Vertex Pharmaceuticals Incorporated

Vertex Pharmaceuticals Incorporated - Q4 2023 Earnings Call

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Event Participants

Executives 4

Susie Lisa, Reshma Kewalramani, Stuart Arbuckle, Charles Wagner

Analysts 10

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Operator Operator

Good day, and welcome to the Vertex Pharmaceuticals Fourth Quarter 2023 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, everyone. 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 and full year 2023 financial results conference call. On tonight's call, making prepared remarks, we have Dr. Reshma Kewalramani, Vertex' CEO and President; Stuart Arbuckle, Chief Operating Officer; and Charlie Wagner, Chief Financial Officer. We recommend that you access the webcast slides as you listen to this call.

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

In addition, the impact of foreign exchange is presented inclusive of our foreign exchange risk management program. I will now turn the call over to Reshma.

Reshma Kewalramani Executive

Thanks, Susie. Good evening all, and thank you for joining us on the call today. We've delivered another excellent quarter to finish 2023, established a strong foundation for continued growth and started off 2024 with tremendous momentum, with additional approvals for CASGEVY, positive Phase III results for VX-548 in acute pain last week and positive results for the vanzacaftor triple program in CF this afternoon. In 2023, Vertex continued to reach more CF patients and achieved full year CF product revenues of $9.87 billion, representing 11% growth versus 2022. Following the historic approvals of CASGEVY, the first-ever CRISPR/Cas9-based therapy, our launch is off and running globally as we are now approved in both sickle cell disease and beta thalassemia in the U.S., Great Britain, the Kingdom of Saudi Arabia and Bahrain.

CASGEVY is a onetime precise, durable CRISPR/Cas9 gene-edited therapy that is generating strong enthusiasm from physicians and patients and excellent support from payers. We're also working toward multiple additional near-term commercial opportunities driving toward our 5 launches in 5 years ago. The recent approvals for CASGEVY in both sickle cell disease and beta thalassemia deliver the first 2. Now with the positive Phase III results from VX-548 in acute pain and from the vanzacaftor triple therapy in CF, these are potentially the next 2. And with a strong clinical stage pipeline with first-in-class or best-in-class assets, we are well on our way to our goal of 5 launches by 2028.

In addition to the rapidly advancing clinical stage pipeline, the next wave of innovation also continues to make progress. And as we announced last month, we are pleased to be advancing 2 new disease areas into the clinic. First, myotonic dystrophy type 1 or DM1, a serious disease with high unmet need and no approved therapies. This disease affects approximately 110,000 patients in North America and Europe. Our DM1 program represents our ninth disease area to advance into the clinic.

We already initiated a Phase I/II study in patients, that is to say a study that will be able to assess both safety and efficacy, late last year. And second, we expect to advance into our tenth disease area in autosomal dominant polycystic kidney disease or ADPKD, the most common genetic kidney disease that affects approximately 250,000 patients in the U.S. and EU alone, into the clinic, with a healthy volunteer study in the first half of this year. With that overview, let me now turn to a more deep pipeline review. This quarter, I'll limit my comments to the programs with significant recent updates: cystic fibrosis, sickle cell disease, beta thalassemia and pain, so as to leave time for your questions.

Starting with cystic fibrosis and our next-in-class vanzacaftor triple combination therapy. This afternoon, we reported positive results from the Phase III program, including the SKYLINE 102 and 103 studies in patients 12 years and above and the RIDGELINE study in patients ages 6 to 11. We are very pleased with these results and the arc of progress in treating patients with CF as we continue to advance our ultimate goal of bringing all eligible patients to carrier levels of sweat chloride. Treatment with the vanza triple met all primary and secondary endpoints in the 3 Phase III studies, and once again, our proprietary HBE assays were both qualitatively and quantitatively predictive. In the SKYLINE 102 and 103 trials, the vanzacaftor triple combination met its primary endpoint of non-inferiority versus TRIKAFTA

on ppFEV1, consistent with our expectations.

The difference in ppFEV1 in the TRI and vanza treated groups was negligible. In SKYLINE 102, the LS mean difference was 0.2, numerically favoring vanza and meeting non-inferiority with a p-value of less than 0.0001. And in the SKYLINE 103 study, again, the difference in ppFEV1 in the TRI and vanza treated groups was negligible and numerically favored vanzacaftor, with LS mean difference of 0.2, meeting non-inferiority with a p-value of less than 0.0001. Recall the improvement in ppFEV1 in treatment-naive patients in the original TRI Phase III program was approximately 14%. In addition, all key secondary endpoints were met across SKYLINE 102 and 103 and showed a statistically significant and clinically meaningful reduction in sweat chloride.

The sweat chloride results were measured in 3 key secondary endpoints. First, the overall achieved sweat chloride levels in the 2 RCTs were lower in the vanza-treated group versus the TRIKAFTA-treated group. The LS mean difference was minus 8.4 with a p-value of less than 0.0001 in SKYLINE 102. The LS mean difference was minus 2.8 with a p-value of 0.0034 in SKYLINE 103. The key difference of course in SKYLINE 102 and 103 was the genotype studied.

SKYLINE 102 included F/MF patients who have more severe disease and therefore higher sweat chloride levels at baseline, and SKYLINE 103 included F/F and other responsive mutations with lower baseline sweat chloride levels. Next, the second key secondary endpoint, a proportion of sweat chloride less than 60 millimoles pooled across 2 studies. 86% of patients in the vanza-treated groups and 77% of patients in the TRIKAFTA-treated groups achieved sweat chloride levels below 60 millimoles, leading to an odds ratio of 2.21 and a p-value of 0.0001. This means about 2x greater likelihood in the odds of achieving sweat chloride less than 60 with vanza versus TRIKAFTA. Last, the third key secondary endpoint, a proportion of sweat chloride less than 30 millimoles pooled across the 2 studies.

31% of patients in the vanza-treated groups versus 23% of patients in the TRIKAFTA-treated groups achieved sweat chloride levels below 30 millimolars, leading to an odds ratio of 2.87 and a p-value of 0.0001. This means about 3x greater likelihood in the odds of achieving sweat chloride less than 30 with vanzacaftor versus TRIKAFTA. The results were even more pronounced in the RIDGELINE study evaluating children ages 6 to 11. The primary endpoint in this single-arm study was safety, which I will come to in a minute. On efficacy, 95% of patients achieved sweat chloride below 60 millimole, the diagnostic threshold for cystic fibrosis, and more than half reached sweat chloride levels below the carrier level threshold of 30 millimoles.

