Horizon Therapeutics plc
Fourth-Quarter and Full-Year 2020 Conference Call
February 24, 2020

Tina Ventura
Senior Vice President, Investor Relations

Thank you, Ursula. Good morning, everyone, and thank you for joining us.

On the call with me today are:

- **Tim Walbert**, Chairman, President and Chief Executive Officer;
- **Karin Rosén,** Executive Vice President, Research & Development and Chief Scientific Officer;
- **Paul Hoelscher**, Executive Vice President, Chief Financial Officer;
- **Liz Thompson, Ph.D.**, Group Vice President, Clinical Development and External Search; and
- **Andy Pasternak**, Executive Vice President, Chief Strategy Officer

Tim will provide a high-level review of the business, our 2020 performance and 2021 guidance. Karin will then provide a review of our R&D programs, followed by Paul, who will discuss our financial performance and guidance in more detail. After closing remarks from Tim, we will take your questions.

As a reminder, during today's call we will be making certain forward-looking statements, including statements about financial projections, development activities, our business strategy and the expected timing and impact of future events. Our actual results could differ materially due to a number of factors, including the extent and duration of the effects of the COVID-19 pandemic, as well as other factors outlined in our annual report on Form 10-K for the year ended Dec. 31, 2020, and our earnings press release, which we issued this morning.

You are cautioned not to place undue reliance on these forward-looking statements and Horizon disclaims any obligation to update such statements.

In addition, on today's conference call, non-GAAP financial measures will be used. These non-GAAP financial measures are reconciled with the comparable GAAP financial measures in our earnings press release and other filings from today that are available on our investor website at www.horizontherapeutics.com.

I will now turn the call over to Tim.

Tim Walbert
Chairman, President and Chief Executive Officer

Thank you, Tina, and good morning, everyone.

Our fourth quarter capped off an exceptional year for Horizon.

- We achieved record full-year total Company net sales of $2.2 billion, representing year-over-year growth of 69 percent. This was driven by our successful launch of TEPEZZA® for Thyroid Eye Disease, achieving $820 million in its first year on the market, as well as continued double-digit growth of KRYSTEXXA®, our biologic for uncontrolled gout. TEPEZZA and KRYSTEXXA finished the year strong – both growing double digits in the fourth quarter versus the third quarter.
- We also achieved record full-year adjusted EBITDA of approximately $1 billion, which increased more than 100 percent compared to 2019. Our 2020 adjusted EBITDA margin was 45.4 percent, a more than 800-basis-point increase compared to 2019, which we drove a full year ahead of our previous plans.
- This morning we issued full-year 2021 guidance that again represents strong double-digit year-over-year growth. Our full-year net sales guidance of $2.7 billion to $2.8 billion represents 25 percent growth at the midpoint. Our adjusted EBITDA guidance of $1.14 billion to $1.18 billion represents 16 percent growth at the midpoint and includes significant investment in driving TEPEZZA uptake and our pipeline – we are roughly doubling our R&D spend compared to 2020 and initiating 6 trials independent of the Viela acquisition.

Additional milestones achieved in 2020 include:

- The acquisition of Curzion Pharmaceuticals, giving us HZN-825, our $LPAR_1$ antagonist that is expected to enter two Phase 2b pivotal trials this year. We now have 14 programs in total in our pipeline.
- We also advanced our KRYSTEXXA immunomodulation strategy, where we continue to see an increase in the use of KRYSTEXXA plus an immunomodulator, now at more than 35 percent of new patient starts. This led to a strong second-half and fourth-quarter KRYSTEXXA net sales growth, and we finished the year up nearly 20 percent, despite the impact of COVID-19.
- And we significantly strengthened our balance sheet, ending the year with more than $2 billion in cash, which is more than double the principal amount of our outstanding debt. This provided us with significant flexibility to pursue business development opportunities and positioned us well to acquire Viela Bio for a total transaction value of $2.67 billion, net of Viela's cash.

