Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q4 2024 Earnings Call

Monday, February 10, 2025 4:30 PM

Event Participants

Executives 4

Susie Lisa, Reshma Kewalramani, Stuart Arbuckle, Charles Wagner

Analysts 12

Salveen Richter, Evan Seigerman, Jessica Fye, Geoffrey Meacham, Michael Yee, William Pickering, Liisa Bayko, Philip Nadeau, Eliana Merle, Tazeen Ahmad, David Risinger, Olivia Brayer

Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals Fourth Quarter 2024 Earnings Call. [Operator Instructions] Please note, this event is being recorded. I would now like to turn the conference over to Ms. Susie Lisa. 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 fourth quarter 2024 financial results conference call. On tonight's call, making prepared remarks, we have Dr. Reshma Kewalramani, Vertex's CEO and President; Stuart Arbuckle, Chief Operating Officer; and Charlie Wagner, Chief Financial Officer. We recommend that you access the webcast slides as you listen to this call.

The call is being recorded, and a replay will be available on our website.

We will 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'll now turn the call over to Reshma.

Reshma Kewalramani Executive

Thanks, Susie. Good evening all, and thank you for joining us on the call today. Before diving into Q4 and full year earnings, I'd like to provide a quick update on some leadership changes planned for mid-2025, as noted in our press release.

Stuart Arbuckle will be retiring on July 1 of this year, after an almost 40-year career in biopharma and a stellar dozen-plus years at Vertex, first, as Chief Commercial Officer and then as COO. Stuart reimagined the Vertex commercial organization as the company transitioned from hepatitis C and in [CBIC] to establishing itself in CF. And since then, he has led as Vertex's Chief Commercial Officer and Chief Operating Officer, with great skill and innovation.

Stuart has been at the hound through the launches and commercialization of all of our CFTR modulators, beginning with KALYDECO and all the way through to a ALYFTREK. He has also helped develop and lead the organization into this new era of commercial diversification with the launches of CASGEVY and JOURNAVX.

Anyone who has had the privilege to work with Stuart as I have, knows Stuart to be a consummate professional, an incredible leader and an excellent developer of talent. He is uncommonly poised, leads with integrity and always puts patients first.

As part of our carefully planned succession, Stuart is fully on board at Vertex until July, which will allow for a seamless transition. While we still have many months before he retires, I want to take this opportunity to convey my deep gratitude for his partnership and for all that Stuart has done for Vertex. We are very thoughtful and deliberate in how we plan for senior leaders succession, and we always do so with a long time horizon in mind. Thanks to this careful planning, we have never been in a stronger position to pass the baton from Stuart to other experienced senior leaders and we are very confident that the transition will enable us to execute seamlessly on the significant opportunities ahead.

In that regard, I am very pleased to announce that Charlie Wagner, who joined as CFO in April of 2019 and whom all of you know very well, will take on the additional role of COO on July 1.

I am equally pleased to announce that Duncan McKechnie, our longtime SVP and Head of the North American commercial team will be promoted to EVP and Chief Commercial Officer, also on July 1. Duncan had over 20 years' experience in the industry across a wide range of strategic, operational and commercial roles in multiple disease areas and geographies at both GSK and Novartis prior to joining Vertex 12 years ago.

Duncan has been working side-by-side with Stuart since 2013, during which time, he played an instrumental role architecting the successful launches of all of our CF medicines as well as the CASGEVY and JOURNAVX launches in the U.S.

In addition to his role as the commercial head of North America since 2022, Duncan has also led the global health economics as well as the global value and access functions across the entire Vertex portfolio.

I'm proud of the deep bench of outstanding talent we have at Vertex, and I'm looking forward to working directly with Duncan as he joins the executive committee and steps into the CCO role and as Charlie continues as CFO and adds COO responsibilities in July.

Moving to earnings. Fourth quarter performance wrapped up another strong year as the continued outstanding commercial execution in CF helped us drive double-digit revenue growth for our 10th consecutive year and the launch of CASGEVY set us on the course of revenue diversification.

We continue to reach more patients and delivered $2.91 billion in revenue in the fourth quarter, representing 16% growth versus Q4 2023. For the full year 2024, revenue reached a new milestone of just over $11 billion, plus 12% versus 2023 and exceeded our full year product revenue guidance of $10.8 billion to $10.9 billion.

From this strong base in 2025, we are focused on driving a significant expansion in the patients we serve with the ongoing launch of CASGEVY and 2 recent U.S. NDA approvals ALYFTREK, our next-generation fifth CF medicine approved on December 20 and JOURNAVX approved for moderate to severe acute pain on January 30.

The JOURNAVX approval is landmark, as it represents the first oral non-opioid pain signal inhibitor and the first new class of pain medicine in over 20 years. We see this approval as significant for millions of patients, for Vertex, and for society as an important option to support public health efforts to curb the opioid epidemic.

Our R&D teams have worked on this program for many years, and it is indeed my privilege to acknowledge their efforts and also to thank the patients and health care providers who participated in the clinical trials and made this approval possible.

With these 2 recent approvals for ALYFTREK and JOURNAVX in hand and the continuing CASGEVY global launch, we have a keen focus on commercialization and our teams are working to secure broad access and reimbursement for patients who are waiting.

As I detailed in January, as the number of in-line approved medicines grow and the late-stage pipeline advances, we anticipate significantly expanding the number of patients we serve over the coming years. In 2024, our transformative therapies have the potential to serve approximately 160,000 patients with CF, sickle cell disease, and transfusion-dependent beta thalassemia. Now we can add 80 million acute pain patients to that reach, thanks to the approval of JOURNAVX. And beyond moderate-to-severe acute pain, focusing just on the mid- and late-stage pipeline, we seek to serve more than 5 million more patients including those with type 1 diabetes and certain renal diseases and then another 10 million-plus patients with peripheral neuropathic pain in the U.S. alone.

To give you a sense of our momentum, we are on track for key clinical development milestones in 3 pivotal studies this year. First, completing enrollment and dosing in the Zimislecel Phase I/II/III study in type 1 diabetes which would position us to file for regulatory approval once this cohort has follow-up with 1 year of insulin independence.

