

# Evaluating the Effects of KRN23, a Fully Human Anti-FGF23 Monoclonal Antibody, on Functional Outcomes in Children with X-linked Hypophosphatemia (XLH): 40-week Interim Results from a Randomized, Open-label Phase 2 Study

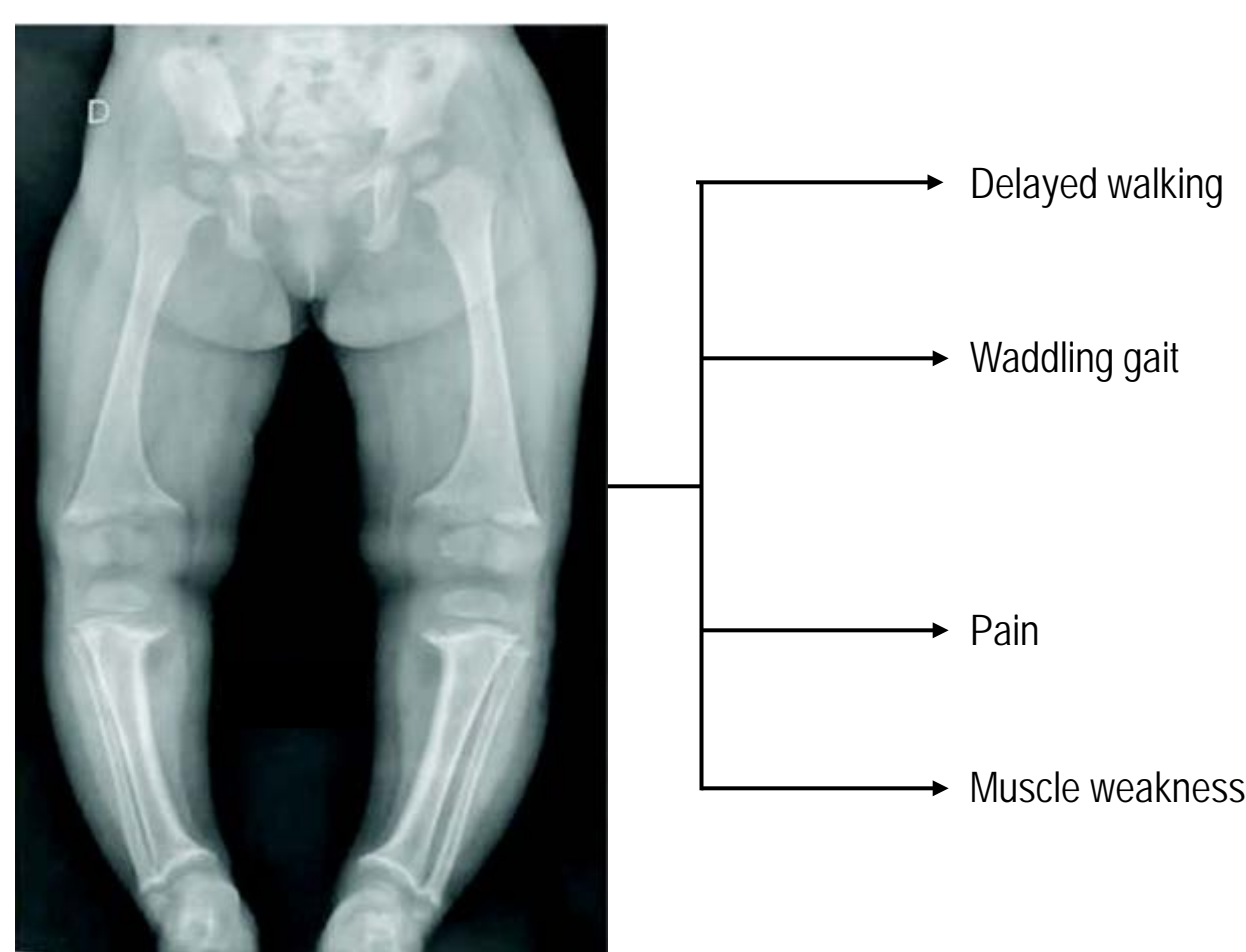
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## INTRODUCTION