These sweat chloride results with the vanza triple are both impressive and important. Let me take a step back to frame the significance of these results. While CF is a systemic multi-organ disease, historically, the focus has been primarily on lung function as measured by ppFEV1, given it is the most visible symptom and typically the cause of death in CF patients. ppFEV1 is also the regulatory enabling endpoint. Given the strides we have made with TRIKAFTA, we believe we may have reached the maximum potential benefit in lung function from CFTR modulators.

Thus, our objective with vanzacaftor moves beyond the focus on lung function to a broader,

more ambitious goal to improve CFTR protein function as measured by lower sweat chloride levels and deliver even greater systemic benefit than TRIKAFTA. To be clear, the goal with the vanza pivotal development program was to show the lung function benefit was non-inferior to TRIKAFTA, and over and above that, to deliver additional benefit on sweat chloride, the direct marker of CFTR protein function. A note on CFTR protein. CFTR protein dysfunction is the underlying pathophysiology in CF. And while CF is often diagnosed by a genetic test at birth, it is confirmed via a sweat chloride test because it is the direct measure of CFTR protein dysfunction.

Simply put, higher levels of sweat chloride associated with more severe disease. Therefore, the ultimate goal is to restore CFTR protein function, as measured by sweat chloride, back to normal or as close to normal as possible so that there is no manifestation of disease. And more specifically, sweat chloride values below 60 millimoles are associated with improved outcomes such as better and more stable lung function, fewer pulmonary exacerbations, better quality of life and improved survival. Vertex' ultimate treatment goal is to restore sweat chloride levels to below 30, which is considered normal and are typical of CF carriers who do not have the disease, for instance, the parents of children with CF. Thus, our goal in designing the vanzacaftor triple therapy studies was to test if even more patients treated with vanza could achieve those sweat chloride thresholds of less than 60 and less than 30 than those treated with TRIKAFTA.

Switching to safety. The vanza triple was generally safe and well tolerated in all studies. The adverse events seen in the vanza triple pivotal development program are consistent with the underlying disease, and with the incidence and nature of adverse events we have seen with previous CFTR modulators. As a reminder and to round out the profile of the vanzacaftor triple, this therapy offers the convenience of once-daily dosing for patients and a substantially lower royalty burden. In summary, we set a goal to establish a new and higher bar in the treatment of CF with CFTR modulators, and with these Phase III vanza triple results, we have the first evidence that we have done so.

And with these results, we now know that the vanza triple has indeed surpassed the very high bar set by TRIKAFTA in people with CF ages 6 and older. And by treating patients early with the vanza triple, we have the potential to possibly prevent systemic manifestations of CF in more people. These results also reaffirm our conviction that continued investment in scientific and serial innovation will allow us to complete our journey to transform CF by bringing all eligible CF patients down to carrier levels of sweat chloride where there are no manifestations of disease. I want to acknowledge the CF patients in our clinical trials who put their trust in us as well as the Vertex San Diego team and the CF R&D teams, some of whom have worked on CF for more than 20 years to deliver yet another potentially transformative medicine. We are working rapidly to compile the regulatory submissions and anticipate filing in both the U.S.

and Europe for patients ages 6 and older by the middle of 2024. We will be using one of our priority review vouchers entitling us to designate the vanza NDA for priority review, which provides an expedited 6-month review versus a standard 10-month review time line. I'll close on CF with VX-522, our CFTR mRNA therapy in development with our partners at Moderna for the more than 5,000 CF patients who do not make any CFTR protein and therefore cannot

benefit from CFTR modulators. Late last year, we completed enrollment in dosing in the single ascending dose portion of our study for VX-522 and initiated the multiple ascending dose portion of the study. This study continues to screen and roll in dose patients, and we expect data late this year or early next.

Turning now to CASGEVY, our precise durable CRISPR/Cas9 gene-edited therapy that delivers a potential onetime functional cure for patients with sickle cell disease and transfusion-dependent beta thalassemia. CASGEVY represents an enormous advancement for the estimated 35,000 people living with severe sickle cell disease and transfusion-dependent beta thalassemia across the U.S. and Europe, as well as thousands of patients in other regions, such as the Kingdom of Saudi Arabia and Bahrain. CASGEVY represents a significant commercial opportunity as well, and Stuart will discuss the strong start to the launch following the rapid approvals in multiple countries. While these launches are underway, we are awaiting approval in the EU, where CASGEVY has received CHMP positive opinion for both sickle cell disease and beta thalassemia.

CASGEVY is also under review in Switzerland, and we anticipate filing in Canada this quarter. Lastly on CASGEVY, recognizing the importance of treating patients with sickle cell disease and beta thalassemia early in life to minimize organ damage and other complications of the disease, we are conducting studies in both sickle cell disease and beta thalassemia to expand the label to younger age groups. To that end, we recently completed enrollment in our 2 global Phase III studies in patients 5 to 11 years of age, and dosing in these studies is underway. Moving to the pain program and VX-548, our novel, highly selective NaV1.8 pain signal inhibitor. With VX-548, we finally have the possibility of a medicine that has the compelling combination of both strong efficacy and strong safety that can be used for multiple moderate to severe pain types across multiple settings of care.

Last week, we detailed the positive results from the 3 Phase III trials that comprise our pivotal program for VX-548 in acute pain, including randomized, placebo-controlled trials in 2 different pain models: abdominoplasty, a soft tissue pain model; and bunionectomy, a hard tissue pain model, and a single-arm safety and effectiveness trial in a broad range of surgical and nonsurgical pain conditions. Both the abdominoplasty and bunionectomy RCTs met the primary endpoint with statistically significant improvement in pain compared to placebo on the primary endpoint of SPID48. The SPID48 is derived from a change in the numeric pain rating scale or NPRS. Practicing physicians tell us that in addition to SPID48, they focus on this reduction in the NPRS from baseline, and this change in baseline in NPRS score is also how clinical meaningfulness is assessed in the field. In acute post-operative pain studies, clinical meaningfulness is defined by at least a 2-point change in NPRS from baseline or at least a 30% reduction in NPRS from baseline.

