Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q1 2025 Earnings Call

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Event Participants

Executives 5

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Analysts 10

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Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals First Quarter 2025 Earnings Call. [Operator Instructions]. Please note this event is being recorded.

I would now like to turn the conference over to Ms. Susie Lisa. Please go ahead, ma'am.

Susie Lisa Executive

Good evening, all. My name is Susie Lisa, and as the Senior Vice President of Investor Relations, it is my pleasure to welcome you to our first quarter 2025 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; Charlie Wagner, Chief Financial Officer; and Duncan McKechnie, SVP North America Commercial Operations and from July 1, Chief Commercial Officer. We recommend that you access the webcast slides as you listen to this call.

The call is being recorded, and a replay will be available on our website. We will make forward-looking statements on this call that are subject to the risks and uncertainties discussed in detail in today's press release and in our filings with the Securities and Exchange Commission. These statements, including, without limitation, those regarding Vertex's marketed medicines for cystic fibrosis, sickle cell disease, beta-thalassemia and moderate to severe acute pain, our pipeline 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 select financial results and guidance that we will review on the call this evening are presented on a non-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. Continuing the momentum from 2024, we've kicked off 25 with another quarter of strong performance across the board. Growing and diversifying revenue as we execute on multiple launches, accelerating programs in pivotal development and advancing the R&D pipeline. We continue to reach more patients with more products and delivered $2.77 billion in revenue in the first quarter, representing 3% growth versus Q1 2024.

This year, we are keenly focused on commercialization, and we are pleased with the early launch dynamics and physician and patient feedback on ALYFTREK, our fifth CF medicine, and JOURNAVX, the first oral non-opioid for moderate to severe acute pain in more than 2 decades, both of which were approved in the U.S. in just the last few months. With these approvals and the continued global launch of CASGEVY, our gene-edited therapy for sickle cell disease in beta thalassemia, we are significantly expanding the number of patients we serve.

We are also sharply focused on advancing the 4 programs currently in pivotal development. Suzetrigine in diabetic peripheral neuropathy, Zimislecel in type 1 diabetes, Inaxaplin in APOL-1 mediated kidney disease and Pove in IgA nephropathy. Importantly, three of these Phase III programs are on track to complete enrollment of the interim analysis cohort or the full study this year, setting up a series of potential filings in 2026. And as we approach the 1-year anniversary of the acquisition of Alpine Immune Sciences, I wanted to highlight 2 big recent Povetacicept related milestones. First, we completed enrollment in the interim analysis cohort in the Phase III RAINIER IgAN trial.

And second, we reached agreement with the FDA to advance Pove to pivotal development in a second indication, primary membranous nephropathy. This is a notable milestone as Pove continues to deliver on its promise as a pipeline in a product with best-in-class potential. The start of the Pove membranous study will also mark our fifth program in pivotal development. Tonight, I'll limit my R&D comments on the pipeline programs with the most significant new information to share, specifically CF, pain, type 1 diabetes and the kidney programs. Starting with CF.

Following our December U.S. approval of ALYFTREK, we have gained MHRA approval in the U.K. and a positive CHMP opinion in the EU -- as a result, we expect potential approval from the European Commission for ALYFTREK in the second half of this year, along with potential approvals in Canada, Australia and Switzerland. These approvals are in addition to the European Commission's early April approval of KAFTRIO for rare mutations, which followed similar approvals for TRIKAFTA rare mutations in the U.S. and Canada late last year.

Adding hundreds of additional eligible patients in North America and thousands in Europe. These approvals are a direct result of the team's decades-long painstaking work to establish and verify the hypothesis that the 3 unique binding sites of our CFTR modulators results in overall protein stabilization and have the potential to transform the lives of nearly 95% of patients with CF. Stuart will share more on the U.S. ALYFTREK launch shortly. Next on the

horizon for our CF small molecule program is the Next-Gen or NG 3.0 CFTR regimen.

With this program, we seek to reach our long-standing goal of bringing most, if not all, patients with CF to normal levels of CFTR function. The backbone of this NG 3.0 combination is VX-828, the most efficacious CFTR corrector that we have ever studied in vitro. It is completing Phase I development, and we remain on track to initiate a study with VX-828 in patients with CF before the end of this year. For the ongoing Phase I/II study of VX-522 for the approximately 5,000 or so patients who cannot benefit from our CFTR modulators, we have recently implemented a temporary pause to the study as we assess the tolerability issue, given that this remains an active clinical trial, we won't be providing any additional details at this time so as to maintain study integrity. We will update you when we know more.

Moving next to the pain programs. First, the Phase III study of Suzetrigine in diabetic peripheral neuropathy, a chronic peripheral neuropathic pain condition that affects over 2 million Americans annually, is well underway with ongoing enrollment and dosing. As a reminder, Suzetrigine has fast track designation for peripheral neuropathic pain and breakthrough designation for diabetic peripheral neuropathy. Next, I'm very pleased to share that the study of oral VX-993, another NaV1.8 inhibitor in acute pain post bunionectomy is on track to complete this quarter, and we expect to report results from this trial in the second half of this year. VX-993 has Fast Track designation for acute pain in both the oral and IV formulations.

Lastly, we continue to make solid progress with additional NaV1.8 inhibitors beyond VX-993 as well as in our NAV1.7 pain signal inhibitor program that may be used alone or in combination with NaV1.8 inhibitors. Transitioning now to type 1 diabetes. Zimislecel remains on track to complete enrollment and dosing of its pivotal study this quarter, positioning us for global regulatory submissions in 2026 if the data are supportive. Recall, we expect about 60,000 severe type 1 diabetics who may potentially benefit from this first Zimislecel submission. Based on the high unmet need in T1D and the transformative nature of this therapy Zimislecel has multiple global regulatory designations, including RMAT and Fast Track in the U.S., Prime in the EU and the Innovation Passport in the U.K.

