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)

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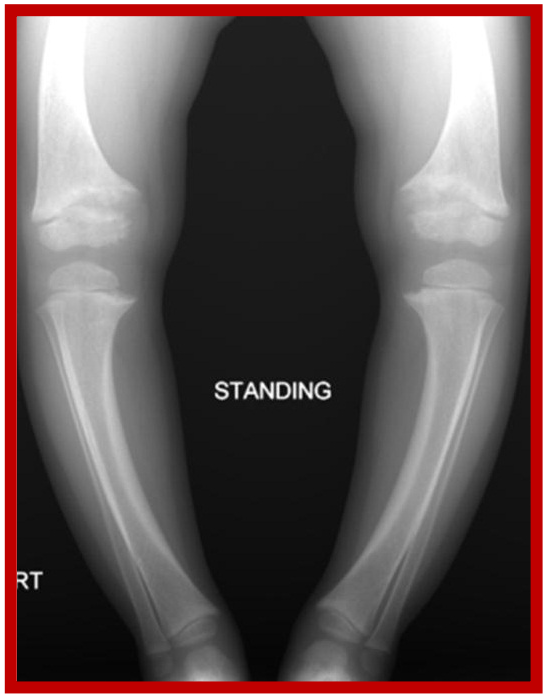
DISCLOSURE

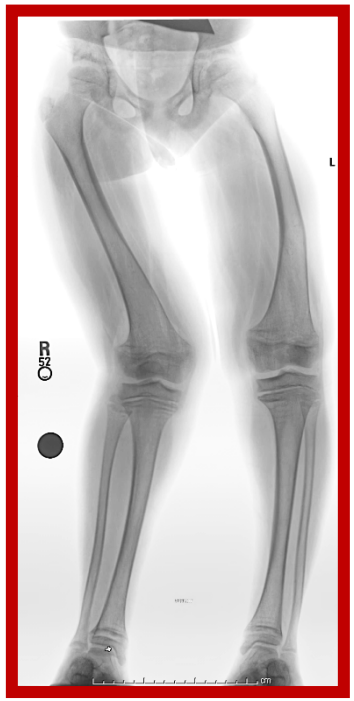
Kyowa Hakko Kirin Pharma, Inc. / Ultragenyx Pharmaceutical:

- Consultant (protocol design); grant recipient

X-linked Hypophosphatemia

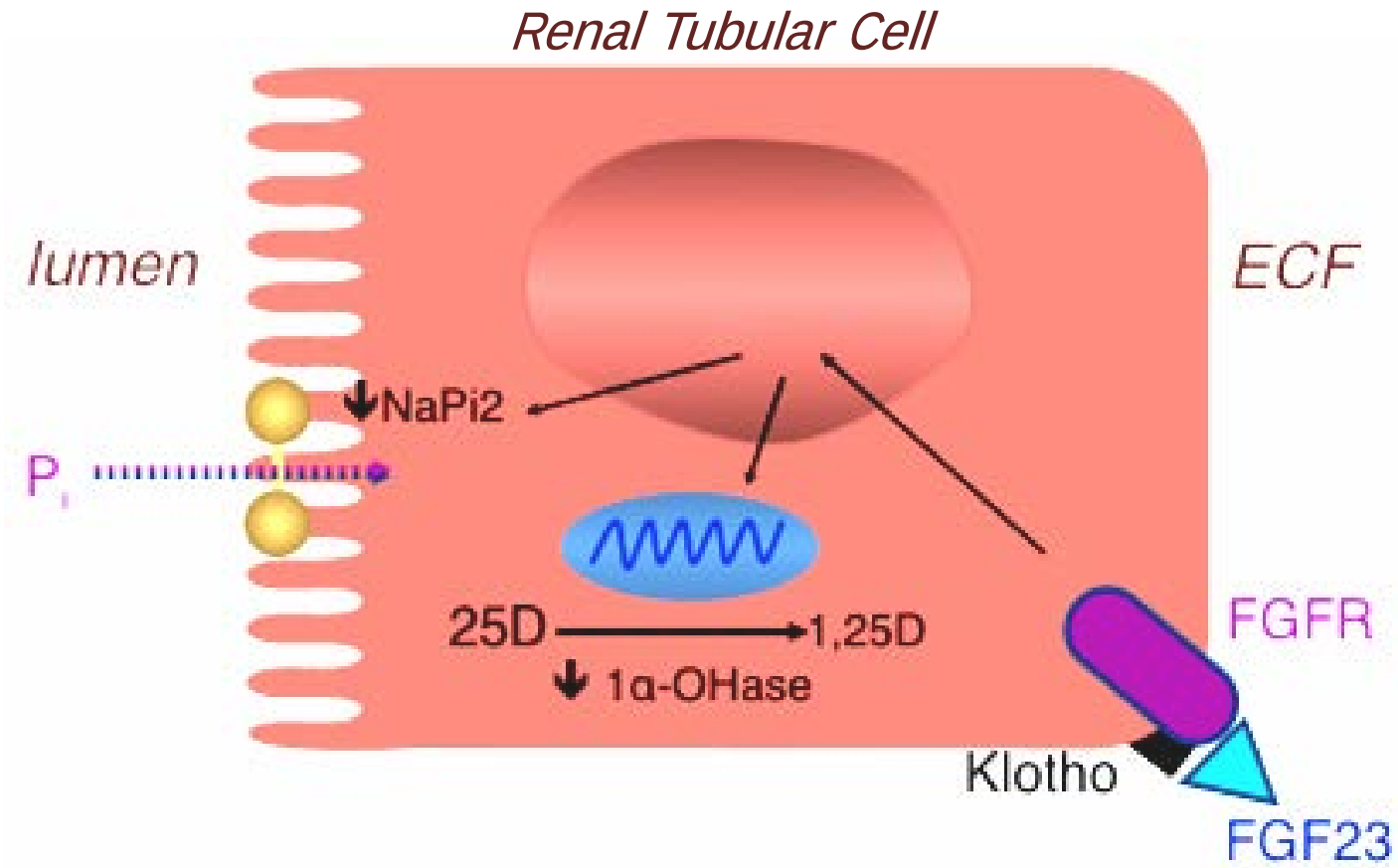
XLH is a chronic disease of renal phosphate wasting presenting with bowing defects in early childhood and biochemical findings of hypophosphatemia, due to low TmP/GFR, and low serum 1,25 dihydroxyvitamin D.





