The First Multi-Dose Trial of a Human Anti-FGF23 (Fibroblast Growth Factor 23) Antibody (KRN23) in Adults with X-Linked Hypophosphatemia (XLH)

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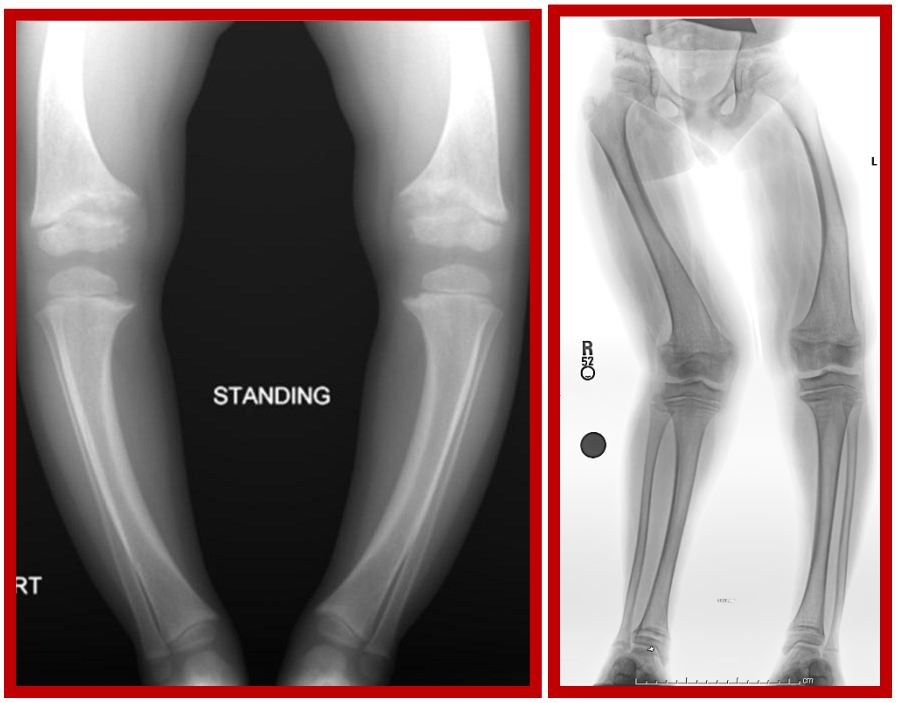
Disclosures

Dr. Erik Imel

- **Kyowa Hakko Kirin Pharma, Inc.**
  - **Consultant (protocol design)**
  - **Research funds**

X-Linked Hypophosphatemia (XLH)

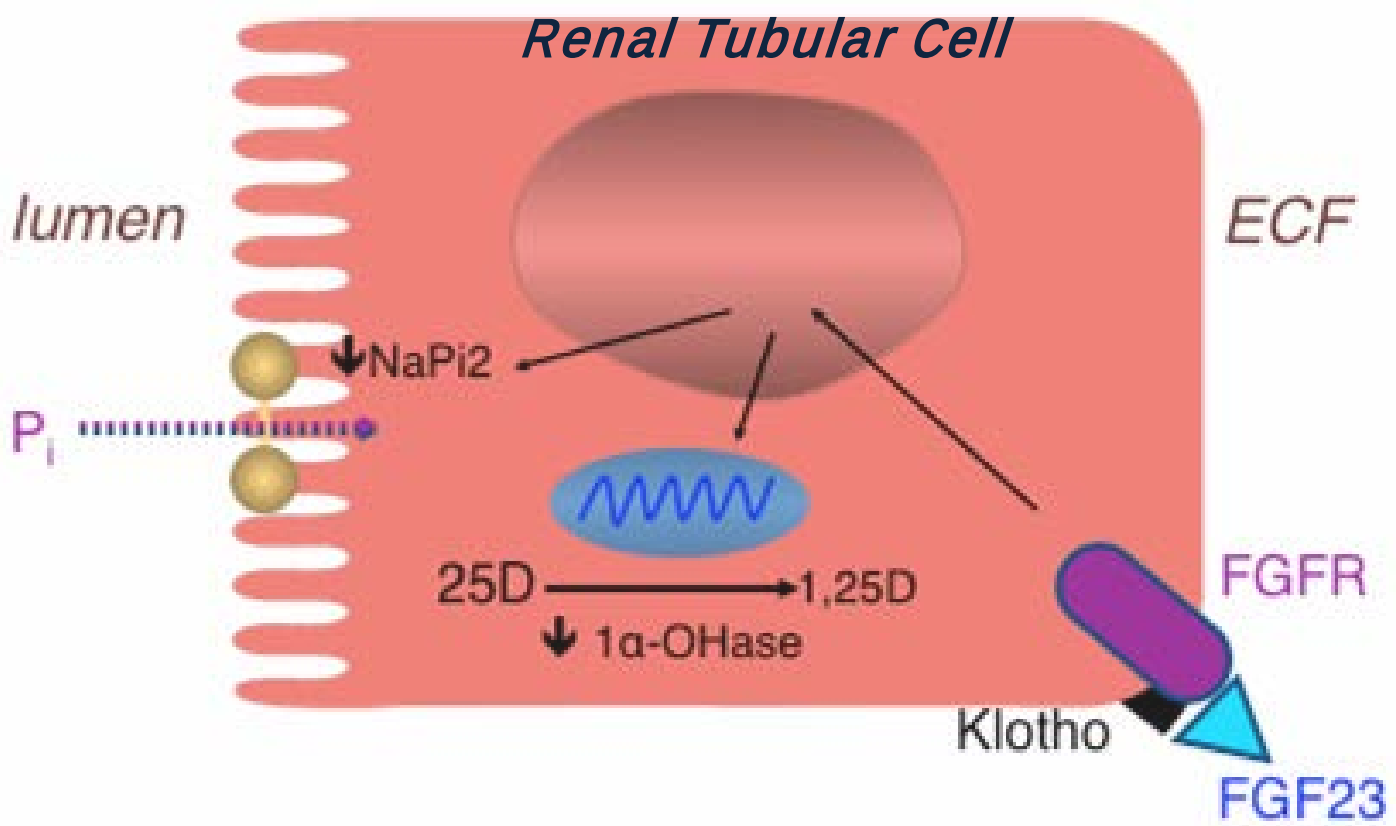
- The most common form of hereditary rickets
- Chronic disease affecting both children and adults
- Bowing deformities of long bones begin in early childhood



