Kyowa Hakko Kirin Announces Positive Interim Data from Pediatric and Adult Phase 2 Studies of KRN23 in X-Linked Hypophosphatemia

Pediatric study demonstrates substantial reduction in bone disease and improvement in growth rates
Adult study demonstrates increase in serum phosphorus and provides evidence of clinical improvement

Tokyo, September 20th, 2016 -- Kyowa Hakko Kirin Co., Ltd. (Tokyo; 4151 President and CEO: Nobuo Hanai; "Kyowa Hakko Kirin") today announced positive interim data from the ongoing pediatric Phase 2 study of KRN23 for the treatment of X-linked hypophosphatemia (XLH), demonstrating that serum phosphorus levels, rickets, growth rates and other functional outcomes improved with continued KRN23 treatment. The bi-weekly dose regimen continued to show a better overall response than patients who were dosed every four weeks, and patients with higher rickets at baseline showed greater improvements in bone disease and growth velocity. Data were also presented from the adult Phase 2 study of KRN23 for the treatment of XLH, demonstrating a significant increase in serum phosphorus levels and evidence of clinical improvement including improvements in walking, mobility, pain and stiffness at 24 weeks of treatment. Adverse events were consistent with what has been previously observed for KRN23 for the treatment of XLH. The studies have been conducted under a collaboration with Ultragenyx Pharmaceutical Inc. (NASDAQ: RARE; "Ultragenyx"). Data from the two studies were presented on September 19th at the American Society for Bone and Mineral Research (ASBMR) 2016 Annual Meeting.

Phase 2 Pediatric Study

The randomized, multicenter, open-label, dose finding study enrolled 52 patients ages five through 12, 49 of whom had been on currently available therapy (oral phosphate/active Vitamin D therapy) for an average of approximately seven years prior to entering the study. The first 36 patients enrolled in the study have completed the full 64-week dose-titration and treatment period. A subset of these patients (n=18) were pre-specified as having higher rickets (greater bone disease), defined by baseline total RSS scores of ≥ 1.5. An additional 16 patients with higher rickets have completed 40 weeks of treatment.

Metabolic Measures

Patients demonstrated increases in mean serum phosphorus, renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels through 64 weeks of treatment. Patients in both dosing groups had mean serum phosphorus levels in the low normal range through 64 weeks of treatment, demonstrating that phosphate wasting, the underlying cause of the disease, improved and patients were able to maintain increased serum phosphorus levels.

Bone Disease Results

Thacher Rickets Severity Scoring (RSS)

Rickets severity was assessed at 40 weeks (n=52) and 64 weeks (n=36) using the RSS scoring system. Rickets improved significantly in all groups, with the greatest improvements in patients with higher baseline rickets (RSS ≥1.5) who received bi-weekly dosing of KRN23.

52 patients/40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
RSS, All Patients			***RSS, High BL RSS ≥ 1.5***		
n	26	52	n	17	34
% reduction (p < 0.0001)	61%	50%	% reduction (p < 0.0001)	71%	61%
36 patients/64 weeks					
RSS, All Patients			***RSS, High BL RSS ≥ 1.5***		
n	18	36	n	9	18
% reduction (p < 0.0001)	51%	38%	% reduction (p < 0.0001)	57%	51%

Radiographic Global Impression of Change (RGI-C) Scale

The change in the severity of rickets was also assessed at 40 and 64 weeks by the RGI-C score. Data show significant improvement in rickets in all groups. Substantial healing (RGI-C score > 2) was observed in all but one patient with higher baseline rickets who received bi-weekly dosing.

52 patients, 40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
RGI-C, All Patients			***RGI-C, High BL RSS ≥ 1.5***		
n	26	52	n	17	34
Score change (p < 0.0001)	1.72	1.56	Score change (p < 0.0001)	2.04	1.91
36 patients, 64 weeks					
RCI-C, All Patients			***RGI-C, High BL RSS ≥ 1.5***		
n	18	36	n	9	18
Score change (p < 0.0001)	1.35	1.35	Score change (p < 0.0001)	1.96	1.91

Growth Velocity

Patients with higher baseline RSS scores ≥ 1.5 showed more growth impairment (baseline height percentile for 40-week group = 5.8%; baseline height percentile for 64-week group = 3.9%), and these patients demonstrated greater improvement in growth velocity and height z-score.