In that context, both RCTs demonstrated that treatment with VX-548 led to rapid clinically meaningful reductions on the NPRS, with more than 3 points of pain reduction or roughly a 50% reduction from baseline in the VX-548 arms. The single arm safety and effectiveness trial was conducted in a broad range of surgical and nonsurgical pain conditions and supported longer-term safety and effectiveness. VX-548 was safe and well tolerated across all 3 studies, including multiple acute pain types and settings. Of importance, with respect to safety, in the 2 RCTs, the incidence of adverse events in the VX-548 arms was lower than

placebo, an uncommon and noteworthy finding. We believe the results of this comprehensive Phase III program support a broad, moderate-to-severe acute pain label, and if approved, should enable prescribing and usage across multiple care settings.

VX-548 has already secured Fast Track and Breakthrough designations, and we are working with urgency to file the NDA by mid-2024. Moving now to neuropathic pain. Two months ago, we also reported positive results from our Phase II study of VX-548 in diabetic peripheral neuropathy, one type of peripheral neuropathic pain and another area of high unmet need. We look forward to our end of Phase II meeting with the FDA towards the end of this quarter and starting our Phase III program thereafter. We also continue to enroll and dose our second Phase II neuropathic pain study of VX-548 in lumbosacral radiculopathy or LSR.

Ultimately, we seek a broad neuropathic pain label and believe by studying 2 of the largest pain segments, DPN and LSR, which together represent more than 60% of all peripheral neuropathic pain, we have a pathway to that broad indication. Just as we transform the treatment of CF, we believe we have the potential to transform the treatment of pain, both acute and neuropathic, based on the compelling and consistent results we have seen with VX-548. We now have results in hand from the Phase III program in acute pain as well as the Phase II results in DPN. We are underway with the Phase II study in LSR, and we are continuing to execute our portfolio approach of serial innovation. We are well on our way to helping address the unmet need of 90 million patients suffering with pain.

With that, I'll now turn it over to Stuart.

Stuart Arbuckle Executive

Thanks, Reshma. With the recent approvals of CASGEVY in sickle cell disease and transfusion-dependent thalassemia in multiple countries and the recent positive results in our pivotal trials for VX-548 in acute pain and for the vanzacaftor triple combination in CF, we are well and truly entering a new era of commercial diversification. As Reshma noted, we delivered strong fourth quarter and full year commercial results in CF as we continue to grow the number of eligible patients receiving our CFTR modulators. Fourth quarter U.S. growth was driven by continued strong performance of TRIKAFTA, including in patients ages 2 to 5 years old following the approval for these patients in April.

Outside the U.S., we saw continued growth from both label expansions and new reimbursement agreements. In the near term, we will continue to focus on reaching more eligible patients, including younger age groups, which will provide revenue growth, and then we expect to drive further growth with the vanzacaftor triple combination. Given the positive Phase III data we released today that demonstrates a strong benefit risk profile and the ability to deliver greater restoration of CFTR function than even TRIKAFTA, we believe the vanzacaftor triple combination will be widely welcomed by the CF community, both as a new treatment option for the greater than 6,000 patients who have discontinued one of our current CFTR modulators, and as an opportunity for TRIKAFTA patients to achieve even greater levels of CFTR function. Longer term, we see additional growth from our mRNA program, VX-522, that we are developing in partnership with Moderna for the more than 5,000 CF patients with mutations that do not respond to CFTR modulators. In addition, we recently updated our estimate of the number of people living with CF in North America,

Europe and Australia to 92,000 from the previous estimate of 88,000.

This increase is in large part due to patients living longer as a result of improvements in CF care, including the advent of CFTR modulators. We expect this trend to continue based on the real-world evidence we have generated on the clinical benefits of CFTR modulators, and this will also drive long-term growth. Now turning to CASGEVY and our launches in sickle cell disease and beta thalassemia. Enthusiasm from patients, physicians and payers is very high around the globe, and we are focused on translating the scientific and medical innovation that CASGEVY represents into transformative patient benefit in the real world. In countries where CASGEVY has been approved, our sales, reimbursement and access teams as well as patient engagement teams have hit the ground running.

Let me provide some insights on the early days of the launch. Starting with physicians. There is tremendous interest in CASGEVY and what it can do for their patients, and we see the impact of that in the rapid activation of authorized treatment centers. Less than 2 months post approval, we already have 12 ATCs in the U.S., 3 in the EU and 1 in the Kingdom of Saudi Arabia, all ready to receive patients. Reaction from payers has also been very positive.

In the U.S., across commercial and government payers, all eligible CASGEVY patients have case-by-case coverage through single case agreements. We continue to see excellent progress from payers on the development of their formal medical policies and reimbursement pathways. We have a contract in place with Synergie for up to 100 million lives and are actively engaged with other commercial payers to finalize medical policies, which would bring the total percentage of covered lives to over 80%. In the government sector, Medicaid state agencies representing over 60% of sickle cell disease lives have established reimbursement pathways for CASGEVY, with an additional 25% of Medicaid sickle cell disease lives in states actively progressing their reimbursement methodologies. In addition, we were pleased to have received the January approval in the U.S.

for CASGEVY for transfusion-dependent thalassemia patients 2.5 months early and are working to achieve a similarly fast trajectory for gaining reimbursement and access for patients. Last week, there was an important update by the Biden administration on the CMMI Cell and Gene Therapy Access Demonstration Model that was originally announced in February of 2023 and was recently accelerated for implementation from 2026 to 2025. We believe the CMMI CGT Access Model could be an important additional path to access, and we now have greater clarity on the scope and process to be employed in the model. The model is intended to provide a comprehensive strategy to address barriers to equitable access to cell and gene therapies for Medicaid beneficiaries as well as the long-standing inequities of care in the sickle cell disease community. Last week's update also confirmed additional federal funding to support access and included a defined scope of manufacturer-provided fertility support in the model in recognition that for patients choosing to embark on the treatment journey, the costs of fertility preservation are a barrier to access.