Carpenter, Imel et al JBMR 2011; 26(7):1381-1388,

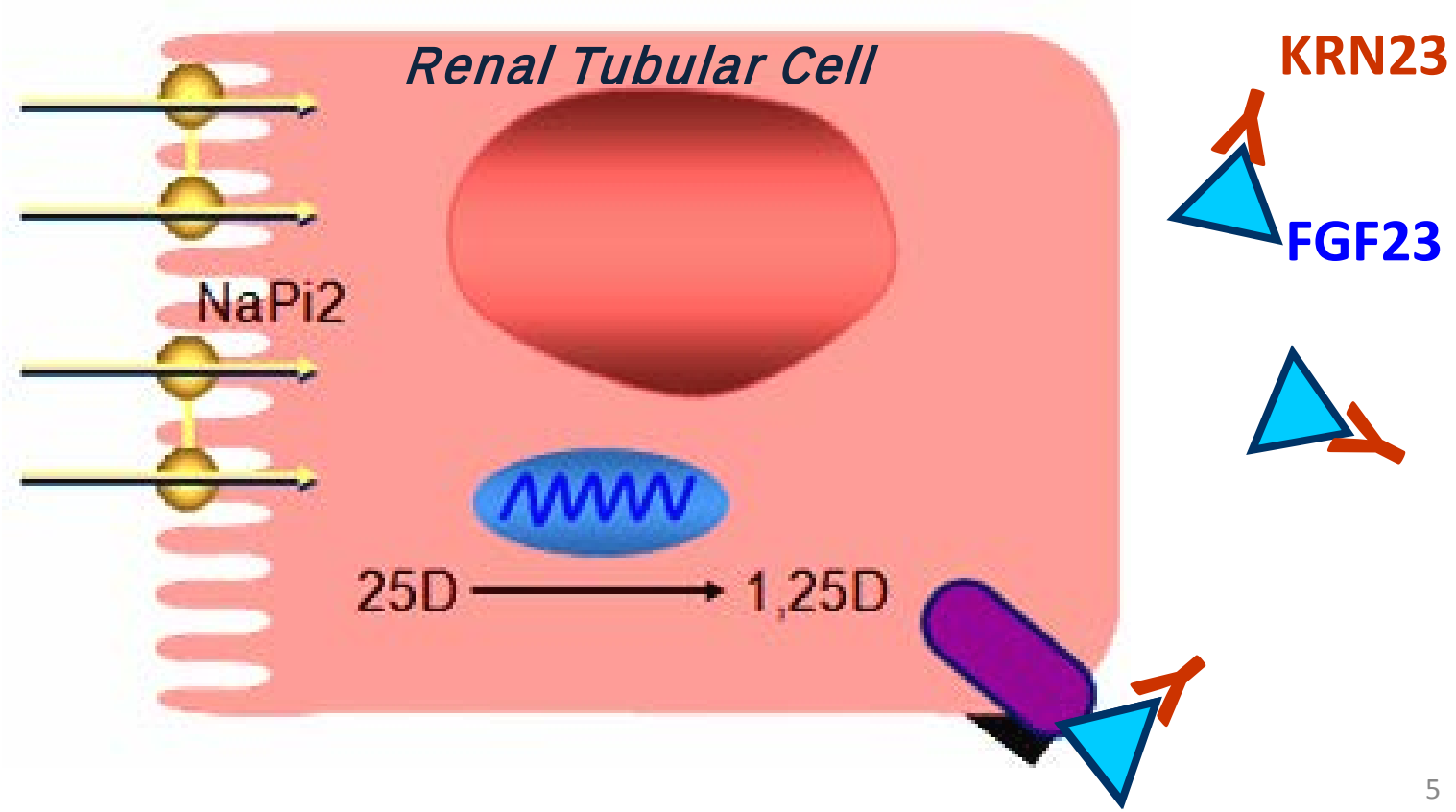
X-Linked Hypophosphatemia

- **Excessive FGF23 mediates**
  - **↓ Renal tubular phosphate reabsorption**
  - **↓ Serum Pi**
  - **↓ Activation of 1,25(OH)$_2$D**



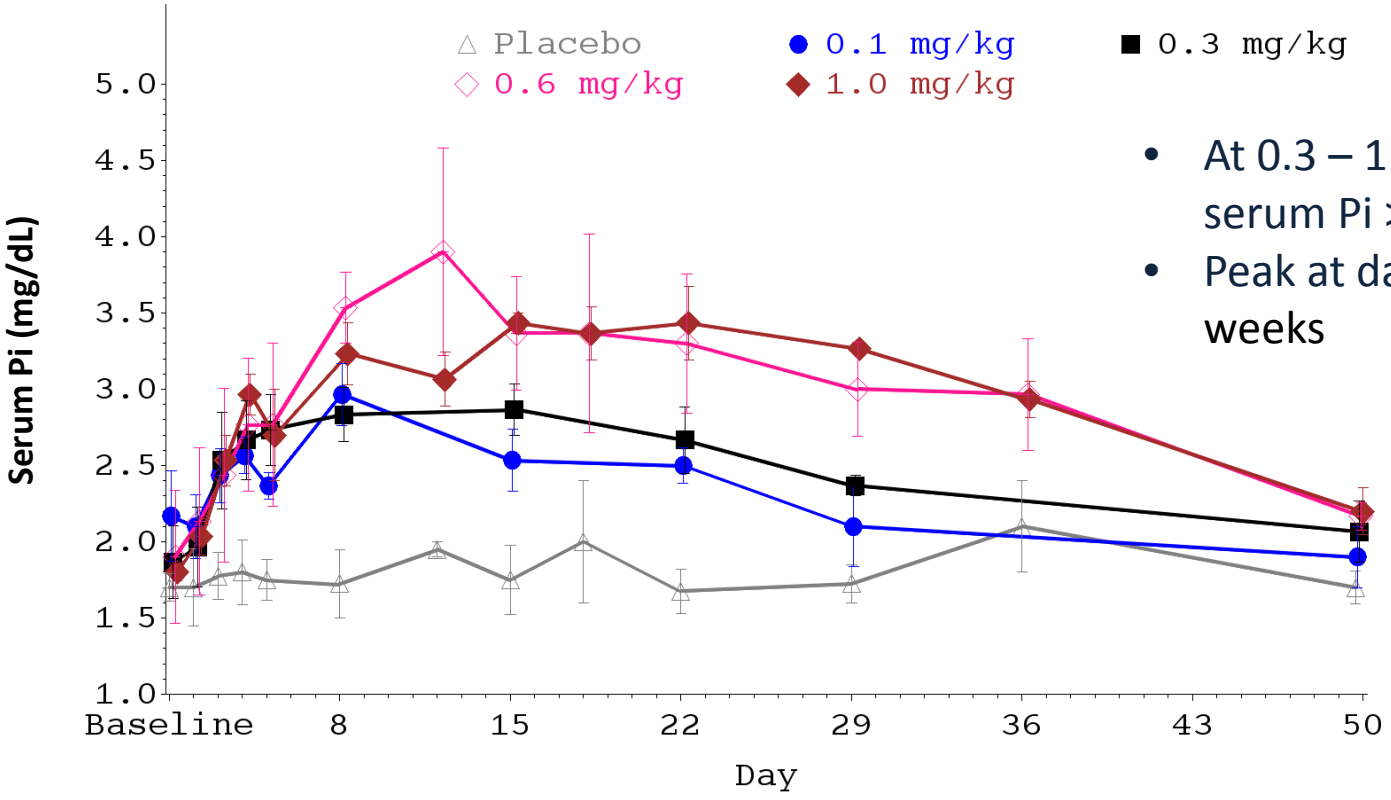
KRN23

A recombinant human IgG1 monoclonal antibody that binds to FGF23 and inhibits FGF23 biologic activity



KRN23: Single Dose Trial in Adult XLH

Serum Pi (inorganic phosphorus) after single SC dose of KRN23:



- At 0.3 – 1 mg/kg, increase in serum Pi > placebo; $p < 0.05$
- Peak at day 8-15, persists ~6-8 weeks

Carpenter TO., Imel EA, Ruppe MD., et al. J. Clin Invest. 2014; 124(4): 1587-97

KRN23-INT-001: The First Multi-Dose Trial of KRN23 in Adults with XLH

Design:

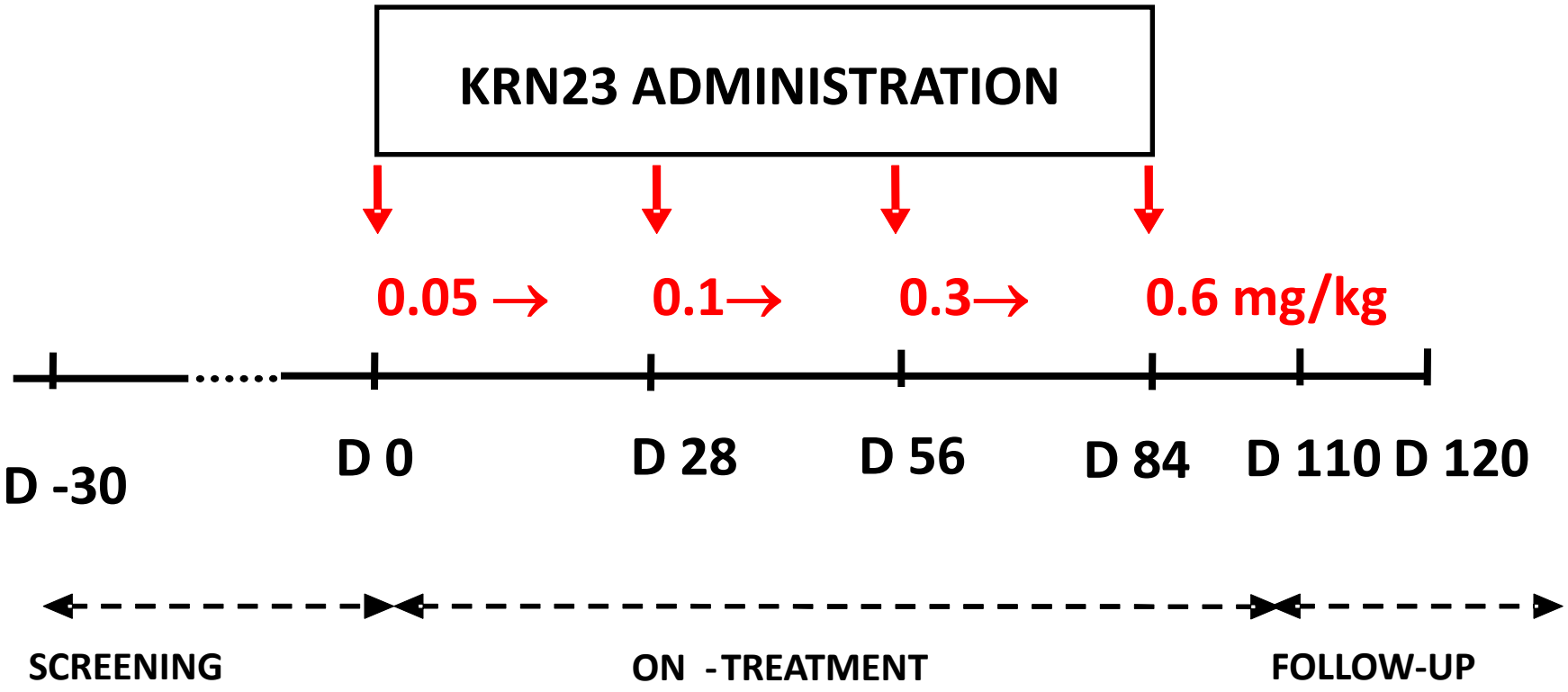
- **Multi-center phase 1/2 open-label, dose-escalation trial**

Subjects

- **28 adults (age ≥18 years) with clinical diagnosis of XLH and**
  - **Intact FGF23 ≥ 30 pg/mL**
  - **TmP/GFR < 2.0 mg/dL**
  - **Creatinine clearance ≥ 60 mL/min**
  - **Serum calcium < 10.8 mg/dL**

* ***Protocol KRN23-INT-001; ClinicalTrials.gov ID: NCT01340482***

KRN23 Dose and Dose Escalation



Dose escalation algorithm for doses 2, 3, and 4 based on serum Pi on day 26 after previous dose

Outcome Measures

- **Primary efficacy outcome: the proportion of subjects with post-dose serum Pi in ranges of:**

  2.5 to ≤ 3.5 mg/dl
  3.5 to ≤ 4.5 mg/dl
  > 4.5 mg/dl

- **Secondary efficacy outcomes: Changes from baseline:**
  - **TmP/GFR**
  - **Serum Pi**
  - **$1,25(OH)_2D$**
  - ***Quality of life (SF-36v2 and WOMAC, see Poster MON210)***
  - ***Pharmacokinetics and pharmacodynamics (see Poster MON0206)***

- **Safety outcomes:**
  - **adverse events, changes in safety laboratory measures, renal ultrasound, and cardiac CT**

Baseline Demographic Characteristics

Characteristics	Value
Age (years), mean ± SD	41.9 ±13.83
Sex (male/female), n	9/19
Race (Caucasian/other), n	27/1
Weight (kg), median (range)	70.1 (46.4, 121.9)
Height (cm), mean ± SD (range)	150.3 ± 12.2 (121.9, 170.2)