52 patients/40 weeks	**Q2W**	**Overall**		**Q2W**	**Overall**
Growth, All Patients			***Growth, Higher BL RSS ≥ 1.5***		
n	26	52	n	17	34
Growth velocity change (cm/yr)	+0.96	+0.68	Change in growth velocity (cm/yr)	+1.69	+1.23
p value	0.0088	0.0321	p value	<0.0001	0.0046
Change in height z-score	0.17	0.13	Change in height z-score	0.22	0.18
p value	<0.0001	<0.0001	p value	<0.0001	0.0003
36 patients/64 weeks					
Growth, All Patients			***Growth, Higher BL RSS ≥ 1.5***		
n	18	36	n	9	18
Growth velocity change (cm/yr)	+0.35	+0.27	Change in growth velocity (cm/yr)	+0.74	+0.58
p value	N.S.	N.S.	p value	0.0173	0.023
Change in height z-score	0.21	0.16	Change in height z-score	0.21	0.19
p value	<0.0001	<0.0001	p value	0.0056	0.0002

Functional measurements: 6 Minute Walk Test (6MWT) and Patient Reported Outcomes (PROs)

Patients with walking impairment at baseline (defined by < 80% predicted normal walk distance in 6MWT) in the bi-weekly dosing group achieved a mean increase of 84 meters (p<0.001) at 40 weeks (n=14), and 97 meters (p<0.001) at 64 weeks (n=7).

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=28, defined as baseline scores < 40 or one standard deviation below the normalized score of 50), a mean improvement of +17.5 (p< 0.0001) was observed at 40 weeks. 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.

Safety and Tolerability

The most common treatment-related adverse events reported by preferred term was injection site reaction in 33% of patients. All of these reactions were considered mild. All other treatment-related adverse events were also considered mild. There was one serious adverse event considered possibly treatment-related. This was a previously reported 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.

Phase 2 Adult Extension Study
The open-label, long-term extension study enrolled 20 adult patients with XLH who had previously participated in the phase 1/2 INT-001 or INT-002 studies of KRN23. All patients had at least a 12-month KRN23 treatment break before enrolling in the extension study. Patients who had resumed oral phosphate and active vitamin D therapy between studies (65%) completed a 21-day washout period. All patients began KRN23 treatment at the last dose received in the INT-001 or 002 study with an option to titrate during the first 12 weeks. An analysis of 24-week data is being presented.

Metabolic Measures
Patients treated with KRN23 demonstrated increased serum phosphorus at 24 weeks of treatment, and maintained levels in the low normal range. Renal phosphate reabsorption (TmP/GFR) and serum 1,25 dihydroxy vitamin D levels also increased from baseline to 24 weeks.

Patient-Reported Outcomes and Physical Function
At baseline, 19 of 20 patients had worst pain scores measured by the Brief Pain Inventory Question 3 (BPI-Q3) of > 4, classified as moderate to severe pain. The mean BPI-Q3 score was significantly reduced from baseline ($p=0.0268$; 1.1 point reduction from 6.6 at baseline to 5.5 at 24 weeks). These patients also demonstrated significant improvements in BPI pain interference ($p=0.0009$) and pain severity ($p=0.0141$) scores.
WOMAC pain, stiffness and physical function domain scores were significantly reduced at 24 weeks in these patients. Patients demonstrating the greatest improvements in stiffness (WOMAC stiffness responders) and pain (BPI-SF worst pain responders) had greater improvements in mobility tests, including the Timed Up and Go (TUG test for balance and agility) and the 6MWT. Mean patient TUG scores improved by 2 seconds ($p=0.04$) at week 24. At baseline, nearly all patients (19/20) were impaired in walking (defined by < 80% predicted normal walk distance in 6MWT). The mean increase in distance walked was 25 meters ($p=0.05$) from baseline.

Safety and tolerability
The most common adverse events were arthralgia (30%), nasopharyngitis (25%), back pain (20%), injection site reaction (20%), and pain in extremity (20%). Treatment-related adverse events occurred in 40% of patients, and were all considered mild. None of the four serious adverse events were considered treatment-related. There have been no deaths or discontinuations from the study.

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 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. XLH is a distinctive 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 active vitamin D

(calcitriol) therapy, which requires multiple divided doses each day and monitoring for potential risks such as nephrocalcinosis, hypercalciuria, and hyperparathyroidism.

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 Ultragenyx and Kyowa Hakko Kirin to treat XLH and TIO, diseases characterized by excess activity of FGF23. FGF23 is a hormone that reduces serum levels of phosphorus and active vitamin D by regulating phosphate excretion and active vitamin D production by the kidney. Phosphate wasting in XLH and TIO 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 and TIO, 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.
A Phase 3 program studying KRN23 in adults and a Phase 2 study in pediatric patients with XLH are 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 biopharmaceutical 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.