Efficacy and Safety of a Human Monoclonal Anti-FGF23 Antibody (KRN23) in a Cumulative 4-Month Dose Escalation (KRN23-INT-001) and 12-Month Long-Term Extension Study (KRN23-INT-002) in Adult Subjects with X-Linked Hypophosphatemia (XLH)

T. Carpenter,1 X. Zhang,2 E. Imel,3 M. Ruppe,4 T. Weber,5 M. Klausner,2 T. Ito,2 M. Vergiere,2 J. Humphrey,2 F. Glorieux,6 A. Portale,7 K. Insogna,1 M. Peacock2

1 Yale University, New Haven, CT; 2 Kyowa Hakko Kirin Pharma, Inc. Princeton, NJ; 3 Indiana University, Indianapolis, IN; 4 The Methodist Hospital, Houston, TX; 5 Duke University, Durham, NC; 6 Shriners Hospital for Children, Montreal, Canada; 7 University of California, San Francisco, CA

2014 ASBMR: Plenary Oral Session Number: 1082
DISCLOSURE

Kyowa Hakko Kirin Pharma, Inc. / Ultragenyx Pharmaceutical:

- Consultant (protocol design); grant recipient
X-linked Hypophosphatemia

XLH is a chronic disease of renal phosphate wasting presenting with bowing defects in early childhood and biochemical findings of hypophosphatemia, due to low TmP/GFR, and low serum 1,25 dihydroxyvitamin D.
X-linked Hypophosphatemia

The defective renal phosphate reabsorption and aberrant vitamin D metabolism is mediated by increased circulating levels of FGF23.
KRN23

- KRN23 is a human monoclonal antibody with FGF23 inhibitory activity.
Serum Pi (mg/dL)

- Serum Pi increase for KRN23 (0.3 – 1 mg/kg) > placebo, $p < 0.05$
- Peak at day 8-15, persists ~6-8 wks

*J.Clin Invest. 2014; 124(4): 1587-97*
KRN23 in XLH adults: Four Doses Every 28 Days (Escalation/Titration)

* p< 0.05, paired t-test, Bonferoni correction
Mean +SD

Source: ICE/ENDO Annual Mtg, June 2014, Chicago
Study Protocol

• Design:
  – Multi-center phase 1/2 open-label, 4 dose-escalation\textsuperscript{a}
  – Multi-center phase 1/2 open-label, 12 dose extension\textsuperscript{b}

• Subjects
  – Dose escalation: 28 adults with clinical diagnosis of XLH
    • Age $\geq$ 18 years
    • Intact FGF23 $\geq$ 30 pg/mL
    • TmP/GFR < 2.0 mg/dL
    • Creatinine clearance $\geq$ 60 mL/min
    • Serum calcium < 10.8 mg/dL
  – Extension: 22 subjects enrolled in the extension study

\textit{ClinicalTrials.gov}: \textsuperscript{a}NCT01340482; \textsuperscript{b}NCT01571596;
• Dose based on serum Pi on day 25/26 after previous dose
• Time between last dose on D84 of first study and Day 0 of second study was 53 days (range: 48-65 days)
Dosing Algorithm for Extension

Serum Pi at Day 25/Day 26 of the 28-day dosing cycle

1. \( \leq 2.5 \text{ mg/dL}, \text{ AND} \)
   a) peak serum Pi < 3.8, dose escalated
   b) peak serum Pi 3.8 - 4.2, previous dose repeated
   c) peak serum Pi > 4.2, dose de-escalated

2. > 2.5, \( \leq 3.5 \), \( \text{AND} \)
   a) peak serum Pi < 3.8, previous dose repeated
   b) peak serum Pi \( \geq 3.8 \), dose de-escalated

3. > 3.5
   a) dose de-escalated; if serum Pi > 3.5 after 28-days, dosing re-evaluated
   b) OR if peak serum Pi \( \geq 4.2 \), dosing re-evaluated
Outcome Measures

• Primary efficacy outcome: proportion of subjects with post-dose serum Pi in the following ranges:
  – 2.5 to ≤ 3.5
  – 3.5 to ≤ 4.5
  – or > 4.5 mg/dl
• Secondary efficacy outcomes: Change from baseline
  – TmP/GFR
  – Serum Pi
  – Serum 1,25(OH)₂D
  – Pharmacokinetics and pharmacodynamics
• Safety outcomes:
  – adverse events, changes in safety lab measures, renal ultrasound, and cardiac CT
## Study Population

