Vertex Announces Statistically Significant and Clinically Meaningful Results From Two Phase 2 Proof-of-Concept Studies of VX-548 for the Treatment of Acute Pain

March 31, 2022

- Treatment with the NaV1.8 inhibitor VX-548 met the primary endpoint in both Phase 2 proof-of-concept acute pain studies following abdominoplasty or bunionectomy surgery -

- VX-548 was generally well tolerated -

- Results further highlight NaV1.8 as a new mechanism that could create an alternative to opioids for the treatment of pain -

- Company plans to advance VX-548 into pivotal development in acute pain in H2 2022 following discussions with regulators –

BOSTON--(BUSINESS WIRE)--Mar. 31, 2022-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive results from two Phase 2 proof-of-concept (POC) studies that investigated treatment with the selective NaV1.8 inhibitor VX-548 for acute pain following abdominoplasty surgery or bunionectomy surgery. Treatment with an initial dose of 100 mg followed by 50 mg every 12 hours of VX-548 (high-dose) compared to placebo resulted in a rapid, statistically significant and clinically meaningful improvement in the primary endpoint of the time-weighted Sum of Pain Intensity Difference over 48 hours (SPID48), which was consistent in both trials. The study also included an active reference arm of the opioid hydrocodone bitartrate/acetaminophen (HB/APAP) to support the evaluation of the VX-548 treatment effect.

VX-548 was generally well tolerated in both studies. Most adverse events (AEs) were mild to moderate and there were no serious adverse events (SAEs) related to VX-548. Fewer patients discontinued treatment in the mid- and high-dose VX-548 arms than in the placebo group or HB/APAP reference arm.

Based on these positive proof-of-concept efficacy results, and the safety and tolerability profile across both the abdominoplasty and bunionectomy studies, Vertex plans to advance VX-548 into pivotal development in the second half of 2022, following discussions with regulators.

VX-548 Results in Patients Undergoing Bunionectomy

Efficacy Results

The bunionectomy study met its primary endpoint, showing a statistically significant improvement in SPID48, as recorded on a Numeric Pain Rating Scale (NPRS), for those treated with VX-548 at the high dose compared to placebo. Higher SPID48 values represent greater improvements in pain relief. The onset of action was rapid and was sustained through the duration of assessment.

Primary Efficacy Outcomes:

Treatment groups:	**Placebo** n=59	**High-dose VX-548** (100 mg first dose/50 mg every 12 hours) n=60	**Mid-dose VX-548** (60 mg first dose/30 mg every 12 hours) n=62	**Low-dose VX-548** (20 mg first dose/10 mg every 12 hours) n=33	**Hydrocodone bitartrate /acetaminophen reference arm** (5 mg/325 mg every six hours) n=60
Mean SPID48	101.0	137.8	86.9	112.9	115.6
Mean SPID48 difference from placebo p-value vs. placebo	N/A	36.8 p = 0.0251	-14.1 p = 0.3859	11.9 p = 0.5379	14.7 p = 0.3706

274 patients were enrolled
All p-values are based on comparison to placebo

Safety Results

VX-548 was generally well tolerated in this study. Discontinuation rates, including discontinuations due to lack of efficacy, were lower in the VX-548-treated mid- and high-dose arms than in the placebo group or HB/APAP reference arm. No patients discontinued treatment due to AEs and no patients had SAEs. All AEs were mild or moderate. The most common AEs (incidence >10% in either placebo, HB/APAP or VX-548 high-dose group, respectively) were headache (12%, 7%, 8%) and nausea (9%, 18%, 8%).

VX-548 Results in Patients Undergoing Abdominoplasty

Efficacy Results

The abdominoplasty study met its primary endpoint, showing a statistically significant improvement in SPID48, as recorded on a NPRS, for those treated with VX-548 at the high dose compared to placebo. Similar to pain relief in the bunionectomy study, the onset of action was rapid and was sustained through the assessment period.

Primary Efficacy Outcomes:

Treatment groups:	**Placebo** n=77	**High-dose VX-548** (100 mg first dose/50 mg every 12 hours) n=76	**Mid-dose VX-548** (60 mg first dose/30 mg every 12 hours) n=74	**Hydrocodone bitartrate /acetaminophen reference arm** (5 mg/325 mg every six hours) n=76
Mean SPID48	72.7	110.5	95.1	85.2
Mean SPID48 difference from placebo	N/A	37.8	22.4	12.5
p-value vs. placebo		p = 0.0097	p = 0.1266	p = 0.3914

303 patients were enrolled
All p-values are based on comparison to placebo

Safety Results

VX-548 was generally well tolerated in this study. Discontinuation rates, including discontinuations due to lack of efficacy, were lower in the VX-548-treated arms than in the placebo group or HB/APAP reference arm. Two patients in the mid-dose VX-548 arm discontinued treatment due to AEs, none of which were related to treatment. There were three patients who experienced SAEs: one patient in the placebo arm, one patient in the HB/APAP arm, and one patient in the VX-548 mid-dose treatment arm, none of which were related to treatment. The majority of AEs were mild or moderate. The most common AEs (incidence >10% in either placebo, HB/APAP or high-dose VX-548 group, respectively) were nausea (36%, 30%, 18%), headache (7%, 7%, 15%), constipation (5%, 12%, 9%), dizziness (18%, 11%, 8%) and vomiting (7%, 11%, 3%).

