Kyowa Hakko Kirin Presented Results of Phase II Study of Bardoxolone Methyl in Japan at the ASN Kidney Week 2017

Tokyo, Japan, November 6, 2017 --- Kyowa Hakko Kirin Co., Ltd. (Tokyo: 4151, President and CEO: Nobuo Hanai, "Kyowa Hakko Kirin") announced that the phase II clinical study (TSUBAKI study) of bardoxolone methyl[*1] (RTA 402) in Japan was unblinded and the results were presented as a Late-Breaking Clinical Trial oral presentation at the American Society of Nephrology Kidney Week 2017. RTA 402 is a small-molecule compound in-licensed from Reata Pharmaceuticals, Inc. (Irving, Texas, USA, CEO and President: Warren Huff, "Reata")

The clinical study was a randomized, double-blind[*2], placebo-controlled, multi-center study in chronic kidney disease (CKD) with type II diabetes, and it evaluated the efficacy and safety of RTA 402 taken once daily for 16 weeks with a titration scheme (5-15mg). The enrolled patients were CKD stages G3 and G4 without identified risk factors of fluid overload such as BNP[*3]>200 pg/mL and previous hospitalization for heart failure. The primary efficacy endpoint was the change in glomerular filtration rate (GFR)[*4] measured by inulin clearance after 16 weeks in stage G3 patients compared to baseline GFR, and a pre-specified interim analysis was conducted. The inulin clearance method[*5], which is the gold standard for measuring GFR, was used for the measurement.

In patients with stage G3, 85 patients were randomly assigned 1:1 to the RTA 402 group and placebo group (three patients discontinued before treatment started), and 82 patients were treated (RTA 402 group: 41 patients; Placebo group: 41 patients). The mean eGFR and GFR at baseline were 46.7 and 48.5 mL/min/1.73 m^2, respectively. The change in GFR after 16 weeks, the primary efficacy endpoint, was evaluated in 40 patients (RTA 402 group: 17 patients; Placebo group: 23 patients), and it was found that there was a significant improvement in GFR (6.64 mL/min/1.73 m^2, p=0.008） in the RTA 402 group compared to the placebo group. In patients with stage G4, 39 patients were randomly assigned 2:1 to the RTA 402 group and placebo group (one patient discontinued before treatment started), and 38 patients were treated (RTA 402 group: 24 patients, Placebo group: 14 patients). The study showed good tolerance in both stages G3 and G4 patients treated with RTA 402, and no symptoms of fluid overload were observed.

Based on these findings, RTA 402 resulted in a clear improvement in GFR (kidney function) measured using the inulin clearance method. Also, by appropriately selecting the target patients, the findings suggest RTA 402 can be used safely. A phase III clinical study, designed to validate the efficacy and safety of RTA 402 targeting a larger number of patients, is planned to be initiated during 2018 in Japan.

"The data from TSUBAKI are very encouraging and indicate that bardoxolone methyl clearly shows true improvements in GFR," said Mitsuo Satoh, Ph.D., Executive Officer, Vice President Head of R&D

Division of Kyowa Hakko Kirin. "On the basis of the data, we are excited to plan a phase 3 study of bardoxolone methyl in diabetic kidney disease patients."

Kyowa Hakko Kirin signed a license agreement with Reata for exclusive right to develop and commercialize RTA 402 in renal and certain other indications in Japan, China, Taiwan, South Korea and Southeast Asia on December 24, 2009. Reata is currently conducting a global Phase III clinical study on RTA 402 in connective tissue disease associated pulmonary arterial hypertension[*6] and a global Phase II/III clinical study in Alport syndrome[*7].

The Kyowa Hakko 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.

*1: Bardoxolone methyl
Bardoxolone methyl activates Nrf2, a transcription factor that controls the production of over 250 antioxidant and detoxification proteins. Activation of Nrf2 protects tissues from inflammation by increasing cellular antioxidant content and suppressing inflammatory signaling pathways. Chronic inflammation has been shown to promote type 2 diabetes and its complications, including cardiovascular events and CKD.

*2: Double-blind study
A double-blind study is where neither the doctor nor the patient know which group the patient is in, and it avoids errors arising from bias, such as the placebo effect, and objectively evaluates the effectiveness of medicinal drugs and procedures.

*3: BNP
BNP is the abbreviation of “brain natriuretic peptide.” It is a hormone excreted by the heart to protect the heart.

*4: Glomerular filtration rate (GFR)
GFR is a marker of renal function and indicates the volume of filtrate through the kidneys per minute. Estimated GFR (eGFR) based on the serum creatinine level is widely used to assess renal function; however, in case of need for accurate evaluation of renal function, for example for kidney transplant donors, the inulin clearance method is used as it is considered the gold standard for measuring GFR.

*5: Inulin clearance method
There are two methods, which are the simple method and standard method, for inulin clearance, and the standard method was used in this study. In the standard method, three sets of 30-min urine samples are collected after the continuous intravenous infusion of 1% inulin. Clearance is calculated by 30-min urine collection and serum concentration at the midpoint of each clearance period. Average of the three clearances is used as the clearance by the standard method.

*6: Pulmonary arterial hypertension
Pulmonary arterial hypertension (PAH) is a condition in which the blood pressure in the pulmonary artery increases, resulting in symptoms such as easy fatigability and shortness of breath. As one of PAH caused by inflammation, autoimmune diseases and systemic vascular disorders, there exists “connective tissue disease associated pulmonary arterial hypertension (CTD-PAH).” CTD-PAH patients do not exhibit a good response to pulmonary vasodilators, and such drugs do not bring significant improvement to functional capacity.

*7: Alport syndrome

Alport syndrome is a hereditary nephritis that progresses to end-stage renal disease. It is caused by a genetic mutation in a type IV collagen, which is an important protein in relation to the structure of the glomeruli in the kidneys. The mechanism of nephritis progression is unknown, and there is no definitive treatment. Also, because type IV collagen also exists in the inner ear and eyes, hearing loss and eye symptoms also occur.