Vertex Announces Positive Results From Phase 2 Study of VX-548 for the Treatment of Painful Diabetic Peripheral Neuropathy

December 13, 2023

– Treatment with the NaV1.8 inhibitor VX-548 led to statistically significant and clinically meaningful reduction in the primary endpoint of change from baseline in the Numeric Pain Rating Scale (NPRS) –

– VX-548 was generally well tolerated –

– Vertex plans to advance VX-548 into pivotal development in diabetic peripheral neuropathic pain following discussions with regulators –

– VX-548 Phase 2 study in patients with painful lumbosacral radiculopathy, another type of peripheral neuropathic pain, has initiated –

– Vertex to host investor call December 13 at 8:00 a.m. ET –

BOSTON--(BUSINESS WIRE)--Dec. 13, 2023-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive results from its Phase 2 dose-ranging study of the selective NaV1.8 inhibitor VX-548 in people with painful diabetic peripheral neuropathy (DPN). Treatment with all doses of VX-548 resulted in a statistically significant and clinically meaningful reduction in the primary endpoint of change from baseline in the weekly average of daily pain intensity on a Numeric Pain Rating Scale (NPRS) at Week 12. The study also included an active reference arm of pregabalin to support the evaluation of the VX-548 treatment effect.

VX-548 was generally well tolerated at all doses tested in the study. Most adverse events (AEs) were mild to moderate and there were no serious adverse events (SAEs) related to VX-548.

“We are very pleased with these results which add to the body of safety and efficacy data for VX-548 and provide further validation of the analgesic effects of NaV1.8 inhibitors,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. “Given the favorable benefit/risk profile of VX-548 seen in this study, we are working with urgency to advance this investigational non-opioid pain medicine into Phase 3 in painful diabetic neuropathy with the goal of changing the standard of care for neuropathic pain, where treatment options are limited. In addition, our Phase 3 studies of VX-548 in acute pain are on track to read out in the first quarter of 2024.”

“I am excited by the results from the VX-548 Phase 2 DPN study, which demonstrate a promising safety and efficacy profile and represent a significant milestone in pain management,” said Roy Freeman, M.D., Professor of Neurology, Director of the Center for Autonomic and Peripheral Nerve Disorders, Beth Israel Deaconess Medical Center and a member of Vertex’s Pain Steering Committee. “Based on these Phase 2 results, VX-548 could offer the potential for a new class of medicine for the millions of patients suffering from neuropathic pain who are desperate for new options.”

Efficacy Results

The study’s primary endpoint was change from baseline in the weekly average of daily pain intensity at Week 12 in patients with painful DPN dosed with VX-548 using the standard pain assessment Numeric Pain Rating Scale, or NPRS. This 11-point scale ranges from 0 (no pain) to 10 (worst pain imaginable). Patients were randomized to four treatment arms: VX-548 once daily at 69 mg (high dose), 46 mg (mid dose), or 23 mg (low dose), or the reference arm of pregabalin 100 mg three times per day (TID) for 12 weeks.

All VX-548 treatment groups showed statistically significant and clinically meaningful reductions from baseline in pain with mean change in NPRS at Week 12 of -2.26, -2.11 and -2.18 at the high, mid and low doses, respectively. The pregabalin reference arm mean change from baseline in NPRS at Week 12 was -2.09 and is provided for context. All VX-548 dose groups had sustained mean reductions in pain from baseline starting at Week 1, with pain continuing to decrease until Week 5, which was then maintained throughout the treatment period.

Secondary and other endpoints were supportive of the study’s primary endpoint. Importantly, in the responder analysis, more than 30% of patients treated with VX-548 achieved ≥50% reduction in all dose groups, and more than 20% of patients in the mid- and high-dose groups achieved ≥70% reduction in weekly average of NPRS at Week 12 compared to baseline. In the pregabalin reference arm, 22% of patients achieved ≥50% reduction and 10% achieved ≥70% reduction in weekly average of NPRS at Week

12 compared to baseline.

Primary Efficacy Outcomes

	Pregabalin 100 mg tid N=47 (Reference Arm)	VX-548 Low Dose 23 mg qd N=24	VX-548 Mid Dose 46 mg qd N=48	VX-548 High Dose 69 mg qd N=48
Baseline				
Mean (SD)	5.98 (1.28)	5.70 (1.32)	5.88 (0.97)	5.79 (1.22)
Change from baseline at Week 12				
LS mean (SE)	-2.09 (0.29)	-2.18 (0.39)	-2.11 (0.28)	-2.26 (0.28)
95% CI	(-2.65, -1.52)	(-2.94, -1.41)	(-2.67, -1.55)	(-2.82, -1.70)
P-value	<0.0001	<0.0001	<0.0001	<0.0001

The three VX-548 doses achieved overlapping exposures at the high end of the expected therapeutic range.

Safety Results

VX-548 was generally well tolerated at all doses studied for up to 12 weeks of treatment. The majority of the AEs were mild or moderate in severity. There were no SAEs related to VX-548 or pregabalin in the study. There was one death in the mid-dose VX-548 group due to atherosclerotic cardiovascular disease, which was not related to study drug.

