Ardelyx Announces Peer-Reviewed Publication of Positive Phase 3 Results of Tenapanor for the Treatment of Hyperphosphatemia in the Journal of the American Society of Nephrology

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- Ardelyx's investigative agent for end-stage renal disease patients on dialysis represents first non-binder innovation to lower patients' phosphate levels, a critically important parameter that is correlated with morbidity and mortality
- Ardelyx's approach leverages newly discovered pathway for the paracellular transport and absorption of phosphate
- Statistically significant reduction in elevated phosphate levels achieved with tenapanor treatment as compared to placebo

FREMONT, Calif., March 7, 2019 /PRNewswire/ -- Ardelyx, Inc. (Nasdaq: ARDX) today announced the publication in the *Journal of the American Society of Nephrology* (JASN) of results from the first of two Phase 3 pivotal trials for tenapanor to treat hyperphosphatemia in patients with end-stage renal disease (ESRD) who are on dialysis. During the treatment period, 164 patients completed treatment in one of three randomized dosing groups (3, 10 and 30 mg titration) of tenapanor twice daily. The data demonstrated that there were significant decreases in serum phosphate in all three treatment groups, with mean reduction of 1.0-1.2 mg/dL over 8 weeks (all P < 0.001). Notably, in a pre-specified secondary analysis of serum phosphate changes in the randomized withdrawal period, there was a statistically significant difference in increases of serum phosphate levels between pooled patients on tenapanor and placebo (n=164; p = 0.003).

"These results, published in one of the most distinguished journals for nephrology worldwide, strongly support the ability of tenapanor to reduce phosphate levels in ESRD patients with a simple regimen of just two small pills twice per day," said chief development officer, David P. Rosenbaum, Ph.D. "We look forward to completing our second monotherapy Phase 3 trial, PHREEDOM, from which we currently expect to receive results in the fourth quarter of 2019. In addition, in the second half of this year, we also expect to receive results from our clinical trial, AMPLIFY, a Phase 3 study to evaluate a combination regimen of tenapanor with phosphate binders. We are excited about the progress we've made and the data that will be forthcoming as we continue to pursue our goal of providing ESRD patients with a much needed, highly differentiated therapeutic alternative for lowering phosphorus."

Dr. Glenn Chertow, Division Chief and Professor of Medicine, Stanford University, and senior author added, "The results from this study demonstrate that tenapanor has a clinically meaningful effect in lowering serum phosphorus in these patients. While ESRD is associated with high morbidity and mortality, the field has not seen significant groundbreaking innovation in many years. I consider tenapanor a major advance in the field, rooted in cutting edge science. I look forward to the results of both PHREEDOM and AMPLIFY and the possibility of having tenapanor in my armamentarium of treatment options for my patients on dialysis."

Ardelyx's second Phase 3 study, the PHREEDOM trial, is fully enrolled, and the company expects to report results from this registration-enabling study in the fourth quarter of this year. Ardelyx's third Phase 3 study, the AMPLIFY trial, designed to evaluate expanded use of tenapanor as adjunctive therapy to phosphate binders, is enrolling patients, and the company expects to report results in the second half of 2019.

About the Phase 3 Trial

The Phase 3 trial described in the JASN paper was an eight-week, double-blind, randomized trial, with a four-week, placebo-controlled, randomized withdrawal period. Ardelyx enrolled a total of 219 ESRD patients with hyperphosphatemia who are on dialysis across 41 U.S. sites. Enrolled patients were randomized evenly into three arms, in which all groups received tenapanor for eight weeks. Tenapanor was administered at fixed doses of 3 mg or 10 mg twice-daily and in a dose-titration arm starting at 30 mg twice-daily with the option to down-titrate once a week during the first four weeks to 20, 15, 10 and 3 mg twice-daily, based on GI tolerability. After the end of the eight-week treatment period, patients were re-randomized 1:1 to either remain on their current tenapanor dose or switch to placebo for a four-week, placebo-controlled, randomized withdrawal period (RWP). Of 219 patients randomized, 164 (75%) completed treatment. Of these, 152 (93%) completed the RWP.

The primary endpoint of the trial is the difference in change in serum phosphorus between the pooled tenapanor-treated patients and placebo-treated patients from the end of the eight-week treatment period to the end of the four-week randomized withdrawal period, in the responder population. The responder population (n=80 out of 164), which was in the statistical analysis plan reviewed by the U.S. Food and Drug Administration, is defined as patients who demonstrate a greater than or equal to 1.2 mg/dL decrease in serum phosphorus from baseline during the initial eight-week treatment period. The study demonstrated a statistically significant difference in serum phosphorus levels from the end of the eight-week treatment period to the end of the four-week randomized withdrawal period between the tenapanor-treated group and the placebo-treated group in the responder patient population (mean -1.01 mg/dL, median of -1.3 mg/dL) and met its primary endpoint (95% CI -1.44, -0.21; LSmean -0.82 mg/dL; p=0.01). Notably, in the responder population there was a mean reduction in serum phosphorus from baseline to the end of the eight-week treatment period of 2.56 mg/dL, with a reduction of up to 5.7 mg/dL and 33 percent of patients experiencing a reduction in serum phosphorus of greater than 3 mg/dL. Only 7.8 percent of patients discontinued treatment due to gastrointestinal side effects.

