission. I'm also pleased to share that multiple modules have already been submitted and we are on track to complete the submission this quarter. Consistent with our serial innovation strategy, the next asset in our acute pain pipeline is VX-993.

We recently received IND clearance for the intravenous formulation of VX-993 and have already started the Phase I trial. We're also planning a VX-993 oral formulation Phase II study in acute pain, which we expect to initiate later this year. Beyond suzetrigine and VX-993, we continue to innovate in the NaV1.8 space and are also making strong progress preclinically with our NaV1.7 pain signal inhibition program that may be used alone or in combination with suzetrigine or other NaV1.8 inhibitors. In peripheral neuropathic pain or PNP, we are very pleased with the outcomes from the recently completed end of Phase II meeting with the FDA and are excited to begin the pivotal program for suzetrigine in painful diabetic peripheral neuropathy or DPN in the second half of this year. The program will consist of 2 randomized sister studies of approximately 1,000 patients each, with 3 arms in each study: a suzetrigine 70-milligram arm once daily, a placebo arm and a pregabalin or Lyrica arm.

The efficacy endpoints are based on the change from baseline to week 12. The primary endpoint is the comparison of suzetrigine versus placebo in the weekly average of the daily pain intensity score or NPRS. The first key secondary endpoint will test for non-inferiority of suzetrigine to pregabalin on the same NPRS pain score, and if successful, we will test for

superiority. And finally, the second key secondary is quality of life measures versus placebo. In order to evaluate the long-term safety and effectiveness of suzetrigine, a subset of patients completing the 12-week study will have the opportunity to roll into a 52-week open-label extension study.

Our goal continues to be a broad peripheral neuropathic pain label. And in support of this goal, we're also studying suzetrigine in lumbosacral radiculopathy or LSR, a PNP condition for which there are no specifically indicated or approved treatments. LSR accounts for approximately 40% of all PNP patients, and together with DPN, make up more than 60% of the PNP segment. We are continuing to enroll and dose our Phase II study of suzetrigine in LSR, and I'm pleased to share that the study is on track to complete enrollment by the end of this year. Just as we've transformed the treatment of CF, we believe we have the potential to transform the treatment of pain, both acute and neuropathic, and look forward to helping address the unmet need of the tens of millions of Americans suffering with these conditions.

Turning now to type 1 diabetes. VX-880 is our stem cell-derived, fully differentiated islet cell therapy for patients with T1D and impaired hypoglycemic awareness who suffer from severe hypoglycemic events. I'm pleased to share that after data review by the independent data monitoring committee, the VX-880 study has resumed. Parts A, B and C of the global 17 patient study are fully enrolled, and we expect to complete dosing soon. We look forward to sharing updated data this June at the American Diabetes Association annual meeting.

VX-264, the next asset in our T1D program, is our cells plus device program. Using the same VX-880 cells, which have already demonstrated efficacy, VX-264 is designed to eliminate the need for immunosuppression by shielding the cells from the immune system in the proprietary device. This Phase I/II study has completed Part A and Part B is underway. Lastly, our hypoimmune program, which aims to evade the immune system by introducing certain edits into the same VX-880 cells, is yet another approach to avoiding the use of immunosuppresses. This program continues to advance in preclinical development.

I'll conclude with a few comments on povetacicept, the lead asset from our pending acquisition of Alpine Immune Sciences. We are excited about the potential of povetacicept across multiple dimensions, including preclinically, with its high affinity and potency against both APRIL and BAFF pathways in preclinical assays as well as high efficacy in cell and animal models of B cell-driven diseases; clinically, with patient data in IgAN through Phase II that look potentially best-in-class; in proteinuria; in hematuria; GFR; and clinical remission; better drug-like properties with direct patient benefit, including once every 4-week dosing, subcutaneously, with low injection volume; a good safety and tolerability profile; the broadest development plan in the field; and a robust IP portfolio. Important upcoming pove milestones in the second half of this year include initiation of the Phase III study in IgAN, and readouts from the ongoing RUBY-3 and RUBY-4 basket studies in autoimmune renal diseases and cytopenias, respectively. With that, I'll turn it over to Stuart for a commercial overview.

Stuart Arbuckle Executive

Thanks, Reshma. I'll first discuss CF, and then as we're entering a new era of commercial diversification, 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 continue to grow the number of eligible patients receiving our CFTR modulators. First quarter year-over-year U.S. growth was driven by continued strong performance of TRIKAFTA, including in patients ages 2 to 5 years old following the approval in this patient population in April of last year.