In our other T1D work, following the recent data from VX-264 or the cells + device program, we have returned this approach to the research stage. We continue to make preclinical progress on our other approaches to clock the VX-880 cells from the immune system. These cells have already demonstrated transformative efficacy. These approaches include alternative immunosuppressive regimens and gene editing to make hypoimmune islet cells, and we look forward to updating you as these programs advance.

Finally, a few updates on our kidney portfolio, which now has clinical stage programs in 4 renal diseases, IgA nephropathy, AMKD, membranous nephropathy and ADPKD, or autosomal dominant polycystic kidney disease, starting with Povetacicept, a potential best-in-class dual antagonist of the BAFF and APRIL cytokines which play a key role in the pathogenesis of B cell-mediated autoimmune diseases. First, in IgAN, as mentioned earlier, I am very pleased to share that we have completed enrollment in the interim analysis cohort of the Rainier Phase III trial. Once this cohort completes 36 weeks of treatment, we will conduct the interim analysis and if positive, it will support filing in the first half of 2026 for potential accelerated

approval in the U.S.

In addition, our program to support the launch of Pove with the subcutaneous auto injector for monthly at-home administration is well underway. And for full approval, we are making strong progress towards our goal of enrolling the complete cohort of 480 patients in whom we will assess eGFR through week 104. Second, based on the positive results from the RUBY-3 basket study, we have reached agreement with the FDA to advance Pove to pivotal development in membranous nephropathy. Beginning in the second half of this year, we are planning to initiate a single Phase II/III adaptive study of Pove versus standard of care with the primary endpoint of complete remission at week 72. Next, 2 highlights on Inaxaplin for APOL-1 mediated kidney disease or AMKD.

First, we remain on track to complete enrollment in the interim analysis cohort of the amplitude pivotal trial this year. Amplitude is a study of primary AMKD. That is to say, patients with 2 APOL-1 variants and no additional renal-related comorbidities. After completing enrollment, when this cohort reaches 48 weeks of treatment, we will conduct an interim analysis. If positive, we will be poised to file for potential accelerated approval in the U.S.

Second, based on the positive proof-of-concept results of Inaxaplin in primary AMKD, the momentum in the Phase III study and interest from the community, we recently initiated the amplified study. Amplified is a Phase II proof-of-concept study of Inaxaplin in patients with AMKD and other comorbidities, including type 2 diabetes. This study is enrolling in dosing patients.

To close on our kidney pipeline, a few comments on VX-407 in autosomal dominant polycystic kidney disease or ADPKD. VX-407 is a first-in-class small molecule protein folding corrector that is designed to target the underlying cause of ADPKD by restoring PC1 protein function, thereby reducing total kidney volume and preventing progression to kidney failure. As a reminder, by way of its mechanism of action, VX-407 addresses up to 10% of ADPKD patients and as in CF, we will seek to expand the eligible patient population with serial innovation over time.

We have completed the Phase I trial of VX-407 and the PK and safety are supportive of advancement. The Phase II proof-of-concept study is designed as a 52-week single-arm study of 24 patients that will evaluate the efficacy of VX-407 as measured by the height adjusted total kidney volume and we are on track to initiate this study in the second half of this year. For 5 years now, at the end of my remarks, I've turned the call over to Stuart. I'll do so for the final time tonight. Let me acknowledge and thank Stuart once again for the incredible run at Vertex and wish him the very best in retirement.

With that, I'll now turn the call over to Stuart, And Duncan for a commercial update.

Stuart Arbuckle Executive

Thanks very much, Reshma. I'll focus my comments tonight on the CF franchise, including the launch of ALYFTREK and the continuing global launch of CASGEVY, building on the foundation we established in 2024. I'll then turn it over to Duncan to provide an update on the U.S. launch of JOURNAVX in acute pain.

Starting with CF with our existing portfolio of CF medicines, KALYDECO, ORKAMBI, SYMDEKO and TRIKAFTA we have continued to grow the number of eligible patients taking our CFTR modulators. As expected, we also continue to make regulatory and reimbursement progress that enables us to expand to younger patients. KALYDECO is now approved down to 1 month old. Patients with rare mutations, TRIKAFTA recently secured U.S. and EMA approvals to expand the label for additional mutations which means that the triple combination is now approved for mutations present in nearly 95% of all CF patients in our core markets and patients in new geographies such as Brazil.

in addition, as a result of better patient care, including the availability of our CFTR modulators, people with CF are now living longer than ever before.

Now turning to the ALYFTREK launch. our fifth CFTR modulator approved to treat the underlying cause of CF. In Phase III studies, when compared head-to-head with TRIKAFTA, ALYFTREK demonstrated noninferiority on lung function and further improvements in CFTR function as measured by sweat chloride. ALYFTREK was also approved by the FDA for an additional 31 mutations, not covered by the TRIKAFTA label and offers the convenience of once-daily dosing. Recall too, that ALYFTREK carries a meaningfully lower royalty burden for Vertex and extends our composition of matter patent protection from 2037 for TRIKAFTA into 2039 for ALYFTREK.