The acquisition of Viela accelerates our strategy to build a robust development-stage pipeline to drive long-term value in four ways:

- First, it adds a deep, mid-stage biologics pipeline with four candidates currently in nine development programs. Each of these molecules target central pathways that are implicated in a wide range of autoimmune diseases providing many avenues for potential growth. We currently have a strong on-market portfolio of medicines with high-growth potential, and the Viela pipeline will position us well to drive growth in the second half of the decade.
- Second, it expands the capabilities of our current strong R&D team, particularly early-stage research and translational capabilities, as well as deep scientific knowledge in autoimmune and severe inflammatory diseases. These capabilities will allow us to continuously innovate beyond what is included in our combined pipeline today.
- Third, Viela allows us to continue to pursue our global expansion strategy that we have initiated with TEPEZZA and HZN-825.
- And finally, Viela further diversifies our on-market medicine portfolio with the addition of UPLIZNA®, an infused biologic medicine indicated for the rare disease, neuromyelitis optica

spectrum disorder, or NMOSD. UPLIZNA is a humanized monoclonal antibody with a well-understood mechanism of action, high efficacy levels and a favorable dosing schedule as well as safety and tolerability profile. As a leader in commercializing rare disease medicines, we see many additional opportunities to add value from a commercial perspective. This includes generating and conveying additional evidence that reinforce the value of UPLIZNA, as well as building the necessary infrastructure to support a favorable physician and patient experience while ensuring the right sites of care are available to treat patients – examples of successful approaches we have used with both KRYSTEXXA and TEPEZZA.

Viela is a strong strategic fit with our portfolio and our therapeutic areas of focus, including ophthalmology, rheumatology and nephrology. We also believe the three currently approved or clinical-stage Viela candidates, which include UPLIZNA, VIB4920 and VIB7734, each represent a more-than-$1-billion annual net sales opportunity. We are on track to close the acquisition by the end of the first quarter.

TEPEZZA

Now moving on to our fourth-quarter results … TEPEZZA fourth-quarter net sales were $344 million, representing sequential quarter-over-quarter growth of 20 percent, with full-year net sales of $820 million. If we had not had the supply disruption at the end of the quarter and had a normalized level of inventory in the channel, we estimate that sequential growth would have been well over 30 percent.

The TEPEZZA launch truly exceeded all expectations and has turned out to be one of the best rare disease medicine launches in history.

As we announced last quarter, based on the potential we see for TEPEZZA and its ability to help many more patients suffering from Thyroid Eye Disease, we are further investing in TEPEZZA to support continued long-term growth. This includes our U.S. infrastructure and marketing initiatives, supply capacity and global expansion.

In the fourth quarter, we doubled the commercial and field-based organization, which includes new sales representatives, patient access liaisons, regional reimbursement liaisons, site-of-care managers and medical liaisons. They all have completed training and are in the field educating physicians on the importance of TED treatment, strengthening the co-management of the disease across key physician specialties and establishing and reinforcing the treatment path, infrastructure and referral network.

Our sales force has continued to drive demand for new patients during supply disruption. Current total pending patient enrollment forms, or PEFs, a leading indicator of demand, exceed the total number of patients who were on therapy in the fourth quarter. We continue to see strong clinical conviction from TEPEZZA prescribers, which drove uptake of TEPEZZA among our roughly 1,000 top-tier, high-volume physician targets and TED specialists. We see significant opportunity for continued growth, given an annual incident population of acute TED patients of 15,000 to 20,000, as well as the prevalent population of 70,000 U.S. patients who have had chronic TED for five years or less.

The expansion of our commercial infrastructure has also served us well during the supply disruption, as our TEPEZZA team has been able to provide valuable support to physicians, patients, sites of care and payers, keeping them updated and helping them navigate through this disruption and be prepared for re-launch.