Outside the U.S., we also saw growth this quarter, driven by the rollout of KAFTRIO in the EU in patients ages 2 to 5 following approval in this age group in November 2023, and we will continue to drive access and uptake in more EU countries over the course of the year. Our outlook in CF is bright in the short, medium and long term. We will drive growth in the near term by reaching more eligible patients, including younger age groups and additional geographies. For example, we recently received EU approval of KALYDECO in patients between the ages of 1 month up to 4 months old. We also expect regulatory approvals for additional rare genotypes for KAFTRIO in the EU and TRIKAFTA in the U.S.

and Canada later this year. And Brazil is a good example of a new geography. Up to now, some patients in Brazil have been able to benefit from our CFTR modulators through named patient sales. We recently secured government reimbursement for TRIKAFTA in ages 6 plus and are in the process of launching TRIKAFTA for all eligible patients there. We will then look to drive further CF growth over the medium term with the vanzacaftor triple combination launch, as many existing TRIKAFTA patients may seek to achieve even greater levels of CFTR function with 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 may be interested in a new treatment option. Furthermore, there are 31 additional rare mutations not previously responsive to our other CFTR modulators that are responsive to the vanzacaftor triple. Our launch preparations are well underway, including pre-approval information exchange with payers, and we are both encouraged by our interactions to date and excited by the opportunity to launch our fifth medicine in CF. Longer term, we expect continued growth in CF from our mRNA program, VX-522, for the more than 5,000 people with CF who do not respond to CFTR modulators. Now turning to CASGEVY and our launches in sickle cell disease and beta thalassemia.

We are making strong progress with ATC activation, physician and patient engagement and payer conversations. Enthusiasm from stakeholders is high in all regions, and our teams are working to translate this historic scientific achievement into meaningful patient benefit in the real world. Let me provide some insights on the launch with 2 key metrics we are sharing externally as important markers of our early launch progress: the number of activated authorized treatment centers or ATCs, and patient cell collections. Recall that Vertex will recognize revenue for CASGEVY near the end of the patient journey at infusion. Starting with ATC activation.

You may recall we are prioritizing approximately 75 ATCs globally and already had 9 ATCs activated at launch, even ahead of knowing the final label or pricing for CASGEVY. We are pleased with our progress as we now have more than 25 activated centers, including centers in all regions where CASGEVY is approved. Even more important than the number of ATCs activated is patient initiations and cell collections. Many patients have begun the treatment journey, and as of mid-April, 5 patients already had cells collected. This is excellent progress

given the short time frame since approval and the complexity and length of the patient journey.

These cells collections have occurred across all regions where CASGEVY is approved: the U.S., Europe and the Middle East. We also continue to make great progress with payers, who recognize the transformative clinical benefits of CASGEVY and are moving quickly to provide rapid and equitable access. In the U.S. commercial market, we have contracts and/or published policies in place for over 200 million lives or nearly 65% of total lives. In the government Medicaid sector, we have policies in place or active contract negotiations ongoing with 18 states.

And in the meantime, all states have confirmed their intent to provide case-by-case coverage. Outside the U.S., we are also making progress with reimbursement and access, either through formal reimbursement agreements or early access programs. In Europe, we see strong traction in France, with a reimbursed early access program in TDT. We're particularly pleased with our progress in the Middle East, which is a new region for Vertex and especially important for CASGEVY given the high prevalence of sickle cell disease in particular, and the government's clear focus on elevating the health of their citizens. Since receiving regulatory approvals from KSA and Bahrain, we have worked with local health care authorities and refined our epidemiology estimates for the region.

Our work indicates that the eligible 12-plus sickle cell disease and beta thalassemia population in KSA and Bahrain that we could serve is in excess of 23,000 patients, a potentially larger opportunity than even the U.S. These regions have the infrastructure to administer medicines like CASGEVY, given the prevalence of the diseases and relatively high volume of allogeneic stem cell transplants performed annually. And importantly, we have already secured reimbursement agreements in KSA and Bahrain, allowing certain eligible patients to access CASGEVY for both sickle cell disease and transfusion-dependent thalassemia. In addition to having activated ATCs and collected cells from our first patients in the Middle East, we continue to work with local health care professionals to increase the number of ATCs and expand patient access in the region. Shifting now to suzetrigine.

We believe this highly selective NaV1.8 pain signal inhibitor has the potential to provide a transformative treatment option for the millions of patients suffering from acute and peripheral neuropathic pain. This quarter, I'm going to limit my commercial comments to the opportunity in acute pain. Throughout its clinical trials to date, suzetrigine has shown a compelling combination of efficacy and safety, with strong potential to be used across a range of moderate to severe acute pain conditions, both surgical and nonsurgical, and across a range of settings. This profile will ideally address the clear unmet need among both patients and physicians: effective pain relief with a favorable safety and tolerability profile. On prior investor webcasts, we provided details on this opportunity, including the magnitude: approximately 80 million patients are prescribed a medicine for moderate-to-severe acute pain each year in the U.S.; and the high concentration, with approximately 2/3 of patients being treated in the institutional setting.