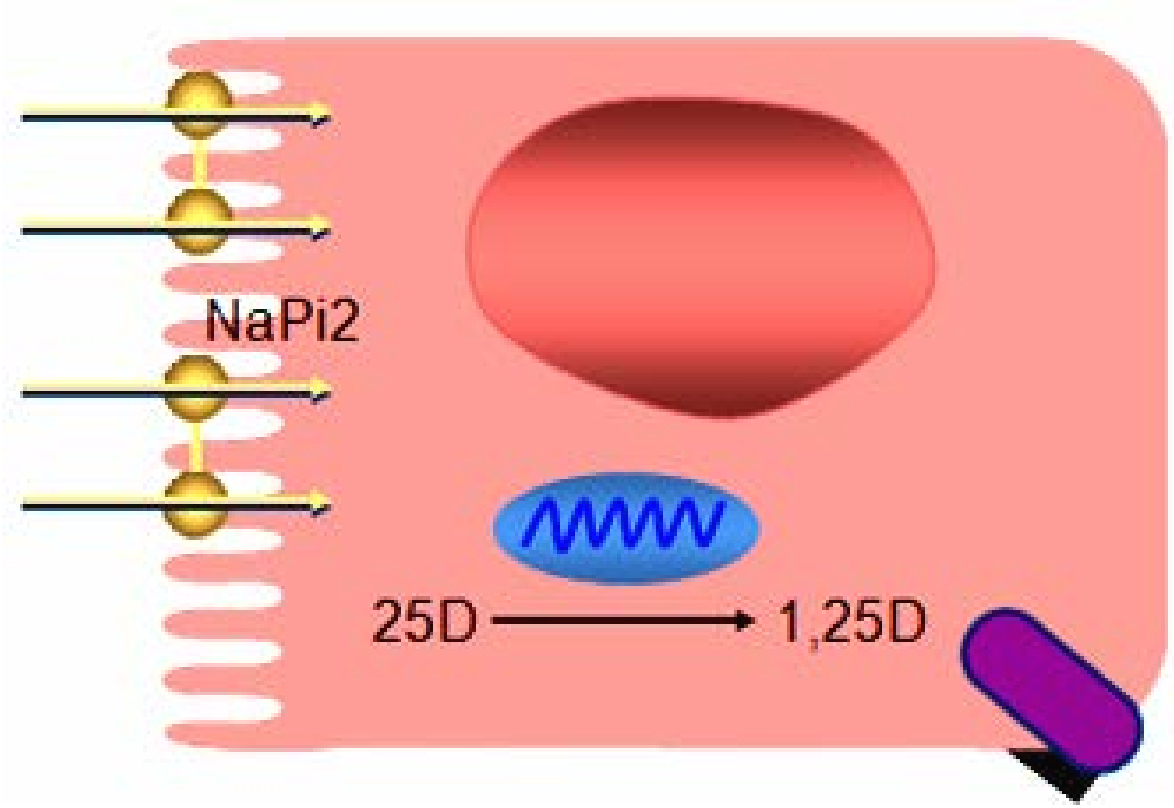
X-linked Hypophosphatemia

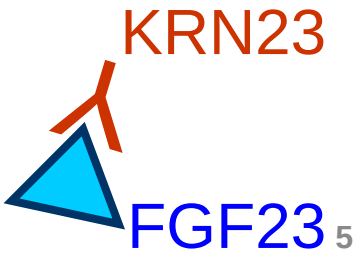
The defective renal phosphate reabsorption and aberrant vitamin D metabolism is mediated by increased circulating levels of FGF23.



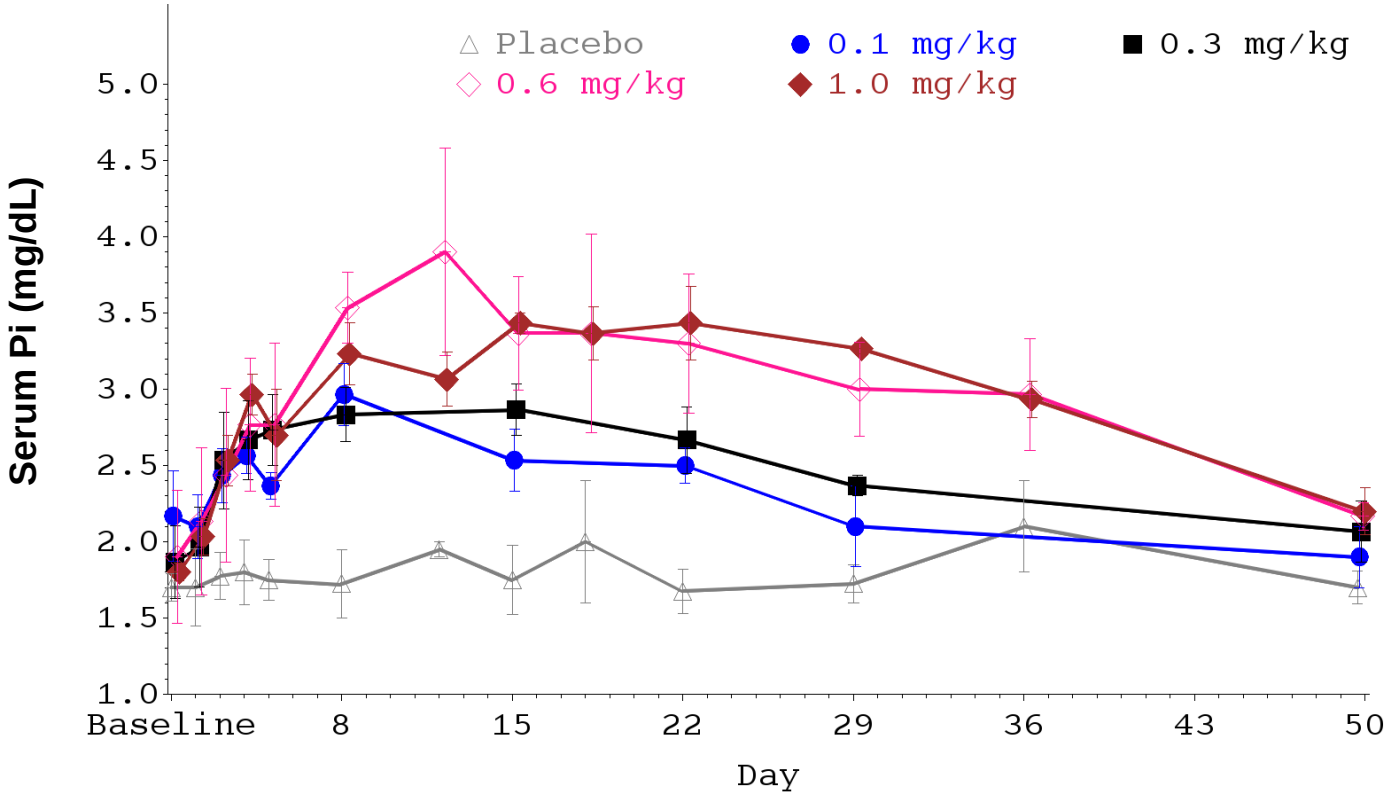
KRN23

- KRN23 is a human monoclonal antibody with FGF23 inhibitory activity.