Second, completing enrollment in the interim analysis cohort of povetacicept in IgAN, which would position us to file for potential U.S. accelerated approval once that cohort reaches 36

weeks of treatment.

And third, completing enrollment in the interim analysis cohort for inaxaplin for AMKD, which would position us to file for potential U.S. accelerated approval once that cohort reaches 48 weeks of treatment.

In addition, we continue to execute the Phase III study of suzetrigine in patients with diabetic peripheral neuropathy. We're also making strong progress with VX-993, the next-generation NaV1.8 inhibitor in both moderate to severe acute pain and diabetic peripheral neuropathy. We also have ongoing trials of potentially transformative medicines like VX-670 in myotonic dystrophy type 1, povetacicept in a basket study in indications beyond IgAN and expect to move VX-407 for autosomal dominant polycystic kidney disease into Phase II this summer.

It's truly an exciting era of broad diversification at Vertex in terms of the revenue base, our pipeline and our geographic presence. Given the detailed clinical update we provided in January, I'll focus the R&D update tonight on CF and our clinical stage renal pipeline.

Starting with CF. The U.S. launch is underway ALYFTREK, the fifth Vertex CFTR modulator regimen, while we are also working to secure approval in international regions. As we work to get ALYFTREK to patients around the globe, we are already in the clinic with our next-generation CFTR modulator regimen. With each CFTR modulator regimen that gains approval, we raised the bar ever higher for ourselves and the field as a whole as we continue our mission to bring all patients with CF to normal levels of CFTR function.

We term TRIKAFTA/KAFTRIO, the next-generation CFTR modulator or NG 1.0. ALYFTREK is NG 2.0. The NG 3.0 regimen consists of VX-828, a CFTR corrector; VX-118, a CFTR potentiator; and tezacaftor. This NG 3.0 triple combo regimen has shown even greater efficacy. In other words, even greater improvement in CFTR dependent chloride transport than ALYFTREK in our CF human bronchial epithelial cell assays, which have been shown to be highly predictive of clinical outcomes.

We expect this regimen to be in the clinic in a study of CF patients this year.

We also continue to enroll and dose the MAD portion of the Phase I/II study of VX-522 for the 5,000-plus patients who cannot benefit from our CFTR modulators. Results from the MAD portion of the study are expected later this year.

Moving on now to what I see as a real renaissance in renal therapeutic drug development. We are focused on advancing potential therapeutics that hold the promise to treat the underlying cause of disease in 3 different severe renal conditions.

First, inaxiplin for APOL1-mediated kidney disease or AMKD. As mentioned, we're working towards our goal of completing enrollment of the interim analysis cohort of the pivotal AMPLITUDE study this year. AMPLITUDE is a study of primary AMKD. That is to say patients with 2 APOL1 alleles and no additional renal comorbidities.

After completing enrollment, when this cohort reaches 48 weeks of treatment, we'll conduct the interim analysis. If positive, we will be able to file for potential accelerated approval in the U.S.

In addition, I am pleased to announce that last month, we initiated a new study AMPLIFIED which is a Phase II proof-of-concept study of inaxiplin in patients with AMKD and other comorbidities, including type 2 diabetes.

Second, povetacicept, a dual antagonist of the APRIL and BAFF cytokines, which play key roles in the pathogenesis of B cell-mediated autoimmune diseases. This tool inhibition mechanism of action, the preclinical and clinical data to date plus pove's once-monthly dosing frequency and small volume subcutaneous route of administration give us high confidence in its promise as a transformative medicine for patients with IgAN and other B-cell-mediated diseases.

As mentioned in January, we expect to complete enrollment of the interim analysis cohort of the pove study in IgAN this year. To this end, I am pleased to report that we have now opened more than 100 clinical trial sites in more than 20 countries, including in the U.S., Europe and Asia, and enrollment in dosing are well underway.

Once this cohort has 36 weeks of follow-up, we'll conduct the interim analysis. And if positive, it would support filing for a potential accelerated approval in the U.S.

And third, an earlier stage renal program that represents an additional significant opportunity. VX-407 in autosomal dominant polycystic kidney disease, or ADPKD, where we are nearing completion of the Phase I trial. ADPKD is the most common severe monogenic disease amongst Caucasians and the most common inherited cause of end-stage renal disease in the U.S. and globally, an estimated 300,000 people in the U.S. and Europe are living with ADPKD, yet there are no treatments that address the underlying cause of disease.

It is a life-shortening disease that is characterized by the growth of numerous cysts that impair kidney function and can ultimately lead to kidney failure. Around half of patients with ADPKD experienced kidney failure by the age of 60. The majority of ADPKD cases are caused by variants in the PKD1 gene, which encodes the polycystin 1 or PC1 protein. These inherited variants lead to the loss of PC1 function that leads to the proliferation of kidney epithelial cells, increased fluid secretion and the formation and expansion of fluid-filled cysts.

The progressive cyst formation causes an increase in kidney size and decline in kidney function. VX-407 is a first-in-class small molecule protein-folding corrector that is designed to target the underlying cause of ADPKD by correcting PC1 folding to restore function. This has the potential to arrest assist growth.

By way of its mechanism of action, VX-407 has potential in a subset of patients with protein-folding mutations of PKD1 estimated at up to 30,000 patients or about 10% of the overall ADPKD population. As we're doing in CF, we seek to serially innovate and over time, reach the full 300,000 patients with ADPKD. For VX-407, we expect to complete our Phase I study soon. And if the results are supportive advance to Phase II later this year.

With that review, I'll turn it over to Stuart for a commercial update.

Stuart Arbuckle Executive

Thank you very much, Reshma. While I admit to having very mixed emotions at retiring from

Vertex in July, I know that the timing is right from both professional and personal standpoint. It's been an amazing journey at Vertex over the last 13 years.

As we've executed on our unique and differentiated strategy to develop and commercialize transformative medicines for patients with CF, sickle cell disease, beta thalassemia and pain, and I'm very confident we will successfully develop many more transformative medicines, such as in diabetes, renal and autoimmune diseases from our broad late-stage clinical pipeline. The business has never been in a better position scientifically and commercially than we are today.