“Our high expectations of achieving therapeutic pain control by inhibiting the NaV1.8 channel have been met with these results from the two acute pain studies,” said Carmen Bozic, M.D., Executive Vice President, Global Medicines Development and Medical Affairs, and Chief Medical Officer at Vertex. “The remarkable consistency in the safety, tolerability and efficacy results in these two studies demonstrate the potential of VX-548 to be a first-in-class non-opioid treatment for acute pain. We are working with urgency to advance the program into Phase 3 with the goal of bringing forward the first novel pain treatment in decades to address the unmet needs of patients suffering from acute pain.”

“There is a tremendous need for innovation in the treatment of pain, specifically non-opioid therapies, and these results provide hope that such an advance may be on the horizon,” said Dr. Paul Frederick White, Former Professor and Distinguished Chair, Department of Anesthesiology, The University of Texas Southwestern Medical Center; Consultant, Department of Anesthesiology, Cedars-Sinai Medical Center, Los Angeles. “A new approach to pain, without addictive qualities or opioid-related side effects, could have a transformative impact on the field of pain management and the millions of patients who experience acute pain.”

Next Steps

As a result of these positive data, Vertex plans to advance VX-548 into pivotal development in the second half of 2022, following discussions with regulators. The full data set from these studies will be presented at a future medical meeting.

About the Phase 2 Study in Patients Undergoing Bunionectomy

The Phase 2 study was a randomized, double-blind, placebo-controlled, dose-ranging trial that evaluated three different doses of VX-548 administered orally over 36 hours in 274 patients with acute pain following bunionectomy surgery. The study also included a hydrocodone bitartrate/acetaminophen reference arm (5 mg/325 mg administered orally every six hours over 42 hours). The primary endpoint was the time-weighted Sum of the Pain Intensity Difference (SPID) over the first 48 hours of treatment, as recorded on the 11-point Numeric Pain Rating Scale (NPRS), compared to placebo. The study evaluated three dosing regimens of VX-548: high-dose – 100 mg first dose, followed by 50 mg every 12 hours (at 12, 24 and 36 hours after the first dose); mid-dose –

60 mg first dose, followed by 30 mg every 12 hours (at 12, 24 and 36 hours after the first dose); low-dose – 20 mg first dose, followed by 10 mg every 12 hours (at 12, 24 and 36 hours after the first dose).

About the Phase 2 Study in Patients Undergoing Abdominoplasty

The Phase 2 study was a randomized, double-blind, placebo-controlled, four-arm trial that evaluated two different doses of VX-548 administered orally over 36 hours in 303 patients with acute pain following abdominoplasty surgery. The study also included a hydrocodone bitartrate/acetaminophen reference arm (5 mg/325 mg administered orally every 6 hours over 42 hours). The primary endpoint was the time-weighted Sum of the Pain Intensity Difference (SPID) over the first 48 hours of treatment, as recorded on the 11-point Numeric Pain Rating Scale (NPRS) compared to placebo. The study evaluated two dosing regimens of VX-548: high-dose – 100 mg first dose, followed by 50 mg every 12 hours (at 12, 24 and 36 hours after the first dose) and mid-dose – 60 mg first dose, followed by 30 mg every 12 hours (at 12, 24 and 36 hours after the first dose).

About VX-548

VX-548 is an 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 clinical proof-of-concept with a small molecule investigational treatment targeting NaV1.8 in multiple pain indications including acute pain, neuropathic pain and musculoskeletal pain. 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 acute pain without the limitations of opioids, including their addictive potential. VX-548 is the most recent molecule 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 multiple approved medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease — and has several ongoing clinical and research programs in CF. Beyond CF,Vertex has a robust pipeline of investigational small molecule, cell and genetic therapies in other serious diseases where it has deep insight into causal human biology, including sickle cell disease, beta thalassemia, APOL1-mediated kidney disease, pain, type 1 diabetes, alpha-1 antitrypsin deficiency and Duchenne muscular dystrophy.

Founded in 1989 in Cambridge, Mass., Vertex's global headquarters is now located in Boston's Innovation District and its international headquarters is 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 12 consecutive years on Science magazine's Top Employers list and one of the 2021 Seramount (formerly Working Mother Media) 100 Best Companies. For company updates and to learn more about Vertex's history of innovation, visit www.vrtx.com or follow us on Facebook, Twitter, LinkedIn, YouTube and Instagram.

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 Dr. Carmen Bozic and Dr. Paul Frederick White in this press release, and statements regarding the potential benefits of VX-548 as a treatment for patients with acute pain, our plans to advance VX-548 into pivotal development in the second half of 2022, our expectation that VX-548 could have a transformative impact on the field of pain management and the patients who experience acute pain, our expectations regarding the number of patients who experience acute pain, our expectations and anticipated timelines for upcoming clinical studies and discussions with regulators, and our plans to present data at a future medical meeting. 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, risks related to the potential future clinical trial design and regulatory review of VX-548, that data from the company's POC studies may not be indicative of final clinical trial results, that data from the company's development programs may not support registration or further development of its compounds due to safety, efficacy, or other reasons, and other risks listed under the heading "Risk Factors" in Vertex's most recent annual report and subsequent filings 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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