Kyowa Hakko Kirin Announces Positive Interim 40-Week Data from Pediatric Phase 2 Study of KRN23 in X-Linked Hypophosphatemia

Substantial reduction in bone disease demonstrated with two different instruments

Tokyo, December 2nd, 2015 -- Kyowa Hakko Kirin Co., Ltd. (Tokyo; 4151 President and CEO: Nobuo Hanai; "Kyowa Hakko Kirin") announced today positive interim data through 40 weeks from the first 36 patients in the ongoing pediatric Phase 2 study of KRN23 for the treatment of X-linked hypophosphatemia (XLH). The study has been conducted under a collaboration with Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE; "Ultragenyx") in the US and EU. The data demonstrated that rickets disease was improved when measured by both Thacher Rickets Severity Scoring (RSS) and Radiographic Global Impression of Change (RGI-C) scoring methods and were further supported by functional improvements measured by patient reported outcomes in more severely affected patients. The data also demonstrated that while both dose groups showed improvements, the bi-weekly dose regimen generally resulted in a better overall response than the monthly dose regimen.. Importantly, patients with more severe disease at baseline had greater improvements on treatment with KRN23.

Study Design

The randomized, open-label, dose-finding Phase 2 study is evaluating safety and efficacy in 52 pediatric XLH patients ages 5 to 12. The study consists of a 16-week individual dose-titration period followed by a 48-week treatment period, for a total of 64 weeks. Patients are divided into three cohorts of escalating starting dose levels of KRN23 with either monthly or bi-weekly dosing regimens. Patients can continue to have their dose increased throughout the duration of the study to reach an individually-optimized dose.

The evaluation of rickets in the study is done via radiographs of the wrists and knees. The scoring was done using the Thacher Rickets Severity Score (RSS) and the Radiographic Global Impression of Change (RGI-C) score. RSS is a pre-specified 10-point scale that measures knee and wrist irregularities. Each radiograph is scored by one central independent reviewer who is blinded to the subject's adherence, dose, dose regimen, and radiographic sequence. The RGI-C score is a 7-point scale that rates changes in a specific list of abnormalities in the wrist, knee, and leg by taking the mean of three independent radiologist readings comparing before and after treatment X-ray images.

Safety, changes in serum phosphorus, and other pharmacodynamic parameters were evaluated at the 40-week analysis. The current interim analysis includes the first 36 patients enrolled in the study. Additional safety, tolerability, and efficacy data, including radiographic evidence of rickets severity, will be evaluated for all patients at the 64-week time point.

Study Results

Patients in the study (n=36) were enrolled at experienced XLH centers, and 35 patients had previously been on standard of care (oral phosphate/Vitamin D therapy) for an average of approximately 7 years prior to entering the study. Patients began a bi-weekly or monthly regimen at low doses and were titrated up to target a low-normal range of serum phosphorus. Data reported today are from the first 36 patients through 40 weeks of treatment. A subset of patients (n=18) were pre-specified as having high rickets severity (greater bone disease) if their baseline total RSS scores were $\geq$ 1.5. For the responder analysis using total RSS, responders were pre-defined as those patients who had baseline total RSS scores $\geq$ 1-0 and had 1.0 or more reduction at Week 40 which is considered a

significant improvement.

Bone Disease Results

Thacher Rickets Severity Scoring (RSS)

RSS is a scoring system originally developed to assess rickets severity in children with nutritional rickets but is used now in genetic bone diseases. In patients who were dosed bi-weekly (n=18), the mean total RSS score decreased from 1.53 at baseline to 0.86 at 40 weeks (-0.67 points; 44% reduction; p=0.0126), and 75% of the patients (9/12) were responders. In the high severity patients who were dosed bi-weekly (n=9), the mean total rickets score decreased from 2.44 at baseline to 1.00 at 40 weeks (-1.44 points; 59% reduction; p<0.0001), and 89% of these patients were responders (8/9).

