Kyowa Hakko Kirin Initiated Phase 3 Clinical Study of Bardoxolone Methyl (RTA 402) for Diabetic Kidney Disease

Tokyo, Japan, May 31, 2018 --- Kyowa Hakko Kirin Co., Ltd. (Tokyo: 4151, President and COO: Masashi Miyamoto, "Kyowa Hakko Kirin") announced the initiation of phase 3 clinical study in Japan (study name: AYAME) for bardoxolone methyl (RTA 402), a small-molecule compound licensed from Reata Pharmaceuticals, Inc. (Irving, Texas, USA; CEO and President: Warren Huff, "Reata").

This multi-center, randomized, double-blind, placebo-controlled study is designed to assess efficacy and safety of RTA 402 for diabetic kidney disease. RTA 402 has been designated "SAKIGAKE Designation" for the treatment of diabetic kidney disease by Ministry of Health, Labour and Welfare on March 27, 2018.

“We are very pleased to start the phase 3 study of bardoxolone methyl for diabetic kidney disease,” said Mitsuo Satoh, Ph.D., Executive Officer, Vice President Head of R&D Division of Kyowa Hakko Kirin. “We believe that this study will prove the potential of bardoxolone methyl to be an important treatment option for patients with diabetic kidney disease.”

Kyowa Hakko Kirin signed a license agreement with Reata for the exclusive rights to develop and commercialize bardoxolone methyl in renal disease and certain other indications in Japan, China, Taiwan, South Korea and Southeast Asia on December 24, 2009. Reata is currently conducting a global Phase 3 clinical study on bardoxolone methyl in connective tissue disease associated pulmonary arterial hypertension and a global Phase 2/3 clinical study in Alport syndrome.

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.

＜Summary of the Study＞

Study Name	RTA 402 Phase 3 Clinical Trial (A Randomized, Double-blind, Placebo-controlled Clinical Trial in Patients with Diabetic Kidney Disease) **A** phase 3 stud**Y** of b**A**rdoxolone **ME**thyl in patients with diabetic kidney disease; AYAME study

	 ※The above is the logo of the AYAME study
Study Population	Patients with diabetic kidney disease (CKD stage G3, G4)
Primary Endpoint	• Time to onset of a ≥ 30% decrease in eGFR from baseline or end-stage renal disease (ESRD)
Secondary Endpoints	• Time to onset of a ≥ 40% decrease in eGFR from baseline or ESRD Other secondary endpoints • Time to onset of a ≥ 53% decrease in eGFR from baseline or ESRD • Time to onset of ESRD • Change in eGFR from baseline at each evaluation time point
Estimated Enrollment	700
Location	Japan
Estimated Study Completion Date	March 2022

About bardoxolone methyl (RTA 402)
Bardoxolone methyl is a low-molecular compound that activates nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that has a key role in the body's protective response to stress. A wide range of anti-oxidative stress and anti-inflammatory effects of this compound could improve renal function. In the phase 2 clinical study conducted in Japan (the TSUBAKI study), administration of bardoxolone methyl resulted in a clear improvement in glomerular filtration rate (kidney function) measured using the inulin clearance method.

About diabetic kidney disease (DKD)
Diabetic kidney disease (DKD) is a chronic kidney disease (CKD) caused by diabetes, the most common reason for patients initiating hemodialysis. CKD, if left untreated, results in end-stage renal disease with a decrease in renal function and ultimately requires hemodialysis or renal transplantation. Reduced renal function in CKD is known to involve excessive oxidative stress and inflammation.