Ardelyx Announces Positive Second Data Analysis from Ongoing NORMALIZE Phase 4 Study Evaluating Tenapanor in CKD Patients on Dialysis

June 15, 2020

Foundational use of tenapanor as monotherapy or with sevelamer enabled up to 47.4% of patients to achieve normal serum phosphorus levels (<4.6 mg/dL), a 58% improvement over current standard of care

NDA submission for tenapanor for the control of serum phosphorus on-track for mid-2020

Separately, Ardelyx's tenapanor partner in Japan, Kyowa Kirin, presented Phase 2 data at ERA-EDTA demonstrating tenapanor enabled a significant reduction in overall pill burden (mean reduction in phosphate binder pill usage by 80%), while maintaining serum phosphorus control

FREMONT, Calif., June 15, 2020 /PRNewswire/ -- Ardelyx, Inc. (Nasdaq: ARDX), a specialized biopharmaceutical company focused on developing first-in-class medicines to improve treatment for people with kidney and cardiovascular diseases, today reported positive data from its ongoing NORMALIZE study, which is designed to evaluate the ability of tenapanor, as monotherapy or in combination with sevelamer, to achieve serum phosphorus levels in the normal range (2.5 – 4.5 mg/dL) in patients with chronic kidney disease (CKD) on dialysis. Tenapanor is an investigational, first-in-class, phosphate absorption inhibitor which, if approved, will provide a completely new approach for the control of serum phosphorus in patients with CKD on dialysis, blocking the absorption of phosphorus at the primary pathway of uptake.

"These data from the NORMALIZE study are unprecedented in terms of the proportion of patients able to achieve serum phosphorus levels < 4.6mg/dL with foundational use of tenapanor," said Stuart Sprague DO, FASN, chief of the Division of Nephrology and Hypertension at Northshore University Health System. "This represents an important advancement in the management of hyperphosphatemia for patients on dialysis. The ability of tenapanor to drive phosphorus levels closer to normal has the potential to completely change the hyperphosphatemia treatment paradigm."

The NORMALIZE extension study allowed patients from PHREEDOM, the positive Phase 3 long-term monotherapy study, to continue therapy with tenapanor, and enabled those in the safety control arm receiving sevelamer, to transition to tenapanor. The planned second analysis demonstrated that the foundational use of tenapanor as monotherapy or in combination with sevelamer carbonate produces a significant phosphorus-lowering effect with a mean serum phosphorous reduction of 2.33 mg/dL, from a mean baseline phosphorus of 7.27 mg/dL at the beginning of the PHREEDOM trial to a mean of 4.94 mg/dL at the time of this analysis. Of the 171 patients in this interim analysis who completed up to 9 months of treatment in this extension study, up to 47.4% achieved a normal serum phosphorus level, and of those, the majority were on tenapanor alone or tenapanor with low dose sevelamer of ≤3 sevelamer tablets per day. These data represent a 58% improvement in the rate of patients who achieve a normal serum phosphorus level, as compared to current treatment practice data as reported in the April 2020 Dialysis Outcomes Practice Patterns Study (DOPPS) Practice Monitor. The DOPPS data demonstrate that, with current standard of care treatment of phosphate binders alone, only 30% of patients have serum phosphorous levels < 4.6 mg/dL. The only adverse event reported in >5% of patients in NORMALIZE was diarrhea, with an incidence rate of 23.3%.

Separately, Kyowa Kirin Co., Ltd., a Japan-based global specialty pharmaceutical company exclusively developing tenapanor in Japan, presented results from a Phase 2 trial of tenapanor at the European Renal Association-European Dialysis and Transplant Association annual meeting (ERA-EDTA 2020). The abstract was entitled:

> A Phase 2 Open-label, Single-arm, First Japanese Study of Tenapanor, a Novel Phosphate Absorption Inhibitor, Focusing on Pill Burden Decrease in Patients with Hyperphosphatemia Undergoing Hemodialysis.

The trial was designed to evaluate if, with tenapanor, patients could achieve at least a 30% decrease in mean pill burden while maintaining their serum phosphorus level. The study results were statistically significant, with 71.6% ($p<0.001$) of patients achieving at least a 30% reduction in mean pill burden. The overall mean reduction in phosphate binder usage was 80% (reduction from 14.7 to 3.0 pills per day), while maintaining serum phosphorus control. The mean phosphorus level of patients entering the study on treatment with binders was 5.2 mg/dL at baseline and 4.7 mg/dL at the end of the 26-week study.

"The compelling results of the NORMALIZE study enhance our robust dataset demonstrating tenapanor's ability to significantly decrease serum phosphorous levels, both as a monotherapy and as part of a dual mechanism approach with phosphate binders," said David Rosenbaum, Ph.D., chief development officer of Ardelyx. "The Phase 2 data reported by our partner in Japan, Kyowa Kirin, shows that with tenapanor we are able to control serum phosphorus with a reduced pill burden as compared to treatment with binders. Together, these data continue to advance our understanding of tenapanor and its potential as a transformative treatment for patients with hyperphosphatemia. Of note, we are in the final stages of preparing our New Drug Application for tenapanor for the control of serum phosphorus, which is on track to be submitted mid-year."