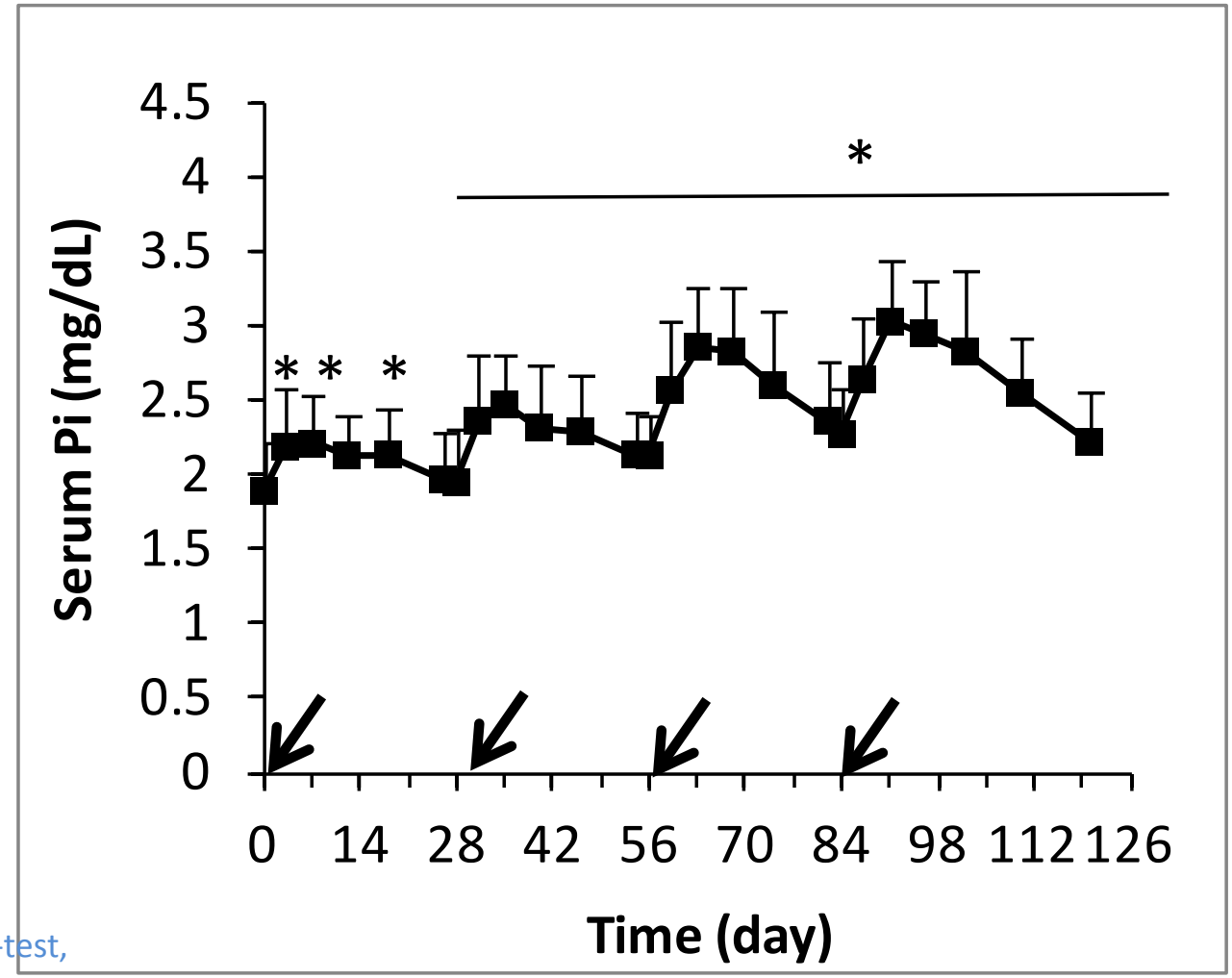
KRN23: Serum Pi after Single SC Doses



- 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)



↙ KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

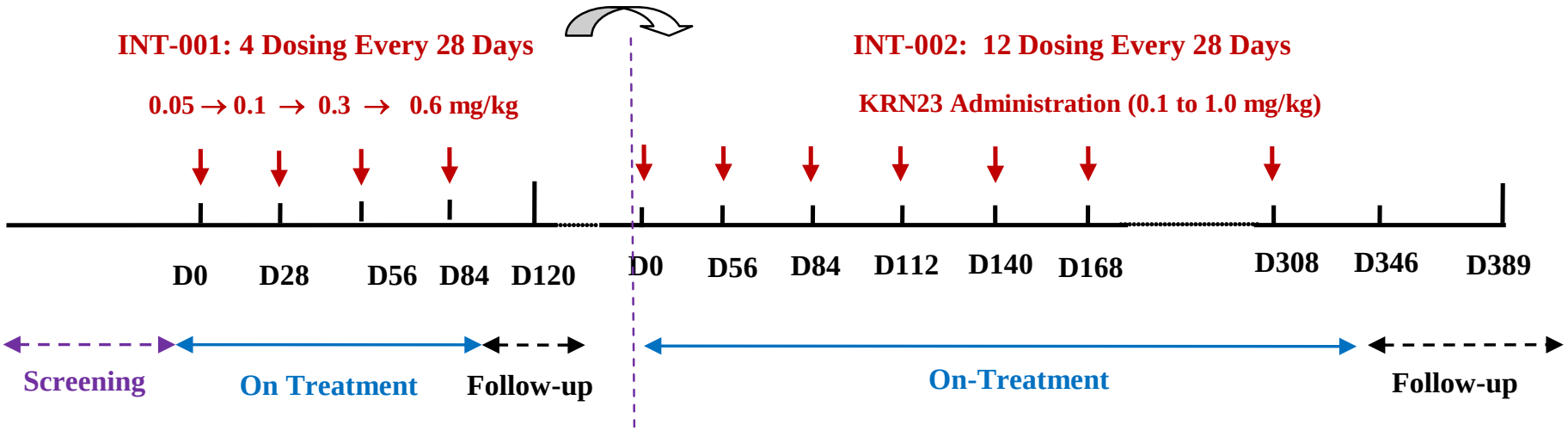
Source: ICE/ENDO Annual Mtg, June 2014, Chicago

Study Protocol

- Design:
  - Multi-center phase 1/2 open-label, **4 dose-escalation**[a]
  - Multi-center phase 1/2 open-label, **12 dose extension**[b]
- Subjects
  - Dose escalation: 28 adults with clinical diagnosis of XLH
    - Age ≥ 18 years
    - Intact FGF23 ≥ 30 pg/mL
    - TmP/GFR < 2.0 mg/dL
    - Creatinine clearance ≥ 60 mL/min
    - Serum calcium < 10.8 mg/dL
  - Extension: 22 subjects enrolled in the extension study

ClinicalTrials.gov: [a]NCT01340482; [b]NCT01571596;

KRN23 Dosing and Titration



- 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. ≤ 2.5 mg/dL, 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, ≤ 3.5, AND
   a) peak serum Pi < 3.8, previous dose repeated
   b) peak serum Pi ≥ 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 ≥ 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

Study (N):	*Escalation (28)*	*Extension* (22)
Age (years)	42 ± 14	42 ± 15
Sex (male/female)	9/19	9/13
Weight (kg)	70 (46 -122) *	75.3 (51.3-124.3)*
Race (Caucasian/Other)	27/1	21/1
Height (cm) (range)	150 ± 12 (122 -170)	151 ± 13 (122 -170)