In the meantime, we continue to actively engage with state Medicaid agencies to finalize medical policies for CASGEVY even in advance of the CGT Access Model to ensure patient access without delay. Outside the U.S., we are pleased that the French National Authority for Health has approved our request for the implementation of an early access program or EAP

for TDT patients ages 12 to 35 years. We are delighted to have secured a path to access and payment in France ahead of a national reimbursement agreement and are also in an EAP review process for sickle cell disease patients. In the U.K., CASGEVY will be reviewed by the highly specialized technology committee in February, and we are advancing our reimbursement discussions in other European countries as well. We also see strong progress in the Middle East, which is especially important for CASGEVY, given the high prevalence of these diseases in the region and the government's clear focus on elevating the health of their citizens.

We are working with local health care authorities in the Kingdom of Saudi Arabia and Bahrain to refine our estimates of the exact number of eligible patients, but there are thousands of patients we could serve, and we are focused on securing access and reimbursement for them. We have established a local presence in the region, have already activated our first ATC and are working with local health care professionals to expand the number of ATCs and establish the required infrastructure to meet patient demand. As we have previously outlined, the CASGEVY patient journey can be broken down into 3 key phases, each of which can take several months: pretreatment; cell collection and manufacturing; and then infusion of the edited cells. We are pleased with the early days of what will be a foundational year for CASGEVY as we work to deliver transformative patient outcomes with the possibility of a lifetime of benefit. We look forward to updating you on the CASGEVY launch over the course of this year.

To help track our progress, our expectation is to provide quarterly updates on the number of activated ATCs as well as the number of patients in the cell collection phase. ATCs have begun assessing their patients for the ability to be treated with CASGEVY, and we expect that the first commercial patients will start the journey in the coming weeks. Shifting now to VX-548. We are very excited about the potential for this highly selective NaV1.8 inhibitor to provide a transformative treatment option for the millions of patients suffering from acute and peripheral neuropathic pain. This quarter, I'll limit my comments to acute pain.

As we discussed last week, when we shared the results from the pivotal program, we are very excited about VX-548's compelling combination of efficacy and safety and the demonstration that it can be used for moderate to severe pain across a range of pain conditions, both surgical and nonsurgical and across a range of settings. If approved, VX-548 will be the first of a new class of medicines that inhibit the pain signal and represent the first new class of medicines for acute pain in over 20 years. The reason we're so excited about the potential for VX-548 to positively impact patient care is because we estimate approximately 80 million patients are prescribed a medicine for moderate to severe acute pain every year in the U.S., representing over 1 billion calendar days of treatment. Given this massive patient population, acute pain is a multibillion dollar market today despite the fact that essentially all prescriptions are generic. We also see upside to this market opportunity, given the significant unmet need that stems from the suboptimal benefit risk profiles of existing agents such as the limited efficacy but acceptable side effects of NSAIDs or the adverse effects and addiction potential of opioids, all of which leads to suboptimal pain management.

What physicians and patients seek is a medicine that combines effective relief of moderate to severe pain with a clear safety and tolerability profile, and VX-548 delivers on that profile.

We've previously shared our go-to-market strategy, and we are now actively recruiting our field force in anticipation of our regulatory filing and approval. The commercial team will focus on the roughly 2,000 hospitals and institutions where a majority of acute pain patients are seen and prescriptions are written. We continue to see a multibillion dollar opportunity for VX-548 in acute pain alone. The well-known risk of opioids have led to widespread restrictions and limitations on their use over the years.

Increasingly, we are seeing a paradigm shift in policy initiatives across various stakeholders to encourage consideration and use of non-opioid alternatives and to remove financial barriers to choosing a branded non-opioid. As an example, late last month, Congress introduced the bipartisan alternatives to Prevent Addiction in the Nation Act or the alternatives to pain act. If enacted, Medicare Part D plans would be required to set co-pays for non-opioids like VX-548 in line with co-pays for generic opioids, which are typically between $0 and $15. The bill would also prohibit Medicare Part D plans from requiring seniors to step through opioids first or requiring prior authorization for non-opioids. In addition, the NOPAIN Act or Non-Opioids Prevent Addiction in the Nation Act, which was enacted in late 2022, provides for an add-on payment for non-opioids in the outpatient and ambulatory surgery center settings and remains on track to go into effect in 2025.

And just recently, 7 states: Maine, Massachusetts, Missouri, Oklahoma, Tennessee, Washington and West Virginia, have pending legislation that would require education on non-opioid options and would remove financial barriers to patient access within state-based health insurance programs like Medicaid. We expect additional states to introduce similar legislation later this year. We believe that these advances in federal and state legislation represent further momentum in Congress and across the U.S. to encourage adoption of and remove any financial barriers to using non-opioid therapies like VX-548. In conclusion, it's an incredibly exciting time at Vertex.

We continue to treat more CF patients around the world, and with the vanza triple, now have visibility to provide an option for the patients who have discontinued CFTR modulators as well as the possibility to bring even more patients below diagnostic levels and even to carrier levels of sweat chloride. We're entering a new era of commercial diversification with the launch of CASGEVY, the first ever gene-edited therapy that brings a potential functional cure to patients with sickle cell disease and beta thalassemia across multiple regions, and we are preparing for additional near-term launches with significant market potential, including VX-548 in acute pain. I'll now turn the call over to Charlie to review the financials.

Charles Wagner Executive

Thanks, Stuart. Vertex' excellent results in the fourth quarter of 2023 demonstrate once again our consistent strong performance and attractive growth profile. Fourth quarter 2023 revenue increased 9% year-over-year to $2.52 billion and was nicely balanced with revenue growth of 8% in the U.S and 12% outside the U.S. Full year revenue of $9.87 billion represents 11% growth versus 2022, our ninth consecutive year of at least double-digit growth. Overall, the primary drivers of revenue growth in 2023 were in line with our expectations.

Fourth quarter 2023 combined non-GAAP R&D, acquired IP R&D and SG&A expenses were $1 billion compared to $872 million in the fourth quarter of 2022. Included in Q4 '23 results

are $18 million of acquired IP R&D charges compared to $23 million of such charges in the fourth quarter of 2022. Note that with the approval of CASGEVY in the fourth quarter, cost for manufacturing capacity for CASGEVY are now being recorded in cost of goods sold rather than in R&D. Full year 2023 combined non-GAAP R&D, acquired IP R&D and SG&A expenses were $4.24 billion compared to $3.07 billion in 2022. Fourth quarter and full year operating expense growth was driven as expected by continued investment in research and our pipeline as we have now advanced assets into the clinic in 9 different disease areas.