There is further concentration within that setting in approximately 2,000 institutions that roll up to around 150 IDNs. Accordingly, they can be served with a specialty commercial

infrastructure. We have also detailed the mix of settings for their over 1 billion calendar days of acute pain treatment: 15% are prescribed and dispensed in an institutional setting, 35% are prescribed at discharge and 50% are prescribed in physicians' offices. This quarter, I'll provide you with some insights on our go-to-market strategy and an update on the legislative and payer landscape. We are focused on the institutional setting, given these approximately 2,000 institutions account for 50% of acute pain prescriptions.

Extensive market research has also helped us identify an initial set of specific acute pain conditions and procedure types with high clinical fit, such as high-volume surgical procedures, pain conditions that typically require prescription pain medicines at discharge, or where we can seek to replace or significantly reduce opioid utilization. And the related physician specialties that are likely to adopt and champion suzetrigine. The key health care professionals we will be targeting include orthopedic, general and plastic surgeons, emergency department physicians, anesthesiologists and pain medicine specialists. Given the dynamics for new medicines to be approved for use in institutions, we expect the earliest uptake of suzetrigine will occur at discharge. Recall this discharge segment represents roughly 35% of the approximately 1.1 billion calendar days of acute pain treatment in the U.S.

each year. The average prescription length in this setting is approximately 2 weeks. Treatment in this setting commonly includes opioids, where prescription length is shorter, 4 to 5 days, due to side effect profile, addiction concerns and prescribing limits at the state and IDN and hospital level. We are already engaging with key decision-makers across the formulary and access landscape, including pharmacists, PBMs, payers, IDNs and GPOs. We expect these stakeholders to make formulary and coverage decisions throughout the first year of the launch, and thus plan to engage in contracting discussions in the second half of this year ahead of launch to support the potential for accelerated formulary adoption.

We've also made great progress in the build-out of our commercial team. Our field leadership team are now on board and fully trained, and having [gated] the hiring of the field force until after the Phase III data, we are now finalizing the hiring of 150 new customer-facing colleagues. Finally, we know the significance of policy in the world of pain treatment, with important legislation like the NOPAIN Act already on track for implementation in 2025 and bills like the Alternatives to PAIN Act recently introduced. Our long-standing efforts continue to help shape state and federal policy initiatives to: one, encourage consideration and use of non-opioid alternatives; and two, remove financial barriers to choosing a branded non-opioid. Overall, we plan for a high science, digitally-enabled commercialization approach with a strong focus on population health decision makers.

In addition, both patient advocacy and public policy efforts complement and supplement our commercial activities. 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 fundamentally redefine the treatment of pain and drive further diversified revenue growth. I'll now turn the call over to Charlie to review the financials.

Charles Wagner Executive

Thanks, Stuart. Vertex' excellent start to the year demonstrates once again our consistent strong performance and attractive growth profile. First quarter 2024 revenue increased 13% year-over-year to $2.7 billion, with solid growth of 8% in the U.S. and 21% outside the U.S. The drivers of this strong start were in line with our expectations, with some outperformance due to channel inventory phasing in select international markets.

First quarter U.S. growth was driven by continued strong performance of TRIKAFTA, including in patients ages 2 to 5 following the approval in this patient population in April of last year, partially offset by the typical pattern of seasonally higher gross to net in the first quarter. Outside the U.S., growth was also driven by KAFTRIO 2 to 5 launch, and a benefit from channel inventory phasing is expected to reverse in subsequent quarters, similar to the dynamics we saw in the first half of 2023. First quarter 2024 combined non-GAAP R&D, acquired IPR&D and SG&A expenses were $1 billion compared to $1.2 billion in the first quarter of 2023. Included in Q1 '24 results are $77 million of acquired IPR&D charges compared to $347 million of such charges in the first quarter of 2023.