In patients who were dosed monthly (n=18), the mean total rickets score decreased from 1.33 at baseline to 1.14 at 40 weeks (-0.19 points; 14% reduction), and 46% of the patients (5/11) were responders. In the high severity patients who were dosed monthly (n=9), the mean total RSS score decreased from 2.17 at baseline to 1.44 at 40 weeks (-0.72; 33% reduction) and 56% of these patients (5/9) were responders. Overall, in all patients (n=36), the mean total RSS score decreased from 1.43 at baseline to 1.00 at 40 weeks (-0.43; 30% reduction; p=0.0076), and 61% of the patients (14/23) were responders. In all the high severity patients (n=18), the mean total rickets score decreased from 2.31 at baseline to 1.22 at 40 weeks (-1.08; 47% reduction; p<0.0001), and 72% of these patients were responders (13/18).

Radiographic Global Impression of Change (RGI-C) Scale

The change in the severity of rickets from baseline to Week 40 was also assessed by the RGI-C score, a 7-point scale that rates changes in a specific list of abnormalities in the wrist, knee, and leg by taking the mean of three independent radiologist readings comparing X-rays before and after treatment. Unlike RSS, clinical significance is explicit in RGI-C. Ratings of -3, -2, and -1 indicate severe, moderate, and minimal worsening, respectively, and ratings of +1, +2 and +3, indicate minimal healing, substantial healing, or complete/near complete healing, respectively.

Patients who were dosed bi-weekly (n=18) experienced a mean improvement in RGI-C score of +1.56 (p<0.0001). Those patients with high severity rickets (n=9) experienced a mean improvement of +2.00 (p<0.0001) at 40 weeks (substantial healing) and 89% (8/9) experienced substantial healing (score $\geq$ 2). Patients who were dosed monthly (n=18) experienced a mean improvement in RGI-C score of +1.20. The patients with high severity rickets (n=9) experienced a mean improvement of +1.70 at 40 weeks and 44% (4/9) experienced substantial healing (score $\geq$2). Overall, all patients (n=36) experienced a mean improvement in RGI-C score of +1.38 (p<0.0001) and those patients who were severe (n=18) experienced a mean improvement of +1.85 (p<0.0001) at 40 weeks. Within the high severity subset, 67% (12/18) experienced substantial healing (score $\geq$2)

Functional measurements: 6 Minute Walk Test (6MWT) and PRO's

The overall patient population (n=36) demonstrated a modest increase in meters walked in the 6MWT at Week 40 as many patients were not impaired in walking at baseline. Patients with walking impairment at baseline (defined by < 80% predicted normal walk distance in 6MWT; n=14) achieved a mean increase of +80 meters (~20% increase from baseline) at Week 40.

Functional disability scores were measured with the Pediatric Orthopedic Society North America/Pediatric Outcome Data Collection Instrument (POSNA/PODCI). When evaluating the Global score of all five domains in those patients with substantial impairment at baseline (n=14, defined as baseline scores < 40, or one standard deviation below the normalized score of 50) or with severe rickets at baseline (n=18), a

substantial mean improvement was observed of about one standard deviation or greater (~10 points) in both dose groups. The Pain/Comfort and Sports/Physical Function domains were the most affected at baseline and also substantially improved in these severely affected subjects treated in both dose groups. Though the magnitude of these changes in functional measurements are substantial, any conclusions must be tempered by the fact that these data are from an uncontrolled, open-label study.

Metabolic Measures
All patients demonstrated increases in serum phosphorus that were consistent with what had been observed previously reaching the low normal or just below normal range. Across both dose groups there were mean increases in both the renal phosphate reabsorption (TmP/GFR) and in serum 1,25 dihydroxy vitamin D levels through 40 weeks of treatment.