We're pleased with the early U.S. launch progress, and we're seeing uptake in all of the patient groups eligible for ALYFTREK. Those naive to CFTR modulators or with newly approved rare mutations where we have seen the fastest initial uptake. Patients who've discontinued one of our other CFTR modulators and patients switching from TRIKAFTA who seek greater improvement in CFTR function and/or the convenience of once-daily dosing. ALYFTREK prescriptions are off to a strong start as patients and physicians familiarize themselves with the ALYFTREK clinical data, including statistically significant lower sweat chloride than TRIKAFTA, the liver monitoring requirements when initiating therapy and the convenience of once-daily dosing.

We continue to expect the majority of patients in the U.S. who are currently on CFTR modulator therapy, will switch to ALYFTREK over time. We also look forward to launching ALYFTREK later this year in the U.K. and other countries pending ongoing regulatory approvals.

Transitioning now to CASGEVY, our transformative onetime treatment for patients with sickle cell disease and beta thalassemia -- since regulatory approvals in late 2023 and early 2024, the rollout of CASGEVY is progressing as we expected and gathering momentum across all regions. ATC activations and patient initiations continue to increase. As we now have more than 65 authorized treatment centers, nearing our goal to activate approximately 75 total ATCs globally. We're also encouraged to see many ATCs have now collected cells from multiple patients. As to specifics on the other important marker of our progress since launch, approximately 90 patients have now had their first cell collections, meaning they have begun the patient treatment journey.

Encouragingly, more than twice that number of patients has been referred by their physicians to ATCs to initiate the treatment process. And in Q1, 8 patients completed their treatment

journey and received their infusions of CASGEVY edited cells.

With regard to access and reimbursement, we continue to make progress on the CASGEVY payer front. In the U.S., formal commercial coverage is either in place or provided through single case agreements. For Medicaid patients who represent about 45% of total patients, the majority of states have joined the CMMI demonstration project for cell and gene therapy access model, enabling fertility coverage for these patients and providing an alternative seamless approach for ATCs and states to the existing case-by-case coverage and state agreements.

In Europe, we have now secured reimbursed access for both sickle cell disease and beta-thalassemia patients in England, Wales, Denmark, Austria and Luxembourg. And in the Middle East, we have reimbursement in Bahrain, Saudi Arabia and recently added coverage in the majority of Emirates in the UAE. The interest in CASGEVY continues to be incredibly high in the sickle cell disease and beta-thalassemia patient and physician communities globally, and uptake is accelerating as access and reimbursement is secured and familiarity with the process for collecting cells and infusing this truly transformative treatment growth. The impact of CASGEVY is best captured by the real-world feedback from patients, caregivers and physicians. It's been inspiring to hear that CASGEVY patients now feel able to live their lives in ways they never have before.

Whether that means having the energy to play with their kids, taking up snowboarding without fear that the cold might bring on a pain crisis or investing in their education and careers given expectations now for a longer and healthier life. It is a privilege to be part of their journey.

I'll close my comments today by saying what a true honor it has been to serve patients, employees and shareholders as the Chief Commercial Officer and Chief Operating Officer at Vertex. The company has never been better positioned from a scientific commercial, financial or people perspective, and I look forward to following its continued success, including with Duncan as the new Chief Commercial Officer. I'll now hand over to Duncan to provide an update on the latest chapter in our commercial diversification with the exciting launch of JOURNAVX in moderate to severe acute pain.

Duncan McKechnie Executive

Thank you, Stuart. It has been a privilege to know you for over 35 years and work with you at Vertex for the last 12. I wish you every happiness in your retirement. JOURNAVX received FDA approval on January 30 and has been available at retailers since mid-March. Although it's early days, we are seeing a strong reception for a novel non-opioid option for the treatment of moderate to severe acute pain.

We are pleased with the early launch, including broad retail pharmacy stocking, progress of reimbursement discussions and payer coverage, P&T committee reviews, the breadth of usage to date and media coverage. To give you a sense of JOURNAVX'S progress thus far, I'll detail several key elements of our launch plan. One, let me start with retail pharmacy stocking, which is crucial given the acute nature of pain. By mid-March, JOURNAVX was available at approximately 33,000 pharmacy locations including nearly every location for the

3 largest pharmacy chains in the country as well as over a dozen regional chains nationwide; two, I'm also happy to report that we've made rapid progress with payers, which is a testament to their appreciation for the JOURNAVX'S clinical profile and the importance of a novel non-opioid option in the treatment of acute pain. As of May 1, across commercial and government payers, 94 million lives already have covered access to JOURNAVX and 42 million have unrestricted access without the need to complete prior authorizations or step edits.

With commercial payers, our negotiations continue to progress favorably. We've recently reached a formal coverage agreement with 1 of the large national pharmacy benefit managers to make JOURNAVX available to their customers, collectively representing 22 million commercial lives. In Medicare, we continue to engage with Medicare plans to secure off-cycle coverage in 2025 and 2026 coverage in line with Medicare bid cycle timing. For Medicaid patients, 10 state Medicaid plans and now providing unrestricted access to JOURNAVX, meaning no prior authorization or step edit requirements and co-pays as low as $3 to $5 as is common practice for Medicaid. We expect the coverage across commercial, Medicare and Medicaid payers will expand through 2025.

Three, A key area of focus is hospital P&T committees. As a reminder, we are prioritizing approximately 2,000 hospitals, many of which will add up to 150 health care systems or integrated delivery networks. More than 1/3 of these target health care systems have already taken steps to initiate P&T reviews of JOURNAVX and some have already added it on to their formulary.