In the fourth quarter and throughout 2023, the most significant areas of increased investment versus prior year included the pivotal studies for VX-548 in acute pain and the vanzacaftor triple in CF, the Phase I/II study for type 1 diabetes as well as the build-out of capabilities for both our expanding pipeline and our anticipated near-term commercial launches. In addition, approximately $400 million of the year-over-year increase in operating expenses was the result of increased AIP R&D costs from new business development. Fourth quarter 2023 non-GAAP operating income was $1.15 billion consistent with $1.15 billion in non-GAAP operating income in the fourth quarter of 2022. Full year 2023 non-GAAP operating income was $4.37 billion compared to $4.79 billion in 2022. Fourth quarter 2023 effective tax rate of 16.3% reflects an increase in our 2023 U.S.

R&D tax credits. This benefit lowered the Q4 rate and brought the full year 2023 effective tax rate to 19.4%, slightly below our guidance range of 20% to 21%. Fourth quarter 2023 non-GAAP earnings per share were $4.20, representing 12% growth compared to $3.76 in the fourth quarter of 2022. Full year 2023 non-GAAP earnings per share were $15.23 compared to $14.88 in 2022. We ended the quarter with $13.7 billion in cash and investments.

Our priorities for cash deployment remain unchanged as we continue to prioritize investment in innovation, including external innovation via business development. During 2023, we completed 10 transactions and recognized over $500 million of AIP R&D. We also deployed over $400 million to repurchase 1.3 million shares over the course of 2023. Now switching to guidance. For 2024, we expect total product revenue in a range of $10.55 billion to $10.75 billion, representing revenue growth of 8% at the midpoint at current exchange rates.

Included in this outlook is our expectation for continued growth in CF as we continue to reach more patients, including younger ones, in core markets and select other countries. Guidance also includes contribution from the commercial launch of CASGEVY in approved indications and geographies. We continue to expect a foundational year for CASGEVY in 2024 as we ramp up patient initiations and build toward a multibillion dollar market opportunity over time. We are providing total product revenue guidance rather than specifics by disease area or product given the inherent uncertainty of new launches as well as the significant disparity and size of our established CF business relative to other revenues. As a reminder, on the accounting for CASGEVY and the CRISPR profit share arrangement, Vertex will book 100% of revenues for CASGEVY.

The profit share with CRISPR calculated after product and commercial costs will be recorded in cost of goods sold. Any ongoing research and development costs will be recorded in operating expenses net of CRISPR's share. For total Vertex operating expenses, we project $4.3 billion to $4.4 billion in full year 2024 combined non-GAAP SG&A, R&D and acquired IP

R&D. This operating expense range includes approximately $125 million in currently anticipated IP R&D charges. We 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.

Note that the costs for multiple Phase III studies have been a significant driver of our growth in our total operating expenses in recent years. Given that a number of Phase III studies were completed as we entered 2024, we were able to fund new additional Phase III studies without the same rate of growth in operating expenses. While we have substantially completed our commercial investments for CASGEVY, we're also funding the expansion of our commercial capabilities in anticipation of other multibillion dollar opportunities represented by our programs with near-term launch potential while continuing to leverage an attractive business model afforded by our focus in specialty markets. With a more normalized impact from U.S. R&D tax credits in 2024, our full year 2024 non-GAAP effective tax rate is expected to be in the range of 20% to 21%.

In closing, Vertex delivered excellent results yet again in 2023, achieving strong revenue growth, important regulatory approvals and commercial launches and positive pivotal trial results that will enable additional near-term launches. We also made progress in our earlier stage pipeline, with proof of concept for VX-548 in neuropathic pain and anticipated advancement of 2 additional disease areas into the clinic. We also made substantial investments behind our programs and commercial capabilities for near-term launches. As we head into 2024, we anticipate further important milestones as highlighted on Slide 20, to mark our continued progress in multiple disease areas. We look forward to updating you on our progress on future calls, and I'll ask Susie to begin the Q&A period.

Susie Lisa Executive

Thanks, Charlie. Just to note, given the multiple positive updates this quarter and thus the longer duration of our prepared remarks, we'll plan to go to about 5:40 this evening, so as to allow 30 minutes for your questions. Chuck, please go ahead and assemble the queue.

Operator Operator

[Operator Instructions] The first question will come from Ms. Salveen Richter with Goldman Sachs.

Salveen Richter Analyst

Congratulations on the data. Two questions for me. One is, with regard to the initial patient you'll be targeting with the next-generation CF program, could you just elaborate whether it's switch patients or patients who have discontinued, naive patients here and where you anticipate the most demand? And then secondly, on the CASGEVY launch, in light of the Innovation Cell and Gene Therapy Access Demonstration Model, how do you work that into the launch at this point? And is there an overhang as you have to determine how these outcome-based agreements may play out?

Reshma Kewalramani Executive

Sure thing, Salveen. Let me turn it over to Stuart for both the question on vanza

commercialization and on the CASGEVY launch with the focus on the CMMI question.

Stuart Arbuckle Executive

Yes, Salveen. So in answer to your first question on vanzacaftor, the answer is both. I think vanzacaftor is going to be an attractive treatment option, both for patients who are currently being treated who might want superior control of their CFTR function, because both patients and physicians know that CFTR function and dysfunction is the underlying cause of CF, and so if you can further improve CFTR function, you're going to get better clinical outcomes down the line. So I think we're going to see interest from those who are currently being treated, but I also think we're going to see a lot of interest from patients who previously discontinued one of our CFTR modulators, given the profile that we've demonstrated today. And then on CASGEVY, a couple of comments, really.

The first one I would make is we're very excited about the demo and the opportunity to work with CMS for those states who are interested in working with CMS and are interested in outcomes-based agreements. I don't particularly see that being a delay for a couple of reasons. One, we're already working with many state Medicaid agencies. We're not waiting for the demo before we secure access for patients who are covered by Medicaid. And then secondly, in terms of do I think it's going to be complex and be a delay to negotiate outcomes-based agreements?