I'm also highly confident that we have developed the right talent to maximize these significant opportunities. I'm thrilled to transition leadership of our outstanding commercial organization to Duncan as the new CCO. I've known Duncan for decades and recruited him to Vertex. He brings a rare combination of outstanding strategic thinking, results focused operational excellence and people management skills, and I have every confidence he will help lead the company to even greater heights.

Although I will see many of you between now and July, I'd like to take this opportunity to thank all our shareholders and analysts for your support and engagement over the years, and I look forward to helping you get to know Duncan over the coming months.

With that, I will focus my comments tonight on our 3 recent launches, including the early U.S. launch of ALYFTREK, the continuing global launch of CASGEVY building on the foundation we established in 2024 and the initial launch of JOURNAVX in acute pain.

Starting with CF. Once again, we delivered strong CF results for the quarter and the full year as we further grew the number of eligible patients taking our CFTR modulators. We made rapid regulatory and reimbursement progress in 2024, enabling us to expand to younger patients, patients with rare mutations and patients in new geographies. ALYFTREK is now our fifth CFTR modulator approved to treat the underlying cause of CF.

We were pleased with the early approval of ALYFTREK which in clinical trials has demonstrated noninferiority on lung function to TRIKAFTA, the current standard of care for eligible patients with CF. ALYFTREK clinical trials also demonstrated further improvements in CFTR function as measured by sweat chloride.

We believe this profile, along with the convenience of once-daily dosing sets the stage for ALYFTREK potentially become the new standard of care in CF. ALYFTREK is also approved for an additional 31 mutations that are not covered by the TRIKAFTA label.

And finally, 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 have received positive feedback from physicians and patients for ALYFTREK.

Early insights show enthusiasm for a new option that offers the convenience of once-daily dosing to simplify treatment and expanded eligibility for many patients who are today not being treated with a CFTR modulator, including those who have 1 of the 31 rare mutations that are not responsive to our other CFTR modulators.

In these early days of the launch, centers are familiarizing themselves with the data and the liver monitoring requirements to frame conversations about initiation with naive, discontinued and potential switch patients. We have seen interest in ALYFTREK from all of these groups of eligible patients, and I'm pleased to report that the first patients have already initiated treatment with ALYFTREK.

As we think about the uptake of ALYFTREK, we are confident that CF patients will seek the best medicine for them. And we believe that for the majority of patients, that is ALYFTREK. We expect that the short-term liver monitoring requirements to initiate ALYFTREK will be considered in the context of the potential for a lifetime of improved CFTR function and the benefits of once-daily dosing.

Outside the U.S., regulatory reviews are underway for ALYFTREK, including in the United Kingdom, European Union, Canada, Switzerland, Australia and New Zealand. We look forward to the potential approvals of this best-in-class medicine in these markets in 2025.

Now turning to CASGEVY, our transformative onetime treatment for patients with sickle cell disease and beta thalassemia. It is just over a year since the historic approval of CASGEVY, which has been enthusiastically received by patients, physicians, payers and policymakers and the launch is gathering momentum across all regions. Two important markers of our launch progress are ATC activations and patient cell collections.

As we reported in January, we exited 2024 with more than 50 authorized treatment centers, well on our way to our goal to activate approximately 75 total ATCs globally. Approximately 50 patients across all regions have their first cell collections in 2024. And patient infusions of CASGEVY-edited cells have already occurred in both the Middle East and the U.S.

We continue to make exciting progress in the Middle East. In November of 2023 and January of 2024, we secured regulatory approvals in Bahrain and KSA, respectively. And on December 31, 2024, we secured regulatory approval in the United Arab Emirates. We are working to expand further in the region with anticipated filings in Kuwait and Qatar later this year.

In this region, we now have national reimbursement in Bahrain, hospital-based coverage in Saudi Arabia and are working towards coverage in the United Arab Emirates. Continuing with the payer landscape, we recently reached a reimbursement agreement with NHS England for the treatment of patients with sickle cell disease. This means that eligible sickle cell disease and beta-thalassemia patients now have access to CASGEVY in England.

In the U.S. Both SCD and TDT patients have access either through private insurance, where over 250 million lives are covered or through single case agreements. And in the Medicaid segment, as of last month, States may now begin to apply to participate in the CMMI cell and gene therapy access model, which we believe will further expand access for eligible patients as States may then subsequently opt in to the CMS negotiated agreements.

We are focused on leveraging the foundation we established for CASGEVY in 2024 to build momentum in 2025 and beyond for this multibillion-dollar opportunity. as we work to get this transformative therapy to more and more patients around the world.

Shifting now to JOURNAVX in acute pain as we are currently 10 days post the milestone

approval of this first selective oral non-opioid pain signal inhibitor. The approval is so critical because JOURNAVX represents the first new class of pain medicine in over 20 years. It combines effective pain relief with a favorable safety profile. And based on its MoA, it does not have addiction potential. It is indicated for use across all types of moderate to severe acute pain.

For example, post surgery, broken bones, sports injuries and has the potential to establish a new standard of care for the 80 million patients who seek a prescription therapy to treat moderate to severe acute pain each year in the U.S.

Half of those seeking out for their acute pain or approximately 40 million Americans each year are prescribed opioids, which although effective, have significant safety and tolerability concerns and addictive potential.

In fact, tragically an estimated 85,000 people each year will develop opioid use disorder within the first year of being prescribed an opioid for acute pain. We believe we now have the opportunity to transform how acute pain is treated in the U.S. and to build another multibillion-dollar franchise for Vertex.

We were launch-ready for the PDUFA date and have now begun commercialization of JOURNAVX. Our focus for 2025 is to engage with health care professionals, formulary decision makers and payers to establish the conditions for rapid patient access that will deliver long-term commercial success for our pain franchise.

To that end, while still just a few days into the launch, we believe that the incredibly broad positive media coverage JOURNAVX has received since approval is one measure of the high unmet need and an indication of the societal importance of providing both physicians and patients with a new non-opioid option for the treatment of acute pain.

We've already seen tremendous interest and requests for information from both doctors and patients, and we look forward to being able to serve them. Our 150-person sales force is actively engaging with health care providers and physicians on the compelling efficacy and safety data of JOURNAVX and its role in all types of moderate to severe acute pain.