The most common AEs (incidence >5% in either VX-548 combined or pregabalin group, respectively) were creatinine clearance decrease (5.1%, 1.9%), dizziness (0.7%, 9.3%), peripheral edema (0.7%, 5.6%) and weight increased (0%, 7.4%). Related AEs were 14.5% in patients treated with VX-548 and 27.8% in patients treated with pregabalin.

Next Steps for the Pain Portfolio

Vertex plans to advance VX-548 into pivotal development following discussions with regulators.

Vertex has also initiated a second Phase 2 study of VX-548 in peripheral neuropathic pain. This trial will evaluate VX-548 in patients with painful lumbosacral radiculopathy, or LSR, which is pain caused by impairment or injury to nerve roots in the area of the lumbar spine.

Additionally, the three Phase 3 studies of VX-548 in acute pain are on track to read out in the first quarter of 2024.

In line with its portfolio strategy, Vertex continues to advance preclinical and clinical development of additional NaV1.8 and NaV1.7 inhibitors, for use alone or in combination, in acute and neuropathic pain.

Conference Call and Webcast

The company will host a conference call and webcast at 8:00 a.m. ET on December 13. To access the call, please dial (833) 630-2124 (U.S.) or +1 (412) 317-0651 (International) and reference the “Vertex Pharmaceuticals Conference Call.”

The conference call will be webcast live and a link to the webcast can be accessed through Vertex's website at www.vrtx.com in the "Investors" section. To ensure a timely connection, it is recommended that participants register at least 15 minutes prior to the scheduled webcast. An archived webcast will be available on the company's website.

About the VX-548 Phase 2 Study in Diabetic Peripheral Neuropathy

The Phase 2 study was a randomized, double-blind, active-controlled, dose-ranging study evaluating the efficacy and safety of VX-548 in people aged 18 to 80 years with painful diabetic peripheral neuropathy. A total of 192 patients with bilateral pain in the lower extremities due to diabetic peripheral neuropathy for at least one year were enrolled in this study. Patients were randomized to four treatment arms: VX-548 once daily of 69 mg (high dose), 46 mg (mid dose) or 23 mg (low dose), or the reference arm of pregabalin 100 mg three times per day. The primary endpoint of the study was the change from baseline in the weekly average of daily pain intensity on a Numeric Pain Rating Scale (NPRS) at Week 12.

About Peripheral Neuropathic Pain

Peripheral neuropathic pain, or PNP, is a significant area of unmet need for patients suffering from pain. PNP is a collection of chronic conditions including painful diabetic peripheral neuropathy (DPN), painful lumbosacral radiculopathy (LSR), painful small fiber neuropathy and trigeminal neuralgia. Painful DPN and LSR are two of the largest segments within the estimated 10 million

patients who are prescribed a medicine for peripheral neuropathic pain every year in the U.S.

About VX-548

VX-548 is an investigational oral, selective NaV1.8 inhibitor that is highly selective for NaV1.8 relative to other NaV channels. NaV1.8 is a voltage-gated sodium channel that plays a critical role in pain signaling in the peripheral nervous system. NaV1.8 is a genetically validated target for the treatment of pain, and Vertex has previously demonstrated positive proof-of-concept results and a well-tolerated profile with VX-548 in two Phase 2 studies of acute pain following abdominoplasty and bunionectomy surgeries. Vertex's approach is to selectively inhibit NaV1.8 using small molecules with the objective of creating a new class of medicines that have the potential to provide superior relief of pain without the limitations of opioids, including their addictive potential. VX-548 is one of the most recent molecules to enter clinical development from Vertex's portfolio of NaV1.8 inhibitors.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious diseases. The company has approved medicines that treat the underlying causes of multiple chronic, life-shortening genetic diseases — cystic fibrosis, sickle cell disease and transfusion-dependent beta thalassemia — and continues to advance clinical and research programs in these diseases. Vertex also has a robust clinical pipeline of investigational therapies across a range of modalities in other serious diseases where it has deep insight into causal human biology, including APOL1-mediated kidney disease, acute and neuropathic pain, type 1 diabetes and alpha-1 antitrypsin deficiency.

Vertex was founded in 1989 and has its global headquarters in Boston, with international headquarters in London. Additionally, the company has research and development sites and commercial offices in North America, Europe, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including 14 consecutive years on Science magazine's Top Employers list and one of Fortune's 100 Best Companies to Work For. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on LinkedIn, Facebook, Instagram, YouTube and Twitter/X.

Special Note Regarding Forward-Looking Statements
This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements by Carmen Bozic, M.D., and Roy Freeman, M.D., in this press release, our beliefs about the potential benefits of VX-548, our plans to advance VX-548 into pivotal development following discussions with regulators, our plans to evaluate VX-548 with painful LSR, the expectation that our three Phase 3 studies of VX-548 in acute pain will read out in the first quarter of 2024, and our plans to continue to pursue preclinical and clinical development of additional NaV1.8 and NaV1.7 inhibitors. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that data from a limited number of patients may not be indicative of final clinical trial results, that clinical trial data might not be available on the expected timeline, that data from the company's research and development programs may not support registration or further development of its compounds due to safety, efficacy, and other risks listed under the heading "Risk Factors" in Vertex's most recent annual report and subsequent quarterly reports filed with the Securities and Exchange Commission at www.sec.gov and available through the company's website at www.vrtx.com. You should not place undue reliance on these statements, or the scientific data presented. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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