I don't, really. If you look at the profile of CASGEVY, it is so incredibly strong that really we're talking about an outcomes-based agreement, which is looking at whether a very, very small number of patients may not respond. And so I don't think it's an outcomes-based agreement where there's lots of uncertainty and difficulty with the outcomes and metrics and endpoints. And so I don't expect that to be particularly challenging.

Operator Operator

Next question will come from Geoff Meacham with Bank of America.

Geoffrey Meacham Analyst

Congrats on the data. On vanza, I just have a couple of questions. Can you follow SKYLINE or RIDGELINE in an extension? I'm just trying to think if you can pick up more differentiation versus TRIKAFTA just in terms of maybe exacerbations or measuring pancreatic sufficiency over a longer period. I guess ultimately, where I'm going is that sweat chloride isn't readily used in the clinic for treatment decisions, so I'm trying to see rationale for maybe switching a patient away from TRIKAFTA if they're stable.

Reshma Kewalramani Executive

Yes. Thanks, Geoff. This is Reshma. Let me take that one. When we think about the patients who were enrolled in both the SKYLINE trial, so the 12-year olds and above, and the RIDGELINE patients, 6 to 11, there are already extension studies.

So those patients have the opportunity to roll over into open-label extended studies just like we did with TRIKAFTA. And I do suspect you're right about the ability to evaluate and document the overall improvements in patients with CF lives over time. And just to give you a

sense for what I'm looking at and why I say that, if you look in the safety tables that were one of the slides, unsurprisingly, the most common or one of the most common AEs in this patient population is pulmonary exacerbation. And if you look, there are less pulmonary exacerbations numerically in those safety tables in the patients on vanza than on the patients who are on TRIKAFTA. And TRIKAFTA is an amazing drug that has already documented improvements in pulmonary exacerbation and other longer-term outcomes.

So I do think you're very correct that we'll be able to pick up these long-term outcomes as these patients are followed in the open-label extension studies and then as they are followed in registries, and we are very fortunate in CF that the registries already exists and the vast majority of patients with cystic fibrosis are followed in registries.

Operator Operator

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

Mohit Bansal Analyst

Just following up on Geoff's question. So how commonly doctors check sweat chloride levels as part of -- I know it is for diagnostic purposes, but do they check it for -- do they test it for prescribing as well? Or it is something that you will have to educate these adopters on that? And then my follow-up is actually on the COGS for Charlie, cost of goods sold. As you think about 2024, what happened in 2023 fourth quarter was a onetime movement from R&D to COGS which drove it?

Or is this something that we to continue more going forward?

Reshma Kewalramani Executive

Let me ask Charlie to tackle the COGS question first, and I'll come back and tell you about sweat chloride in clinical practice.

Charles Wagner Executive

Yes, Mohit. In the fourth quarter, because CASGEVY was approved in the U.S., we started treating it as a commercial product, and therefore we took some of the manufacturing costs that previously had been recorded in R&D and moved them up to cost of goods sold. Those manufacturing costs will remain in cost of goods sold going forward.

Reshma Kewalramani Executive

Mohit, with regard to sweat chloride measurement in clinical practice, you're very correct. In terms of diagnosis, patients in the Western world are diagnosed by a gene test, a genetic test, when -- oftentimes when patients are born or when people are born, and then that's confirmed with the sweat chloride test. If the number is above 60, that diagnosis of CF, if it's between 30 and 60 millimoles for sweat chloride, that's indeterminate and if it's less than 30, that is not diagnosed as CF. This is not a metric. Sweat chloride is not a measure that's followed routinely in clinical practice.

But what physicians understand very well, especially pulmonologists who are CF experts, is that the underlying cause of disease in CF is dysfunction of the CFTR protein. That's very well

understood. And further, that a direct readout of that CFTR protein function is sweat chloride. So I think the concepts are very well understood, but sweat chloride other than the diagnosis is not a commonly used test in the clinic.

Operator Operator

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

Philip Nadeau Analyst

Let us add our congratulations on another positive pivotal program. One on sweat chloride, then one actually on the pain data that you released last week. First, on the sweat chloride, it does look like TRIKAFTA gets a decent proportion of patients to below 60 millimole per liter and below 30 millimole per liter. Do you have data following the patients who've been on TRIKAFTA for a long time to show better outcomes for those TRIKAFTA patients who got to low levels of sweat chloride, which then presumably you could extrapolate to the vanza triple and show a higher proportion of patients would have good outcomes? That's the first question.

And then the second question on the pain data released last week. It does seem like the bunionectomy Phase III trial underperformed the Phase IIs that you had previously released as well as the abdominoplasty Phase III released last week. Was there anything different about that trial which would have caused 548 to act less potently there than it had in the prior studies?

Reshma Kewalramani Executive

Yes. Phil, let me take bunionectomy, abdominoplasty, VX-548 first, and then we'll come back to sweat chloride. You know what I actually find remarkable, Phil, is the -- how consistently 548 has performed. That, to me, is more striking than the smaller differences in bunionectomy readout Phase II to Phase III or across from bunionectomy to abdominoplasty. So if I look at the totality of the VX-548 evidence, and it's easy enough to do because the structure of the study design was very similar in Phase II as Phase III and we have the same dose, the high dose from Phase II, you'll see that bunionectomy and abdominoplasty performed virtually identically.

Like the SPID48 was something like 40 points or something like that. I think that was the actual number. And then when you move to Phase III, again, positive studies against placebo. In the grand scheme of things, this is remarkable because as you know, the conduct of clinical trials in the pain field is notoriously difficult. Placebo effects move around significantly.

The effect of any comparator group moves around significantly. So when I look at the totality of the data, and for me, that means looking at the data from Phase II to Phase III, and it also means looking at the SPID48, let's focus on bunionectomy, in bunionectomy, and connecting that with the NPRS. Remember, the NPRS is the actual score that feeds the SPID48, which is an integration of NPRS over time. So if you look at the NPRS data, it's -- the decrease in the NPRS is 3.4 points in bunionectomy, it's 3.4 points in abdominoplasty start to hour 48. And it's about a 50% decrease in terms of the relative decrease.