In the institutional setting, we are engaging with roughly 2,000 high-volume hospitals and approximately 150 related health systems. We have line of sight to accelerate the typical P&T committee processes in many networks to support the use of JOURNAVX in this setting. We are advancing our discussions with national and regional payers and group purchasing organizations to provide access to JOURNAVX, building on our work preapproval to accelerate formulary reviews and limit inappropriate utilization management controls. And lastly, with retail pharmacies, we are working to secure broad stocking agreements at national retail pharmacies and regional chains to ensure availability of JOURNAVX for patients across the country. We have also now begun our nonpersonal promotional initiatives to physicians and patients to promote broad awareness of the first oral non-opioid pain signal inhibitor for moderate to severe acute pain, such as embedded content in relevant websites like Medscape for physicians and WebMD for consumers, along with point-of-care marketing.

Furthermore, we continue to see momentum and interest by policymakers both on the federal and the state level in providing equal access to non-opioid options for pain relief. The

NOPAIN Act launched on January 1 and provides a Medicare add-on payment for non-opioids used in the hospital outpatient or ambulatory surgery center settings.

We expect JOURNAVX to be added near term to the list of medicines approved for this add-on payment. The alternatives to pain act had 78 cosponsors from both parties last year and is expected to be reintroduced in the new Congress with similar and growing support. Additional federal and state initiatives also continue to progress.

For example, just 6 weeks into 2025, 17 states have already introduced legislation to support the use of non-opioid options. adding to the 7 states that enacted legislation for Medicaid and state-regulated plans in 2024. We expect more states to join this movement.

On the pricing front, we have priced JOURNAVX at $15.50 per pill or $31 per day at list price. We believe this price strikes a balance between ensuring broad access with the benefits it brings to patients and society, including the cost offsets that JOURNAVX may provide. It also recognizes our 20-plus year investment in pain.

And significantly, we feel that this pricing enables us to continue to invest so that we can be the leader in serving patients with acute and chronic pain for decades to come. As previously discussed, in the early months of the launch, we are strategically investing in initiatives, including financial assistance programs for eligible patients that enable smooth, rapid access for patients prescribed JOURNAVX, which is critical given the acute nature of the condition. And lastly, we expect to start shipping JOURNAVX to wholesalers by the end of this month with retail availability a few days later.

To conclude, we had a very strong commercial execution throughout 2024 and are already executing on the multiple launches and growth opportunities ahead of us in 2025. we are in a new and exciting era of commercial diversification with the ongoing global launch of CASGEVY, the launch of ALYFTREK in CF and JOURNAVX in moderate to severe acute pain in the U.S.

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

Charles Wagner Executive

Thanks, Stuart. Vertex's excellent results in the fourth quarter of 2024 demonstrate once again our consistent strong performance and attractive growth profile. Fourth quarter 2024 total product revenue increased 16% year-over-year to $2.91 billion, including revenue growth of 17% in the U.S. and 14% outside the U.S. The exceptional U.S.

CF revenue growth in the quarter resulted from continued strong patient demand and the effect of the January 2024 price increase as well as a favorable gross to net dynamic. Ex U.S. revenue growth was driven by strong CF performance in many established markets as well as in newer markets where we have recently transitioned to long-term reimbursement agreements.

Revenue in the quarter also benefited from certain nonrecurring items. Full year revenue of $11.02 billion represents 12% growth versus 2023, our tenth consecutive year of double-digit growth.

Fourth quarter 2024 combined non-GAAP R&D, acquired IPR&D and SG&A expenses were $1.3 billion an increase of 29% compared to $1 billion in the fourth quarter of 2023. The most significant areas of increased investment versus prior year included the pivotal studies for type 1 diabetes, IgAN, AMKD and DPN as well as the build-out of capabilities for both our expanding pipeline and ongoing commercial launches. Also included in Q4 2024 results are $88 million of acquired IPR&D expenses, including for the Orna collaboration to develop next-generation in vivo therapeutics for sickle cell disease and beta thalassemia.

This compares to $18 million of such charges in the fourth quarter of 2023. Full year 2024 combined non-GAAP R&D, acquired IPR&D and SG&A expenses were $8.82 billion compared to $4.24 billion in 2023. Included in full year 2024 results are $4.63 billion of acquired IPR&D charges with the vast majority resulting from the Alpine Immune Sciences acquisition. Acquired IPR&D charges were $527 million for the full year 2023.

The year-over-year increase in R&D expenses were driven by continued investment in our pipeline, including 4 ongoing pivotal studies. The year-over-year increase in SG&A costs was primarily driven by investments in our commercial organization to support the launches of JOURNAVX and CASGEVY.

Fourth quarter 2024 non-GAAP operating income was $1.2 billion compared to $1.15 billion in non-GAAP operating income in the fourth quarter of 2023. Full year 2024 non-GAAP operating income was $696 million compared to $4.37 billion in 2023. Recall that full year 2024 non-GAAP operating income reflects a $4.4 billion charge for acquired IPR&D from the acquisition of Alpine.

Fourth quarter 2024 non-GAAP effective tax rate of 21.3% was in line with our expectations, while our 16.3% tax rate in Q4 '23 benefited from higher U.S. R&D tax credits. Our full year 2024 effective tax rate of 91% reflects the nondeductibility of the Alpine acquired IPR&D charge. Our non-GAAP effective tax rate in 2023 was 19.4%.

Fourth quarter 2024 non-GAAP earnings per share were $3.98 compared to $4.20 in the fourth quarter of 2023, largely as a result of lower interest income and the tax rate differential previously noted. Full year 2024 non-GAAP earnings per share were $0.42 compared to $15.23 in 2023. For reference, the Alpine AIPR&D charge equates to roughly $17 on a per share basis.

We ended the quarter with $11.2 billion in cash and investments. Our priorities for cash deployment remain unchanged as we continue to prioritize investment in innovation, including external innovation by business development. We also continued our share repurchase program and deployed approximately $1.2 billion to repurchase 2.7 million shares over the course of 2024, including 961,000 shares in the fourth quarter.

Now switching to guidance. For 2025, we expect total revenue in a range of $11.75 billion to $12 billion, representing growth of approximately 8% at the midpoint at current exchange rates with the U.S. as the main driver of total revenue growth.