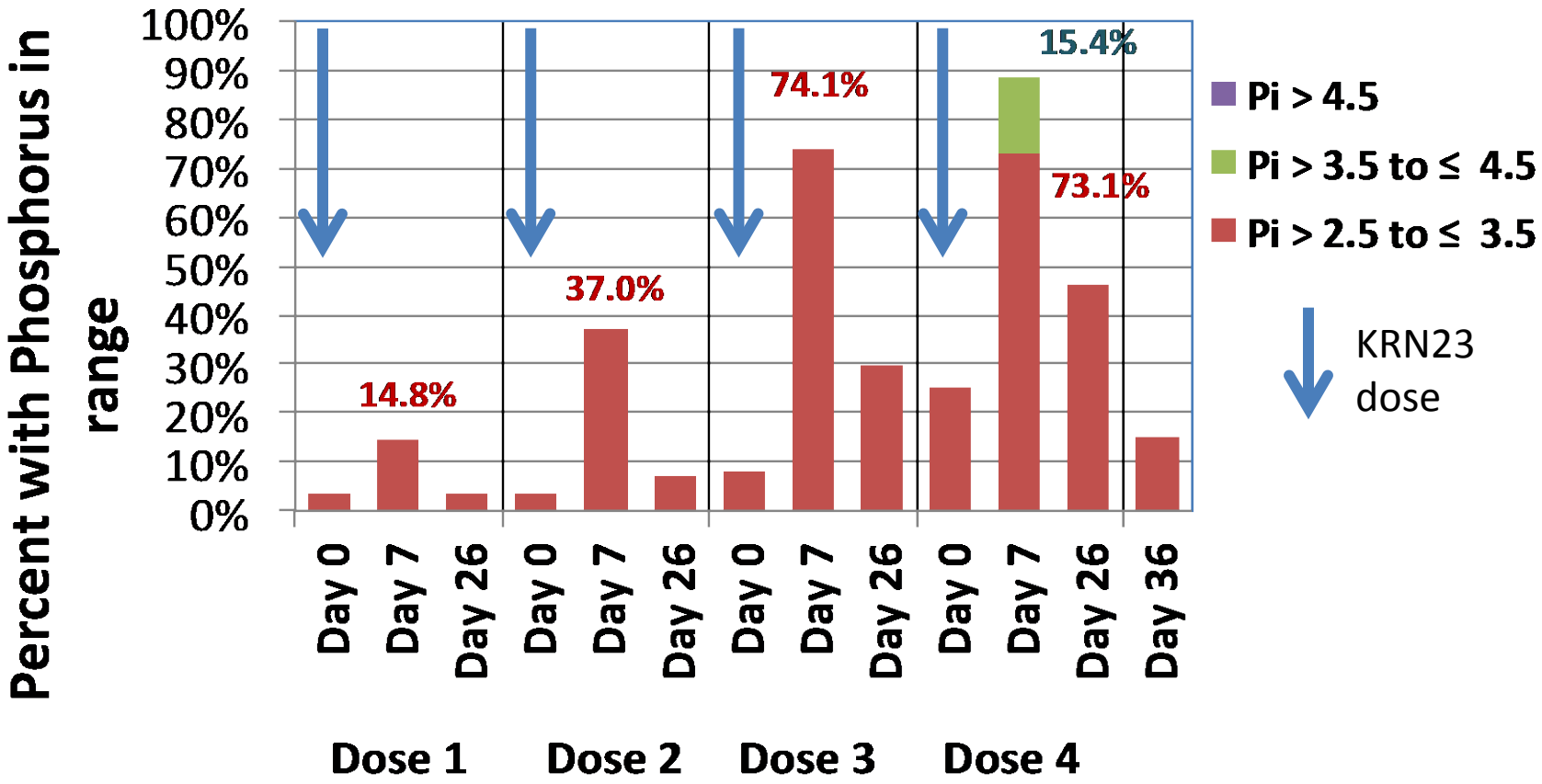
Baseline Biochemistry Characteristics

Characteristic	Value	Reference Range
Intact FGF23 (pg/mL), median (range)*	95 (36, 3520)	8 - 54
Serum Pi (mg/dL)	1.9±0.3 (1.2, 2.8)	2.5 - 4.5
TmP/GFR (mg/dL)	1.6±0.4 (0.8, 2.3)	2.5 - 4.2
Serum 1,25(OH)$_2$D (pg/mL)	36.6 ± 14.3 (10, 62)	15.9 - 55.6
Serum 25(OH)D, ng/mL	25.0± 9.1 (12, 44)	32 - 100
Serum total calcium (mg/dL)	9.1±0.4 (8.5, 10.2)	8.5 - 10.3
Serum PTH (pg/mL), median (range)*	74 (38, 143)	10 - 65
BALP (µg/L)	28.3±12.8 (8.2, 52.4)	M: 3.7 - 20.9 F: 3.8-22.6 (Postmenopausal)

Mean ± SD (range) are presented unless noted

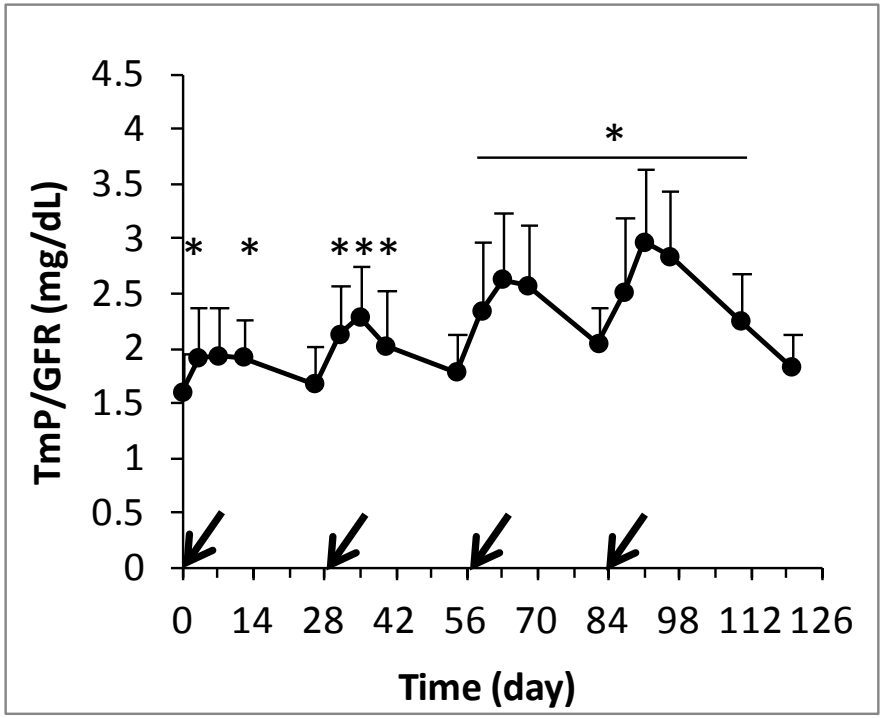
** Median is presented due to a skewed distribution*