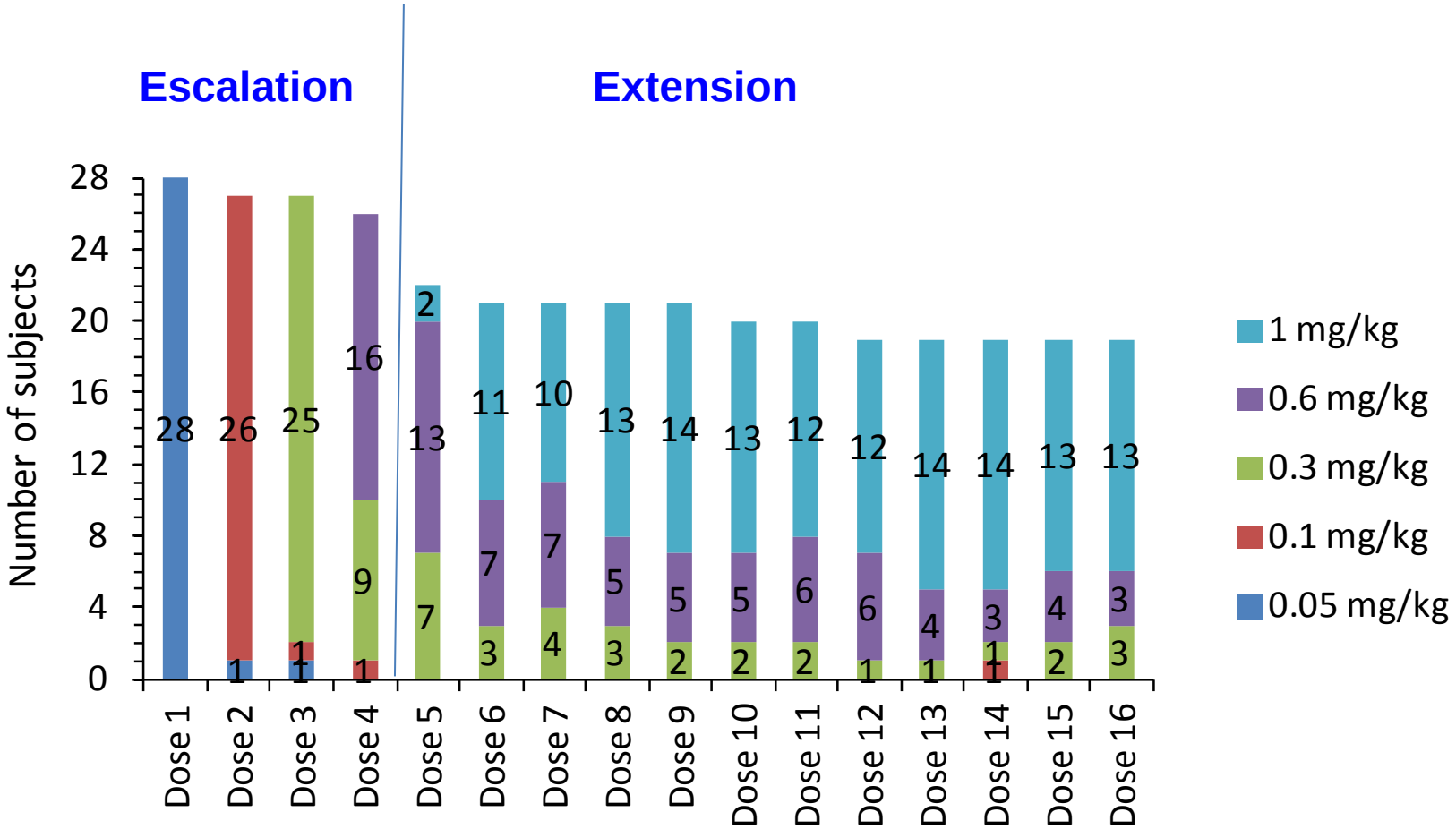
Mean ± SD (except weight)
* *Median (95% Confidence Interval)*

Baseline Biochemistry

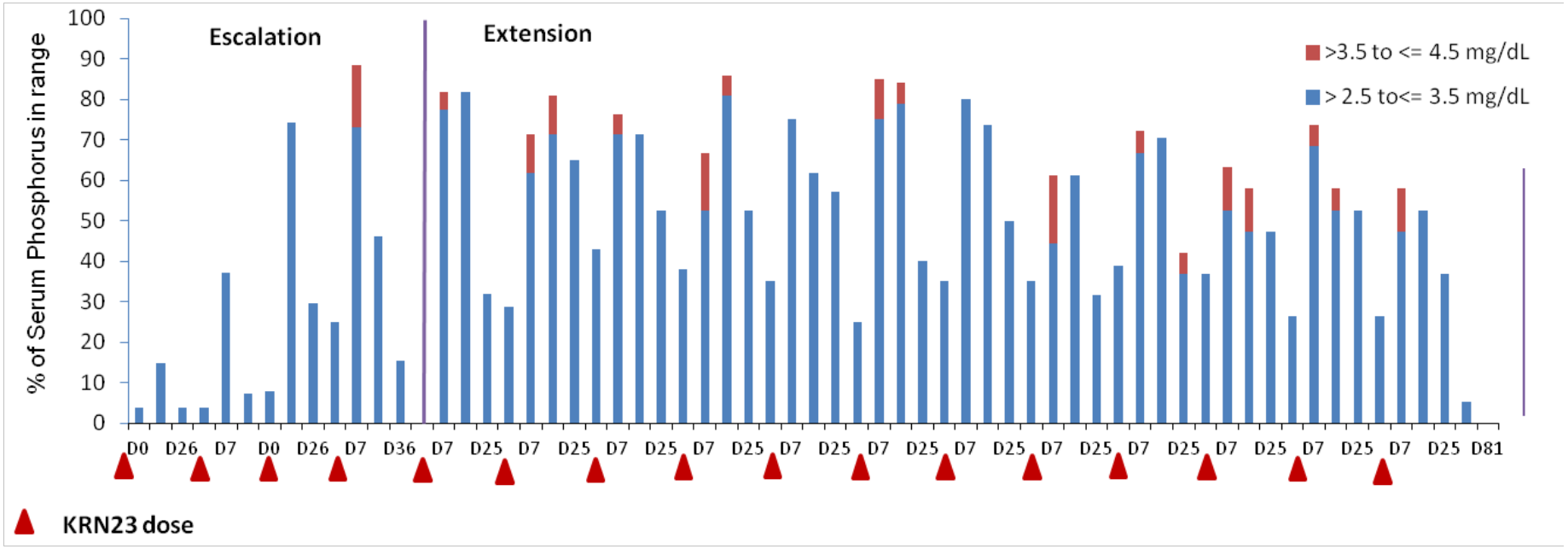
Study (N)	*Escalation (28)*	*Extension (22)*
Serum Pi (mg/dL)	*1.9 ± 0.3*	*1.9 ± 0.28*
1,25D (pg/mL)	*36.6 ± 14.3*	*36.4 ± 12.6*
25D (ng/mL)	*25.0 ± 9.1*	*23.1 ± 8.68*
Total calcium (mg/dL)	*9.1± 0.4*	*9.1± 0.4*
PTH (pg/mL)	*74 (38, 143)**	*68.5 (40, 143) **
BALP (µg/L)	*28.3 ± 12.8*	*31.1 ± 12.3*
Intact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