The PHREEDOM trial

The PHREEDOM trial, the company's second Phase 3 clinical trial of tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis, is currently underway. The study's design includes a 26-week open-label treatment period, with a 12-week placebo-controlled, randomized withdrawal period followed by an additional 14 week open-label safety extension. Topline results from this trial are expected in the fourth quarter of 2019.

The AMPLIFY trial

The AMPLIFY clinical trial is a randomized, double-blind, placebo-controlled study evaluating tenapanor in combination with phosphate binders as adjunctive therapy for the treatment of hyperphosphatemia in patients with ESRD on dialysis. Approximately 215 patients on a stable phosphate binder regimen with a serum phosphorus greater than or equal to 5.5 mg/dL and less than or equal to 10 mg/dL at screening, and after an up to 3-week run-in period will be randomized into the clinical trial 1:1 to receive tenapanor or placebo twice daily. Patients will be allowed to titrate their dose of tenapanor (or placebo) from a starting dose of 30 mg to 20 mg or 10 mg and then back up to 30 mg twice-daily, based on GI tolerability and serum phosphorus levels. The primary endpoint will be the difference in change of serum phosphate levels between the tenapanor and placebo treated groups from randomization to the end of the 4-week treatment period. Results from the AMPLIFY clinical trial are currently expected in the second half of 2019. If the company's AMPLIFY trial is successful, tenapanor would, if approved, be the first and only phosphate lowering therapy to be indicated as adjunctive therapy for use in combination with binders.

About Hyperphosphatemia

Hyperphosphatemia is a condition resulting in an abnormally elevated level of phosphorus in the blood that is estimated to affect more than 745,000 people in major developed countries. Phosphorus, a vital element required for most cellular processes, is present in almost every food in the Western diet, and, in individuals with normal kidney function, excess dietary phosphorus is efficiently removed by the kidneys and excreted in urine. In adults with functioning kidneys, normal serum phosphorus levels are 2.5 to 4.5 mg/dL. With kidney failure, elevated phosphorus becomes harmful and is diagnosed as hyperphosphatemia when serum phosphorus levels are greater than 4.5 mg/dL, according to KDIGO guidelines[1]. Although patients with end-stage renal disease (ESRD) rely on dialysis to eliminate harmful agents, these patients cannot adequately handle a typical daily phosphate intake and other means of managing phosphorus levels must be employed. In addition to dialysis, ESRD patients are put on restrictive low phosphorus diets and are currently prescribed medications called phosphate binders, the only interventions currently marketed for the treatment of hyperphosphatemia.

About Tenapanor

Tenapanor is a minimally absorbed inhibitor of intestinal sodium/hydrogen exchanger 3 (NHE3) that is being evaluated to reduce phosphate absorption and lower elevated serum phosphate concentrations in patients with ESRD on dialysis. A recent discovery by Ardelyx scientists, in collaboration with global academic experts, revealed phosphate absorption in humans occurs primarily through a dynamically regulated paracellular pathway. This pathway of phosphate flux is inhibited by tenapanor in a manner that appears largely specific for phosphate, whereas the overall absorption of other ions and large molecules appear not to be affected. The effect of tenapanor on phosphate absorption is mediated by transiently increasing the intracellular proton concentration in cells lining the gastrointestinal lumen, a result of NHE3 inhibition, which induces a conformational change in tight junction proteins, thereby decreasing permeability to paracellular phosphate transport. Notably, in clinical trials, tenapanor has not affected the absorption of other ions (except sodium) or nutrients. A consequence of intestinal NHE3 inhibition is that systemic sodium absorption is reduced leading to an increase in stool sodium and water content, loosening stool consistency and increasing bowel movement frequency.

Ardelyx, Inc.

Ardelyx is focused on enhancing the way people with cardiorenal diseases are treated by developing first-in-class medicines. Ardelyx's cardiorenal pipeline includes the Phase 3 development of tenapanor for the treatment of hyperphosphatemia in people with end-stage renal disease (ESRD) who are on dialysis, 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 has completed Phase 3 development of tenapanor for the treatment of irritable bowel syndrome with constipation (IBS-C) and submitted a new drug application, or NDA, to the U.S. Food and Drug Administration, or FDA, for the treatment of patients with IBS-C which has been granted a target action date under the Prescription Drug User Fee Act (PDUFA) of September 12, 2019. To efficiently bring its treatments to market, Ardelyx is pursuing strategic collaborations for tenapanor for IBS-C and hyperphosphatemia in certain territories. Ardelyx has established agreements with Kyowa Hakko Kirin in Japan, Fosun Pharma in China and Knight Therapeutics in Canada. For more information, please visit http://www.ardelyx.com/ and connect with us on Twitter @Ardelyx.

[1] KDIGO CKD-MBD Guidelines 2017. https://kdigo.org/wp-content/uploads/2017/02/2017-KDIGO-CKD-MBD-GL-Update.pdf

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 Ardelyx's product candidates in treating the diseases and conditions for which they are being developed; the potential for Ardelyx's product candidates to receive approval from the FDA for marketing for the indications for which they are currently being developed; Ardelyx's current expectations regarding the timing of receipt of results from its ongoing Phase 3 clinical trial evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis; and Ardelyx's current expectations regarding the timing of receipt of results from its ongoing Phase 3 clinical trial evaluating tenapanor in combination with phosphate binders for the treatment of hyperphosphatemia in ESRD patients 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 inherent in 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 November 7, 2018, and its future current and periodic reports to be filed with the Securities and Exchange Commission.

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