NORMALIZE Study Design
Patients completing the Phase 3 PHREEDOM trial from both the tenapanor arm and the sevelamer safety control arm had the option to participate in NORMALIZE, an ongoing open-label 18-month extension study.

Patients entering the study from the tenapanor arm with serum phosphorus levels in the normal range are followed with no medication changes. Patients entering the study from the tenapanor arm with serum phosphorus > 4.5 mg/dL have sevelamer tablets added incrementally to achieve normal serum phosphorus levels. Patients entering the study from the sevelamer safety control arm have tenapanor tablets added to their treatment regimen while reducing sevelamer tablets based on their serum phosphorus value, to achieve normal serum phosphorus levels.

The primary objective of the study is to evaluate the ability of tenapanor alone or in combination with sevelamer to achieve serum phosphorus levels within the normal range (2.5 to 4.5 mg/dL) in patients with chronic kidney disease on dialysis whose serum phosphorus levels were greater than 6.0 mg/dL at baseline.

Kyowa Kirin's Phase 2 Study Design
A multicenter, open-label, single-arm Phase 2 study consisted of a screening period, a 3-week observation period, and a 26-week treatment period. Patients whose serum phosphorus level was 3.5 to 7.0 mg/dL, taking at least two phosphate binder pills three times a day were enrolled. Patients received 30 mg of tenapanor twice daily. Phosphate binder treatment was continued according to individual regimens; however, the dose was adjusted to maintain serum phosphorus level within ±0.5 mg/dL from baseline. The primary endpoint was the achievement of at least a 30% decrease in the mean total number of phosphate binder and tenapanor pills compared to the number of phosphate binder pills at baseline.

About Tenapanor for Hyperphosphatemia
Tenapanor, discovered and developed by Ardelyx, is a first-in-class, proprietary, oral medicine for which the Company is preparing a New Drug Application for submission to the FDA in mid-2020 for the control of serum phosphorus in patients with CKD on dialysis. Tenapanor has a unique mechanism of action and acts locally in the gut to inhibit the sodium hydrogen exchanger 3 (NHE3). This results in a conformational change of the epithelial cell junctions, thereby significantly reducing paracellular uptake of phosphate at the primary pathway of phosphate absorption. Three successful Phase 3 studies demonstrating tenapanor's ability to reduce phosphate levels, as monotherapy and as part of a dual mechanism approach with phosphate binders, have been reported.

About Hyperphosphatemia
Hyperphosphatemia is a serious condition resulting in an abnormally elevated level of phosphorus in the blood that is estimated to affect more than 745,000 dialysis patients in major developed countries. The kidney is the organ responsible for regulating phosphorus levels, but when kidney function is significantly impaired, phosphorus is not adequately eliminated from the body. As a result, hyperphosphatemia is a nearly universal condition among people with CKD and especially those on dialysis. Despite treatment with phosphate binders (the only approved therapy for hyperphosphatemia), approximately 70% of CKD patients on dialysis continue to experience elevated phosphorus levels at any point in time (Spherix Global Insights: RealWorld Dynamix, Dialysis 2018). Phosphorus levels greater than 5.5 mg/dL have been shown to be an independent risk factor for cardiovascular morbidity and mortality in patients requiring dialysis (Block 2004), and internationally recognized treatment guidelines recommend lowering elevated phosphate levels toward the normal range (<4.6mg/dL).

About Ardelyx, Inc.
Ardelyx is focused on enhancing the way people with kidney and cardiovascular diseases are treated by developing innovative first-in-class medicines. Ardelyx's pipeline includes tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis, for which the Company is preparing for NDA submission mid-year, and RDX013, a potassium secretagogue program for the potential treatment of high potassium, or hyperkalemia, a problem among certain patients with kidney and/or heart disease. In addition, Ardelyx received FDA approval of IBSRELA® (tenapanor) on September 12, 2019. Ardelyx has established agreements with Kyowa Kirin in Japan, Fosun Pharma in China and Knight Therapeutics in Canada for the development and commercialization of tenapanor in the respective territories.

Forward Looking Statements
To the extent that statements contained in this press release are not descriptions of historical facts regarding Ardelyx, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor of the Private Securities Reform Act of 1995, including the potential for the use of tenapanor as monotherapy and as part of a dual mechanism approach with phosphate binders for the control of serum phosphorus in adult chronic kidney disease patients on dialysis; the potential for tenapanor with binders to achieve serum phosphorus levels of less than 4.6 mg/dL; and Ardelyx's expectation regarding the timing of the submission of a NDA to the FDA seeking approval for tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis. Such forward-looking statements involve substantial risks and uncertainties that could cause the development of Ardelyx's product candidates or Ardelyx's future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, the uncertainties associated with the clinical development process, including the regulatory approval process. Ardelyx undertakes no obligation to update or revise any forward-looking statements. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Ardelyx's business in general, please refer to Ardelyx's quarterly report on Form 10-Q filed with the Securities and Exchange Commission on May 7, 2020, and its future current and periodic reports to be filed with the Securities and Exchange Commission.

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