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

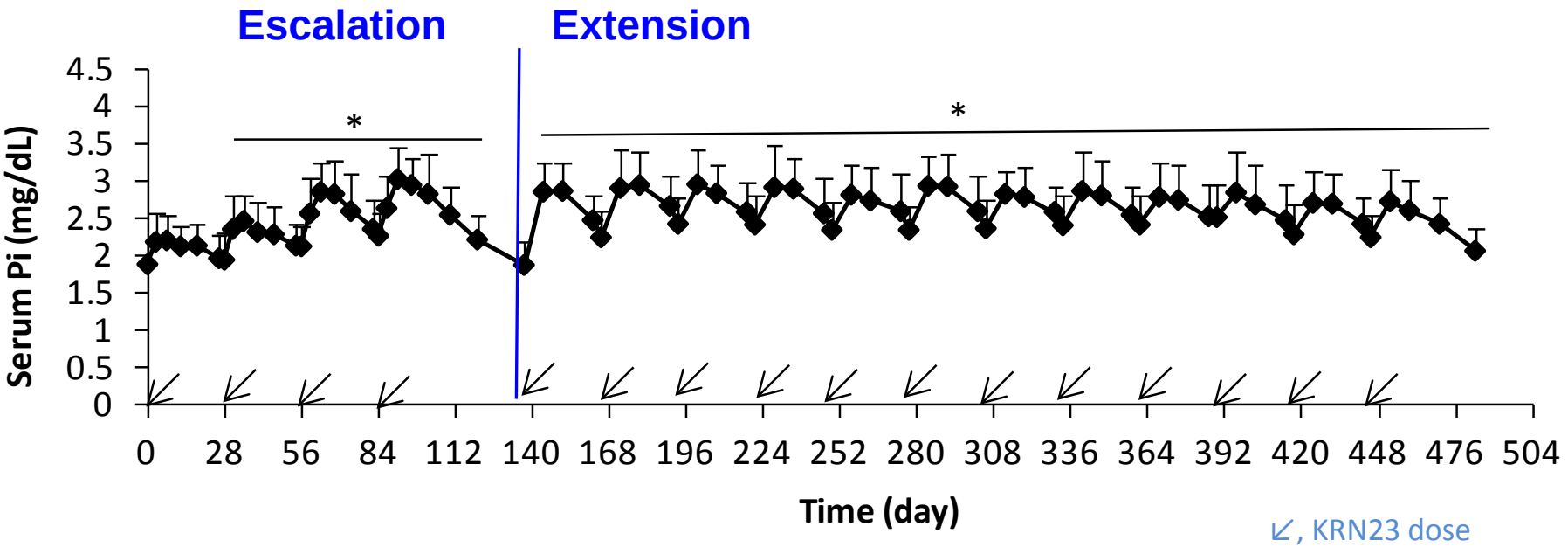


Primary Efficacy Results



- 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

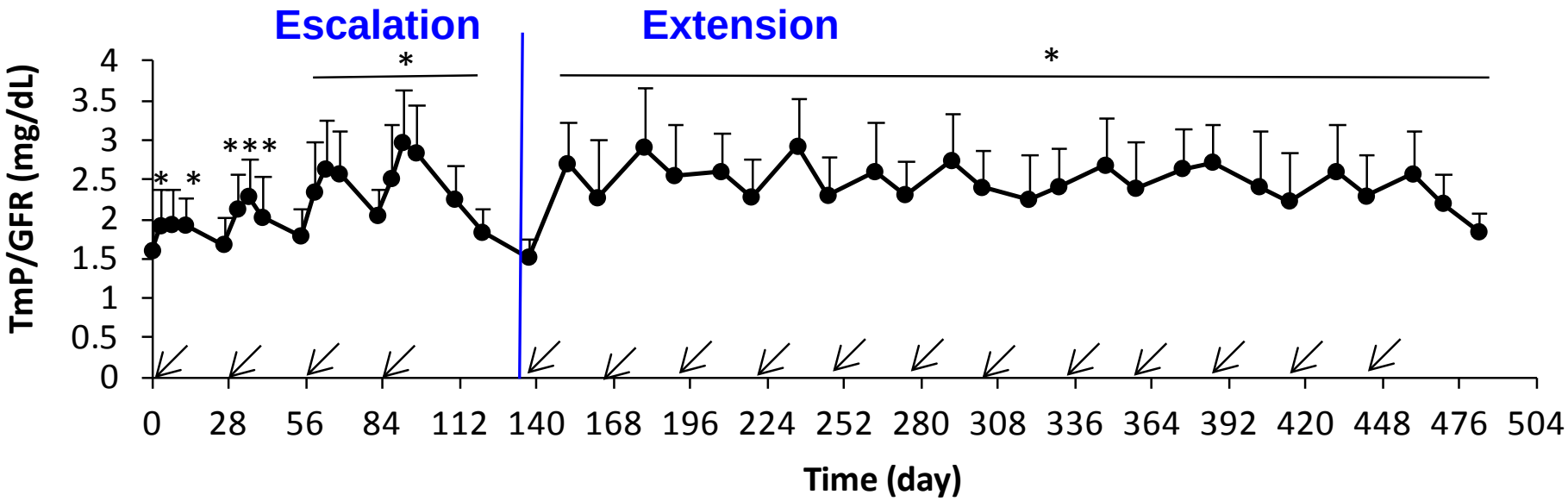
KRN23: Effect on Serum Pi



↙, KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

- 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%)

