Unique mechanism of action inhibiting paracellular phosphate absorption

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Ardelyx, Inc. today announced that the novel mechanism of action for tenapanor for the treatment of hyperphosphatemia, or elevated serum phosphorus, has been published in the peer-reviewed journal *Science*

Translational Medicine. Tenapanor is a sodium/hydrogen exchanger 3 (NHE3) inhibitor currently being evaluated in a second Phase 3 registration trial, the PHREEDOM trial, for the treatment of hyperphosphatemia in patients with end-stage renal disease (ESRD) who are on dialysis. The paper, titled "Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability," can be accessed in the current online edition of the publication.

"The elucidation of tenapanor's mechanism is a landmark discovery in our field, causing us to completely rethink our understanding of phosphate transport and absorption," said Geoff Block, M.D., director of clinical research at Denver Nephrology Research, and a PHREEDOM trial investigator. "Nearly all patients with ESRD have elevated serum phosphorus, a problem that if not managed properly through diet changes and prescription medication, can lead to an increase in morbidity and mortality in patients. Today, our only therapeutic option is to use phosphate binders, which are inadequate in reducing serum phosphorus in the majority of patients and associated with a number of challenges, including low rates of compliance because of the large number of pills that must be taken each day, significant tolerability issues and long-term concerns related to the safety of our patients. I believe tenapanor could shift our treatment approach and offer a significant benefit to patients, who absolutely need better options."

Ardelyx scientists, in collaboration with global academic experts, established the mechanism by which tenapanor reduces gastrointestinal phosphate absorption using in vivo studies in rodents, as well as Ardelyx's human stem cell-based translational technology called the Ardelyx Primary Enterocyte and Colonocyte Culture System (APECCS). In the past, the literature has described two pathways of phosphate absorption in the gut: active transcellular transport directly through the cells lining the gut and passive paracellular flux through tight junction

protein pores between cells. Historically, the science has focused almost exclusively on the transcellular transport pathway where specific transporter proteins bring phosphate into and through intestinal cells and into the blood. Ardelyx's discoveries conclude that phosphate absorption in humans actually 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. Tenapanor's phosphate mechanism is due to its direct action on NHE3, which exchanges sodium from the lumen of the gut for an intracellular proton. Inhibition of NHE3 by tenapanor results in proton retention in the cell, which modulates tight junction proteins to decrease permeability to phosphate, reducing paracellular phosphate absorption. Dynamic regulation of the permeability characteristics of the tight junction pore has only very recently been recognized, and tenapanor is the first agent to demonstrate this dynamic regulation of paracellular phosphate permeability.

Tenapanor's novel mechanism of action has translated into meaningful reductions in serum phosphorus in humans, as reported in the findings from Ardelyx's first Phase 3 clinical study evaluating tenapanor for the treatment of hyperphosphatemia in ESRD patients on dialysis. That trial met its primary endpoint, demonstrating a statistically significant difference in change in serum phosphorus between 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. Tenapanor was also well-tolerated in the trial, with limited discontinuations due to GI-related adverse events in the treatment period and no discontinuations related to GI events in the randomized withdrawal period.

"Tenapanor's dynamic mechanism of lowering phosphate by tight junction modulation with just two small pills has the potential to offer a

first-of-its-kind approach to treating this large and growing patient population," commented David Rosenbaum, Ph.D., chief development officer of Ardelyx. "This important publication showcases our commitment to scientific innovation, unique insights into the biology of the gut and chemistry capabilities that enable us to design and optimize gut-restricted compounds. Tenapanor, if approved, would offer an entirely new way of treating ESRD patients who need a convenient, effective and tolerable medicine for managing phosphorus."

Ardelyx's Phase 3 PHREEDOM trial is enrolling patients, and the company expects to report results from this registration study in 2019.

About hyperphosphatemia

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 guidelines1. 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.

More information: Andrew J. King et al. Inhibition of sodium/hydrogen exchanger 3 in the gastrointestinal tract by tenapanor reduces paracellular phosphate permeability, *Science Translational*

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