Ardelyx Announces Positive Topline Results from Pivotal Phase 3 PHREEDOM Study Evaluating Tenapanor in CKD Patients on Dialysis

December 3, 2019

The primary endpoint was met (p<0.0001)
77% of tenapanor-treated patients in the intent-to-treat population had a mean reduction in serum phosphorus of 2.0 mg/dL from baseline
NDA submission for tenapanor for the treatment of hyperphosphatemia on-track for mid-2020
Additionally, initial results from Phase 4 NORMALIZE study show that 42% of patients achieved normal serum phosphorus, a 45% improvement over DOPPS current practice data
Conference call to be held today at 8:00 AM ET

FREMONT, Calif., Dec. 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 topline results from PHREEDOM, a long-term Phase 3 study evaluating the efficacy and safety of tenapanor as monotherapy for the treatment of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis. In the study, patients randomized to the tenapanor arm were treated in a 26-week open-label treatment period and were then re-randomized to a 12-week double-blind, placebo-controlled randomized withdrawal period. The PHREEDOM study met its primary endpoint demonstrating a statistically significant difference in least square (LS) mean serum phosphorus change (-1.4 mg/dL, p<0.0001), as compared to placebo. During the 26-week treatment period, 77% of tenapanor-treated patients in the intent-to-treat population (n=408) had a decrease in serum phosphorus, with a mean reduction from baseline of 2.0 mg/dL. Tenapanor is an investigational, first-in-class, phosphate absorption inhibitor being developed to treat hyperphosphatemia in patients with CKD on dialysis. If approved, tenapanor will be the only non-binder treatment for the control of serum phosphorus in patients with CKD on dialysis.

"If approved, tenapanor is poised to change the way we manage hyperphosphatemia in patients on dialysis," said Myles Wolf, M.D., MMSc, Charles Johnson, M.D. professor of medicine and chief of Duke Nephrology. "Tenapanor would be a first-in-class therapy that targets the primary pathway of phosphate absorption to significantly lower serum phosphate while requiring patients to take just one small pill twice per day. This would make tenapanor an important innovation and potentially an ideal first-line therapy for patients receiving dialysis for whom new effective treatments are desperately needed."

"These results are very exciting and represent a capstone to our tenapanor clinical development program, which is focused on the development of a new and important therapy for patients with hyperphosphatemia," said Mike Raab, president and chief executive officer of Ardelyx. "Based on the PHREEDOM data that demonstrate tenapanor as an effective monotherapy, and the previously released AMPLIFY data that demonstrate the benefits of a dual mechanism approach with tenapanor plus binders in those who require more aggressive phosphate management, it is clear that tenapanor has a role to play in the management of all dialysis patients with hyperphosphatemia. With these results in hand, our focus will now turn to completing and submitting our NDA, which we expect in mid-2020."

PHREEDOM
Key Topline Results

Primary Endpoint:

As compared to patients treated with placebo, patients in the efficacy analysis set treated with tenapanor had a statistically significant difference in LS mean serum phosphorus change from the end of the 26-week treatment period to the endpoint visit in the 12-week randomized withdrawal period (-1.4 mg/dL, p<0.0001).

Safety:

Tenapanor was generally well-tolerated. As anticipated due to the mechanism of action, the most common self-reported adverse event was loose stools/diarrhea at an incidence rate of 52.5%, with approximately 90% of these events judged by the investigator to be mild to moderate in nature. The majority of the events were reported within the first five days of treatment and were transient notwithstanding continued treatment with tenapanor. In the 26-week open-label treatment period, 16% of the tenapanor-treated patients discontinued treatment due to diarrhea. Additionally, during the randomized withdrawal period, only 0.8% of tenapanor-treated patients discontinued due to diarrhea.

In the safety analysis set of the 26-week open-label treatment period, which included tenapanor (n=419) and sevelamer (n=137), 17.2% of tenapanor-treated patients compared to 22.6% of sevelamer-treated patients experienced a serious adverse event. The median dose for tenapanor was 60 milligrams per day throughout the study and the median dose for sevelamer was 4.8 grams per day after randomization and increased to 7.2 grams per day by the end of the 26-week open-label treatment period.

