News release

Kyowa Kirin Announces a Phase 2 Study Result of tenapanor (KHK7791) for Hemodialysis Patients with Hyperphosphatemia in Japan Presented at European Renal Association-European Dialysis and Transplant Association

TOKYO, June 8, 2020 – Kyowa Kirin Co., Ltd. (TSE:4151, President and CEO: Masashi Miyamoto, Kyowa Kirin) announced that tenapanor's[*1] effect of decreasing pill burden[*2] of phosphate binders (PB), which is the outcome of a phase 2 study of tenapanor (KHK7791) for hemodialysis patients with hyperphosphatemia in Japan, was presented in a poster session virtually at European Renal Association-European Dialysis and Transplant Association (ERA-EDTA 2020), June 6 ~ June 9, 2020.

ERA-EDTA 2020　Poster session：P1404

Title：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.

・Method

This is a multicenter, open-label, single-arm phase 2 study, consisting of a screening period, a 3-week observation period, and a 26-week treatment period. Patients whose serum phosphorus level was ≥ 3.5 and ≤ 7.0 mg/dL, taking at least two PB pills three times a day were enrolled. The patients started to receive 30 mg of tenapanor twice daily. PB treatment was continued according to individual regimens, and the dose could be adjusted appropriately to maintain serum phosphorus level within ±0.5 mg/dL from the baseline. The primary endpoint is an achievement of at least a 30% decrease in the mean of the total number of PB and tenapanor pills compared to the number of PB pills at baseline.

・Results

The primary endpoint was met. Of 67 enrolled patients at the timing of analysis, 48 patients (71.6%, [95% CI: 59.3% - 82.0%], $p<0.001$) achieved a 30% decrease in the total number of PB and tenapanor pills, and 18 patients (26.9%) no longer required the use of any PB at week 26 (their PB tablets is zero at last evaluation). Mean phosphorus levels were maintained during the study from 5.2 mg/dL at the baseline to 4.7 mg/dL at week 26. The most frequent adverse event was diarrhea (76.1%), which was mostly mild to moderate. Four patients discontinued the study due to diarrhea. Serious adverse events were reported in five patients.

・Conclusion

Tenapanor provided effective phosphorus control with significantly fewer pills compared to PB. The Adverse Event (AE) profile was similar to previous US studies conducted by Ardelyx, Inc. (Nasdaq: ARDX). This result suggests that tenapanor, a first-in-class, non-binder, phosphate absorption

inhibitor that provides a novel approach to the management of hyperphosphatemia could potentially reduce PB pill burden while maintaining effective phosphorus control.

This study showed that tenapanor is able to reduce pill burden with hyperphosphatemia treatment in hemodialysis patients. Kyowa Kirin expects tenapanor to be a new, unique approach, for treating hyperphosphatemia. Kyowa Kirin also conducted a monotherapy study and a combination study with PB in Japan.

"Many patients with hyperphosphatemia have difficulty in taking many pills to control the level of phosphorus and it is very important to reduce the pill burden." said Yoshifumi Torii, Ph.D., Executive officer, Vice President Head of R&D Division of Kyowa Kirin. "I'm very pleased with the result that tenapanor may help patients who have this difficulty."

In the United States, Ardelyx conducted monotherapy and combination therapy studies of tenapanor[*3].

The Kyowa Kirin Group companies strive to contribute to the health and well-being of people around the world by creating new value through the pursuit of advances in life sciences and technologies.

About tenapanor (KHK7791)
Tenapanor, discovered and developed by Ardelyx, is a NHE3 inhibitor. It has a unique mechanism of action that, in hyperphosphatemia, acts by blocking the NHE3 sodium transporter in the GI tract, reducing the absorption of dietary sodium and resulting in increased protons within the cells. The increase in protons causes a reduction in phosphate uptake by tightening junctions or pores that regulate phosphate absorption in the GI tract. And it is absorbed minimally in oral administration. Overall, this mechanism appears to be specific to phosphate absorption given that Ardelyx has not observed any significant changes in other ions, other than sodium, in preclinical or clinical studies. According to the license agreement with Ardelyx on Nov. 2017, Kyowa Kirin has the exclusive rights to develop and commercialize tenapanor for the treatment of cardiorenal diseases, including hyperphosphatemia, in Japan.

About PB pill burden
It has been reported that patients undergoing dialysis treatment have to take a lot of pills daily, and in particular, they have a large number of PB pills.
Ref. 1 Fissell RB, Karaboyas A, Bieber BA, Sen A, Li Y, Lopes AA, et al. Phosphate binder pill burden, patient-reported non-adherence, and mineral bone disorder markers: Findings from the DOPPS. Hemodial Int. 2016;20:38-49.
Ref. 2 Wang S, Alfieri T, Ramakrishnan K, Braundhofer P, Newsome BA. Serum phosphorus levels and pill burden are inversely associated with adherence in patients on hemodialysis. Nephrol Dial Transplant. 2014;29:2092-9.

About previous US studies
Ardelyx conducted phase 3 studies including monotherapy study, long-term study and combination study with PB in the United States. Main outcome of each study was published as a journal or Ardelyx's news releases below.

- Block GA, Rosenbaum DP, Yan A and Chertow GM. Efficacy and Safety of Tenapanor in Patients with Hyperphosphatemia Receiving Maintenance Hemodialysis: A Randomized Phase 3 Trial. Journal of the American Society of Nephrology 2019;30(4): 641-652
- http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-announces-positive-topline-

results-pivotal-phase-3

- http://ir.ardelyx.com/news-releases/news-release-details/ardelyx-announces-positive-results-pivotal-phase-3-amplify-study