Non-GAAP R&D expenses in Q1 '24 were relatively flat year-over-year and reflect growing investment in the advancement of our broad earlier-stage R&D portfolio offset by reduced costs from the recent successful completion of multiple late-stage clinical trials for CASGEVY, vanzacaftor and suzetrigine as well as the associated transition of certain costs from R&D to COGS and inventory. The increase in non-GAAP SG&A costs versus Q1 '23 includes investment in the commercial organization and launch activities for CASGEVY and acute pain. We anticipate the quarterly non-GAAP R&D and SG&A expenses will increase over the remainder of 2024 as we advance inaxaplin into Phase III development in AMKD, initiate the suzetrigine Phase III program in painful diabetic peripheral neuropathy and continue to invest in preparation for upcoming potential new commercial launches, including the further build-out of our suzetrigine team. First quarter 2024 non-GAAP operating income was $1.3 billion, a 48% increase compared to $902 million in non-GAAP operating income in the first quarter of 2023. First quarter 2024 non-GAAP effective tax rate of 17.4% compares to 21.3% in Q1 '23 and includes a benefit from a discrete adjustment to Vertex' income tax reserves.

First quarter 2024 non-GAAP earnings per share were $4.76, including benefits from revenue and expense phasing as well as a lower tax rate, compared to $3.05 in the first quarter of 2023. We ended the quarter with $14.6 billion in cash and investments. We will use a portion of this cash on hand to fund the $4.9 billion acquisition of Alpine Immune Sciences, which is expected to close this quarter, subject to certain customary conditions. Alpine is a prime example of our priority for capital deployment: to invest in innovation, including external innovation via business development. We see multibillion-dollar potential for Phase III-ready povetacicept given its transformative and best-in-class potential in IgAN, a disease area with high unmet need.

We also look forward to exploring pove's full potential in other serious diseases. Additionally, we deployed over $140 million of cash in the first quarter to repurchase 336,000 shares. Now switching to guidance. There is no change to our 2024 total product revenue guidance range of $10.55 billion to $10.75 billion, representing revenue growth of 8% at the midpoint at

current exchange rates. We have high visibility into this revenue outlook.

We expect continued growth in CF as we continue to reach more patients, including younger ones in core markets and select other countries as well as contribution in the second half of the year from the commercial launch of CASGEVY in approved indications and geographies.

For total Vertex operating expenses, we continue to project $4.3 billion to $4.4 billion in full year 2024 combined non-GAAP SG&A, R&D and acquired IPR&D. This operating expense range continues to include approximately $125 million in currently anticipated IPR&D charges. Upon the close of the Alpine acquisition, we expect Alpine's projected non-GAAP operating expenses for the remainder of 2024 to be absorbed within this guidance range, but note the potential impacts of transaction accounting, including any potential acquired IPR&D charges, will be determined at the time of closing. There's also no change to our full year 2024 non-GAAP effective tax rate guidance range of 20% to 21%. In closing, Vertex posted excellent results yet again to start off the year as we delivered strong revenue growth, regulatory approvals and commercial launches.

We also strengthened our capabilities in preparation for additional near-term launches, progressed our mid- and earlier-stage pipeline and entered the clinic in our 10th disease area of ADPKD. Importantly, we also announced the anticipated acquisition of Alpine Immune Sciences, a compelling fit with Vertex' strategy. Post close, we aim to leverage Vertex' clinical, regulatory and commercial capabilities to accelerate development and commercialization of pove. We are targeting approval in IgAN in 2027 and contribution to Vertex' revenue growth and diversification beginning in 2028, leveraging a specialty market approach with attractive margins. As we move through 2024, we anticipate further important milestones as detailed on Slide 18 to mark our continued progress in multiple disease areas.

Please note that this pipeline slide will not reflect programs from Alpine Immune Sciences until post transaction close. We look forward to updating you on our progress on future calls, and I'll now 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.

Geoffrey Meacham Analyst

I had a few on the filings. So the first question is for vanza. Do you think you guys will get a claim for the sweat chloride benefit? It seems like, obviously, you'll have the Phase III data on the label. I'm just curious what you can do from a regulatory perspective to kind of elevate the sweat chloride benefit.

So that's the first question. The second one, kind of the same question for 548 in acute pain. Do you think that -- are you guys going to push to make a claim for -- as an option to opioids or to Lyrica? I wondered if the regulatory climate can drive that.

Reshma Kewalramani Executive

Yes. Geoff, this is Reshma. Let me take those questions. On the vanzacaftor triple, if you go

back and look at all of the CFTR modulated labels, you'll see that we always have sweat chloride in the labels, and they are reflected because it is indeed a pharmacodynamic or PD marker. So I fully expect that the sweat chloride data from the vanza triple studies will be reflected in the label.

Obviously, we are just at the point of having submitted the filing, so we're not at the point of label negotiations yet. But if history serves as a guide, I expect the sweat chloride will absolutely be in the label. On VX-548, Geoff, I think your question was about the DPN, diabetic peripheral neuropathy, study, but let me broaden the question about 548 and acute pain because that's the filing that we have already initiated the rolling submission. We've already submitted a few of the modules, and we expect, as I said in my prepared remarks, to complete the filing this quarter. We are submitting all of the data that we generated in acute pain, and the same will be true when it comes to the diabetic peripheral neuropathy data.