And when you look at that in comparison to Norco, the opioid we used in the trial, that number is 3.2 in abdominoplasty, 3.6 in bunionectomy and it's approximately a 50% reduction in terms of the relative change. So I put that all together, and I see quite a bit of consistency and very good therapeutic effectiveness and efficacy. On sweat chloride. So it's a really, really great question. And in order to sort of really understand this, you have to triangulate a couple of different data points.

One data point is around just the natural history and the genetics of this disease. So take, for example, patients who are F/MF versus those who are F/RF, F/MF patients have very high sweat chlorides and have more severe disease. F/RF patients, the residual function patients, have relatively better sweat chloride levels and relatively less severe disease. That's one set of data. And then to your point, if you look at interventional data, the data that we have, the greatest reduction in ppFEV1, sweat chloride and long-term evidence is TRIKAFTA.

And if you compare that to KALYDECO, for example, you can see where TRIKAFTA does even better than KALYDECO. And the best example I can give you is on rate of decline. The TRIKAFTA real-world data on rate of decline shows there is no decline. And until we got to TRIKAFTA, what we could show is we slowed the rate of decline. And so I have every reason in the world to believe as the vanzacaftor triple is used over a longer time point and we get CFTR protein function to higher levels, and the Vanza triple has given us the best, highest achieved CFTR protein levels, I do think we're going to see long-term benefit.

And yes, you can do all of that math and triangulation from the available data.

Operator Operator

Next question will come from Robyn Karnauskas with Truist.

Robyn Karnauskas Analyst

So commercialization, I know it's really hard switching from one drug to the next. Can you walk me through switching from TRIKAFTA to the next drug. And like given that people are stable, their lung functions are great, how would you think about what motivates commercial Europe as well as U.S. to allow people to stay on drug and like move to a next-generation drug? And I think -- I'm coming from the point of like I remember from a long time ago, the people had a hard time switching from one drug to the other.

And I want to understand like more like how you actually help people, help commercial organizations switch from one to the next.

Reshma Kewalramani Executive

Stuart?

Stuart Arbuckle Executive

Yes, Robyn, thanks. So I must confess our experience is a little bit different to that. We've seen very rapid transitions from our medicines as we've serially innovated and delivered better and better medicines. And even, for instance, when we introduced TRIKAFTA and patients who had been on KALYDECO, for instance, for a very long time, and obviously,

KALYDECO had set a very, very high bar for efficacy. We did see rapid adoption with TRIKAFTA, even in those patients, given that it had a clear benefit/risk profile.

So I think we've seen relatively rapid transitions for our medicines as we've serially innovated. And interestingly, the design of the study actually gives a proof for the fact that patients can effectively transition from TRIKAFTA to vanzacaftor because, as Reshma mentioned in her remarks, the design of the study was to have people stable on 4 weeks of TRIKAFTA therapy to establish a baseline, and they were then randomized to either continue on TRIKAFTA or transition to vanzacaftor. So we have, within the study, real-world evidence of people being able to transition. And then you'll ask me what do I think is going to motivate people to want to consider the vanzacaftor triple combination? I think it's the benefit/risk profile that we've been able to demonstrate here.

We're achieving higher levels of sweat chloride reduction than with any of our previous medicines, including now TRIKAFTA, and the fact that this is a once-a-day therapy. So as I've said a number times, I think with this profile, we're going to see a lot of enthusiasm from the CF community.

Robyn Karnauskas Analyst

So follow-up question for you is what about the payers and the governments in Europe? Do they believe -- and like you've had very stable levels of lung function with TRIKAFTA, do you think that people will focus on like that? Or do they need more data moving forward?

Stuart Arbuckle Executive

Well, I mean, I think we've had a long track of working with payers on cystic fibrosis for again of well over a decade now. So I think there's a significant amount of understanding about the disease. Obviously, we'll be presenting the data to vanzacaftor to payers in a compliant manner at the right time. The one other thing would I note about the vanzacaftor triple combination is it's likely to be indicated for a very similar population of patients to TRIKAFTA, which I do think is going to make this launch, from a payer perspective, a bit different to previous launches, as you will recall, because you've been on this journey with us for a while. When we launched ORKAMBI, we were moving from kind of single-digit numbers of eligible patients to a medicine that could potentially treat up to 50% of CF patients.

When we then brought TRIKAFTA forward, we were moving it towards being able to treat 90% of patients. Vanza is going to likely have a very similar label to TRIKAFTA, and so it's not likely to be as scary, I would suggest to payers, in terms of a big budget impact hit.

Operator Operator

Next question will come from Jessica Fye with JPMorgan.

Jessica Fye Analyst

Great. Can you set expectations around how you see the cadence of patients initiating the CASGEVY journey for us?

Reshma Kewalramani Executive

Sure thing. Stuart?

Stuart Arbuckle Executive

Yes, Jess. So I think we've described the patient journey for CASGEVY. It has kind of these multiple phases from patients being evaluated by their physician and deciding with their physician that this is the journey that they want to go on. You then have to go through the cell collection and manufacturing process and then the cells are infused. Each of those steps can take a number of months.

And as you know, we've said that we'll be recognizing revenue at the point of infusion. So in contrast to our cystic fibrosis launches, which have really seen incredibly rapid uptake, we have said that we are expecting this launch to be more like a traditional biopharma launch, but we are expecting this, and we have said we are expecting this, to be a foundational year for us as we build momentum around CASGEVY. Having said that, in terms of the destination, we continue to believe that the destination for CASGEVY is going to be used in thousands of patients and represents a multibillion dollar opportunity.

Operator Operator

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

Evan Seigerman Analyst

I know there's a lot on the vanza triple, but kind of -- can you maybe walk us through some of the clinical considerations as you would get to maybe have a physician switch patient? And then thinking about kind of potential TRIKAFTA quitters returning on drug, what does that conversation look like? And I guess, maybe more specifically, why would a patient discontinue TRIKAFTA and why would they want to reinitiate with the vanza triple?

Reshma Kewalramani Executive

Sure thing, Evan. I think Stuart has talked about this, and maybe I'll shorthand it by saying we have the approximately 6,000 patients who are in the system. They are known to have CF. They are seen by a CF provider. They used to be on TRIKAFTA.