NORMALIZE
Initial Results

Patients completing the PHREEDOM trial from both the tenapanor arm and the sevelamer active safety control arm had the option to participate in NORMALIZE, an ongoing open-label 18-month extension study. The goal of this study is to obtain real-world evidence regarding the dual mechanism of tenapanor and sevelamer to reduce patients' serum phosphorus levels to normal (<4.6 mg/dL) while minimizing medication burden.

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 ³4.6 mg/dL have sevelamer tablets added incrementally to achieve normal serum phosphorus levels. Patients entering the study from the sevelamer active safety control arm have tenapanor tablets added to their treatment regimen and have sevelamer tablets withdrawn based on their serum phosphorus value, to achieve normal serum phosphorus levels.

In this initial analysis, 96% of eligible patients have chosen to enroll into NORMALIZE. Of the 73 patients thus far treated for more than one month of treatment, 42% have achieved normal serum phosphorus of less than 4.6 mg/dL and of those, 58% have accomplished this with either tenapanor alone or with tenapanor in combination with only one to three sevelamer tablets per day. These data represent a 45% improvement compared to current treatment practice data reported in the June 2019 Dialysis Outcomes Practice Patterns Study (DOPPS) Practice Monitor.

PHREEDOM Study Design

PHREEDOM is a one-year study with a 26-week open-label treatment period and a 12-week double-blind, placebo-controlled randomized withdrawal period followed by a 14-week open-label safety extension period. The study randomized a total of 564 patients with CKD on dialysis who had a serum phosphorus level between 6.0 mg/dL and 10.0 mg/dL and had an increase in serum phosphorous of at least 1.5 mg/dL after an up to 3-week phosphate binder wash-out period. Patients were randomized 3:1 to either the tenapanor arm (n=423, n=408 intent to treat) or the active safety control arm (sevelamer n=141). Those patients randomized to the active safety control arm are treated with sevelamer for 52 weeks. Patients in the tenapanor arm received tenapanor twice daily at a starting dose of 30 mg with dose adjustments allowed based on serum phosphorus level and gastrointestinal tolerability. At the end of the 26-week treatment period, patients in the tenapanor arm were randomized 1:1 to enter the randomized withdrawal period and either remain on the tenapanor dose they were taking or receive placebo for up to an additional 12 weeks. After the randomized withdrawal period, patients then continued on the study for an additional three months as part of the long-term safety extension. Patients in the active safety control arm received sevelamer at an initial dose based on its package insert with dose changes allowed at the discretion of the principal investigator for up to one year.

The primary efficacy endpoint of the study was the difference in change in serum phosphorus between the pooled tenapanor-treated patients and placebo-treated patients in the efficacy analysis set from the end of the 26-week treatment period to the endpoint visit of the 12-week randomized withdrawal period. The efficacy analysis set (n=131), which was accepted by the U.S. Food and Drug Administration as the primary analysis set, included patients who completed the 26-week treatment period and achieved a 1.2 mg/dL decrease in serum phosphorus in the same period.

About Tenapanor for Hyperphosphatemia

Tenapanor, discovered and developed by Ardelyx, is a first-in-class, proprietary, minimally absorbed, 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 to the positive results of the PHREEDOM trial, the company previously reported results from its first Phase 3 monotherapy study with tenapanor in patients with CKD on dialysis, reporting that the primary endpoint was met (p=0.01).

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).

Conference Call Information
The company will host a conference call today, December 3, 2019 at 8:00 AM ET to discuss the PHREEDOM findings. To participate in the conference call, please call (855) 296-9612 (toll-free) or (920) 663-6277 (toll) and reference call ID number 8065608. A webcast of the call and accompanying slides 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 way people with cardiorenal diseases are treated by developing first-in-class medicines. Ardelyx's cardiorenal pipeline includes tenapanor, a treatment of hyperphosphatemia in people with chronic kidney diseases (CKD) 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 received approval of IBSRELA® (tenapanor). 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 (formerly known as 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.

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 as part of a dual mechanism approach with tenapanor and binders for the treatment of hyperphosphatemia, the potential for tenapanor with binders to achieve serum phosphorus levels of less than 5.5 mg/dL and less than 4.6 mg/dL, and Ardelyx's expected timing for an NDA submission for tenapanor for hyperphosphatemia. 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 6, 2019, and its future current and periodic reports to be filed with the Securities and Exchange Commission.

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