This outlook reflects our expectation for continued growth from our portfolio of CF medicines, including the U.S. launch of ALYFTREK. Note that ex U.S. CF revenue growth will be impacted by a reduction of revenue in one country outside our core markets where certain

intellectual property rights are being violated. This impact will be most pronounced in Q1 as the increases in international channel inventory that occurred in Q1 of 2024 will not repeat in Q1 2025.

Guidance also includes a continued ramp-up in CASGEVY revenue as we treat more patients in approved geographies. Given the very recent approval of JOURNAVX, guidance also reflects a contribution from this launch in the U.S., primarily in the back half of the year. We expect JOURNAVX volumes to ramp up ahead of revenue as a result of financial assistance programs that are designed to provide eligible patients with immediate access while we work to secure broad sustainable payer coverage.

To give you context on the launch progress of JOURNAVX, we will provide metrics on total covered lives and prescription data over the course of 2025. Also note that the expected benefit to gross margin in 2025 from the lower royalty rate on ALYFTREK will largely be offset by the higher cost of goods on our other new product launches as they scale towards their long-term margins.

For combined non-GAAP R&D, acquired IPR&D expenses and SG&A, we project a range of $4.9 billion to $5 billion for the full year 2025. This guidance includes approximately $100 million in currently anticipated IPR&D charges. We will continue to invest a majority of our operating expenses into R&D given the momentum in our multiple mid- and late-stage clinical development programs.

The cost for 4 Phase III studies were a driver of increased investment in Q4 '24, and this trend will continue over the course of 2025 with the 4 Phase III studies continuing and multiple Phase IIs ongoing as well. The increase in commercial costs in 2025 supports our increasingly diversified commercial portfolio and reflects a full year of investments to support the launch of JOURNAVX as well as targeted spending on commercial capabilities for future potential multibillion dollar opportunities in renal therapies and zimislecel, for example.

Given our differentiated business model and focus on specialty markets, we can make these targeted investments while maintaining attractive profitability and cash flow. Our full year 2025 non-GAAP effective tax rate is expected to be in the range of 20.5% to 21.5%.

In closing, Vertex delivered excellent results yet again in 2024, achieving strong revenue growth, advancing our CASGEVY launch and gaining important regulatory approvals that position us for commercial launches, all while continuing to make significant pipeline progress across the portfolio. We are now launching 2 new products in the U.S., driving the CASGEVY global launch and enrolling 4 Phase III studies with 3 of them expected to reach significant enrollment milestones this year. These and other anticipated milestones of continued progress in multiple disease areas are detailed on slide 16.

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 our first question will come from Salveen Richter with Goldman

Sachs.

Salveen Richter Analyst

On JOURNAVX, and actually, Stuart, we really are going to miss you and Duncan welcome here. Maybe just going back to my question on JOURNAVX, can you further elaborate on prelaunch efforts in the retail pharmacies and the P&T committee review processes and how you can work to accelerate these aspects? And then secondly, on your mRNA program in cystic fibrosis, maybe frame for us how you think of success here.

Reshma Kewalramani Executive

Yes. Salveen, let me turn it over to Stuart first, and then I'll come back to the mRNA question. Stuart?

Stuart Arbuckle Executive

Yes. Salveen, thanks for the kind words. Yes, so in terms of our work with retail, we've been working with the largest national retail chains and also regional chains to ensure that we get broad availability of JOURNAVX across the U.S. And it's very important, obviously, to have broad availability because we want the product to be there when a patient in acute pain turns up with their prescription because they obviously can't wait.

And as I said in my prepared remarks, we are expecting to have the product with wholesalers by the end of this month and in retail shortly thereafter. And I am expecting that we will have broad availability across the entire U.S.

In terms of our work with both payers on their approval processes and also institutions on their pre-approval. We are working on them compliantly to provide them with information that they need, such as the full clinical profile of the medicine. Obviously, now. We also have the established price, which is an important component for them as well. And we do have indications that people are looking to move quickly to provide access to JOURNAVX given the benefit risk profile, and we'll keep you updated on our progress with that over the next few weeks and months.

Reshma Kewalramani Executive

And Salveen, on your question with regard to mRNA. So these are the last 5,000 or so patients, they have no options available to them. And so if I think about the approved medicines ORKAMBI on the one hand, with about a 3% improvement in ppFEV1 and then TRIKAFTA and ALYFTREK on the other side with about a 14% improvement on ppFEV1. And because the mRNA, VX-522 is an inhaled therapeutic, we're not expecting any movement on sweat chloride. So this would be a readout on ppFEV1.

And any number between 3% and 14% would be just fine. And of course, if it's more than that, that would be acceptable as well. But based on the approved medicines, I think you could look at a range from 3% to 14% as what would be important. If you translate the 3%, let's say, that's what ORKAMBI had into long-term outcomes. Remember that the 3% in acute improvement in ppFEV1 translated to a 50-plus percent improvement or reduction in pulmonary exacerbations.

Operator Operator

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

Evan Seigerman Analyst

Congrats on a strong '24 and a great start to 2025. Also Stuart, congrats on your retirement. It's been an honor to watch you really transform this company. So I want to touch on JOURNAVX. Can you talk to me a little bit about how your early discussions with payers have been progressing?

How many covered lives do you expect to have, access to therapy when it is a retail channel? And how is that going to change over the course of the year?

Stuart Arbuckle Executive

Again, thanks for the kind words. I appreciate it. And let me just reassure everybody, I'm going to be here until July 1 and 100% focused on driving the JOURNAVX launch and CASGEVY and ALYFTREK as well. In terms of our payer discussions, we were having payer discussions prior to the approval. And obviously, we've continued to have them post approval, Evan.

They've gone really well. I think it's no surprise. Everybody is acutely aware of the unmet need to have better treatment options and opioids and everybody is excited about the fact that this is the first non-opioid for decades.

I am expecting that we will get broad access over time, and I expect it to grow over time. We're not giving specific expectations or guidance on exactly how many covered lives we expect at what point through the year. But obviously, we are expecting it to grow throughout the year as more payers choose to put JOURNAVX on their formulary.