Four, turning to patients. Our patient support programs are working as designed to provide a smooth and positive patient experience so that eligible patients who are prescribed JOURNAVX for their acute pain get access to the medicine for an interim period while payer coverage decisions are made. Five, shifting to the policy landscape, we are encouraged by the continued momentum and interest by federal and state policymakers to provide equal access to non-opioids. The critical need for non-opioid options was underscored by the presentation of new research at the American Academy of Pain Medicine in April. Our health economics analysis indicates that replacing just 25% of current acute pain prescriptions for opioids with non-opioids like JOURNAVX could deliver annual cost savings of $4.5 billion to the health care system and could prevent up to 260,000 cases of opioid use disorder and approximately 9,000 overdose deaths over the next 15 years.

With respect to state legislation, to date, nearly 35 states have already either enacted or proposed legislation to support the use of nonopioids. At the federal level, I'll highlight the NOPAIN Act, which in January, began providing an add-on payment for non-opioids used in Medicare patients in the hospital outpatient or ambulatory surgery center settings. We continue to expect JOURNAVX to be added near term to the list of medicines approved for this add-on payment. Lastly, an important indicator of our launch progress and a reflection of the unmet need in moderate to severe acute pain is that more than 20,000 prescriptions were successfully filled for JOURNAVX as of April 18. While it is early days in the launch, we are very encouraged by the breadth of physician types writing prescriptions for JOURNAVX as well as the wide range of pain types being treated, which is aligned with JOURNAVX broad label.

We continue to execute on the opportunity to transform the treatment of pain while also creating another multibillion-dollar franchise for Vertex. To conclude, we are in a new era of commercial diversification at Vertex, and we look forward to bringing our transformative therapies to more and more patients and to keeping you updated on our progress.

I'll now turn the call over to Charlie to review the financials.

Charles Wagner Executive

Thanks, Duncan. Vertex's Q1 2025 results demonstrate our consistent strong performance and attractive growth profile. First quarter 2025 total revenue increased 3% year-over-year to $2.77 billion. U.S. revenue growth of 9% year-over-year was driven by ongoing patient demand, higher net realized pricing and the early launch of ALYFTREK.

As expected, ex U.S. revenue in the quarter declined and was down 5% year-on-year. Recall that outside the U.S., Q1 2024 benefited from increased channel inventory due to the majority of Russia shipments occurring early in that year. In Q1 2025, Russia revenue was negatively impacted by the availability of an illegal copy product. Excluding the impact of the revenue decline in Russia, ex U.S.

CF revenue growth would have increased in the low single digits. Included in Q1 total revenue was $14 million from CASGEVY and $10 million of collaboration revenue. First quarter 2025 combined non-GAAP R&D, Acquired IPR&D and SG&A expenses were $1.23 billion, an increase of 21% compared to $1.02 billion in the first quarter of 2024. The most significant increases in R&D and SG&A expenses versus prior year were due to rapid advancement of our broad pipeline, including clinical trials for IgAN, pain and type 1 diabetes as well as the build-out of commercial capabilities in pain. First quarter 2025 non-GAAP acquired IPR&D expenses were $20 million compared to $77 million in the first quarter of 2024.

First quarter 2025 non-GAAP operating income was $1.18 billion compared to $1.34 billion in non-GAAP operating income in the first quarter of 2024. First quarter 2025 non-GAAP effective tax rate was 18.8%. First quarter 2025 non-GAAP earnings per share were $4.06 compared to $4.76 in the first quarter of 2024 and primarily due to increased operating expenses as well as lower interest income. We ended the quarter with $11.4 billion in cash and investments after deploying approximately $425 million to repurchase more than 930,000 shares in the first quarter. Overall, our priorities for cash deployment remain unchanged.

Now switching to guidance. Given the strong start and clear line of sight to the balance of the year, we are raising the low end of our 2025 total revenue guidance from $11.75 billion to a revised range of $11.85 billion to $12 billion, representing growth of approximately 8% at the midpoint at current exchange rates. This outlook reflects our expectation for continued growth from our portfolio of CF medicines, including the ongoing launch of ALYFTREK in the U.S., followed by other regions later this year. We believe the illegal copy issue is isolated to Russia and is fully included in our outlook. Guidance also includes a continued ramp-up in CASGEVY revenue as we treat more patients in geographies where we have secured regulatory approval and reimbursement.

In addition, guidance reflects a revenue contribution from JOURNAVX primarily in the second

half of 2025. And as a reminder, we expect volumes will ramp ahead of revenue due to financial assistance programs that are designed to provide eligible patients with immediate access while we work to secure broad sustainable payer coverage. Recently announced positive coverage decisions are included in our revenue guidance. As a result of these positive trends and as implied in our guidance range, we expect growth to accelerate over the remainder of the year delivering another strong year for Vertex in 2025. For combined non-GAAP R&D, Acquired IPR&D expenses and SG&A, there is no change to our guidance range of $4.9 billion to $5 billion for the full year 2025.

Consistent with prior guidance, this includes approximately $100 million in projected IPR&D charges.

We will continue to invest the majority of our operating expenses into R&D given the momentum in our multiple mid- and late-stage clinical development programs with 4 and soon to be 5 Phase III studies ongoing and multiple Phase IIs. The planned increase in commercial costs in 2025 supports our increasingly diversified commercial portfolio, a full year of investments to support the launch of JOURNAVX and potential near-term launches.

Given our differentiated business model and focus on specialty markets, we can make these targeted investments while maintaining attractive profitability and cash flow. We expect an immaterial cost impact from tariffs based on what we know today due to our low exposure to China and a geographically diverse supply chain. Additionally, much of our intellectual property is either in the U.S. or the U.K. Of course, given the dynamic nature of the tariff situation, including the potential for sector-specific tariffs, this outlook is subject to change.