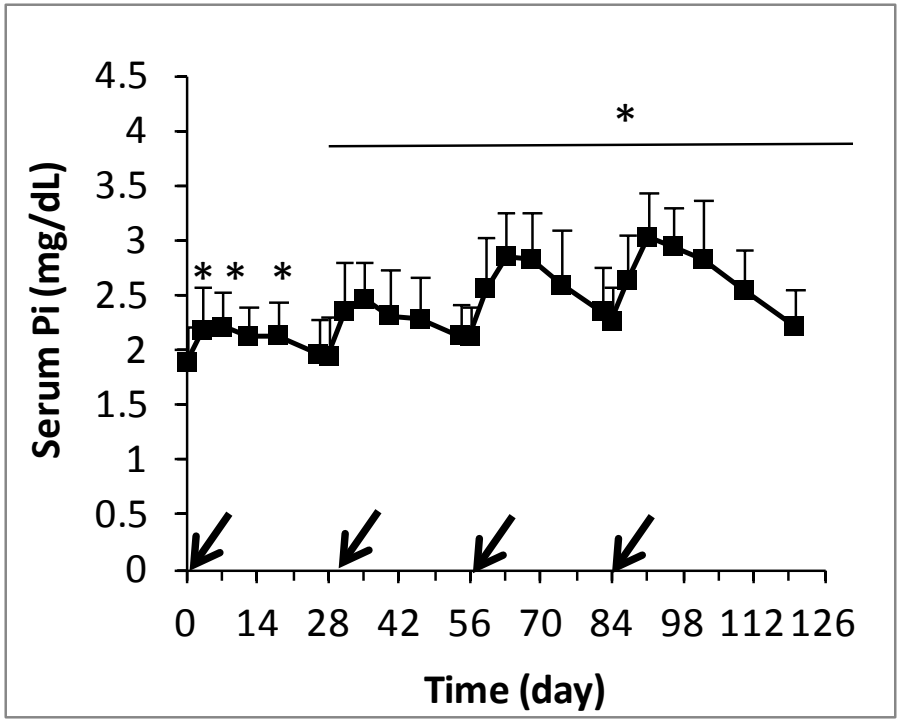
Primary Efficacy Results



- **Serum Pi did not exceed 4.5 mg/dL in any subject**

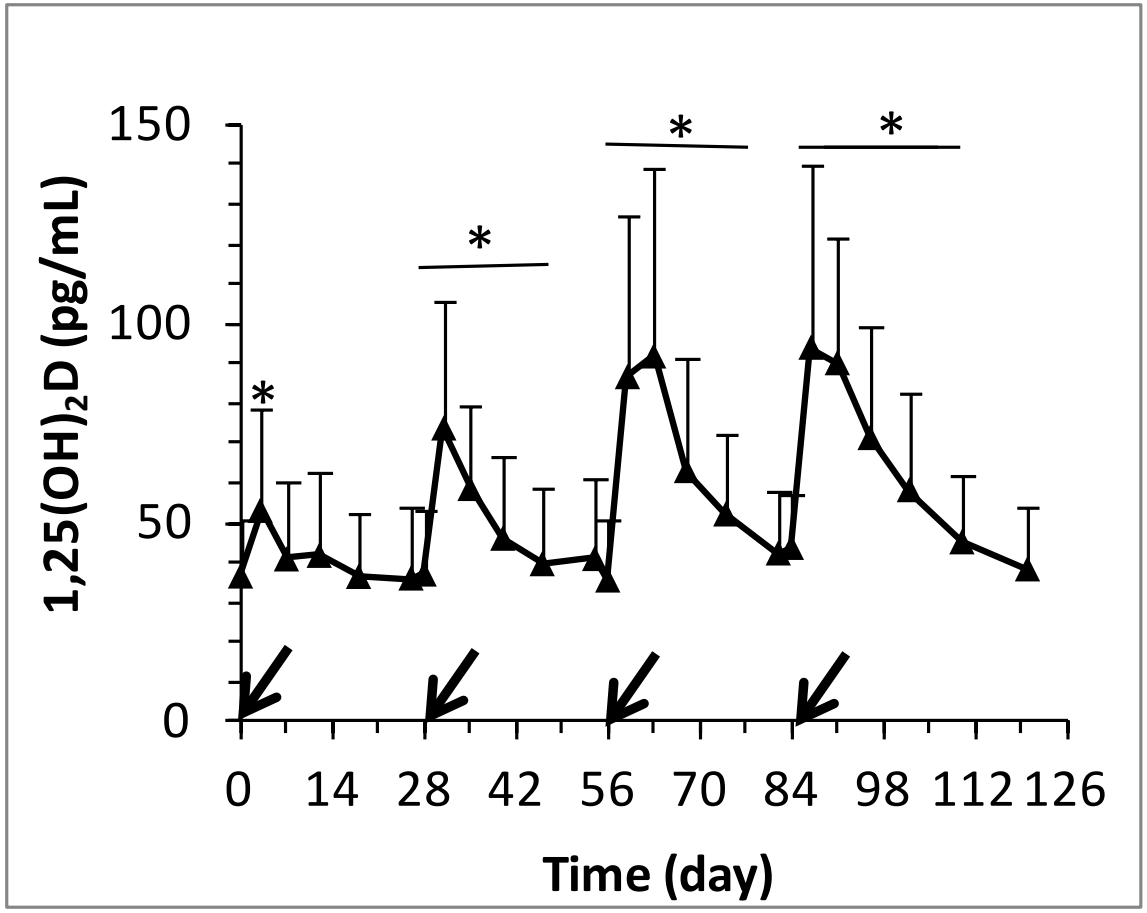
KRN23 Effects: TmP/GFR and Serum Pi





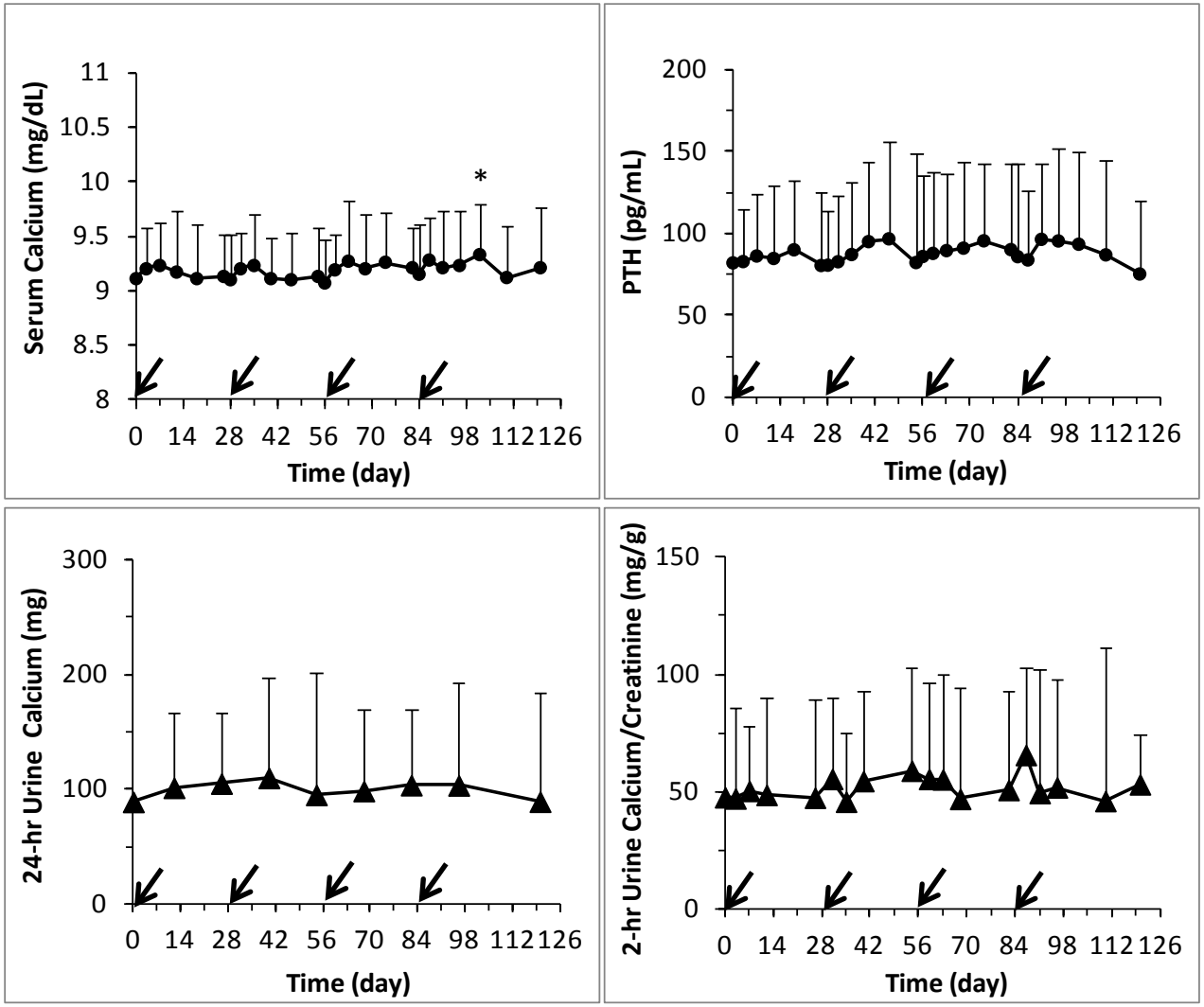
↙ KRN23 dose; Mean + SD presented; * $p < 0.05$ compared to baseline