Operator Operator

Your next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

Thinking about the 2025 top line guidance, it seems like that's largely driven by CF. I was wondering if you could talk about how we should think about the U.S. versus ex U.S. contribution to that growth rate in the CF business? And kind of what's driving those respective growth rates in the U.S.

and outside the U.S.

Susie Lisa Executive

Charlie?

Charles Wagner Executive

Yes, Jess, thanks for the question. Our guidance range of $11.75 billion to $12 billion, as we highlighted in the prepared remarks, represents 8% at the midpoint. We did call out in the prepared remarks sort of the differential between the U.S. and ex U.S. If you think about what's

going on, I think about 2024, obviously, we continue to see very strong growth in the CF business around the world.

We expect that to continue into 2025. The U.S. has the benefit of the ALYFTREK launch as well as the JOURNAVX launch in addition to ramping CASGEVY and the ongoing growth in CF. If you think about international, we'll see strong growth in CF.

In most markets, we did call out that there is one country where our IP is not being respected. That has an impact on the ex U.S. growth rate that will be most pronounced and visible in the first quarter, so we thought we would call that out for you. And then obviously, the CASGEVY launch continues to ramp ex U.S. as well.

So with those dynamics, there is a little bit of a difference between the U.S. and ex U.S. in 2025. But overall, a very healthy growth rate on the top line for us.

Jessica Fye Analyst

Great. And can I just throw on a follow-up. I think you also mentioned the 4Q revenue benefited from some nonrecurring items. Possible to quantify that at all?

Charles Wagner Executive

Yes. I'm not going to get into that. I'll just qualitatively, I'll tell you, the fourth quarter was very strong. Growth in the U.S. was driven by strong volume in CF as well as the benefit from the price increase that we took earlier in the year.

In addition, we saw a very favorable gross to net dynamic in the U.S.

Gross to net fluctuates, honestly from quarter-to-quarter. Typically, it's a little more negative in the first quarter. But we did see a meaningful benefit in the fourth quarter. Outside the U.S., again, strong volume growth in CF. We did also have the benefit of some onetime items, things like VAT rebates and some other settlements that we worked out in different markets, those don't reoccur necessarily every quarter.

Operator Operator

The next question will come from Geoff Meacham with Citibank.

Geoffrey Meacham Analyst

I also want to offer up congrats to Stuart as well as Charlie and Duncan just on all the announcements today. So just on JOURNAVX and LSR. I know you guys have taken a deep dive into the Phase II and maybe you've gotten some KOL feedback. Are there any more considerations you're thinking about for Phase III design?

I know you're still awaiting regulatory feedback, but I want to get your perspective on that? And then second question is on ALYFTREK. I want to get maybe any early anecdotes from you guys on new patients coming into care either just qualitative or quantitative feedback on those that are perhaps not on TRIKAFTA or unmet need populations.

Reshma Kewalramani Executive

Sure thing. Geoff I'll take the LSR question, and then I'll ask Stuart to comment on ALYFTREK. So you actually have it exactly right. The big thing that we're waiting for is our end of Phase II meeting with the regulators. Where we are with our analyses is, our teams are very deep into their analyses of everything we can possibly glean from the Phase II.

We are out talking to not only key opinion leaders, but PIs and those who are very involved in doing LSR studies, and we are preparing ourselves for our regulatory meetings.

I'll have more to share with you this summer, but I don't have an update. I'd rather collect all of this and present it to you all at once in the summer after we've gone through our regulatory interactions. And obviously, the really big thing that we are looking to understand is what the FDA would like to see what are the packages, what we need to include in the package for this broad PNP indication that we seek. Stuart?

Stuart Arbuckle Executive

Yes. On ALYFTREK, Geoff, we've seen strong interest from patients who are either kind of naive have never been on a CFTR modulator and in particular, those who are now eligible for a CFTR modulator, ALYFTREK is approved, which, as you know, has additional mutations over and above even TRIKAFTA. So we've seen strong interest there, as you might expect.

But we've also seen interest in transition patients, either those who are on something like TRIKAFTA, but also those who previously discontinued. So we've seen interest across all 3 of the population that we were expecting. And I'm pleased to say that the first patients have already received their first prescriptions and already received their first packs of ALYFTREK, which is great to see.

Operator Operator

Your next question will come from Michael Yee with Jefferies.

Michael Yee Analyst

Stuart, hopefully, you're not making the nervous going into the acute pain launch. But thinking about reimbursement, which is I know something you're working on with JOURNAVX, can you just comment about your thoughts around public payer coverage as it relates to Medicare, Medicaid and the understanding that. Presumably, the administration know that, that's an important thing in the opioid, as well as the commercial side where you would think that bad headline coverage of not paying for that is probably not a good thing. And so given those 2 things, are you fairly confident that reimbursement is something that should not be an issue on the launch of JOURNAVX.

Stuart Arbuckle Executive

Yes. Well, Mike, let me first address your first comment. I've never been more excited to be at Vertex. I have never been more confident about the future of this company. It is firing on all cylinders, both scientifically and commercially.

And so I wouldn't want you to have any doubts about my confidence in either the launch of JOURNAVX or the launch of any other things that we have ongoing right now.

It is a purely personal decision that the time is right for me to move on to the next chapter of my life. In terms of payer coverage, I am expecting us to get broad coverage for JOURNAVX over time across all segments. For the reasons that you described, Mike, to be perfectly honest with you. Everybody is aware of the enormous unmet need. Everybody has been waiting for a truly effective non-opioid pain reliever that did not have the adverse events, including addictive potential of opioids.

And so I'm expecting us to get broad access over time. In addition to individual discussions we've been having, I think we've talked a number of times about the many both federal and state policy moves, which are already in flight to create, if I can put it this way, sort of to the availability of JOURNAVX.

So I'm incredibly excited. We're obviously only 7 days, 7 business days into the launch, but the feedback has been absolutely tremendous and I'm sure JOURNAVX is going to be a huge success.

Operator Operator

Your next question will come from William Pickering with Bernstein.

William Pickering Analyst

Congrats on all the progress, and Stuart, congrats on your retirement. I had a question about the DPN Phase III what placebo effect did you assume in designing that study? And how does that compare to the 2 points placebo effect we saw in LSR? Is 1.5 points placebo effect a reasonable ballpark? And what delta versus placebo would be clinically meaningful for suzetrigine?