And finally, on guidance, there is no change to our expected full year 2025 non-GAAP effective tax rate in the range of 20.5% to 21.5%. In closing, Vertex yet again delivered strong results in line with our expectations in Q1 2025, growing and diversifying our revenue with the launch of 2 new products in the U.S., ALYFTREK and JOURNAVX continuing the global launch of CASGEVY and making significant pipeline progress across the portfolio. In addition, we now have 5 programs that are in Phase III or soon will be and multiple additional programs with first-in-class and/or best-in-class potential in the clinic in our early and mid-stage pipeline. 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.

Before turning the call to Susie to begin the Q&A period, let me also add my thanks and congratulations to Stuart. Stuart is a talented executive and team player who has contributed enormously to Vertex. He's also a friend. As Stuart passes the baton, we look forward to welcoming Duncan to the executive team and to future earnings calls.

I'll now ask Susie to begin the Q&A.

Susie Lisa Executive

Thanks, Charlie. Chuck, can you get us started, please?

Operator Operator

[Operator Instructions]. And the first question will come from Geoffrey Meacham with Citibank.

Geoffrey Meacham Analyst

Stuart, congrats again on the retirement, Duncan, looking forward to working together. I just had a couple of quick ones. One on ALYFTREK on the launch -- what's been the feedback on utilizing sweat chloride as a biomarker more in practice. I wasn't sure if the conversations that you guys are having with pulmonologists on switching from TRIKAFTA is more related to the dosing differential or the sweat chloride or maybe a combination? And then just on JOURNAVX, to get an update -- maybe give us a sense for how you're thinking about the chronic pain indications and the design of those studies.

I know you haven't had full FDA discussions, but as you look at the prior data maybe give us a sense for where you are with implementing maybe more novel strategies for that study.

Reshma Kewalramani Executive

Geoff, it's Reshma. Let me start with the JOURNAVX and chronic pain work, and then I'll turn it over to Stuart to talk ALYFTREK. Really no new news to report to you, Geoff. We're on track to have our end of Phase II meeting with the FDA this summer. I really like the study designs the team has come up with.

We've done a lot of work on innovating and optimizing the clinical trial designs. And I do expect that we'll have an update for you this summer. Separately, but on a related note, the DPN study, the diabetic peripheral neuropathy study with VX-548 is well underway enrollment dosing in that study is going well. Stuart, ALYFTREK?

Stuart Arbuckle Executive

Yes, Geoff, on ALYFTREK, I would say sweat chloride is not routinely used in clinical practice to assess CFTR function, although it's well understood as a measure of CFTR function, but it's not something that's being increasingly adopted in clinical practice despite the ALYFTREK data. And in terms of what do people find compelling about the ALYFTREK profile, I would say it's really the sum of the parts, Geoff. So it's firstly, the fact that it's demonstrated in large, long, robust clinical trials that it's noninferior to TRIKAFTA, which, as we all know, sets a very high bar in terms of FEV1 and then it is the improvements in CFTR function that people have the potential to access as measured by sweat chloride then reinforcing that improved potential efficacy. It's the additional 31 mutations in the ALYFTREK label that the FDA granted us versus the TRIKAFTA label. And then lastly, but still very importantly for CF patients, it's the once a day versus the twice a day for TRIKAFTA.

So I wouldn't say it's one thing more than the others. It's really that combination of benefits that I think people are finding attractive about the ALYFTREK profile.

Operator Operator

Your next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

Stuart, congrats again. First, when you -- maybe for Charlie, when you said you expect immaterial impact from tariffs, just to confirm, is that from the current tariffs? Or is that if biopharma specific tariffs are implemented? And maybe just for our comfort, can you give us a little more detail on Vertex's manufacturing footprint, particularly for a ALYFTREK, TRIKAFTA and JOURNAVX and how you think about the company's potential exposure to tariffs if they are implemented? And then just separately on the CF business, can you recap how we should think about the impact of the Russia issue and just lapping last year sales that included Russia.

Is that impact largely contained to 1Q? Or is it also impacts 2Q and subsequent quarters? Can you just quantify what that headwind is?

Charles Wagner Executive

Yes, Jess, I'm going to start with the CF impact. Listen, the year is off to a great start, and it's very much in line with our internal expectations. We commented in the fourth quarter about this isolated issue in Russia. And it's worked out exactly as we expected. The impact in the first quarter is about $100 million.

And for the full year, it's $200 million total. And so all of that is included in our current guidance, which, as you know, is 8% growth at the midpoint, which implies acceleration over the balance of the year. So we feel really good about where we're at, and we can talk more about some of the drivers. I'm going to move on to the second part of your question on tariffs. Given how dynamic the situation is, just I have to limit my comments to what we know today.

And so for tariffs that have been announced and are in effect, there is an immaterial impact to Vertex. We have, I think, a very well-balanced global supply chain. We have minimal exposure to China. The vast majority of our drug product manufacturing for CF is in the United States and most of our IP is concentrated in the U.S. and the U.K.

So for those reasons, the impact is immaterial. Again, there are all sorts of different tariff concepts that are being discussed including sector-specific tariffs until we know more about what might be implemented, I can't really size the impact for you.

Operator Operator

Next question will come from Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

Just following up on ALYFTREK. Could you just walk us through who the early adopters are, whether there's -- there seems to be a significant portion coming from a certain pool of patients. And then on JOURNAVX, with regard to the commercial payers here. Can you speak to the nuances with regard to tiered and preferred versus nonpreferred status in your overall plan for positioning.