I'll now give an update on TEPEZZA supply. We've been investing in our long-term manufacturing supply capacity since the acquisition of TEPEZZA and have continued our efforts since it was approved. The fact that we were able to meet the significantly higher demand for the launch – 23 times our initial guidance

– is a testament to our comprehensive supply strategy and our talented team. Our strategy included increasing both drug substance manufacturing, through our partner AGC Biologics, and drug product manufacturing, or the filling and finishing of TEPEZZA vials, with our drug product manufacturer Catalent. Following approval, we began efforts to increase the scale of each drug product manufacturing lot. This effort proved particularly important in December, when the U.S. government-mandated COVID-19 vaccine production at Catalent dramatically restricted capacity for the production of TEPEZZA. We have been out of supply since the end of December and have continued to make good progress toward bringing TEPEZZA back to market.

We submitted a prior approval supplement to the FDA for this new manufacturing process. With the supply produced to date, plus the manufacturing capacity currently planned at Catalent, we expect to be able to serve existing patients and new patients, allowing us to relaunch TEPEZZA following FDA approval. We continue to have good dialogue with the FDA, including answering several series of questions from them, and we are hopeful that the agency approves the supplement on an expedited basis. We continue to estimate that the disruption could last through the first quarter. We also remain on track to receive FDA approval to start producing TEPEZZA supply from our second drug product manufacturer by the end of the year.

We are looking forward to being able to again provide TEPEZZA to patients who have no other options available to them to treat their TED, a highly debilitating and sight-threatening rare disease.

With our expanded commercial organization, an improving COVID-19 environment, a return of TEPEZZA supply and a lack of any other approved options for TED patients, we remain highly confident in TEPEZZA's long-term potential peak annual net sales target of more than $3.5 billion globally.

KRYSTEXXA

With KRYSTEXXA, we reported record full-year 2020 net sales of $406 million, representing year-over-year growth of 19 percent. We significantly exceeded the guidance we provided at the onset of the pandemic, a testament to the efforts of the KRYSTEXXA commercial organization and our immunomodulation strategy.

This strategy is key to the long-term success of KRYSTEXXA. A body of evidence has been building that demonstrates the response rate of KRYSTEXXA plus immunomodulation is significantly higher than the response rate with KRYSTEXXA alone. This data is resonating with physicians, with more than 35 percent of new patients now starting KRYSTEXXA plus immunomodulation. It's quickly becoming the preferred treatment option for patients with uncontrolled gout, driven by the data published to date that shows an approximate doubling of the patient response rate using KRYSTEXXA plus immunomodulation versus KRYSTEXXA alone. This was demonstrated in the first randomized controlled trial to study KRYSTEXXA plus an immunomodulator. In this trial, called RECIPE, patients on KRYSTEXXA plus the immunomodulator mycophenolate mofetil achieved an 86 percent response rate at the 12-week primary endpoint.

Our MIRROR randomized controlled trial is a 12-month trial evaluating the efficacy and safety of the use of KRYSTEXXA plus methotrexate. The trial completed enrollment in August of 2020, and we remain blinded to the results of the trial to date. The primary endpoint is at six months, and secondary endpoints go out through 12 months. As we have discussed in the past, we dad planned to approach the FDA to potentially submit the six-month results for inclusion in the KRYSTEXXA prescribing information. In our ongoing dialogue with the FDA, the agency recently informed us that they want the trial to continue unblinded through the full 12-month period without unblinding at six months, given that patients could be on KRYSTEXXA plus methotrexate for a longer period of time in clinical practice. We therefore expect the primary and secondary endpoint results, along with key safety

information, to be available in the fourth quarter of 2021. We expect to submit the data to the FDA for potential inclusion in the KRYSTEXXA prescribing information in the first quarter of 2022.

Our strategy for KRYSTEXXA is working, exemplified by our expectation for strong growth again this year. We are well on track to achieve our peak U.S. annual net sales estimate of more than $1 billion.