Safety and Tolerability
The most common treatment-related adverse event reported by preferred term was injection site reaction in 39% of patients. All of these reactions were considered mild. All other treatment-related adverse events were considered mild. There was one serious adverse event considered possibly treatment-related. This was a patient with fever and muscle pain who improved without complication and is still in the trial. There have been no deaths or discontinuations from the study for any reason.
No clinically meaningful changes were observed in mean serum calcium, urinary calcium and in serum intact parathyroid hormone. None of the patients had serum phosphorus levels above the upper limit of normal at any time point. No clinically significant changes were observed in renal ultrasounds pre- and post-treatment.

Kyowa Hakko Kirin and Ultragenyx plan to file for a conditional marketing authorization in the EU on the basis of these data and on prior feedback from the EMA suggesting that we could do so if the data indicated a positive benefit-to risk-profile. In addition, we plan to proceed with a pediatric Phase 3 study in 2016. The exact design details are yet to be determined but will likely utilize RGI-C as the primary endpoint and would include a standard of care reference arm. This study is expected to be required for potential approval in the US and could also serve as a confirmatory study in the EU if a conditional marketing authorization were granted.

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.

About X-Linked Hypophosphatemia (XLH)
XLH is a disorder of phosphate metabolism caused by phosphate wasting in the urine leading to severe hypophosphatemia. XLH is the most common heritable form of rickets (the softening and weakening of bones) that is inherited as an X-linked dominant trait affecting both males and females, though some reports indicate that the disease may be more severe in males. XLH is a distinctive bone disease characterized by inadequate mineralization of bone that leads to a spectrum of abnormalities, including rickets, progressive bowing of the leg, osteomalacia, bone pain, waddling gait, short stature, gross motor impairment, muscle weakness, frequent/poorly healing pseudofractures, spinal stenosis, enthesopathy, and osteoarthritis.
Most pediatric patients and some adult patients are managed using oral phosphate replacement and vitamin D (calcitriol) therapy, which requires frequent divided doses and careful medical monitoring.

About KRN23

KRN23 is an investigational recombinant fully human monoclonal IgG1 antibody, discovered by Kyowa Hakko Kirin, against the phosphaturic hormone fibroblast growth factor 23 (FGF23). It is being developed by Kyowa Hakko Kirin and Ultragenyx to treat XLH, a disease characterized by excess activity of FGF23. FGF23 is a hormone that reduces serum levels of phosphorus and vitamin D by regulating phosphate excretion and vitamin D production by the kidney. Phosphate wasting in XLH is caused by excessive levels and activity of FGF23. KRN23 is designed to bind to and thereby inhibit the excessive biological activity of FGF23. By blocking excess FGF23 in patients with XLH, KRN23 is intended to increase phosphate reabsorption from the kidney and increase the production of vitamin D, which enhances intestinal absorption of phosphate and calcium.

Multiple clinical studies of KRN23 in adult patients with XLH have been completed and Kyowa Hakko Kirin and Ultragenyx intend to continue development of KRN23 in adults with XLH. In addition, a Phase 2 study in pediatric patients with XLH is ongoing.

KRN23 is also being developed for tumor-induced osteomalacia (TIO), a disease characterized by typically benign tumors that produce excess levels of FGF23, which can lead to severe osteomalacia, fractures, bone and muscle pain, and muscle weakness.

About Ultragenyx

Ultragenyx is a clinical-stage biotechnology company committed to bringing to market novel products for the treatment of rare and ultra-rare diseases, with a focus on serious, debilitating genetic diseases. Founded in 2010, the company has rapidly built a diverse portfolio of product candidates with the potential to address diseases for which the unmet medical need is high, the biology for treatment is clear, and for which there are no approved therapies.

The company is led by a management team experienced in the development and commercialization of rare disease therapeutics. Ultragenyx's strategy is predicated upon time and cost-efficient drug development, with the goal of delivering safe and effective therapies to patients with the utmost urgency.

For more information on Ultragenyx, please visit the company's website at www.ultragenyx.com.