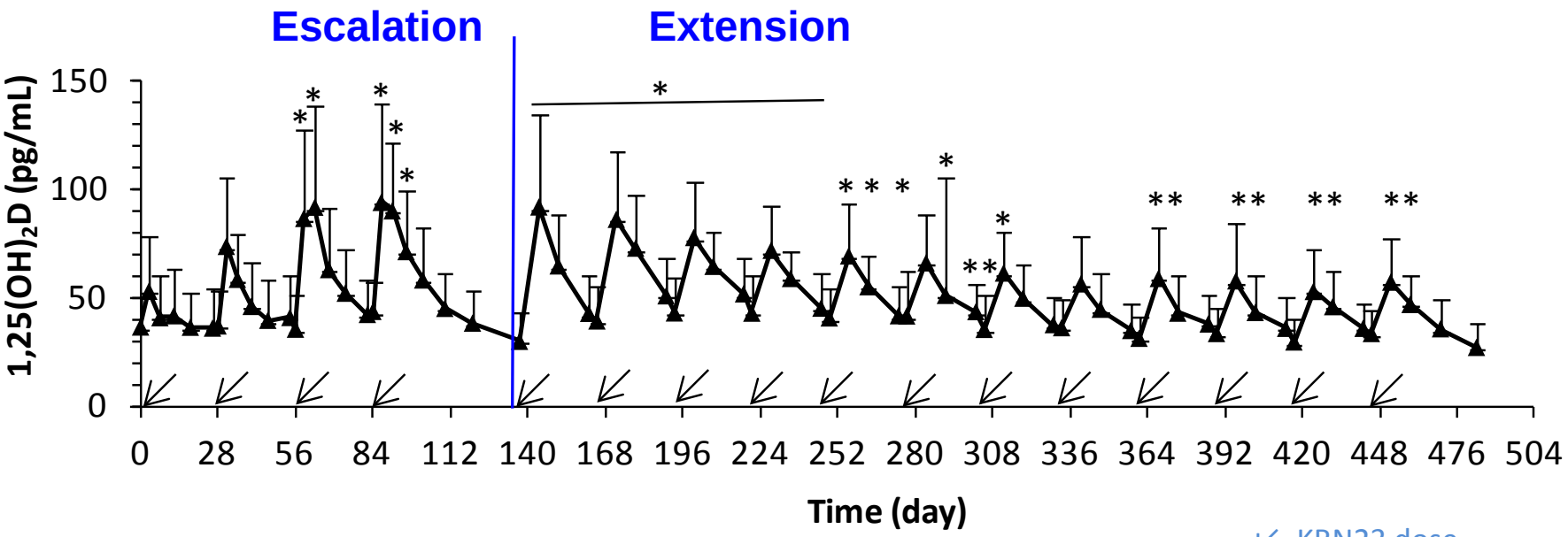
KRN23: Effect on TmP/GFR



↙,KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

- 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

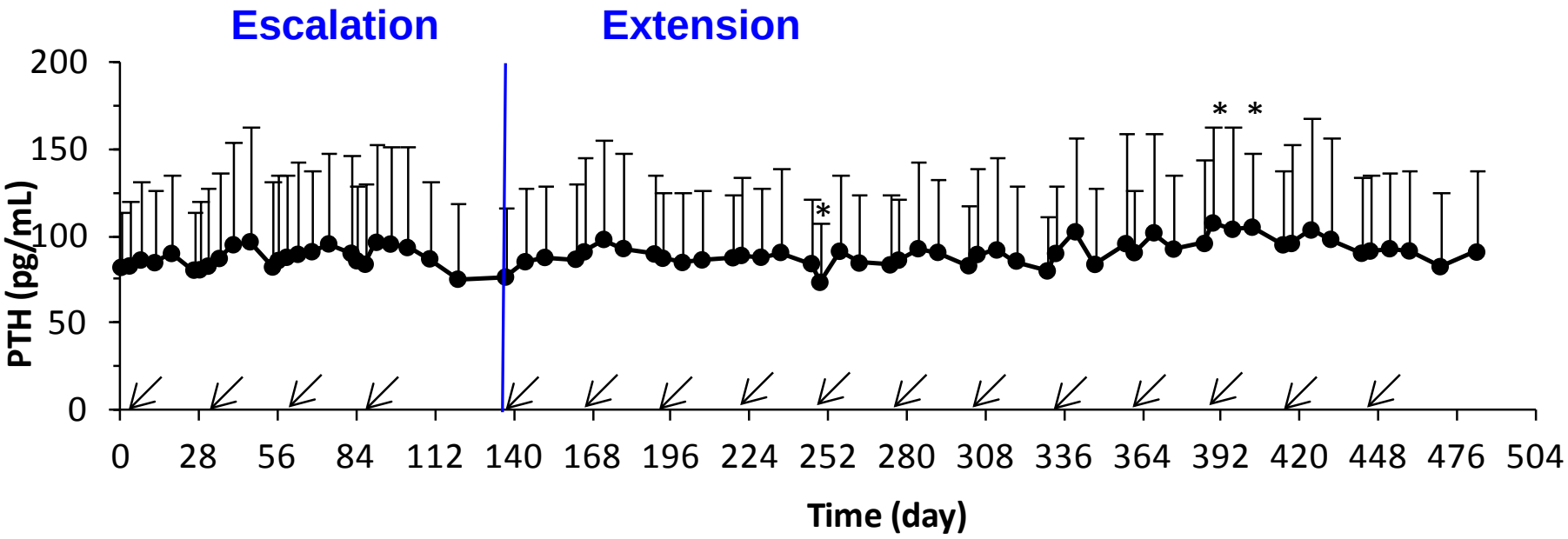
KRN23: Effect on $1,25(OH)_2D$



↙, KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

- Serum $1,25(OH)_2D$ peaked on Day 3- 7
- Escalation: serum $1,25(OH)_2D$ increased as dose increased
- Extension: serum $1,25(OH)_2D$ increased after each dose and decreased toward pre-dose level by next dose, with tendency to decrease over time