<table>
<thead>
<tr>
<th></th>
<th>Escalation (28)</th>
<th>Extension (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>42 ± 14</td>
<td>42 ± 15</td>
</tr>
<tr>
<td><strong>Sex (male/female)</strong></td>
<td>9/19</td>
<td>9/13</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>70 (46 -122) *</td>
<td>75.3 (51.3-124.3)*</td>
</tr>
<tr>
<td><strong>Race (Caucasian/Other)</strong></td>
<td>27/1</td>
<td>21/1</td>
</tr>
<tr>
<td><strong>Height (cm) (range)</strong></td>
<td>150 ± 12 (122 -170)</td>
<td>151 ± 13 (122 -170)</td>
</tr>
</tbody>
</table>

*Mean ± SD (except weight)*

*Median (95% Confidence Interval)
## Baseline Biochemistry

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Escalation (28)</th>
<th>Extension (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Pi (mg/dL)</td>
<td>1.9 ± 0.3</td>
<td>1.9 ± 0.28</td>
</tr>
<tr>
<td>1,25D (pg/mL)</td>
<td>36.6 ± 14.3</td>
<td>36.4 ± 12.6</td>
</tr>
<tr>
<td>25D (ng/mL)</td>
<td>25.0 ± 9.1</td>
<td>23.1 ± 8.68</td>
</tr>
<tr>
<td>Total calcium (mg/dL)</td>
<td>9.1 ± 0.4</td>
<td>9.1 ± 0.4</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>74 (38, 143)*</td>
<td>68.5 (40, 143) *</td>
</tr>
<tr>
<td>BALP (µg/L)</td>
<td>28.3 ± 12.8</td>
<td>31.1 ± 12.3</td>
</tr>
<tr>
<td>Intact FGF23 (pg/mL)</td>
<td>95 (36, 3520)*</td>
<td>81 (54, 268) *</td>
</tr>
<tr>
<td>TmP/GFR (mg/dL)</td>
<td>1.6 ± 0.4</td>
<td>1.6 ± 0.3</td>
</tr>
<tr>
<td>24- hour urine calcium (mg/day)</td>
<td>67 (11, 253)*</td>
<td>78.5 (11,253) *</td>
</tr>
</tbody>
</table>

Mean ± SD except PTH, FGF23, urinary Calcium
* Median (95% Confidence Interval)
Baseline: prior to initial dose in escalation study
KRN23 Administered During Escalation and Extension

Number of subjects

Escalation

Extension

Dose 1
Dose 2
Dose 3
Dose 4
Dose 5
Dose 6
Dose 7
Dose 8
Dose 9
Dose 10
Dose 11
Dose 12
Dose 13
Dose 14
Dose 15
Dose 16

28
26
25
16
13
11
10
13
14
13
12
12
14
14
13
13

1 mg/kg
0.6 mg/kg
0.3 mg/kg
0.1 mg/kg
0.05 mg/kg
• During each dosing cycle of the extension study, peak serum Pi reached target range:
  – > 2.5 and ≤ 3.5 mg/dL in 44.4% - 81.8% of subjects
  – > 3.5 to ≤ 4.5 mg/dL in 4.5% - 16.7% of subjects
• Serum Pi did not exceed 4.5 mg/dL in any subject
**KRN23: Effect on Serum Pi**

- Serum Pi peaked on Day 7 - 14
- Escalation: serum Pi increased as dose increased
- Extension: serum Pi increased after each dose and returned toward pre-dose level by next dose
- Fluctuations between peak and trough serum Pi levels were small after each dose (range: 9.97% - 21.5%)
KRN23: Effect on TmP/GFR

- TmP/GFR peaked on Day 7-14
- Escalation: TmP/GFR increased as dose increased
- Extension: TmP/GFR increased after each dose and returned toward pre-dose level by next dose
Serum $1,25(\text{OH})_2\text{D}$ peaked on Day 3-7

Escalation: serum $1,25(\text{OH})_2\text{D}$ increased as dose increased

Extension: serum $1,25(\text{OH})_2\text{D}$ increased after each dose and decreased toward pre-dose level by next dose, with tendency to decrease over time
No consistent trend was noted in mean serum PTH.
KRN23: Effects on Serum Calcium

- Minor increases in serum calcium during extension phase

KRN23 dose
*p < 0.05, paired t-test, Bonferoni correction
Mean ± SD
KRN23: Effects on 24-h Urine Calcium

- No consistent trend was noted in mean 24-hour urine calcium

*KRN23 dose
*p < 0.05, paired t-test, Bonferoni correction
Mean + SD
Bone Turnover: P1NP and Osteocalcin

