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**Bardoxolone Methyl (RTA 402) Data Show Improvement in Renal Function by Inulin Clearance in a Phase II Clinical Study in Japan**

Kyowa Hakko Kirin Co., Ltd. (Tokyo; 4151 President and CEO: Nobuo Hanai; “Kyowa Hakko Kirin”) announced today the results of an interim efficacy analysis of a phase II clinical study (TSUBAKI study) in Japan of bardoxolone methyl[*1] (RTA 402), which is a small-molecule compound in-licensed from Reata Pharmaceuticals, Inc. (Irving, Texas, USA; CEO and President: Warren Huff; “Reata”).

The clinical study is a randomized, double-blind[*2], parallel group, placebo-controlled study in patients with chronic kidney disease (CKD) and type II diabetes, and has been evaluating the safety and efficacy of once-daily administration of RTA 402 for 16 weeks. Inulin clearance method[*3] as the gold standard for measuring glomerular filtration rate (GFR)[*4] was used in the efficacy evaluation to make a precise assessment of GFR, which is an indicator reflecting kidney function. Data from interim analysis were assessed by an Independent Data Monitoring Committee[*5] and demonstrated that a significant improvement in GFR was seen in the RTA 402 compared with the placebo group. This is the world's first result showing improvement in renal function by inulin clearance. There are no safety concerns with RTA 402. Kyowa Hakko Kirin will continue to evaluate RTA 402 toward the completion of the study.

Kyowa Hakko Kirin signed a license agreement with Reata for exclusive right to develop and commercialize RTA 402 in Japan, China, Taiwan, Korea and Southeast Asia on Dec. 24, 2009. Reata has been conducting a Phase II clinical study on RTA 402 in pulmonary hypertension in the US, and its initial positive data were presented at the annual meeting of the 2015 American College of Chest Physicians (CHEST). Reata is proceeding into a global Phase III clinical study on RTA 402 including Japan in connective tissue disease associated pulmonary arterial hypertension.

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 avoids errors arising from bias, as the placebo effect, and objectively evaluates the effectiveness of medicinal drugs and procedures.

*3: **Inulin clearance method**
There are two methods, which are the simple 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.

*4: **Glomerular filtration rate (GFR)**
GFR is a marker of renal function and indicates the volume of filtrate through 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: **Independent Data Monitoring Committee**
Independent Data Monitoring Committee is established by the sponsor to assess periodically the progress of this clinical study, safety data and critical efficacy variables. The committee recommends to the sponsor whether to continue, modify, or discontinue the study.