Reshma Kewalramani Executive

Yes. Will, first, I did read your note from earlier in the week and I appreciate that you were doing primary research, while going through your own surgical procedure. On DPN Phase III, I will share the specifics with you, Will. But what I will tell you is that in the DPN area, there are many Phase II studies and many Phase III studies and there are several medicines that have been approved. And we have taken full advantage of that rich data set to appropriately size our Phase III trial, and you will note that the Phase III trial has not only a placebo group, but also has a gabapentin group in addition to the JOURNAVX group.

And we've taken all that into account as we think about the outcomes there. So while I won't share with you the specifics, please note that we have taken full advantage of all that's available out there. the general ranges that you have suggested are indeed what the literature tells you. And the study that we've designed, including the sample size, well takes care of that level of a placebo effect, yes, you bet.

Operator Operator

Next question will come from Liisa Bayko with Evercore ISI.

Liisa Bayko Analyst

I'll just get in line and offer my congratulations to both -- to everybody involved actually. It's a

great transition and have fun. We'll be living vicariously through you. So I wanted to ask about the pain program. Just a couple of questions.

Can you maybe describe sort of any like stocking? It seems like you are trying to get stocks available in the different channels. So just wanted some commentary there.

And also, how are you thinking about who is the right patient? We did a pain call earlier this week and a big topic was onset of action and kind of like where it falls in line in the ambulatory care setting if the onset of action is a little bit longer. So where are you thinking of -- how it is positioned in terms of first, second or third line? And what is the right patient for suzetrigine.

Reshma Kewalramani Executive

Liisa, I'm going to turn it over to Stuart to give you some color, but I just want to say upfront, our goal here is for JOURNAVX to be the first line prescribed pain medicine for moderate to severe acute pain. Stuart?

Stuart Arbuckle Executive

Yes. So Liisa, just to address your first question on stocking. Yes, we are looking to get the product broadly stocked in retail across the country in addition to in hospital pharmacies as well. So yes, we are striving to do that, and I feel very confident that, that will happen as I said, our product would be with the wholesalers by the end of this month and then in the channel shortly thereafter.

As Reshma said, the great thing about JOURNAVX is we got a broad label for the treatment of moderate to severe acute pain. And we've heard people from across the spectrum of different physicians talking about how they think they're going to be using it in many, many different populations. I do think some of the early ones might be procedures where after a procedure somebody feels like they often need to prescribe a product for a week or 2 weeks afterwards. And in those situations that's where they are most concerned about prescribing opioids in the discharge setting there.

So I think that will certainly be an area where there will be patients treated relatively early on. But as Reshma said, our goal and I think how people are seeing JOURNAVX is that it is for the treatment of moderate to severe acute pain regardless about etiology. And so I expect it's going to be used broadly across the spectrum.

Reshma Kewalramani Executive

Liisa, we have just one more comment from Charlie on your question.

Charles Wagner Executive

What I would add to Stuart's comment, we'll absolutely seek stocking in the first half of the year, which is why we commented that you'll see volumes increasing ahead of revenues. The reason for that is the impact of our patient assistance programs while we work to secure broad access. And so while there will be stocking in the channel in the first half of the year, the revenue contribution will really be more loaded to the second half of the year.

Operator Operator

Next question will come from Phil Nadeau with TD Cowen.

Philip Nadeau Analyst

Stuart, Charlie and Duncan, [indiscernible] congratulations on today's announcements and your transitions. In terms of our questions, a couple on JOURNAVX and one on ALYFTREK. On JOURNAVX, can you give us some sense of will the prescription data that we see from third-party sources be accurate, and what are Vertex's on expectations for the average duration of a script.

Now on ALYFTREK, there is a dispute going on between you and Royalty Pharma as to exactly what Royalty is owed. Can you give us some sense of the milestones in that dispute. When could we hear something? And what are the procedures to getting that resolved?

Reshma Kewalramani Executive

So let me take your second question first, and then I'll turn it over to Stuart to talk about JOURNAVX. On ALYFTREK, this is really not a matter of opinion. We have a contractual agreement with the CF Foundation and the contract very clearly spells out what our responsibilities are. And so I don't see any room for interpretation or opinion on that. Stuart, on JOURNAVX, a few questions on that.

Stuart Arbuckle Executive

Yes. JOURNAVX. On lens of therapy, Phil, so the first thing I would say is that the label is for moderate to severe acute pain. It does not have a time limitation or a days of therapy limitation contained within the label, although acute pain is considered to be pain lasting for less than 90 days. In terms of -- in the -- obviously, in the inpatient setting, it's very short length of therapy there in the discharge or outpatient setting for non-steroidals, you see length of therapy at around about 14 days.

For opioids, it's markedly less somewhere in the 7- to 8-day range for all the reasons that we probably expect I would expect JOURNAVX is going to be more like the nonsteroidals because it doesn't have the sort of baggage that the opioids have, which is what leads people to want to give out as little days of therapy as they possibly can.

Reshma Kewalramani Executive

And Stuart, there's a quick question in there about will the prescription data be accurate, maybe split them out into the retail and what happens in the inpatient.

Stuart Arbuckle Executive

Yes. So it depends a little bit on what prescription data you buy, Phil. So it's a little bit hard to comment on exactly what how good it will be. But prescription data overall in the retail setting is very robust in the hospital setting. It's more volume-related data that's available.

We will be providing, as Charlie said in his prepared remarks, information on prescriptions as a -- one of the markers of our success in ongoing calls for 2025. We'll also be providing

updates on the number of covered lives as well as 2 of the most important markers of our early launch success.

Operator Operator

The next question will come from Eli Merle with UBS.

Eliana Merle Analyst

You mentioned with ALYFTREK, you've seen starts from all the different patient segments. Can you give any color on the new starts that are coming from the patients who had previously been on a CFTR modulator but no longer were and what their rationale had been for discontinuing other CFTR modulators, but coming back to ALYFTREK? And basically, taking a step back, I guess, what drives your confidence that you can recapture this segment of 6,000 patients globally.