Rare Disease Medicines
Our rare disease medicines – RAVICTI®, PROCYSBI® and ACTIMMUNE® – had an impressive year and finished 2020 with total growth of approximately 11 percent compared to 2019. We continued to see strong combined active shipping patients and high rates of compliance and adherence.

Our Clinical Programs
In addition to the acquisition of Viela, which represents a significant transformation of our R&D organization, we also continued to advance our other clinical programs:

- With TEPEZZA, we partnered with Halozyme to develop a subcutaneous formulation of TEPEZZA, which may offer additional flexibility and convenience for patients.
- With HZN-825, we have finalized the protocol for our diffuse cutaneous scleroderma trial, and we are on track to start this trial in the first half of this year. We are also pursuing interstitial lung disease, starting with idiopathic pulmonary fibrosis, or IPF, as a potential indication for HZN-825. If we are successful in the development of HZN-825 for these indications, we estimate that HZN-825 could generate more than $1 billion in peak annual net sales globally.
- With KRYSTEXXA, we recently announced two new trials, the monthly dosing and the retreatment trials. We now have five trials to maximize the value of KRYSTEXXA.

Employee Engagement
Finally, I want to note that our success this year is a testament to our talented employees. We continue to receive multiple recognitions as a "best workplace" – 13 total in 2020 – reflecting the high level of engagement of our employees. In addition, we are taking steps to foster inclusion and combat racism. We've donated $500,000 to community organizations that are addressing racial inequality and racism and $1 million to endow scholarships for students of color. We've also instituted diversity and inclusion efforts within Horizon to further embed inclusion, diversity, equity and allyship at all levels of the organization.

Our progress in 2020 underscores our position as one of the fastest-growing biotech companies with a top-tier growth profile, and we remain focused on continuing to drive significant value for our shareholders, patients and all of our stakeholders moving forward.

I will now turn the call over to Karin for an update on our R&D programs.

Karin Rosén
Executive Vice President, Research & Development and Chief Scientific Officer

Thank you, Tim, and good morning, everyone.

I will start with a summary of the Viela pipeline and then move to our Horizon programs.

Viela Acquisition
The Viela acquisition will add a portfolio of novel medicine candidates ranging from Phase 1 to Phase 3.

Viela's first commercially available medicine, UPLIZNA, an anti-CD19 humanized monoclonal antibody, obtained FDA approval for the treatment of NMOSD last June. Viela is also pursuing three additional indications for the medicine:

- An ongoing Phase 3 trial in myasthenia gravis, or MG, which is a chronic, rare, autoimmune neuromuscular disease that affects voluntary muscles, especially those that control the eyes, mouth, throat and limbs.
- An ongoing Phase 3 trial in IgG4-related disease, a group of disorders marked by tumor-like swelling and fibrosis of affected organs, such as the pancreas, salivary glands and kidneys.
- And finally, a Phase 2 proof-of-concept trial in kidney transplant desensitization, which is currently paused due to COVID-19.

VIB4920 is a CD40 ligand antagonist and is being studied by Viela in three potential indications:

- An ongoing Phase 2b trial in Sjögren's Syndrome, a chronic, systemic autoimmune condition that impacts exocrine glands, including the salivary and tear glands. Sjögren's Syndrome is the second most common rheumatic disease after rheumatoid arthritis.
- A Phase 2 trial in active rheumatoid arthritis patients.
- And a small Phase 2 proof-of-concept study in kidney transplant rejection.

VIB7734 is a human monoclonal antibody that has the potential to become a novel treatment for autoimmune diseases in which plasmacytoid dendritic cells, or pDCs, overproduce interferons and other types of cytokines and chemokines.

- In systemic lupus erythematosus, or SLE, Viela recently decided to move into a Phase 2 trial after demonstrating encouraging results from their Phase 1b cutaneous lupus erythematosus trial.
- VIB7734 is also in Phase 1 development for COVID-19-related acute lung injury.

And finally, VIB1116 is a monoclonal antibody that is expected to move into Phase 1 development in mid-2021 for autoimmune diseases, and we look forward to exploring the potential of this candidate.