Reshma Kewalramani Executive

Sure thing, Salveen. Let me split that question and ask Stuart to comment on ALYFTREK and

the segments we've talked about on the kinds of patients. And then I'll ask Duncan to give you a little bit more color and texture behind the JOURNAVX launch in general, including where we are with payers. Stuart?

Stuart Arbuckle Executive

Yes. So we are seeing uptake from ALYFTREK in all of the patient groups that we identified. There are those that are newly eligible for a CFTR modulator, people who are sort of truly naive have never been on one previously, which includes the rare mutations that TRIKAFTA was approved for and the additional mutations that ALYFTREK was approved for.

And perhaps not surprisingly, we're seeing the fastest uptake as a percentage of the total pool in that group. But we are also seeing patients who've discontinued coming back to a CFTR modulator, now that a new option like ALYFTREK is available. And we are also seeing transitions primarily from TRIKAFTA because that is where the lion's share of CF patients are. And on those transitions, we continue to expect the majority of patients will transition to ALYFTREK over time. So we're really seeing uptake in all 3 of those patient groups.

The fastest perhaps not surprisingly in people who've never had a treatment option to treat the underlying cause of their disease before. Duncan?

Duncan McKechnie Executive

Thank you, Stuart. So to provide you with a little bit of context to the overall launch of JOURNAVX to date, we are incredibly pleased with the early progress, although it's early days, we're seeing tremendous receptivity to a novel non-opioid option for the treatment of moderate to severe acute pain. And over the last 3 months, we've made great progress in terms of broad retail pharmacy stocking, advancing discussions with payers, initiating P&T committee reviews as well as broad usage of the product by physicians in multiple different pain settings and conditions in line with the label. To get to your question specifically with regard to tiers and preferred versus nonpreferred, I would say there's an enormous number of payers in the U.S. with an enormous number of different plan designs.

And even within the same payer different tiers can mean different things. So what I would focus on are our goals in this area, and that is to ensure that we have payer coverage in line with label, but to ensure that, that coverage has a few restrictions as possible for physician prescribing and that we ensure the product is affordable for patient -- patients and that we get to all of those outcomes whilst ensuring, of course, that we're optimizing the long-term value for Vertex. And so in terms of the progress to date, of the 3 big PBMs in the U.S. We have one of those 3 big PBMs now are covering JOURNAVX for a total of 94 million lives. And I can tell you that the progress that we're making is in line with those overall goals to minimize restrictions for physicians, maximize access for patients and optimize long-term value for Vertex.

Operator Operator

Your next question will come from Tazeen Ahmad with Bank of America.

Tazeen Ahmad Analyst

I wanted to ask one a couple actually on JOURNAVX. You talk about the momentum that you've been seeing in the early innings of uptake. I'm just curious as to what the profile of the patients are that are the earliest onboarders and where in the treatment regimen are these scripts being written?

Are they being written for patients on their way home from the hospital? Are they being written while in the hospital for use in the hospital? Or is there any other scenario that we're not thinking about -- and as you think about the second half of the year, in terms of acceleration of recorded sales, would you expect to start to see that already in 2Q? Or is most of that going to be back-end loaded towards the end of the year?

Reshma Kewalramani Executive

All right. Duncan, can I ask you a comment on settings of care types of pain on the one hand and then a comment on the volume versus revenue that we've talked about.

Duncan McKechnie Executive

Absolutely. So in terms of the settings of care that we're seeing at this point, we're seeing JOURNAVX used in surgery settings, in non-surgery settings. So for example, we're seeing it used in knee, hip, shoulder replacement, for example, all the way through to ankle sprains, fractured risks, et cetera. So we're seeing broad uptake of JOURNAVX in line with its broad indication and it's being used by a broad range of physicians, for example, orthopedic surgeons, plastics, general surgeons, anesthesiologists and of course, pain specialists and perhaps importantly, we're also seeing repeat use by physicians, and we're seeing very, very positive feedback from physicians in terms of the clinical effect of JOURNAVX to date. In terms of the recorded sales, I think we've always said that we would see volume ramp in the first half of the year and then revenue in the latter part of the year as we secure payer coverage and can thus payer back some of our patient support programs.

Operator Operator

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

Evan Seigerman Analyst

I really wanted to touch on the uptick of CASGEVY and really, what are some of the key hurdles that are accelerated -- that are kind of preventing the acceleration of the uptake? Is it fertility issues, health system trust issues, involvement intensity of the procedure. How can you really work to overcome those so we can see really this product hit its maximal potential?

Reshma Kewalramani Executive

Evan, let me ask Stuart to take that one.

Stuart Arbuckle Executive

Yes. Evan, thanks for the question. So we did see acceleration in CASGEVY in the first quarter, building on the foundation that we built in 2024. The things that I think are leading to that acceleration and that we expect to continue as we work through the balance of 2025 is firstly, establishing authorized treatment centers. Obviously, we need to have those so that patients

can get treated.

Securing access and reimbursement. We've done that in large part here in the U.S. in both commercial and government paid. And increasingly, we are securing reimbursed access for sickle cell disease and beta-thalassemia outside of the U.S., and we announced a number of those in my prepared remarks. We're also seeing centers get more familiar with the treatment process.

Clearly, this is a very innovative medicine. This is a very innovative a new treatment process for them and their patients to consider and as they get more experience with the process, then that's also encouraging them to treat more patients. And I mentioned again in my prepared remarks that we've seen a number of our authorized treatment centers that have treated multiple patients now. So I think all of those things contribute to the acceleration we saw in the first quarter, and we expect that to continue through the balance of 2025 and beyond, and it's that which gives me confidence that CASGEVY truly does have the potential to be a multibillion-dollar product for Vertex.