And insofar as the acute pain Phase III results are versus placebo as the primary end point but there are data that have the opioid arm in there, I expect that it will be a discussion with the regulators about how exactly they want to display it. We are not at the point for the acute pain studies to have label negotiations and quite a bit far away from it for the DPN studies, which are just starting Phase III. But I will say that the reason we have a pregabalin arm in the Phase III DPN study is exactly for that reason, for us to be able to share the data with prescribers.

Geoffrey Meacham Analyst

Reshma, just a quick follow-up to that. Just on the alternative to opioids. I mean, obviously, you don't know yet when it comes to the label, but do you think you'll need that to help with Medicare kind of reimbursement?

Reshma Kewalramani Executive

Yes. So on the acute pain side, Geoff, I think that the most important data are going to be the primary endpoint data, and I'll ask Stuart to comment on that in a minute. And with regard to securing reimbursement and ensuring that there are no barriers to prescribing a non-opioid, we see that as a very important place for policy. Stuart?

Stuart Arbuckle Executive

Yes. Thanks, Reshma. So first thing I would say, Geoff, is remember, we are seeking a broad moderate to severe acute pain label so that the product could be used, if the physician decides and the patient wants to, for any type of acute pain, and so we're not really looking for a label that's looking to niches or pre-position us relative to other agents that are out there. We want physicians to have the broadest possible ability to use the product in the patients they see fit. As Reshma said, the primary endpoint, which talks to the really strong efficacy we see in moderate-to-severe acute pain, is clearly very important as is all the additional safety and tolerability data that we have to support VX-548 in combination with the fact that given its mechanism, it doesn't have addictive potential.

So we're really looking at the full range of efficacy and safety, which I think is going to be the most important thing that's going to allow physicians to decide who they want to prescribe

the product for.

Operator Operator

Your next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

I'm curious. For your various NaV1.8 and 1.7 programs, would you consider advancing maybe another molecule for musculoskeletal pain, perhaps engaging a commercial partner to the extent it's not a Vertexian sales detail? Just curious if you kind of have any thoughts about that, so as to like not leave potential value on the table.

Reshma Kewalramani Executive

Yes. Thanks for that question, Jess. So just to set the stage, we see 3 distinct areas in pain: acute pain, neuropathic pain and then everything else. And in everything else, I would add, musculoskeletal pain. It's the kind of osteoarthritis kind of pain.

We fully intend to serve all patients, and I fully do expect that our NaV1.8, and when the time is right, the NaV1.7 or the NaV1.7, 1.8 combinations, our pain assets, will serve patients with musculoskeletal pain. And I say that because, as you know, the predecessor molecule to VX-548, VX-150, already demonstrated that potential. But we want to go one step at a time here. So first, we're going to do acute and neuropathic pain, and we see the research development and commercialization is completely Vertexian. And then for the musculoskeletal pain, whether that's with VX-548, the next-in-class medicine, VX-993, or the ones that come after that, again, either NaV1.8 or NaV1.7 alone or in combination, any of those for musculoskeletal pain.

We will get them to patients, but we will not be commercializing that ourselves because it is a primary care sell. But we do absolutely see value there, and we see a need to help those patients. But one step at a time. First, neuropathic and acute pain, and that, we will do ourselves.

Operator Operator

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

Salveen Richter Analyst

Two part here on the acute pain program. With regard to engaging with key decision makers, can you help us to understand the importance of the hospital administrators who are taking into account the legislative tailwinds versus the physician treaters here in the specific verticals that you cited and how they might make -- or work together here to make a decision? And my second question is what hospitals really need to make an argument for using it in lieu of opioids, and whether outcomes data is required, be it reduction in recovery room time or lower usage of opioids or rates of addictions being reported?

Reshma Kewalramani Executive

Sure, Salveen. Let me ask Stuart to comment.

Stuart Arbuckle Executive

Yes. So Salveen, all of the stakeholders that you described are going to be important in making decisions on the use of a new medicine in the institutional setting. So administrators are certainly going to be important, but as are our physician advocates who are going to advocate based on the efficacy and safety of the medicine. And the process is a relatively standardized process. It's not going to be created newly for suzetrigine.