The Viela acquisition will also add a talented team skilled in the development of medicines that treat autoimmune and inflammatory diseases, with important early research and translational capabilities that will position us for growth now and in the future.

We intend to explore the full potential of Viela's pipeline to leverage our combined capabilities to maximize the potential of these molecules.

HZN-825
Moving on now to discuss HZN-825, our oral selective $LPAR_1$ antagonist that has shown early signs of clinical impact in fibrotic diseases. $LPAR_1$ signaling has been implicated in fibrosis and inflammation, and preclinical and clinical evidence support the antifibrotic potential of LPAR antagonism across organ systems including both lung and skin.

We are on track to initiate our first pivotal Phase 2b trial in HZN-825 in diffuse cutaneous systemic sclerosis in the first half of this year. Diffuse cutaneous systemic sclerosis is a rare, chronic, progressive autoimmune disease that often causes internal organ damage and has a high mortality rate. Given there are no FDA-approved treatments for patients today, diffuse cutaneous systemic sclerosis presents a significant unmet medical need. Current treatments provide symptomatic relief, but nothing actually slows disease progression. A more comprehensive treatment is needed to address the inflammation and fibrosis that drive this progressive disease and its high mortality rate. We expect to enroll approximately 300 patients who will be randomized in a 1:1:1 ratio to receive HZN-825 300 mg once daily, HZN-825 300 mg twice daily, or placebo for 52 weeks. The primary endpoint of the trial will be change in forced vital capacity, or FVC, after 52 weeks. This is an objective endpoint that measures lung capacity and is used to assess the progression of lung disease and the effectiveness of the treatment. Key secondary endpoints include the Health Assessment Questionnaire-Disability Index, or HAQ, modified Rodnan skin score and ACR-CRISS. We expect enrollment to take approximately two years, and with a one-year endpoint, we expect data to be available in 2024.

Mid this year, we expect to start a second pivotal Phase 2b trial with HZN-825 in idiopathic pulmonary fibrosis, which is the most common interstitial lung disease. FVC will be the primary endpoint here as well.

TEPEZZA in Chronic TED

Moving to TEPEZZA, and our placebo-controlled trial in chronic TED, the aim of this trial is to generate clinical data to better inform payers and physicians who use TEPEZZA to treat their chronic patients. We expect this trial to begin in the second quarter assuming TEPEZZA supply normalizes.

Until data are available from our chronic TED trial, case reports can help inform physicians who may wish to use TEPEZZA in treating their chronic TED patients. Case reports of approximately 30 TED patients with chronic disease were presented at the virtual Fall Symposium of the American Society of Ophthalmic Plastic and Reconstructive Surgery, or ASOPRS, in November last year and at other forums that showed chronic TED patients benefited after treatment with TEPEZZA.

Also, this week a poster was included in the North American Neuro-Ophthalmology Society, or NANOS, 2021 Annual Meeting of a patient with longstanding TED who underwent decompression surgery to treat her TED. Five months later, the patient experienced worsening diplopia and proptosis. Averse to a second decompression surgery, the patient began TEPEZZA therapy. Upon completion of her treatment, she had significant reduction in her proptosis of between five and six millimeters, and her lid retraction subsided substantially.

TEPEZZA Subcutaneous Administration

We are also working on additional administration options for TEPEZZA, and in November we partnered with Halozyme to begin work to develop a subcutaneous formulation, which may offer additional flexibility and convenience for patients. This year we'll be starting our early clinical work on TEPEZZA with the Halozyme technology, initially to understand the pharmacokinetics, bioavailability, tolerability and dosing regimen. We will work with regulatory agencies to agree on the full required data package, which we anticipate will include a confirmatory trial to demonstrate safety and efficacy of TEPEZZA co-formulated with Halozyme's PH20 molecule for subcutaneous delivery.