- P1NP and osteocalcin increased during 16 months of treatment and were statistically significant after the 1st and 4th dose through completion (p < 0.05)

*p < 0.05, paired t-test, Bonferonni correction

*Mean +SD
Most Common AEs Reported by Investigators as Drug-related

- Injection site reaction (5)
- Diarrhea and arthralgia (3)
- Injection site erythema, injection site pain, upper abdominal pain, headache, restless legs syndrome, and decreased neutrophil count (2)
- No life threatening AEs or deaths occurred

Both cases of low neutrophil count were observed at baseline
Calcification and ECG Monitoring

• Renal ultrasound
  – No worsening of nephrocalcinosis in any subject

• Cardiac CT
  – 2 had modest increase in coronary artery calcification score*

• ECG
  – No subject developed clinically significant ECG abnormalities
  – No subject demonstrated left ventricular hypertrophy

* Both subjects have minimal changes and were considered not clinically relevant
Laboratory Parameters

• No discernible pattern of clinically significant or persistent laboratory abnormalities
• No treatment-related changes in PTH
• Slight increase in mean serum calcium (mean $\leq 0.39$ mg/dL, and $< 1.4$ mg/dL in all subjects); mild intermittent hypercalcemia in 2 subjects
• Mean 24-hour urine calcium remained stable; transient hypercalciuria in 4 subjects
• No subject developed anti-KRN23 antibodies
Summary

• All subjects responded to KRN23 by increasing serum Pi, TmP/GFR, and 1,25(OH)₂D
• Majority of subjects (58% to 86%) reached serum Pi levels within the normal range by day 7-14 throughout the study
• Majority of subjects (60 to 73.7%) stabilized at 1.0 mg/kg
• Biomarkers of bone turnover increased significantly (P1NP and osteocalcin)
• KRN23 was well-tolerated for up to 16 monthly doses
• No subject developed anti-KRN23 antibodies
Conclusions

• KRN23, a monoclonal antibody to FGF23, restored phosphate homeostatic in patients with XLH

• Blocking FGF23 activity by SC administration of KRN23 every 28 days for up to 16 doses demonstrated both efficacy and a favorable safety profile

• Results support further studies of KRN23 in both adults and children with XLH
Acknowledgements

• Dedicated participation of XLH patients
• Research Unit staffs at Yale, Indiana, Duke and University of Texas-Houston, University of California San Francisco, and Shriners Hospital for Children Montreal.
• Study coordinators at research sites:
  – Marian Hart
  – Elizabeth Olear
  – Margaret Stewart
  – Becky Sullivan
  – Connie Sullivan
  – Nathaniel Jacob Harrison
  – Monika Ruscheinsky
  – Michaela Durigova
  – Stephanie Lemp
  – Vinodhini Lakshman
• Sponsored by Kyowa Hakko Kirin Pharma, Inc.
Back-up Slides
No consistent trend was noted in mean values for 2-hour urine calcium/creatinine ratio after 16 months of KRN23 treatment.

乏, KRN23 dose
*p<0.05, paired t-test, Bonferoni correction
Mean +SD
Bone Turnover Marker: BALP and CTx

Pooled data from KRN23 INT-001 and KRN23-INT-002 Study

- BALP and CTx appeared to increase during escalation period and were maintained during extension.
- Changes in BALP were not statistically significant.
- Changes in CTx were statistically significant after 9th and 12 doses.

*p< 0.05, paired t-test, Bonferoni correction Mean +SD
Bone Turnover Marker: NTx/Creatinine

Pooled data from KRN23 INT-001 and KRN23-INT-002 Study

Changes in NTX/creatinine ratio were not statistically significant

* p< 0.05 for paired t-test compared to baseline with Bonferoni correction

- Changes in NTX/creatinine ratio were not statistically significant
X-linked Hypophosphatemia

- Treatment for XLH: oral phosphate salts + calcitriol.

- This regimen is fraught with difficulties including limited compliance, suboptimal outcomes, and complications (e.g., hyperparathyroidism, nephrocalcinosis, and vitamin D intoxication).
Standard Treatment of XLH

- High dose oral phosphate salts and calcitriol
  - Addresses the consequences of FGF23 excess
  - Does not fix the underlying defect
- Limited by:
  - Poor compliance
  - Persistent bowing and short stature
  - Complications:
    - Hyperparathyroidism, nephrocalcinosis, & vitamin D intoxication.