Operator Operator

Next question will come from Michael Yee with Jefferies.

Michael Yee Analyst

We had 2 questions on pain. I guess a lot of Wall Street is looking at third-party data, actually the script data in total tracks with what you guys are talking about, but a lot of people are seeing it sort of decelerate week over week. So maybe could you just confirm or talk to what you see week-over-week -- and are you seeing an acceleration and don't pay too much attention to the data there. And then on 993, we have historically talked about with David and Fred about how that could have significantly better exposure than Susie. So could you just tell us about the data coming up in acute pain in the second half?

And how would you compare that to the acute pain data we've already seen and figure out what to do with that?

Reshma Kewalramani Executive

Yes. Mike, it's Reshma. I'll take your second question first on VX-993 and then I'll turn it over to Duncan to tell you a little bit about JOURNAVX, the momentum, the data we see and help you sort of think through the commonly available IMS data and the data that we see, which also includes hospital. On VX-993, so the big news from my prepared remarks on this 1 is the Phase II trial in acute pain post bunionectomy is going to complete in the near term. And I do expect to be able to share results with you in the second half of this year.

What we're looking for in this program, it is a more potent molecule. It is a molecule where we can dose higher. And so we're looking forward to exploring the full dose range of 993 and what we're really looking for here is 2 things. One is to have yet another safe and efficacious NaV1.8 inhibitor, and we want that because we are looking for options and for NAV1.7, which is making its way preclinically. Certainly, our NAV1.7 inhibitor, when it makes its way into the clinic could be co-formulated with dynamics, that's one possibility and a different possibility

is that we have additional options like VX-993.

So that's one thing we're looking for. And second is, of course, if it is possible to do better than JOURNAVX on efficacy, boy, we're going to be the ones who do that, and 993 is the first option behind JOURNAVX to tell us if that's possible. Clearly, that will require cross-study comparisons and the limits that come with that. But I'm really happy to see this program move as fast as it has and to share results when available.

Duncan, can you say a few words about the momentum of the JOURNAVX scripts and the data sources.

Duncan McKechnie Executive

Yes. Thank you, Mike, for the question. So maybe just to step back briefly quickly. Our goals in 2025 are really focused on securing payer coverage for JOURNAVX as well as P&T wins whilst providing, of course, a seamless experience for patients.

And as you've seen from our prepared remarks. We're incredibly encouraged by the progress we're making with payers and in terms of P&T coverage as well. In terms of the prescription data, I would make a couple of points. Firstly, the latest total prescription data ending the week of April 25, so Friday, April 25, is 25,000 prescriptions, but I suspect that in the data you're seeing, you're seeing the IMS retail date, which does not include usage in hospitals where we are seeing, of course, uptake. So the total number we're giving you includes both the retail data as well as hospital usage.

I would say also that we are incredibly early in the launch, and it is incredibly common to see variability week by week in prescription numbers, for example, actually last week's data showed the fastest growth in retail since JOURNAVX became available. So overall, I think as the payer coverage improves and our formulary adoption increases in hospitals, and as physicians get more experience with JOURNAVX, we'll continue to see growth of the products. So overall, we're incredibly happy with the progress, happy with the 25,000 prescriptions to date and looking forward to seeing those numbers grow over time.

Operator Operator

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

Liisa Bayko Analyst

Congratulations on the quarter. I was wondering if you could just provide a little more granularity as a follow-up question to one of the earlier ones on JOURNAVX. In terms of the prescriptions, how many of those patients were kind of fully paying patients? What are gross to nets? And how do you anticipate that evolving as the year goes on?

What should be the target gross to net, say, by the end of the year?

And just then one on type 1 diabetes. If you could just give us a little bit of color on the product in Zimislecel the 60k patients, who those patients are exactly? I know there's a certain blood type within that as well.

Reshma Kewalramani Executive

Yes. Thanks so much, Lisa. Let me ask Charlie to comment on gross to net, and I'll come back and tell you a little bit about Zimislecel.

Charles Wagner Executive

Yes, Lisa. Keep in mind that we're only reporting our first quarter results here and the approval was only in the first quarter as well. So -- gross to net is impacted by our patient assistance program. That's going to have a significant impact early in the launch while we work to secure broad and sustainable access as we gain access, the patient assistance programs will fall away and gross to net will start to normalize over the balance of the year. So I'm not going to get any more specific than that.

But as we exit 2025 and into '26 we should be approaching something that's a bit more normalized.

Reshma Kewalramani Executive

And then, Lisa, on the Zimislecel program, you'll remember that this first program targets about 60,000 people in the U.S. and Canada and Europe that are the most severe of our type 1 diabetics. These are people who have very brittle diabetes high highs in terms of sugar and low lows and multiple SHEs or symptomatic hypoglycemic episodes.

So this first filing that we're looking for, the enrollment in dosing should be done in the near term. I said by the end of the quarter, we'll set us up for that filing sometime next year that is for about 60,000 patients. We're then looking to expand that not only in terms of the patient numbers that can be served, including immunosuppression, but also then moving to alternative immunosuppression and then, of course, our gene-edited programs and other programs to clock our cells so that immunosuppression is not necessary. So that's sort of the trajectory that we're looking at.

First filings, I expect we'll start next year, and that's for about 60,000 patients. Those are the most severe of T1D patients.

Operator Operator

Next question will come from Eliana Merle with UBS.