KRN23 Effect: $1,25(OH)_2D$



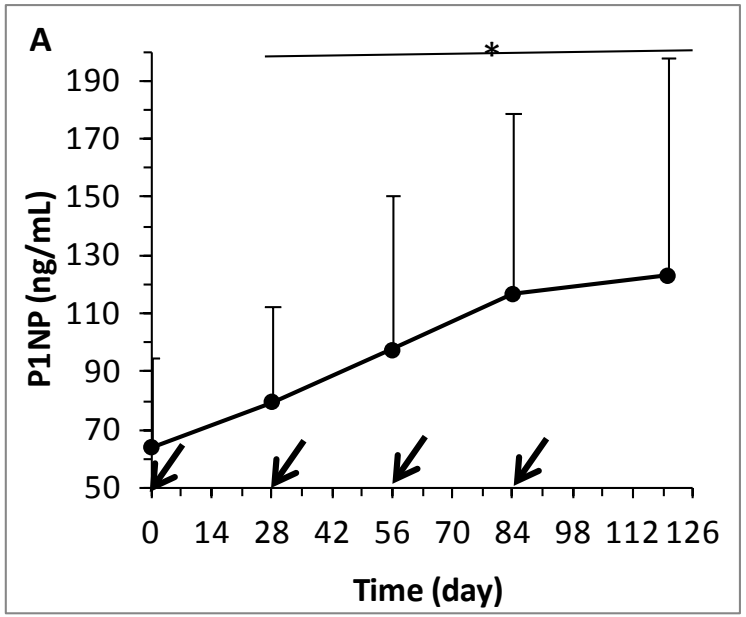
↙ KRN23 dose; Mean + SD presented; * $p < 0.05$ compared to baseline

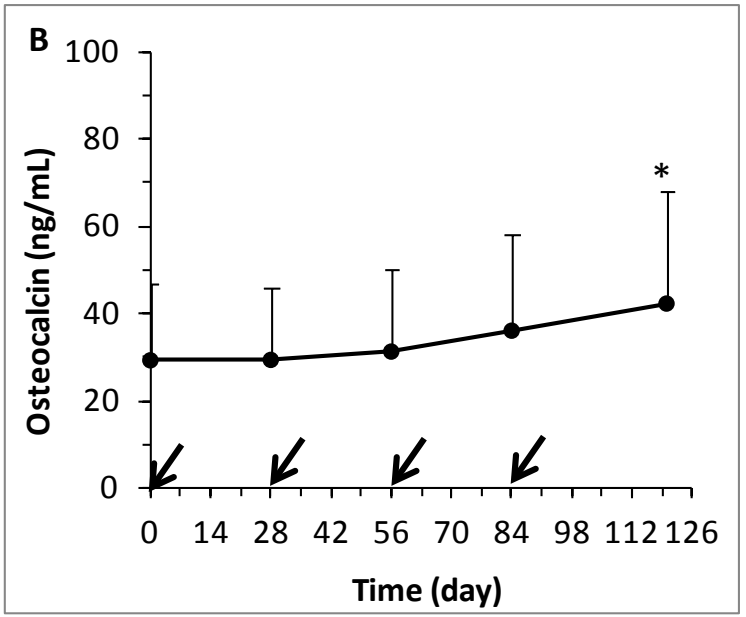
KRN23 Effects: Calcium and PTH



↙ KRN23 dose; Mean + SD presented; * $p < 0.05$ compared to baseline

Bone Turnover Markers





- **P1NP increased during treatment**
- **Osteocalcin increased by the end of treatment**

- **BALP, and serum CTx appeared to increase with successive doses**
- **Changes in BALP, CTx and NTX/creatinine ratio were not statistically significant**

↙ KRN23 dose; Mean + SD presented; * $p < 0.05$ compared to baseline

Safety Results

- **Adverse events (AEs) reported in 25 (89.3%) out of 28 subjects**
  - **Nasopharyngitis (8 subjects, 28.6%)**
  - **Arthralgia (7 subjects, 25%)**
  - **Diarrhea (5 subjects, 17.9%; *only 2 were treatment-related)***
  - **Back pain (5 subjects, 17.9%)**
  - **Restless leg syndrome (5 subjects, 17.9%)**
  - **Injection site urticaria (1 subject, discontinued)**
  - **Two subjects had severe AEs unrelated to study drug (subjects continued in study)**
    - **Severe myalgia**
    - **Severe back pain due to trauma**
- **No anti-KRN23 antibody was detected in any subjects**

Calcification

- **Renal ultrasound: Obtained in all subjects pre and post treatment**
  - **Baseline nephrocalcinosis in 5/28**
  - **No clinically significant post-treatment changes**
- **Cardiac CT: Obtained in 11 subjects pre and post treatment**
  - **Baseline: Coronary and aortic calcification scores 0 in all subjects**
  - **Post treatment: no change in 10/11**
    - **1 subject had a post-treatment change**
      - **Coronary calcification score of 3 Agastron units**
      - **Aortic calcification score of 0 Agastron units**
      - **(For comparison, 1-10 is low risk, >400 is high risk)**

Long term Extension Study (KRN23 INT-002)

- **22 subjects received KRN23 every 4 weeks for up to an additional 12 doses.**
- **Total treatment duration up to 16 months**
- **KRN23 continued to show favorable safety profile and sustained clinical effects.**
- **These results have been submitted to the American Society for Bone and Mineral Research Annual Meeting in Houston, TX in September.**

Summary

- **Four monthly injections of KRN23 in adults with XLH resulted in:**
  - **Increased TmP/GFR, serum Pi, and 1,25$(OH)_2D$**
  - **Most subjects increased serum Pi into normal range**
  - **Increased bone turnover markers**
  - **Improved quality of life scores [Poster MON-0210].**
- **KRN23 had a favorable safety profile**
- **Data supports ongoing investigation of KRN23 in both adult and pediatric clinical trials**

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.
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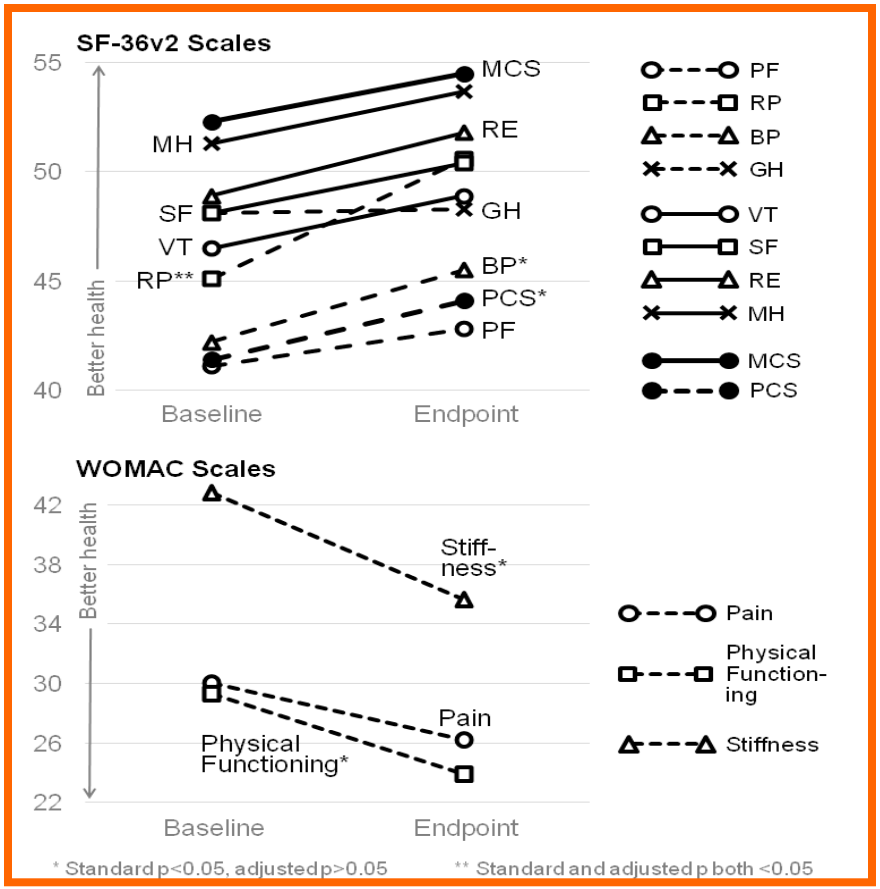
  - Elizabeth Olear
  - Margaret Stewart
  - Becky Sullivan
  - Connie Sullivan
  - Nathaniel Jacob Harrison
  - Monika Ruscheinsky
  - Michaela Durigova
  - Stephanie Lemp
  - Vinodhini Lakshman
- Sponsored by Kyowa Hakko Kirin Pharma, Inc.