Stuart Arbuckle Executive

Yes. So I mean, the first thing that drives our confidence that we have a good shot at getting those patients back is the clinical profile of ALYFTREK itself. Obviously, it has terrific efficacy and it's once a day as well. So it really is the profile and the fact that we know that all CF patients want to be on the best CFTR modulator. They certainly want to be on a CFTR modulator if they can.

And these patients unfortunately have not been able to stay on a CFTR modulator for a whole range of reasons.

So that's what gives us the confidence that a lot of those people are going to come back and be initiated on ALYFTREK. I can't give you any granularity on the patients to date. It's a relatively small number of patients in the grand scheme of things, and I don't have the granularity to know exactly what those individual patients were thinking when they came back on to ALYFTREK or even why they discontinued at this stage.

Operator Operator

Next question will come from Tazeen Ahmad with Bank of America.

Tazeen Ahmad Analyst

One on CF. So for this year, just to clarify, are you expecting to see cannibalization of TRIKAFTA from ALYFTREK? And if so, how should we be thinking about that rate of switching? And then from your pipeline, I just wanted to get a sense of expectations for the type 1 diabetes data that you're set to show and how we should be thinking about the opportunity there.

Reshma Kewalramani Executive

All right. Let me turn it over to Stuart.

Stuart Arbuckle Executive

Yes. So on ALYFTREK, yes, we are expecting patients to transition from TRIKAFTA and even

patients who may be on one of our older CFTR modulators to ALYFTREK given the benefit/risk profile it has and the benefit it has of being once a day. We haven't set expectations or given any guidance on what we think the rate of switching will be.

Reshma Kewalramani Executive

On the T1D question, maybe the best way to summarize it is this, the lead program is the VX-880 program, let's call it the naked cell program, that's now in the Phase II portion of the development. That's the trial that we talked about is going to have enrollment complete this year, and we'll be in a position to file when that group of patients has 1 year of follow-up being insulin free.

We are estimating that opportunity, maybe something like 60,000 people or so. And the reason we say that is that it's maybe 45,000 people or so who are brittle diabetics, very high, highs in terms of their sugars and low, lows and maybe 15,000, something like that patients who have already been transplanted with a kidney transplant because of their type 1 diabetes and are therefore already on immunosuppressants.

And then the next program, which is in Phase I/II, that's the same cells encapsulated with the device no immunosuppression required there. And of course, with that program, we aim to get to all of the type 1 diabetic patients. And we have programs in research that aim to make the same VX-880 cell hyporemute with certain gene edits, and we're also working on alternative immunosuppressions. All of those latter programs, our goal would be to get them to all patients.

Operator Operator

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

David Risinger Analyst

So I wanted to add my congrats to Stuart, Charlie and Duncan as well. And I have 2 questions. So first, with respect to the plans to secure broad formulary access, I'm hoping that you can discuss that in a little bit more detail. So if a drug is on formulary, but there are hassles for the physicians. It just won't be prescribed all.

Surgeons don't have time to go through step edits and other challenges. So do you expect to be able to pay the rebates that are necessary to get broad unfettered access to suzetrigine?

And then second, with respect to the country that is violating Vertex's IP, what are the company's plans to take action to prevent other countries from doing the same as that single country?

Reshma Kewalramani Executive

David, let me ask Stuart to go first and then Charlie will comment.

Stuart Arbuckle Executive

Yes, Dave, okay. So you're right, getting broad access if you have significant utilization management controls is really not getting broad access if you're putting lots of hurdles in the

way of prescribers to actually use your medicine, 100% agree with you.

And so our goal is not just broad access, but it's broad access in both commercial and government channels, but with minimal utilization management controls, and that's certainly been the nature of the discussions that we've been having with them preapproval and since the approval because I absolutely agree with your broad access on its own is insufficient. And so that is a key part of what we are talking to payers, as I say, in both the government and indeed the commercial area.

And it's actually what you see in some of the policy initiative that's been introduced as well. So for instance, the alternatives to pain act, which was actually reintroduced to Congress just last week. One of the things that it includes is there for Medicare Part D patients, it's 2 things. One, no utilization management controls and also no equal co-pays for a branded non-opioid with generic opioids to the point that you are making.

Reshma Kewalramani Executive

Charlie, a quick word.

Charles Wagner Executive

Yes, Dave, we have an incredibly strong and robust IP portfolio around CF, and you know that it goes out to the late 2030s. We've been very successful in defending and enforcing our IP in every market. The one country in question is Russia, where they have made a decision to disregard the IP and allow an unauthorized copy. We are taking every measure possible to enforce our rights. But that is a sort of, let's say, a unique market for that reason.

I feel that this issue is very isolated.

Operator Operator

Next question will come from Olivia Brayer with Cantor Fitzgerald.

Olivia Brayer Analyst

Do you know yet whether there will be quantity limits or any other utilization management parameters put in place for JOURNAVX? Maybe just any feedback you're getting so far from those payer conversations? And do you have a sense yet around how long it will take before P&T committees actually officially recommend formulary coverage? Or maybe just asked another way, what would you consider to be an expedited process?

Stuart Arbuckle Executive

Yes, Olivia, I'll kind of repeat a little bit of what I said in my answer to Dave, just a second ago. We certainly are very aware of the fact that utilization management controls can get in the way of physicians wanting to prescribe and patients getting access to a new medicine and certainly our discussions with payers, as I said, on the government and on the commercial side, have involved discussions about minimizing those utilization management controls and certainly not considering things like step edits through generic opioids, which I think would be medically and ethically inappropriate. So that is a discussion that we've been having prior to launch, and we are continuing to have.

In terms of the P&T formulary committees, particularly in the institutional setting, again, one of the things that we were doing in the run-up to the approval in a compliant way as making sure we understood those processes, we were providing the institutions with everything that we could compliantly prior to the approval to allow them to think about how quickly they wanted to review JOURNAVX when it was approved.

We've obviously reengaged with those institutions post approval. I do believe a number of them will accelerate their processes faster than they typically do. They can certainly take up to 12 to 18 months in some cases. for some new products, and we are looking to significantly accelerate that everywhere that we can.

Susie Lisa Executive

Seth, That'll do it if you could wrap this up please?

Operator Operator

Yes, ma'am. This will conclude 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 10187033. Thank you for your participation today.

You may now disconnect.