So they're not lost, they simply have discontinued it either because of an adverse event or perhaps because of compliance. TRIKAFTA [indiscernible]. Vanza is, of course, once a day. So we see those 6,000 patients potentially coming back, and the short version of the conversation would be they're coming to see their doctor, usually CF patients are seen by their doctor once a quarter, so when they return, the conversation might be something like, if and when vanza is approved, there's a new drug. It has this safety.

It has this efficacy. Do you want to try it? You had tried a medicine before. This is a new one. And the doctor and patient would have a communication about that.

So the patients who are already on TRIKAFTA and are doing well, I suspect it's going to be just like it was from SYMDEKO and ORKAMBI to TRIKAFTA or from KALYDECO to TRIKAFTA. Our CF patients are very educated patients. They know what clinical trials are going on. They know what potential medicines might be coming down the pipe, and they are interested in

being treated with the most effective medicine, the medicine with the best benefit/risk. And they do this because it is a disease that starts at birth and is with them their entire life.

Now with the life expectancy, based on modeled data, being in the 80s, I do think the idea is that we can get patients to as close to normal as possible, at least we're on that journey with vanza is an attractive option for physicians and patients. And I suspect that's what that conversation is going to be about.

Operator Operator

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

Christopher Raymond Analyst

Congrats from us as well on the data. Just 2 questions, if possible. First maybe on CASGEVY. We've gotten some physician feedback that, of course, access is a barrier to uptake. But maybe a surprise that we got from some of the questions we've asked is that transplant center capacity and prioritization of non-oncology patients is also sort of a consideration.

Just curious, as you activate these ATCs, maybe talk about transplant capacity. Does this factor into the discussions as you're activating these sites? And then maybe on vanzacaftor, I know you guys have described the royalty differential. I think TRIKAFTA is in the low double digits, and you've described vanzacaftor as down in the single digits. But are there plans to put some guardrails around this leverage improvement as you get closer to launch of the vanza triple?

Reshma Kewalramani Executive

I'm sorry, Chris, I didn't follow the question on the vanza triple. I got you on CASGEVY. Is it about the royalties?

Christopher Raymond Analyst

Yes, sorry. On -- yes, just on the leverage and the royalty differential. I think you guys described the difference, but are there plans to put guardrails around that leverage as people model that?

Reshma Kewalramani Executive

Yes. Yes. Sure thing. Let me take CASGEVY quickly, turn it over to Stuart and then we'll just do one minute real quick with Charlie, and he'll tell you about the royalty structure for vanza. Real quickly on CASGEVY, we have not heard of there being a center capacity issue.

And honestly, we have not heard about challenges for reimbursement. We've actually had very positive reception from payers. But I'll turn it over to Stuart to make a quick comment on activation and his perspective.

Stuart Arbuckle Executive

Yes. And we're making great progress, Chris, I would say, activating authorized treatment centers just here in the U.S. We're now up to 12, and I don't think those centers would be

going through the effort of becoming an activated treatment center if they weren't fully intending to treat patients with CASGEVY. And then as Reshma said, the reaction we've had from payers has been really positive. I think they're incredibly impressed with the clinical data.

They are well aware of the unmet need in sickle cell disease and indeed transfusion-dependent thalassemia and the burden that places on patients and indeed the health care system. They like the label that we've got, and they like our value-based price. And so I've been very encouraged by the conversations we've been having with payers, and I'm fully expecting us to be able to secure great access for sickle cell disease and TDT patients.

Reshma Kewalramani Executive

Charlie, a word on royalties.

Charles Wagner Executive

Yes, just briefly on the royalties bit, Chris. The blended royalty rate on our current CF portfolio is just under 10%. And so high single digit, call it. And we expect with the vanza triple, that royalty burden will be meaningfully lower in the single digits. No additional color to add today.

And then, of course, if you want to model the impact of that, you have to factor in the rate of switching from TRI and other medicines again. So as we get closer to commercialization, we'll have more to say.

Operator Operator

The next question will come from Colin Bristow with UBS.

Colin Bristow Analyst

Congrats on all the data. Maybe first on the vanza triplet. Can you say if there are any cases of AST or ALT elevations greater than 3 or 5x the upper limit of normal? And then secondly, I see that you've now got 3 follow-on pain assets in clinic: 993, 973 and 708. Could you just give us more color on how you expect them to be differentiated and just elaborate a bit more on the strategy from here?

Reshma Kewalramani Executive

Yes. Sure thing, Colin. Quickly on LFT elevations with the vanzacaftor triple. As with all of the CFTR modulators, there are some elevations in LFTs. They're approximately the same with the vanzacaftor triple as with TRIKAFTA.

On the pain program, Colin, this is exactly what you saw us do in CF and frankly, what you should expect from us across the portfolio. And that is to say a portfolio approach to every disease in our sandbox. If there is a way to improve on our assets, we aim to be the ones who do so. So a couple of examples of what we're doing with 993, for example. 993 is a medicine that may be able to be dosed both oral and IV, and we're pursuing both.

We believe that there is a real opportunity here for a patient to come into hospital and have 993 or one of our NaV1.8 inhibitors be the medicine that they get for pain relief, let's say, intraoperatively. And then when they can take by mouth, then they can switch to 548, 993, as

an example. Another example that we're working on, you know that we also have a pipeline of NaV1.7 inhibitors. Those are still in preclinical development, but they are making good progress. So one of the other elements we're working on is formulations in terms of drug-drug interactions and the possibility to combine.

So NaV1.7 could be a molecule as a single agent therapy or it could also be a therapy in combination with the NaV1.8. That's kind of a sense for what we're doing with our follow-on approach.

Operator Operator

Our last question for the evening will come from Myles Minter with William Blair.

Myles Minter Analyst

You just mentioned the first commercial patients on CASGEVY are expected to start the journey in the coming weeks. Can you clarify what geographies they are in? And do you have a sense of how many patients you've screened out at those ATCs to identify those first patients?

Reshma Kewalramani Executive

Sure thing. Myles, we're not going to comment in detail on the first patients, but as Stuart said in his prepared remarks, we're expecting our first patient shortly.

Operator Operator

This concludes our question-and-answer session as well as our conference call for today. I want to thank everyone 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 10178829. Thank you, and have a great day.