Back-up Slides

KRN23 Improved Quality of Life

Mean PRO Scores at Baseline and Endpoint Among Completers



Ruppe MD, Zhang A, Imel EA, et al,
2014 ICE/ENDO Poster Number: MON-0210

Table 1. SF-36v2 Scales

	Acronym
Physical Functioning	PF
Role Limitations due to Physical Health	RP
Bodily Pain	BP
General Health Perceptions	GH
Vitality	VT
Social Functioning	SF
Role Limitations due to Emotional Problems	RE
Mental Health	MH

KRN23 PK and PK-PD Relationship

Figure 1. Serum KRN23 concentration over time (A) and dose proportionality for KRN23 (B)

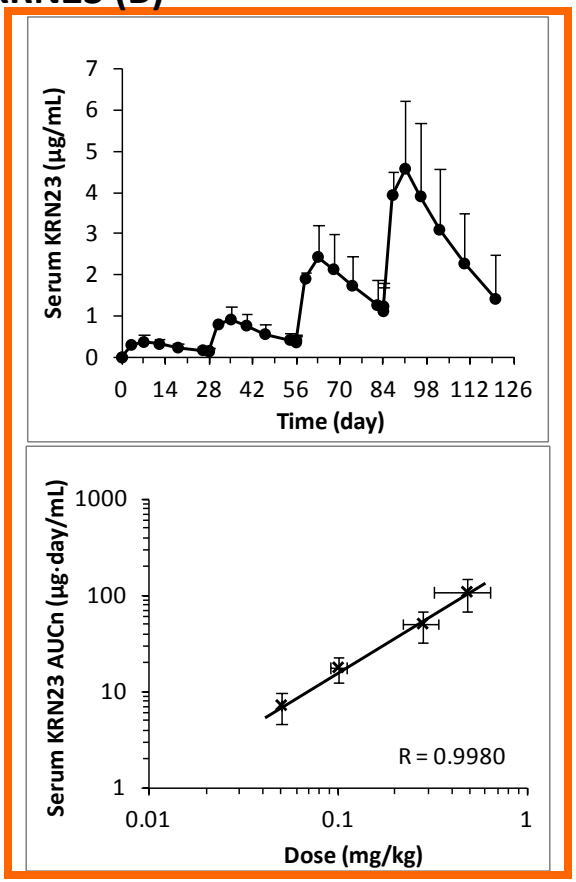
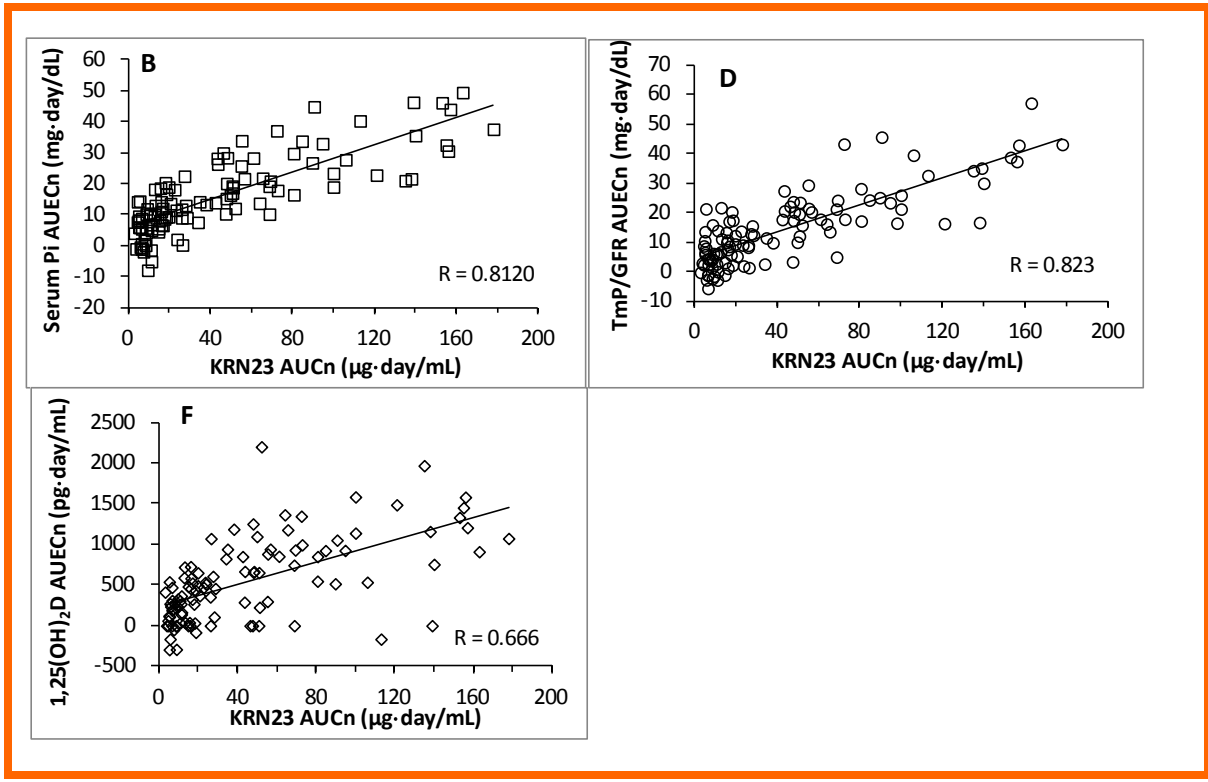


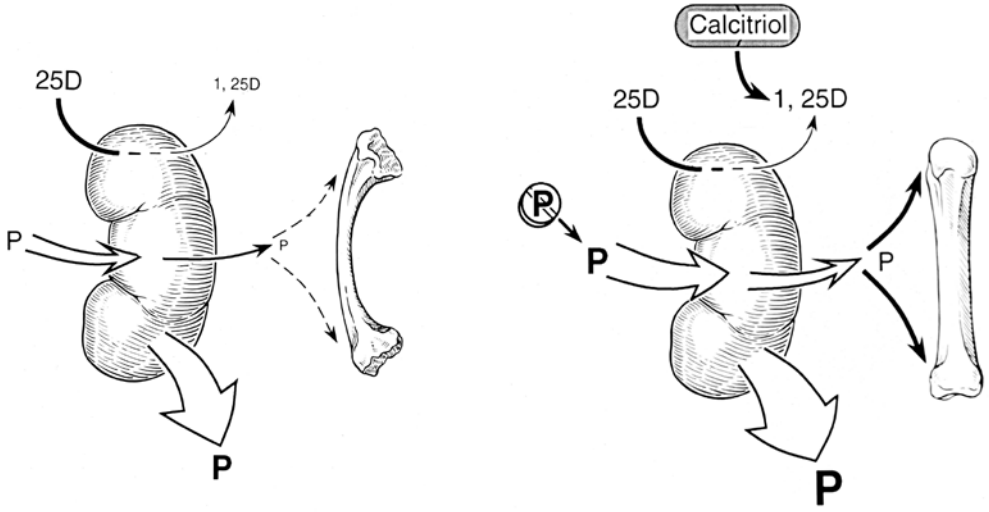
Figure 2. Linear correlation between $AUEC_n$ for Serum Pi (B), TmP/GFR (D) $1,25(OH)_2D$ (E) with AUC_n for KRN23 PK exposure.R is correlation coefficient