Eliana Merle Analyst

For JOURNAVX, the retail pharmacy stocking you mentioned stocking now at around 30,000 retail locations. Can you put this in the context relative to the total number of retail locations you hope to be stocked at? And then in terms of the mix of scripts being filled in the retail versus the hospital setting? How do you expect that to trend over the course of the year? And then just lastly, what's the average duration for the script that you're seeing for JOURNAVX in terms of those that are being written so far?

Reshma Kewalramani Executive

Sure thing. Duncan, all 3 of you.

Duncan McKechnie Executive

Okay. Thank you for the question, Ali. So to take them in order, in terms of retail pharmacy stocking, -- it has always been a key part of our launch plan to ensure that JOURNAVX is easily available for patients. Obviously, they are being treated for acute pain and need to be able to get the medicine rapidly. So at the point of retail stocking, we were in about 95% of retail locations across the U.S.

Obviously, that number varies day by day. Depending on when JOURNAVX has been used and prescribed and comes out of the pharmacy store. But overall, we're looking for broad coverage and thus easy access in retail for patients throughout the year. In terms of the retail and hospital setting, maybe to step back a little bit, you may remember that in the acute pain market, about 15% of patients are in the pure hospital setting, about 35% of treatment days in discharge and about 50% are in retail, and we have always communicated that we expected to see the initial prescriptions for JOURNAVX focused heavily in the discharge setting as the hospital formularies get up to speed. And that essentially is exactly what we are seeing.

That trend will, we think, persist for the rest of the year.

And in terms of the average duration of a prescription in moderate to severe acute pain, it, of course, varies by setting of care as to whether someone is inpatient or whether they are outpatient or in the retail setting and also by type of medicines, say, an opioid versus an NSAID, but the average is about 14 days. And essentially, that is what we're seeing, the prescription duration for JOURNAVX at this point.

Operator Operator

The next question will come from David Risinger with Leerink.

David Risinger Analyst

Yes. So I'm just hoping to clarify -- regarding the PBM with 22 million lives, are those within the 94 million figure or on top? And are they unrestricted or restricted lives. And then separately, just a higher-level question, please, Reshma. How is Vertex engaging with Washington leadership to educate elected leadership about the importance of both proven medical science and biotechnology innovation to the United States?

Reshma Kewalramani Executive

Yes. David, thanks for the question. Let me take the second question first, and then I'll turn it over to Duncan to tell you a little bit more about the lives covered. We are and have been engaged with D.C. as well as with state governments on all of our medicines, CF, CASGEVY, JOURNAVX as well as the pipeline.

I found those meetings to be constructive. And as far as our ability to ensure that the programs are reviewed in a timely fashion that we get feedback from regulators and that we are able to speak with those providing coverage, that has also continued. It's been business as usual and nothing out of the ordinary for us. Duncan, over to you.

Duncan McKechnie Executive

Dave, thank you for the question. So yes, the 22 million lives that you're referring to are included in the total 94 million and in general, those 22 million lives fall into our definition of unrestricted where we're looking for either no prior authorizations or no step edits.

Susie Lisa Executive

Last question, Chuck.

Operator Operator

The last question will come from Gena Wang with Barclays.

Huidong Wang Analyst

Maybe one regarding the VX-522. I know you cannot comment too much. But for the temporary pause, was that due to the -- so I don't know if you can give a little bit more color regarding what are the tolerability issue that raised and then -- yes, so that's the first question.

And then second question is regarding the ALYFTREK. If we look at the first quarter revenue and when we compare to the other CF launch in the past, how do you see this compared to the past? And do you expect the trend to pick up in the next few quarters?

Reshma Kewalramani Executive

Yes. Gena, let me take the question on 522 and then I'll ask Stuart to comment about the ALYFTREK launch. Obviously, we have the great benefit of having Stuart here, who has been involved in every single CF launch, so he'll have good line of sight on that. I don't have much more to add, Gena, because VX-522 is an active program. And because we want to maintain study integrity, I'll just leave it at the fact that the team is assessing a tolerability issue.

And once we're able to say more, we certainly will. And I'll turn it over to Stuart to tell you about ALYFTREK.

Stuart Arbuckle Executive

Yes, Gena, I think it's a little bit difficult to compare ALYFTREK to other of our CFTR modulator approvals for one main reason. If you think about ORKAMBI when it was first approved, it was approved for mutations, which accounted for approximately 50% of CF patients where previously all we had was KALYDECO, which at the time, I think, was probably around 7%-ish of genotypes for all CF patients.

And then if you think back to when TRIKAFTA came along, TRIKAFTA took us from the sort of the 50% to the -- on its first approval to almost 90%. So there was such a lot of newly eligible patients who had never had a treatment to treat the underlying cause of their disease. ALYFTREK slightly different to that, right? There are additional mutations. There are additional patients who are now eligible for a CFTR modulator with the approval of ALYFTREK.

I talked about the 31 additional mutations here in the U.S., but that's really hundreds of

patients, whereas for ORKAMBI and TRIKAFTA, we were talking about thousands, if not tens of thousands of newly eligible patients. So I think it's really difficult to compare and contrast the approvals this early on. What I can tell you is we're seeing uptake in all the groups of patients that we anticipated naive patients, those who are discontinued and those who are already on a CFTR modulator. And so we're very pleased with the launch of ALYFTREK to date, and we look forward to keeping you updated over coming quarters.

Susie Lisa Executive

That will conclude. Chuck, if you could please relay the information.

Operator Operator

Yes, ma'am. 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 here by dialing 1-877-344-7529 or 1-412-317-0088 using replay access code 101-96550. Thank you for your participation today.

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