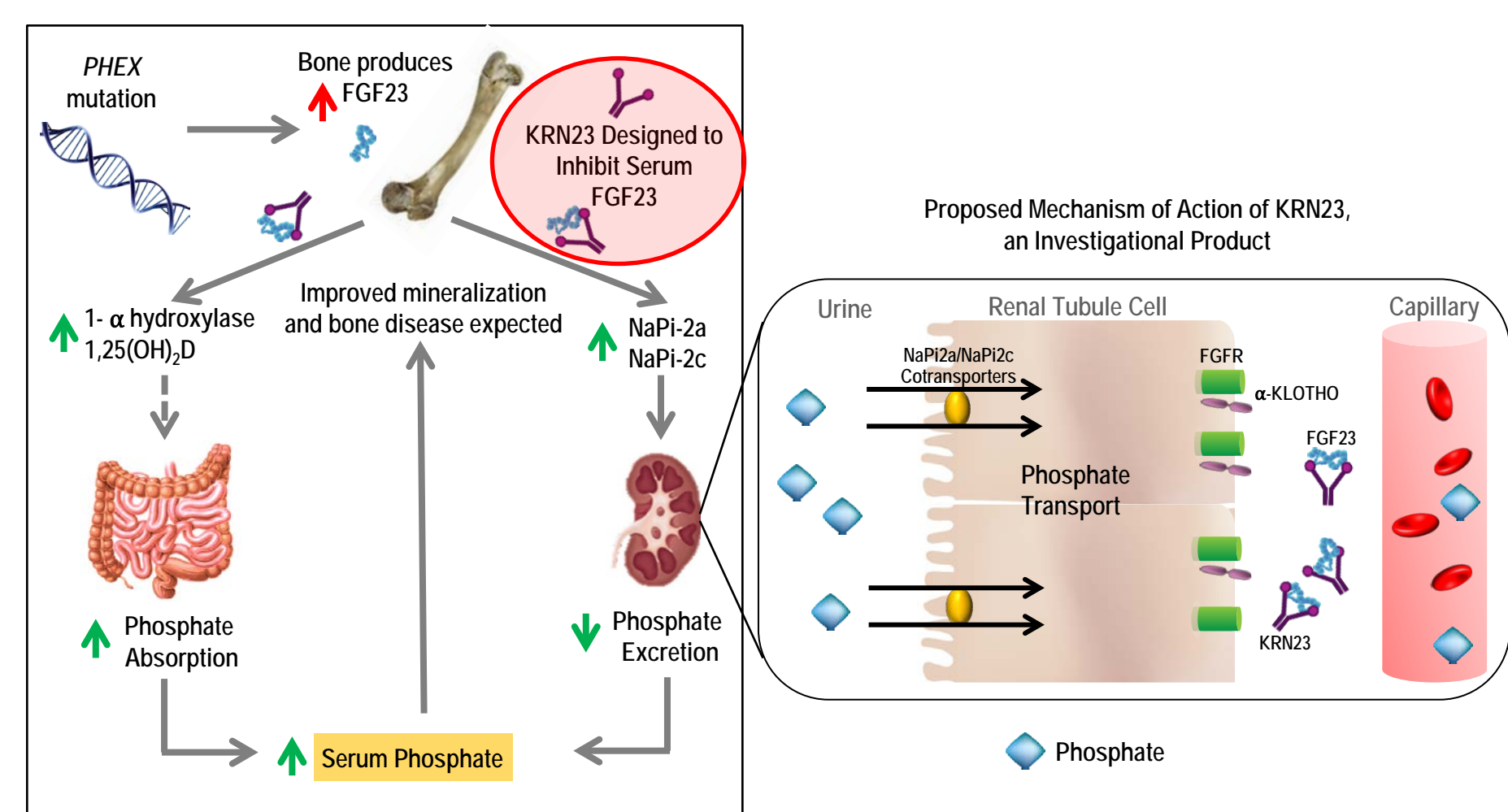
- X-linked hypophosphatemia (XLH) is a rare, lifelong, chronically debilitating, and deformative bone disease mediated by high circulating fibroblast growth factor-23 (FGF23) (Carpenter et al, 2011; Linglart et al, 2014).
- The resulting skeletal abnormalities, including rickets and bowing of the legs, can significantly impair gross motor function and quality of life in childhood or adulthood.