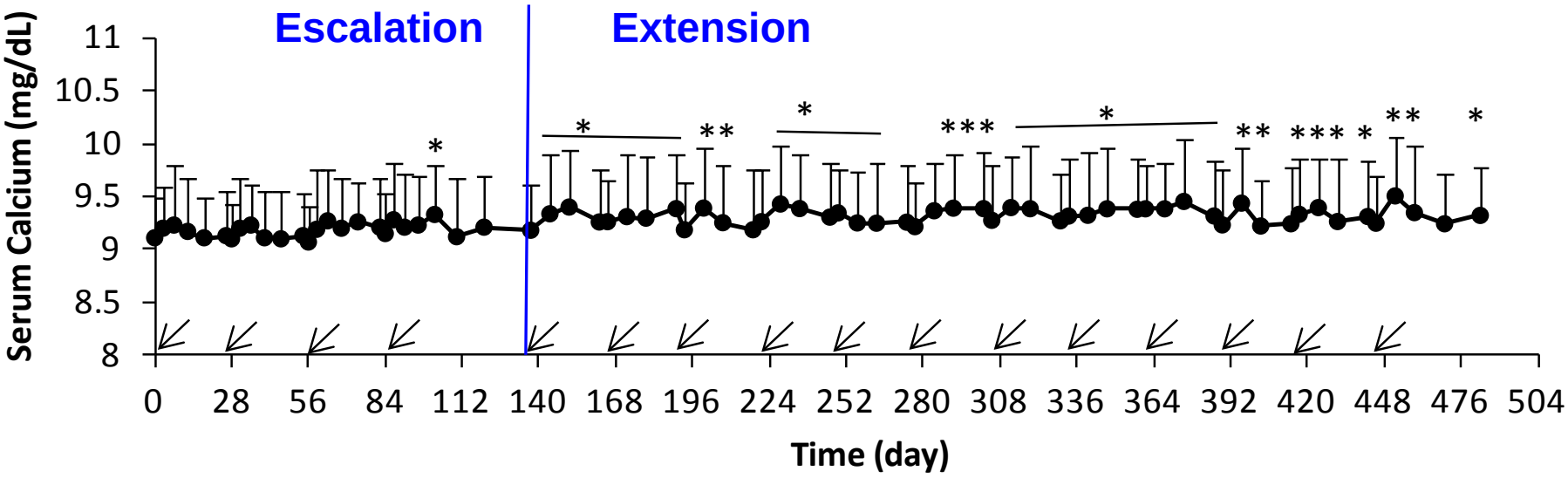
KRN23: Effect on PTH



- No consistent trend was noted in mean serum PTH

↙ KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

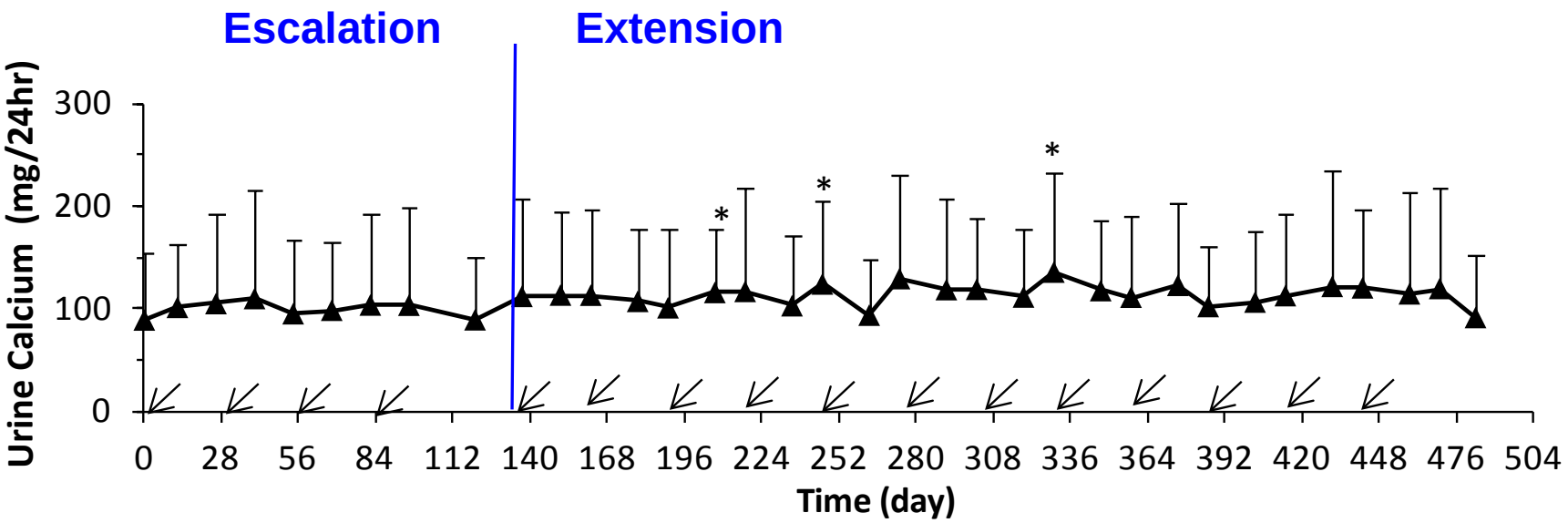
KRN23: Effects on Serum Calcium



- Minor increases in serum calcium during extension phase

↙ KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean+ SD

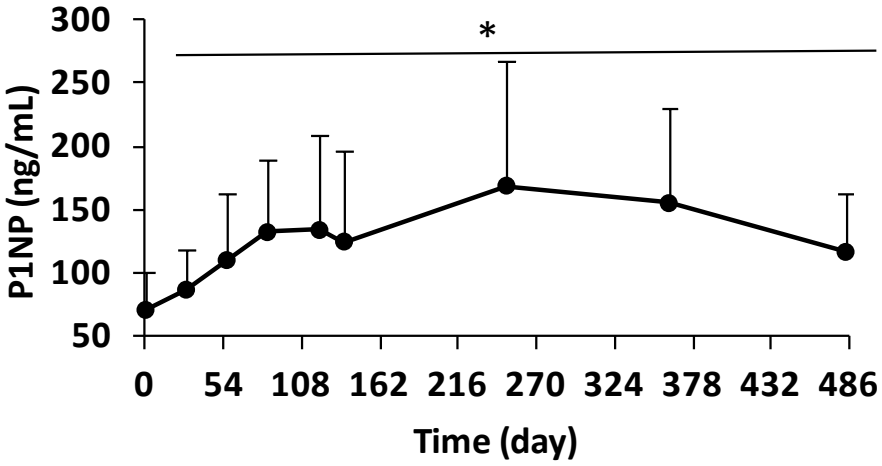
KRN23: Effects on 24-h Urine Calcium

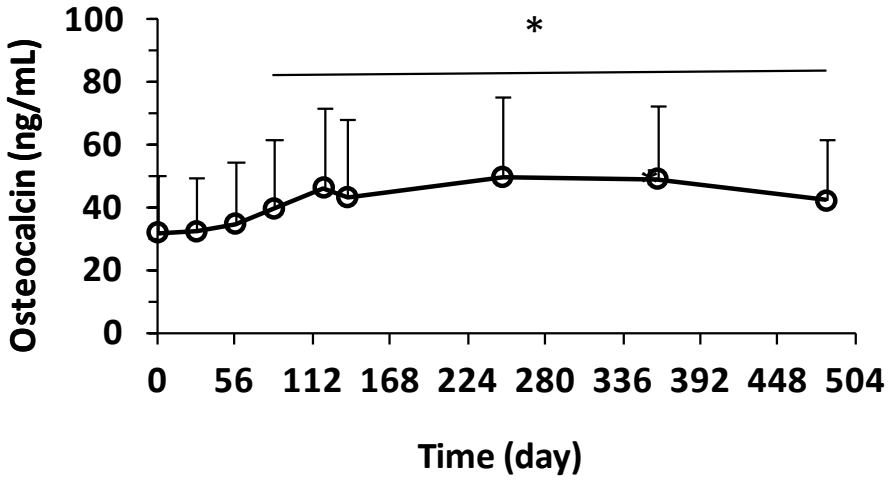


- No consistent trend was noted in mean 24-hour urine calcium

↙ KRN23 dose
*p< 0.05, paired t-test, Bonferoni correction
Mean +SD

Bone Turnover: P1NP and Osteocalcin





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

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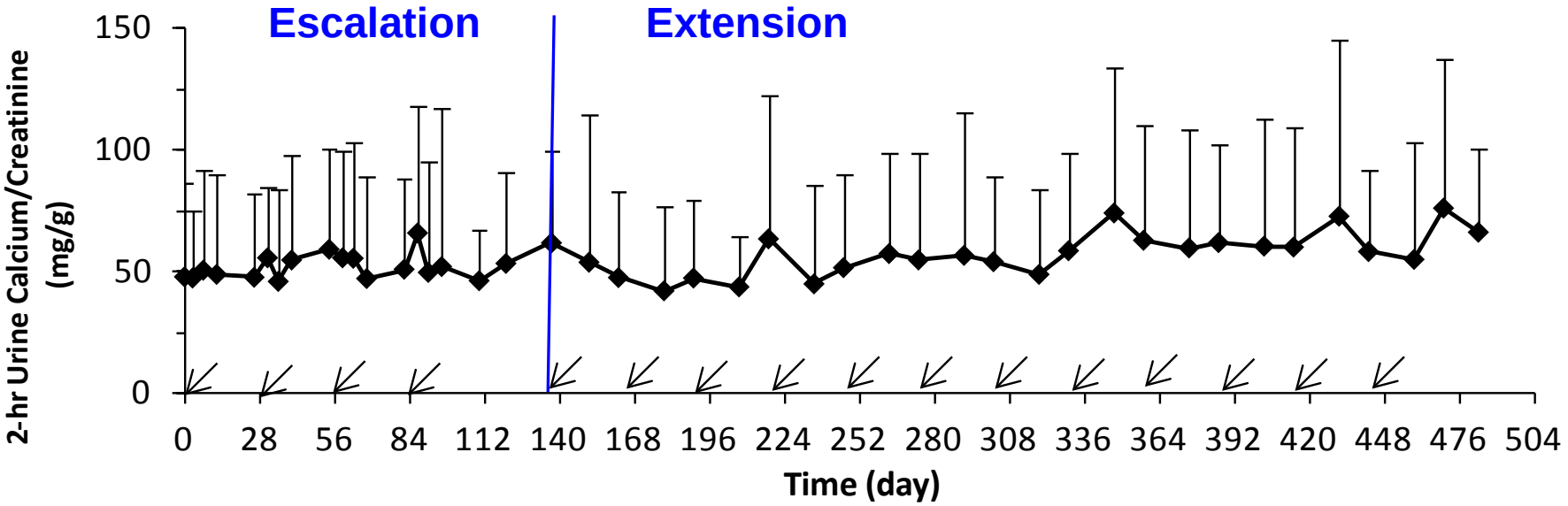
  - Elizabeth Olear
  - Margaret Stewart
  - Becky Sullivan
  - Connie Sullivan
  - Nathaniel Jacob Harrison
  - Monika Ruscheinsky
  - Michaela Durigova
  - Stephanie Lemp
  - Vinodhini Lakshman
- Sponsored by Kyowa Hakko Kirin Pharma, Inc.