This is a standard process that hospitals go through to decide whether they're going to put it on their formulary, and typically go through some sort of P&T committee process where all of the various stakeholders, be it physicians, be it the pharmacy team, be it the administrators, are all going to be making that decision collectively. They're particularly interested in the use, obviously, within the institutional setting. Use in the discharge setting is typically something which is a little bit more straightforward, and that's why I suggested in my prepared remarks that we see that as the likely setting where there is going to be the earliest uptake of a medicine like suzetrigine. In terms of some of the outcomes data that you were referring to, I think the clearest way of describing is every patient that is treated with suzetrigine when the other choice would have been an opioid is essentially providing opioid-sparing for that patient. So that data, in many ways, is kind of already sort of readily available just from the data that we've already shared, and I think that data in addition to all the other efficacy and safety data we've got is going to be pretty impactful and compelling to the various stakeholders we've described.

Operator Operator

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

Evan Seigerman Analyst

Love to know if you to provide any additional color on how many patients in the United States have gotten their cells collected, and maybe how we should think about the growth of cell collections in the U.S. going forward. I'm just trying to understand what the trajectory of this could be like this year and next year.

Reshma Kewalramani Executive

Yes. Evan, just to set expectations, we're not going to comment very specifically on patients and exactly where they are in the cell collection process in each region, but I will ask Stuart to give you a little bit of color commentary on what we're seeing. And if I was stealing Stuart's thunder, if you really think about when CASGEVY was approved, which is December and January, I am so very pleased that the number of ATCs that are activated around the globe and the number of patients who have already started cell collection. Stuart, is there anything you want to add?

Stuart Arbuckle Executive

Only that we are expecting the momentum to build based on all of the feedback that we've got and the trends that we're seeing in activations and cell collections, as Reshma said. We're delighted to have had 5 cell collections already. As she also mentioned, that represents

patients in every region in which we are operating, including obviously, the United States, and we expect those trends to continue to ramp up during the course of 2024, which we've always said was going to be a foundational year for CASGEVY.

Operator Operator

The next question will come from Colin Bristow with UBS.

Colin Bristow Analyst

Maybe first on the pain pipeline. I see you're advancing 993 to Phase 2. Could you just give us any sort of color or detail on how you expect this to be differentiated? And does this advancement mean you won't be taking 973 forward, which I think also recently completed Phase I? And then if I may, a quick housekeeping one.

Any inventory moves in the quarter that we should be aware of?

Reshma Kewalramani Executive

Colin, let me break that up into 2 questions. One on inventory, which I will ask Charlie to comment on first, and then I'll come back on 993 and 973.

Charles Wagner Executive

Colin, in my prepared remarks, I mentioned that we saw some benefit in the first quarter from phasing of international channel inventory, so I assume that's what you're talking about. That benefit was on the order of $75 million to $100 million in the quarter, and I expect that to begin to reverse in the second quarter.

Reshma Kewalramani Executive

On 993, 973, Colin, this is all part of serial innovation. 993 is a little bit further ahead than 973 in terms of the preclinical package, the manufacturing and all of the things we need to do to get our medicines ready to go into Phase II. That's why that one is ready to go. 973 is just a little bit further behind. What are we looking for in terms of differentiation?

There's really 2 major elements other than our overarching serial innovation strategy. But very specifically, one, we are looking for molecules that can be both oral and IV, VX-548 is oral only, because our goal here is to own the waterfront on pain management, including for those patients who may be just coming out of surgery or for other reasons, not able to take by mouth. The second big goal here is to ensure that we have medicines with the right drug-like properties that can be therefore combined with the NaV1.7, which is also making good progress in preclinical development. So that's what we're really looking for. And why 993 next?

It's because it's a little bit further ahead. And 973, we're going to be working on just as soon as all of the data already there.

Operator Operator

Your next question will come from Terence Flynn with Morgan Stanley.

Terence Flynn Analyst

Great. Maybe a two-part for me as well. I was just wondering if you can give us any insight on a potential presentation venue for the 548 Phase III data. And then the second question relates to CASGEVY. I was just wondering, any directional insight on pricing and reimbursement in the Middle East?

Reshma Kewalramani Executive

Yes, on VX-548, fall meetings, shall we say. You should expect more data on 548 with those Phase III results. certainly not only in Congress form but in publications. So I'd say fall meetings. And let me ask Stuart to comment on CASGEVY in the Middle East.

It is a really exciting opportunity for us.

Stuart Arbuckle Executive

Yes, super exciting opportunity for us, Terence, which is why we provide a little bit more color on it. Specifically to answer your question, we don't provide pricing data at an individual country level, but suffice to say, the price we are receiving in the existing reimbursement agreements that we've signed there reflect the transformative value of the product and the lifetime benefits that patients can accrue from it. And that's going to be the same kind of philosophy we're going to have everywhere around the world where we're commercializing CASGEVY.