### Rickets and Skeletal Impairments Lead to Significant Symptoms and Physical Disabilities



- KRN23 is an investigational fully human IgG1 monoclonal antibody designed to specifically bind to and inhibit excess FGF23.

### KRN23 Is Designed to Inhibit Excess FGF23



Razzaque MS. *Nat Rev Endocrinol*. 2009;5:611-9. Martin A, et al. *Physiol Rev*. 2012;92:131-55.

## OBJECTIVE OF PRESENTATION

- To assess the effect of KRN23 on functional outcomes in pediatric patients with XLH.

## REFERENCES

Carpenter TO, Imel EA, Holm IA, et al. A clinician's guide to X-linked hypophosphatemia. *J Bone Miner Res*. 2011;26:1381-88.  
Linglart A, Blosse-Duplan M, Briot K, et al. Therapeutic management of hypophosphatemic rickets from infancy to adulthood. *Endocr Connect*. 2014;3:R13-30.

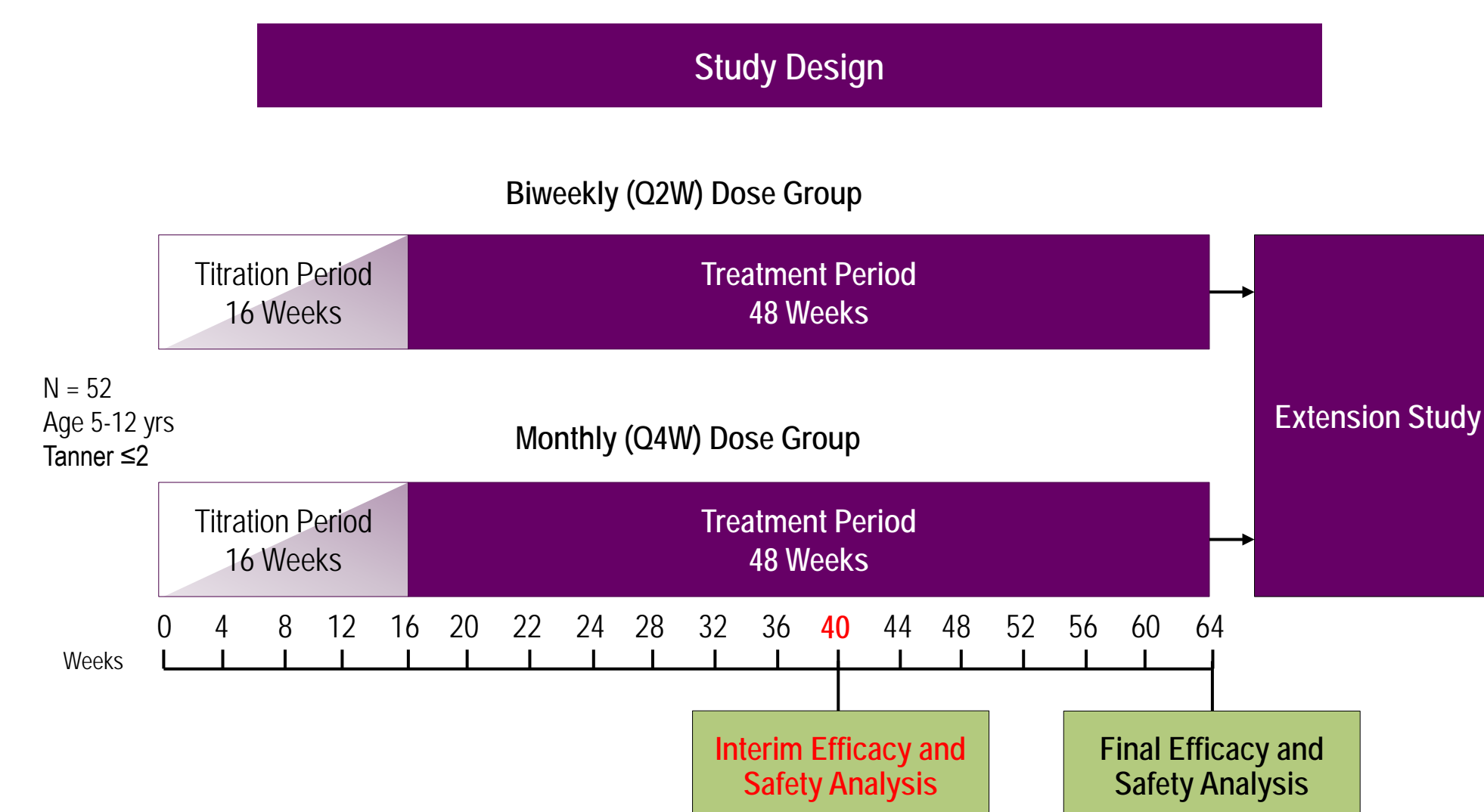
## DISCLOSURES

- This study was sponsored by Ultranex Pharmaceuticals, Inc.
- EI, TC, AL, AB, WH, RP, AvH, AP, MW: travel, consulting, and/or research funding from Ultranex and/or Alexion.
- CYC, AS, JSM: employees of Ultranex.
- Ting Chang (Ultranex) and Rebecca Lew (ProScribe) provided medical writing support.

## METHODS

- In our Phase 2 study, 52 XLH children (ages 5-12 years, Tanner  $\leq 2$ ) were randomized to receive KRN23 subcutaneously biweekly (Q2W) or monthly (Q4W).
- Serum phosphate (Pi) was measured biweekly.
- KRN23 dose was titrated (maximum 2 mg/kg) targeting age-appropriate serum Pi concentrations.
- In this interim analysis, data are presented for the first 36 enrolled subjects.

### Pediatric Phase 2 Study Design (UX023-CL201; ClinicalTrials.gov NCT02163577)

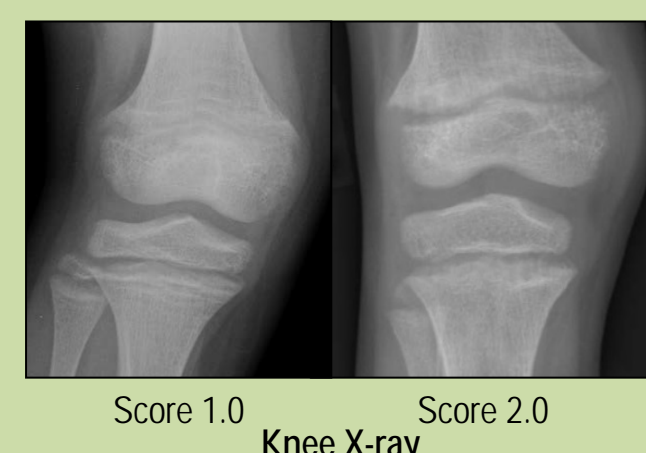


- Data available for 36 subjects through 40 weeks
  - Pre-specified subgroups based on baseline Total RSS