KRYSTEXXA R&D Programs

For KRYSTEXXA, we currently have five R&D programs aiming to maximize its value in three ways: increasing the response rate, benefiting more patients with uncontrolled gout and improving the patient experience.

As Tim mentioned, we expect the readout from the MIRROR placebo-controlled trial in the fourth quarter of 2021. The PROTECT trial, which is studying the use of KRYSTEXXA for people who are living with uncontrolled gout and have undergone a kidney transplant, is now fully enrolled. We have already presented encouraging interim data for this trial and are on track for final results by the end of this year.

We are progressing with our trial evaluating the impact of administering KRYSTEXXA over a shorter infusion duration. We are also on track to initiate our newest KRYSTEXXA pipeline trials – monthly dosing and retreatment – in the first half of 2021. The goal of the monthly dosing trial is to explore whether that dosing regimen can provide similar outcomes as the current dosing schedule, while the KRYSTEXXA retreatment trial will evaluate whether patients can benefit from KRYSTEXXA plus methotrexate, after developing an immune response to KRYSTEXXA when taken alone.

Conclusion

In conclusion, it's a transformational time for R&D at Horizon. We look forward to integrating the Viela R&D organization once the transaction closes, as well as deploying the extensive experience of our combined team to pursue the full potential of our development-stage candidates and our on-market medicines.

With that, I will turn the call over to Paul.

Paul Hoelscher
Executive Vice President, Chief Financial Officer

Thanks, Karin.

My comments this morning will primarily focus on our non-GAAP results, unless otherwise noted.

Fourth-Quarter 2020 Financial Results
I will start with our fourth-quarter results followed by our 2021 financial guidance.

Fourth-quarter net sales were $745 million, a year-over-year increase of 105 percent and a record for the company.

Our orphan segment generated net sales of $628 million, an increase of 151 percent year-over-year, representing nearly 85 percent of our total company net sales. This growth was driven by the exceptional TEPEZZA launch, with fourth-quarter TEPEZZA net sales of $344 million, along with strong growth for KRYSTEXXA, with record quarterly net sales of $129 million, representing quarterly sequential growth of 19 percent. Our fourth-quarter operating margin for the orphan segment was 48 percent, a year-over-year increase of 1,500 basis points.

Net sales for the inflammation segment were $117 million, with segment operating income of $67 million. Though net sales in this segment declined by 8 percent for full-year 2020, inflammation segment operating income was roughly flat, evidence of the successful execution of our strategy to maximize profitability in this segment. We continue to reinvest the resulting cash flow of this segment into our growth drivers and expanding pipeline.

Our fourth-quarter non-GAAP gross profit ratio was 87 percent of net sales. Non-GAAP operating expenses for the fourth quarter were $279 million. This included non-GAAP R&D expense of $38 million and non-GAAP SG&A expense of $241 million, reflecting our increased investments in TEPEZZA. Adjusted EBITDA was $371 million for the fourth quarter, significantly exceeding expectations.

The non-GAAP income tax rate in the fourth quarter was 17.1 percent, resulting in a 9.9 percent non-GAAP tax rate for the full year.

Non-GAAP net income was $298 million, and non-GAAP diluted earnings per share were $1.28. The weighted average shares outstanding used to calculate fourth-quarter non-GAAP diluted EPS were 233 million shares. Non-GAAP operating cash flow was $411 million, benefiting from the collection of significant TEPEZZA receivables in the fourth quarter.

Cash Flow and Balance Sheet
As of December 31, our cash and cash equivalents were $2.08 billion, and the total principal amount of our debt outstanding was $1.018 billion.

We plan to fund the Viela acquisition with $1.3 billion of new debt plus available cash on hand. The Hart Scott Rodino waiting period expired yesterday, in line with our expectations to complete the acquisition by the end of the first quarter. As Tim noted, the total value of the transaction is $2.67 billion, net of Viela's cash and cash equivalents. Based on this, our pro-forma gross leverage ratio is expected to be about 2.6 times. We expect our gross leverage ratio to be near our target of 2 times by the end of 2021. We significantly strengthened our capital structure over the last two years, and we were very pleased that S&P recently recognized our efforts, upgrading our company rating to double-B, a rating they affirmed following our announcement of the Viela acquisition.