Operator Operator

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

Philip Nadeau Analyst

Two from us. So first on the suzetrigine formulary and access discussions. Stuart, I think you made an interesting comment that you thought enabling reimbursement ahead of opioids in the acute pain setting will be something that government programs could help incentivize it or something to that effect. Could you speak a bit more about that? And in particular, are your formulary and access discussions suggesting that in the absence of legislative initiatives, it's likely that 548 will be reimbursed after opioids in the acute pain setting?

And then second, small commercial question. Can you give us some sense of how big Brazil could be for the CF franchise?

Reshma Kewalramani Executive

Yes. Phil, I will ask Stuart to comment on both CF in Brazil. You know that we have regulatory approval and reimbursement there as well as formulary discussions on suzetrigine. But just to make sure we are on the same page, the formulary discussions are separate from our discussions with policymakers. The common theme is that both of those stakeholders, and frankly, all of the stakeholders are very aware of the opioid crisis.

They have high awareness of suzetrigine, and there is enthusiasm to using non-opioids. But those discussions are separate. Over to you, Stuart.

Stuart Arbuckle Executive

Yes. So just to add to that, Reshma, what I would say, Phil, is that the policy initiatives that we've seen so far are really looking at trying to reduce financial disincentives for patients and indeed for institutions to selecting a branded non-opioid in a market which is obviously currently dominated by generic opioids. And so that's why things like NOPAIN, which is providing an additional payment above the DRG in the outpatient and ambulatory surgical center setting, is important there. And then on the patient side, the Alternatives to PAIN Act is looking at in Medicare Part D, ensuring that there are no co-pay disadvantages to a patient for using a branded non-opioid in a market where there are already generic opioids. So I'd say that's the kind of the policy landscape.

Those are kind of slightly different discussions that we're having with the institutions and the stakeholders there, which were much more clinically based on whether this is the right medicine to be using in the patients who are being prescribed and dispensed medicines in the institutional setting. So that's how I would describe the difference between the conversations. They're obviously linked in some ways, but they are -- they have a different focus from the policy side to the institutional side.

Philip Nadeau Analyst

Maybe just a follow-up. The basis for our question is we recently did a survey, and 75% of physicians thought that patients would have to step through a generic opioid. Is that Vertex' expectation as well?

Stuart Arbuckle Executive

I can't really speculate on exactly what's going to happen with, for instance, 2,000 institutions. But my hope would be that, that's not what's happening. I don't think it's very reasonable to expect a patient to have to step through a therapy which has significant side effect liability, including addictive potential, when there is a product available, which has very good efficacy from a pain control perspective and has an excellent safety and tolerability profile, including lack of addictive potential. So I don't think that would be something that we would -- certainly wouldn't be advocating and I don't think would be particularly medically reasonable. I didn't answer the second part of your question, which was around Brazil.

We estimate there's around 1,500 patients who are eligible for TRIKAFTA. That's 6 and over in Brazil. As I mentioned in my prepared remarks, a number of those patients did already have access to TRIKAFTA through named patient sales, but we now have a reimbursement agreement with the national government there, which is going to allow us to launch the medicine and make it available for all of those patients now.

Operator Operator

The next question will come from Olivia Brayer with Cantor Fitzgerald.

Olivia Brayer Analyst

What's your level of confidence that you'll get priority review in acute pain? And Stuart, I know you've talked about the commercial build-out, but what's your base case for when you'll start

to actually see revenue recognition from that program? And just a quick clarification on CASGEVY. Just wanted to clarify that I heard 5 patients have already finished collection versus just having initiated the cell collection process.

Reshma Kewalramani Executive

Olivia, this is Reshma. Let me take 1 and 3, and then I'll ask Stuart to take the question on where are we exactly with paying commercialization. On number 3, again, just to set expectations on CASGEVY. We're thrilled with the number of ATCs, 25 since approval, which has been in just the last few months, and we commented on the cell collection, but we're not going to comment any further on exactly where each one patient is in their journey. On VX-548 and acute pain, 3 things to say.

Maybe the most important thing is we'll know whether or not we've received priority review in about -- after we complete the submission, and then it takes some 60 days or so for the FDA to tell us what the final review time lines will be. However, the leading indicators of whether or not we will get priority review are all quite favorable. We have Fast Track status, we have Breakthrough Designation and our conversations with the FDA have shown me that they have high enthusiasm for a medicine that has high efficacy and does not have addictive potential. I'll turn it over to Stuart for the question about where are we with the acute pain launch, and when we're going to be out there.