Back-up Slides

KRN23 Effects: 2-h Urine Calcium/Creatinine Ratio

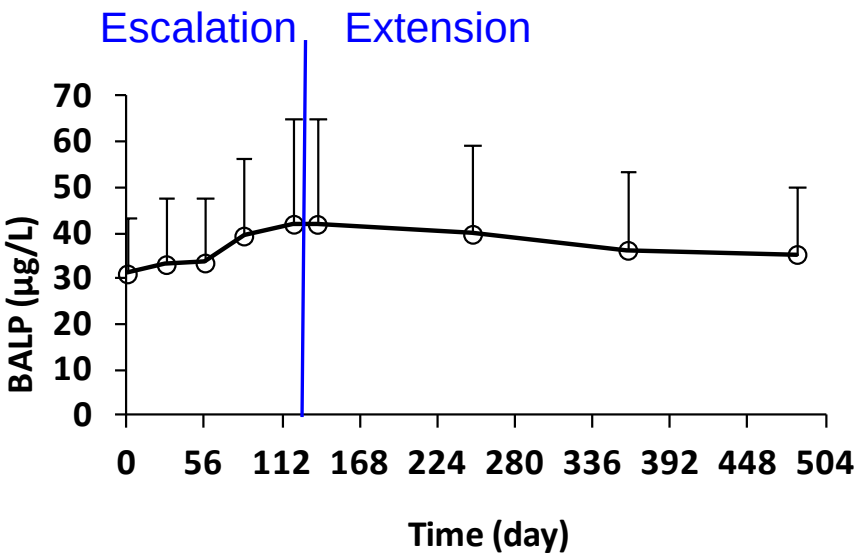


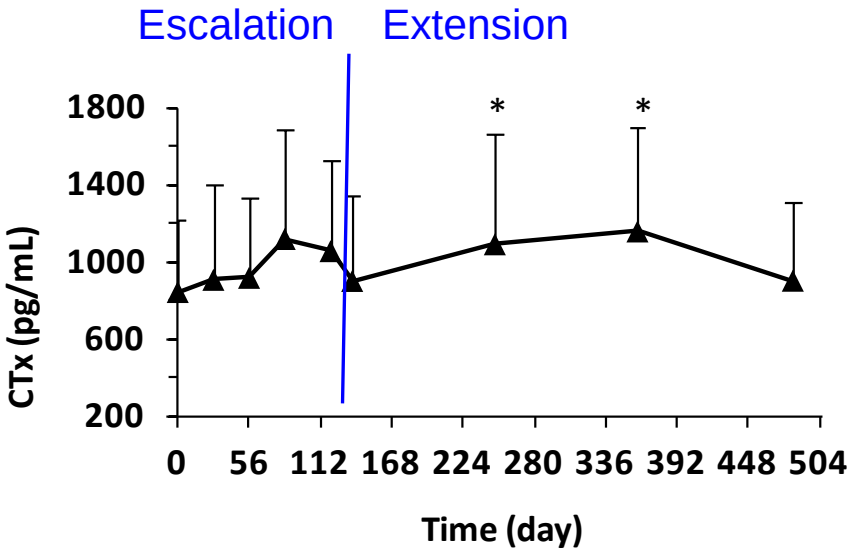
- No consistent trend was noted in mean values for 2-hour urine calcium/creatinine ratio after 16 months of KRN23 treatment

↙, 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



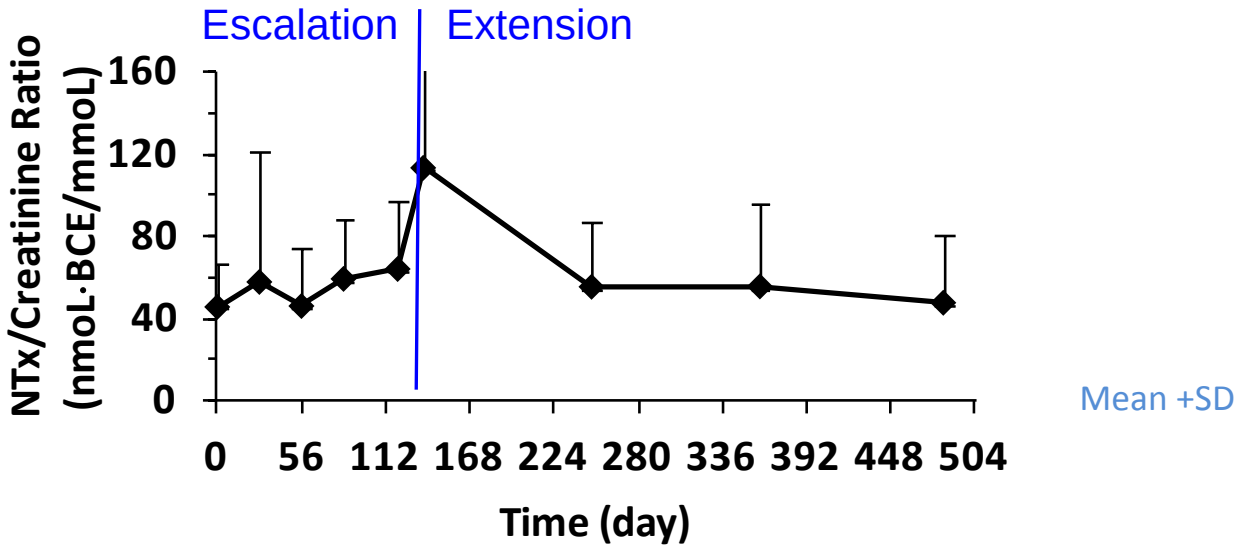


- BALP and CTx appeared to increase during escalation period and were maintained during extension
- Changes in BALP were not statistically significant
- Changes in CTx were statistically significant after 9th and 12 doses

*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

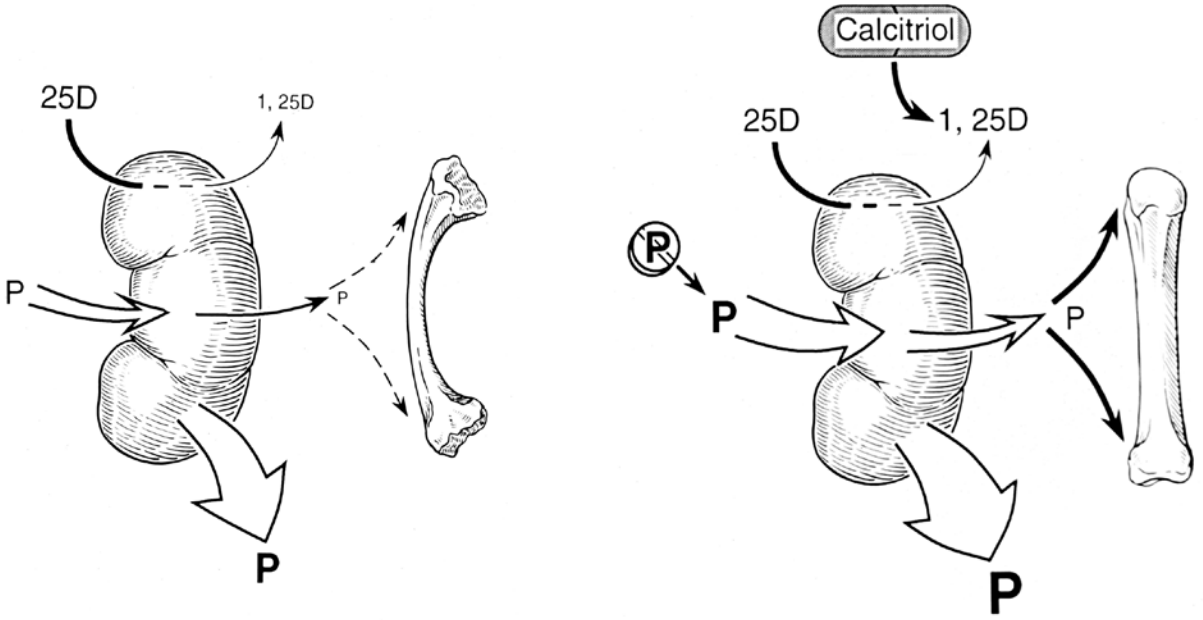


*** p< 0.05 for paired t-test compared to baseline with Bonferoni correction**

- 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.