Ardelyx Announces Positive Results from the Pivotal Phase 3 AMPLIFY Study Evaluating Tenapanor in Dialysis Patients Who Have Uncontrolled Hyperphosphatemia Despite Phosphate Binder Treatment

September 3, 2019

The primary and all key secondary endpoints were met.
Tenapanor in combination with binders met the primary endpoint demonstrating a statistically significant (p=0.0004) reduction of serum phosphorus compared to binders alone.
Approximately two times more patients achieved the established serum phosphorus treatment goal of less than 5.5mg/dL in the tenapanor arm compared to binders alone (p -values≤0.0097) for each week of treatment.
Conference call to be held today at 8:30AM ET.

FREMONT, Calif., Sept. 3, 2019 /PRNewswire/ -- Ardelyx, Inc. (Nasdaq: ARDX), a specialized biopharmaceutical company focused on developing first-in-class medicines to improve treatment for people with cardiorenal diseases, today reported positive results from AMPLIFY, a pivotal Phase 3 study of tenapanor in combination with phosphate binders in patients with chronic kidney disease (CKD) on dialysis whose hyperphosphatemia was not previously controlled with binders alone. The AMPLIFY study met the primary endpoint and all key secondary endpoints, including demonstrating a statistically significant (p=0.0004) reduction in serum phosphorus levels for patients treated with tenapanor and phosphate binders compared to phosphate binders alone. Tenapanor is an investigational, first-in-class, small molecule, non-binder, phosphate absorption inhibitor being developed to treat hyperphosphatemia in patients with CKD on dialysis.

"I believe tenapanor has the potential to change the landscape of hyperphosphatemia treatment – finally, a novel agent that can lower serum phosphorus alone or in conjunction with binders," said Glenn Chertow, M.D., M.P.H., division chief of nephrology and professor of medicine at Stanford University. "Faced with an extremely high mortality rate of approximately 18% per year in dialysis patients, we are very focused on managing and treating elevated serum phosphorus. Elevated serum phosphorus is associated with mortality, cardiovascular events and bone fracture among patients receiving dialysis, and more than half of patients cannot achieve control of hyperphosphatemia despite taking a fist full of binders three times daily with meals. The AMPLIFY study results provide convincing evidence that controlling hyperphosphatemia will soon be within our reach."

Mike Raab, president and chief executive officer of Ardelyx added, "We are thrilled with the positive results from the AMPLIFY study demonstrating that tenapanor can help significantly more patients achieve the established serum phosphorus treatment goal of less than 5.5 mg/dL. This result is striking as serum phosphorus levels above 5.5 mg/dL are associated with increased mortality. For too long, hyperphosphatemia management has been an enormous challenge for patients and clinicians. With tenapanor, patients may finally be able to achieve their treatment goal. We look forward to reporting results from our second Phase 3 monotherapy study, PHREEDOM, in the fourth quarter of this year. With additional positive results from that trial, we will complete our New Drug Application for tenapanor, encompassing two indications: monotherapy and combination therapy for the treatment of hyperphosphatemia. The promising results from AMPLIFY bring us one step closer to providing this important medicine to patients with CKD on dialysis."

Key Study Results

Efficacy
For the primary endpoint, patients treated in the tenapanor arm (tenapanor in combination with phosphate binders, n=116) had a statistically significant (p=0.0004) mean reduction in serum phosphorus from baseline to the end of the four-week treatment period of 0.84 mg/dL, as compared to those treated in the binder arm (placebo in combination with phosphate binders, n=119) who had a mean reduction of 0.19 mg/dL. Patients in the tenapanor arm had statistically significant decreases in serum phosphorus during all four weeks ranging from 0.84 to 1.21 mg/dL (p-values≤0.0004). During the treatment period, up to 49.1% of patients in the tenapanor arm achieved a serum phosphorus of <5.5 mg/dL which was statistically significant compared with up to 23.5% in the binder arm (p-values≤0.0097). There was a statistically significant 22% to 24% reduction (p-values≤0.0027) in FGF23 levels in the tenapanor arm as compared to the binder arm. Elevated levels of FGF23 are associated with an increased risk of major cardiovascular events.