Stuart Arbuckle Executive

Yes. So the recruitment of our teams is going very well. Obviously, we are in the middle of our rolling submission here. Obviously, once we've completed that, we'll get an indication from the regulators on when we could expect our PDUFA date to be, and we are going to be launch ready. In terms of the question around revenue recognition, this is unlike CASGEVY, I would say, which has an extended treatment process where revenue recognition is at infusion.

This is a small molecule, and therefore, we're going to be kind of selling and distributing it in the normal way. And so there really isn't going to be that kind of lag, I would suggest, around revenue recognition that people are aware of with CASGEVY.

Operator Operator

Next question will come from Debjit Chattopadhyay with Guggenheim Securities.

Debjit Chattopadhyay Analyst

I got a couple. First on IgAN, when Vertex is ready to launch in IgAN, it's likely Otsuka will have GFR data. How are you thinking about navigating this commercially? And then on DM1, with the IND cleared and the Phase I/II underway, do you think myotonia is an approvable endpoint? Or is the agency going to ask for [splicing] correction with strength or force measurements?

Reshma Kewalramani Executive

Debjit, let me take both of those. On DM1 or myotonic dystrophy type 1, we actually haven't had a chance to talk about it extensively. But this is a program that is in Phase I/II in patients.

So we are going to have the opportunity in this study to not only assess safety, but to assess efficacy as well. With regard to what the agency might want to see for the endpoint for approval, the real answer is I don't know yet because we haven't gotten to that phase in the clinical trial.

But your point around, is myotonia possible? Insofar as this is a disease that is a rare disease, a serious disease and one that doesn't have any therapies that target the underlying cause of the disease or very specifically works on the genetic defect, I think that opportunity is there. And I've seen -- and we've seen a lot of openness for accelerated end points in these kinds of rare serious diseases. On IgA nephropathy, so the most important thing to know about IgA nephropathy is that it's a serious chronic disease, and this is a disease that over time leads to decline in GFR and end-stage renal disease, death or transplantation. The most important thing that I would be looking at as a nephrologist is efficacy.

Because proteinuria is known to translate to GFR and therefore, the decline in renal function, so if we have a medicine that has high reductions in proteinuria, and as I said in my prepared remarks, everything that we've seen from pove, preclinically and clinically through Phase II, is best-in-class across many dimensions, but certainly including efficacy. I think that's the drug that physicians will choose.

Susie Lisa Executive

One last quick question, please, Chuck.

Operator Operator

That will come from Ms. Liisa Bayko with Evercore ISI.

Liisa Bayko Analyst

So just 2 from me. Just a follow-up on IgA nephropathy. Have you thought any more about how you might highlight having [BAFF]? Because in addition to APRIL, I think that's one kind of key differentiator of this program. And just wondering how you're thinking about how you could differentiate on that point.

I don't know if there's biopsies or some kind of different points that you could really highlight the potential benefits of BAFF. And then just for the -- for CF and TRIKAFTA for the quarter, I noticed you had your price increase yet sales looked slightly down quarter-over-quarter. Can you kind of just describe in the U.S. what's going on? Was there some higher gross to net inventory changes, whatnot?

Maybe -- great for some color there.

Reshma Kewalramani Executive

Let me take the IgAN question first, and then I'll ask Charlie to comment on CF. On IgAN, you are correct in pointing out that it's a dual inhibitor. It's an inhibitor of BAFF as well as APRIL. And this is one of the most attractive features of povetacicept is this dual inhibition. Yes, preclinically, we can certainly share when we have information, and you'll certainly see all of this with the fullness of time, the inhibition of BAFF and the measurement of that, and how we

can show that preclinically.

We can also do that with APRIL. However, I think the data that's more interesting is the clinical data which is already available, and that is with this dual APRIL, BAFF inhibitor on proteinuria, but I'd encourage you to look at the poster from the WCN meeting that Alpine showed. It has proteinuria results, it has hematuria results, it has GFR results, and it has a composite of remission. And I find those data very, very interesting, particularly the hematuria results clinically, because as you know, hematuria is a hallmark of this disease along with proteinuria. Let me turn it over to Charlie on the question about CF and U.S.

Charles Wagner Executive

Yes, Liisa. On the quarter, I wouldn't read too much into sequential quarter fluctuations. We saw strong volume growth in the U.S. year-over-year. As we normally do, we see some seasonal gross to net in the first quarter, and the benefit of the price increase really isn't fully reflected in the quarter that comes throughout the balance of the year.

So all of those factors affect the comparison. But overall, very, very strong year-over-year growth in the U.S. and outside the U.S.

Susie Lisa Executive

Thanks. Chuck?

Operator Operator

This concludes our question-and-answer session as well as our conference call for today. Thank you for attending today's 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 10186968. Thank you for your time today. You may now disconnect.