2021 Guidance
Moving to our outlook for 2021. Our 2021 guidance excludes the impact from the operations of Viela, which we currently estimate will reduce our adjusted EBITDA by approximately $140 million. Our guidance also assumes FDA approval of the increased-scale drug product manufacturing process of TEPEZZA and the successful completion of future committed manufacturing slots for TEPEZZA.

This morning, we provided full-year 2021 net sales guidance of $2.7 billion to $2.8 billion, representing year-over-year growth of 25 percent at the midpoint.

For TEPEZZA, we expect full-year 2021 net sales of greater than $1.275 billion, which continues to assume the supply disruption could last through the first quarter.

For KRYSTEXXA, we project net sales of more than $500 million, representing continued strong growth.

We expect full-year 2021 adjusted EBITDA of between $1.14 billion and $1.18 billion, representing growth of 16 percent at the midpoint. This reflects our expectations for strong growth in our net sales, partially offset by the roughly doubling of our R&D dollar spend compared to last year, as well the investments we recently made to expand the TEPEZZA commercial organization and marketing initiatives.

We expect our non-GAAP gross profit ratio for the full year to be between 86 percent and 87 percent.

Non-GAAP net interest expense is expected to be approximately $45 million, which does not include the interest on the new debt to be issued to fund the Viela acquisition.

We expect our full-year non-GAAP tax rate to be in the low double digits. As with every year, we anticipate variability in our non-GAAP tax rate on a quarterly basis. We estimate that our cash tax rate will be in the low-to-mid single digits in 2021. And as always, our tax rates could change significantly as a result of any acquisitions or divestitures made by the Company or any changes in tax laws.

We expect our full-year 2020 weighted average diluted share count to be in the range of 232 million to 234 million shares.

First-Quarter 2021
Let me now touch on the first quarter. As we discuss every year, first-quarter net sales are generally the lowest of the year, impacted by seasonality as patients experience changes in their health insurance coverage. Therefore, we expect the typical sequential step-down for our medicines. Additionally, operating expenses will increase as we approach mid-year, as additional marketing efforts for TEPEZZA continue to increase, and our two Phase 2b trials in HZN-825 begin.

And finally, we expect operating cash flow to increase significantly year over year, although as usual, we expect first-quarter cash flow to be the lowest of the year.

With that, I'll turn it over to Tim for concluding remarks.

Tim Walbert
Chairman, President and Chief Executive Officer

Thank you, Paul.

2020 was a breakthrough year for Horizon, with the TEPEZZA launch far exceeding expectations and resulting in one of the best rare disease medicine launches ever. We generated record net sales of $2.2 billion and adjusted EBITDA of approximately $1.0 billion, driven by the tremendous success of TEPEZZA as well as by strong growth of KRYSTEXXA and our rare disease medicines.

We continue to execute on our strategy to maximize the value of TEPEZZA and KRYSTEXXA and expand our pipeline. The Viela transaction is a great example. This acquisition represents a significant step forward in our transformation to an innovative-driven, high-growth biotech company and gives us tremendous potential to help more patients, their caregivers and physicians by bringing to market medicines that truly serve unmet needs.

We have made remarkable progress as a company, transforming Horizon in just a few short years. In just the last two years alone, our market cap has increased six-fold to approximately $20 billion today. Horizon is one of the fastest-growing biotech companies with a top-tier growth profile and we expect the Viela acquisition to build on the value we provide patients and to drive long-term value for our shareholders.

We will now open the call up for questions.

Tina Ventura
Senior Vice President, Investor Relations

Thank you, Ursula. That concludes our call this morning. A replay of this call and webcast will be available in approximately two hours. Thank you for joining us.