Safety
Tenapanor was well tolerated. Only 4.3% of patients in the tenapanor arm discontinued treatment compared to 2.5% in the binder arm. The single adverse event with a placebo-adjusted rate greater than 3% was loose stools/diarrhea at 36%, where most incidents were reported within the first five days of treatment, were transient in nature and the median time to resolution was four days after onset. Notably, only 2.6% of patients in the tenapanor arm discontinued treatment due to loose stools/diarrhea, as compared to 0.8% in the binder arm. There were no serious adverse events related to tenapanor.

About AMPLIFY
AMPLIFY, a double-blind, placebo-controlled, randomized study, enrolled a total of 236 patients with CKD on dialysis, who despite a stable phosphate binder regimen, had a serum phosphorus level greater than or equal to 5.5 mg/dL and less than or equal to 10.0 mg/dL at screening. After a run-in of two to four weeks, patients were randomized 1:1 to receive tenapanor or placebo twice daily while continuing their established phosphate binder regimen. Baseline serum phosphorus at randomization was at a mean level of 6.8 mg/dL. Tenapanor was initiated at a starting dose of 30 mg twice daily with tenapanor dose adjustments allowed based on serum phosphorus level and gastrointestinal tolerability.

The primary endpoint of the study was the comparison of the change from baseline in serum phosphorus levels at week four between the tenapanor and binder arms. The key secondary endpoints included a comparison of the proportion of patients achieving a serum phosphorus level below 5.5 mg/dL at week four and relative change from baseline in FGF23 levels between the tenapanor and binder arms at week four. (NCT 03824587)

About Tenapanor for Hyperphosphatemia
Tenapanor, discovered and developed by Ardelyx, is a first-in-class, proprietary, oral, medicine in late-stage clinical development 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 the tightening of the epithelial cell junctions, thereby significantly reducing paracellular uptake of phosphate, the primary pathway of phosphate absorption. In addition, if approved, tenapanor will be easier than phosphate binders for patients to take with a regimen of just one small pill, taken twice daily. The company previously reported results from its first Phase 3 monotherapy study with tenapanor in CKD patients on dialysis, reporting that the primary endpoint was met (p=0.01) and that 50% of patients (n=164) experienced a mean serum phosphorus reduction of 2.56 mg/dL.

Ardelyx believes that, if approved, tenapanor can become a foundational therapy for all CKD patients on dialysis who experience elevated serum phosphorus.

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 common 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 over time (Spherix 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 dialysis patients (Block 2004), and common treatment goals are to manage serum phosphorus levels to <5.5mg/dL.

About Fibroblast Growth Factor 23 (FGF23)
FGF23 is a protein in humans that is responsible for phosphate and vitamin D metabolism. Prospective clinical studies have demonstrated a linear association between elevated levels of FGF23 and a greater risk of major cardiovascular events and mortality. FGF23 is independently associated with greater left ventricular mass and greater prevalence of left ventricular hypertrophy (Amaral 2012).

Conference Call Information
The company will host a conference call today, September 3, 2019 at 8:30AM ET to discuss the AMPLIFY findings. To participate in the conference call, please call (855) 296-9612 (toll-free) or (920) 663-6277 (toll) and reference call ID number 9789472. A webcast of the call can also be accessed by visiting the Investor page of the company's website www.ardelyx.com and will be available on the website for 60 days following the call.

About Ardelyx, Inc.
Ardelyx is focused on enhancing the lives of people with cardiorenal diseases by developing first-in-class medicines that matter. Ardelyx's cardiorenal pipeline includes the Phase 3 development of tenapanor for the treatment of hyperphosphatemia in people with CKD 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 Kirin Co., Ltd. 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.

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 the use of tenapanor as monotherapy and in combination with phosphate binders for the treatment of hyperphosphatemia, the potential for tenapanor in combination with phosphate binders to achieve serum phosphorus levels of less than 5.5mg/dL, Ardelyx's expected timing for receipt of data from PHREEDOM, its ongoing Phase 3 clinical trial evaluating tenapanor as monotherapy for the treatment of hyperphosphatemia in CKD patients on dialysis, Ardelyx's expectations regarding its plans for the commercialization of tenapanor, Ardelyx's expectations regarding the size of the patient populations for its product candidates, and Ardelyx's expectations regarding the potential for tenapanor to become a foundational therapy for all patients on dialysis who experience elevated serum phosphorus. 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 August 9, 2019, and its future current and periodic reports to be filed with the Securities and Exchange Commission.

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