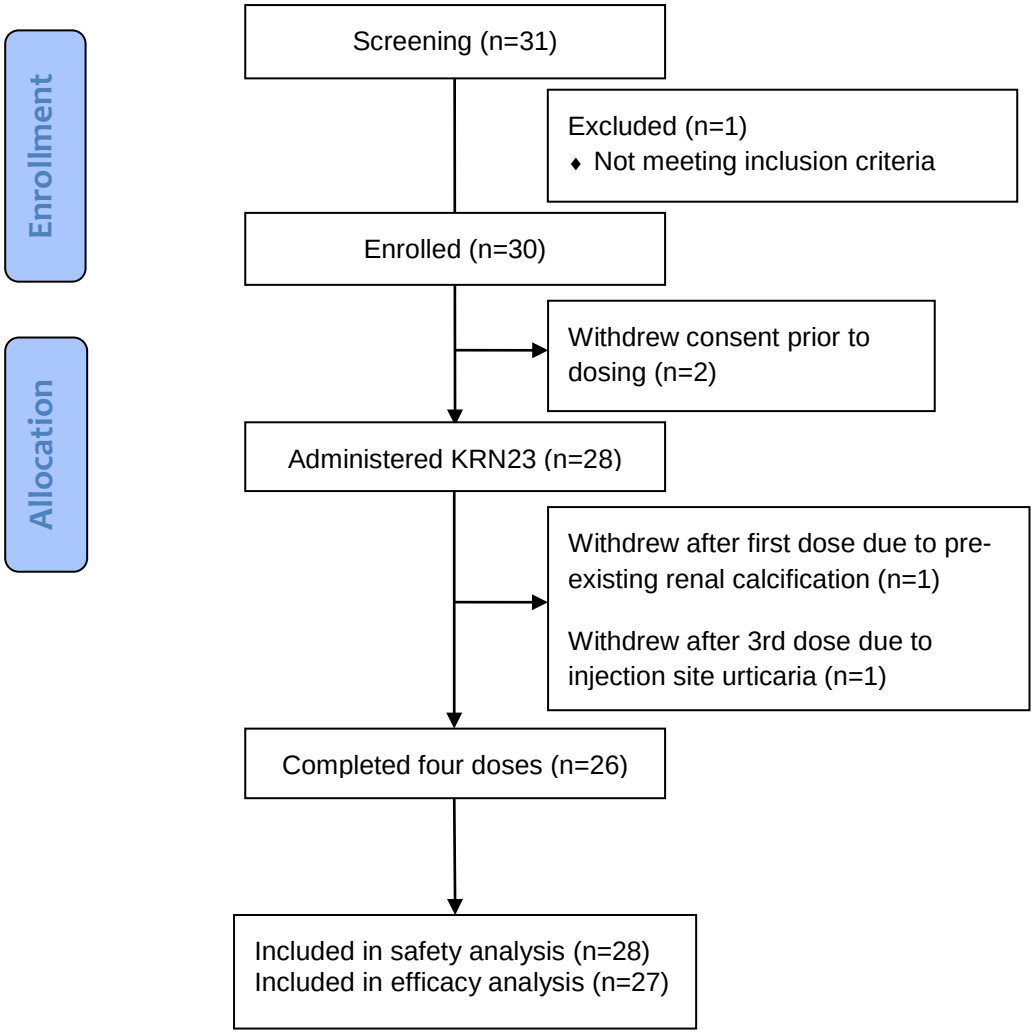
Zhang X, Imel EA, Ruppe MD, et al, 2014 ICE/ENDO Poster Number: MON-0206

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.**



CONSORT Diagram for the Study



Dose Algorithm

- KRN23 0.05 → 0.1→ 0.3→ 0.6 mg/kg
- Dose escalation based on Serum Pi day 26 post-dose
- If Serum Pi day 26 post-dose
  - ≤2.5 mg/dL, the dose was escalated 1 dose level
  - >2.5 mg/dL and ≤3.5 mg/dL, the previously administered dose level was repeated
  - >3.5 mg/dL, dosing was delayed and retested 28 days later.
    - If the repeat serum Pi was:
    - a) ≤2.5 mg/dL, the most recent dose was repeated
    - b) >2.5 mg/dL and ≤3.5 mg/dL, the dose was reduced by 1 dose level
    - c) >3.5 mg/dL, dosing withheld and re-evaluated 28 days later at the discretion of the Investigator and the Sponsor

KRN23 Doses Administered

- **Dose 1:**
  - **All 28 subjects received 0.05 mg/kg.**
- **Dose 2:**
  - **26 (96.3%) escalated to 0.1 mg/kg**
  - **1 remained at 0.05 mg/kg (1 withdrew).**
- **Dose 3:**
  - **25 (92.6%) escalated to 0.3 mg/kg**
  - **1 continued at 0.05 mg/kg**
  - **1 continued at 0.1 mg/kg**
- **Dose 4:**
  - **16 (61.5%) escalated to 0.6 mg/kg**
  - **8 continued at 0.3 mg/kg**
  - **1 increased from 0.05 to 0.1 mg/kg**
  - **1 increased from 0.1 to 0.3 mg/kg (1 withdrew)**
- **No subject required dose reduction.**

Table 2: Proportion of Subjects With Post-dose Serum Pi by Categories

Study Day	Post-dose Day*	Number (%) of Subjects Categories of Serum Pi Levels (mg/dL)			
		≤ 2.5	Phosphorus > 2.5 to ≤ 3.5	Phosphorus > 3.5 to ≤ 4.5	Phosphorus > 4.5
Dosing Interval 1, n=27					
Predose Day 0	Day 0	26 (96.3)	1 (3.7)	0	0
Day 7	Day 7	23 (85.2)	4 (14.8)	0	0
Day 26	Day 26	26 (96.3)	1 (3.7)	0	0
Dosing Interval 2, n=27					
Predose Day 28	Day 0	26 (96.3)	1 (3.7)	0	0
Day 35	Day 7	17 (63.0)	10 (37.0)	0	0
Day 54	Day 26	25 (92.6)	2 (7.4)	0	0
Dosing Interval 3, n=27					
Predose Day 56*	Day 0	23 (92.0)	2 (8.0)	0	0
Day 63	Day 7	7 (25.9)	20 (74.1)	0	0
Day 82	Day 26	19 (70.4)	8 (29.6)	0	0
Dosing Interval 4, n=26					
Predose Day 84*	Day 0	18 (75.0)	6 (25.0)	0	0
Day 91	Day 7	3 (11.5)	19 (73.1)	4 (15.4)	0
Day 110	Day 26	14 (53.8)	12 (46.2)	0	0
Day 120	Day 36	22 (84.6)	4 (15.4)	0	0

* The visits where two serum Pi data were missing.

- **Serum Pi did not exceed 4.5 mg/dL in any subject**