    - 18 subjects with Total RSS  $\geq 1.5$  (Higher RSS)
    - 18 subjects with Total RSS  $< 1.5$  (Lower RSS)
- Endpoints evaluated in this presentation
  - Six-Minute Walk Test (6MWT)
    - Distance walked in 6 minutes, corrected for age, height, and weight
  - Pediatric Orthopedic Society of North America-Pediatric Outcome Data Collection Instrument (POSNA-PODCI)
    - Assesses functional health outcomes in children with musculoskeletal conditions
    - Scores are normalized to a mean of 50 and a standard deviation (SD) of 10
- Key endpoints
  - Rickets
    - Thacher Rickets Severity Score (RSS)
    - Radiographic Global Impression of Change (RGI-C)
  - Pharmacodynamics
  - Safety

### Two Rickets Scoring Systems Utilized

#### Thacher Rickets Severity Score (RSS)

- Total 0-10: wrist (0-4) plus knee (0-6)
- Read centrally by an expert blinded to dose and patient



#### Radiographic Global Impression of Change (RGI-C)

- 7-point scale describing changes at wrist, knee, and leg during treatment
- X-rays read by 3 independent experts blinded to dose

|                  |                    |                   |           |                 |                     |                                   |
|------------------|--------------------|-------------------|-----------|-----------------|---------------------|-----------------------------------|
| -3               | -2                 | -1                | 0         | +1              | +2                  | +3                                |
| Severe Worsening | Moderate Worsening | Minimal Worsening | No Change | Minimal Healing | Substantial Healing | Complete or Near Complete Healing |

## RESULTS

- At study entry, 35 of the first 36 subjects enrolled had received oral phosphate/active vitamin D for a mean of 6.6 years.

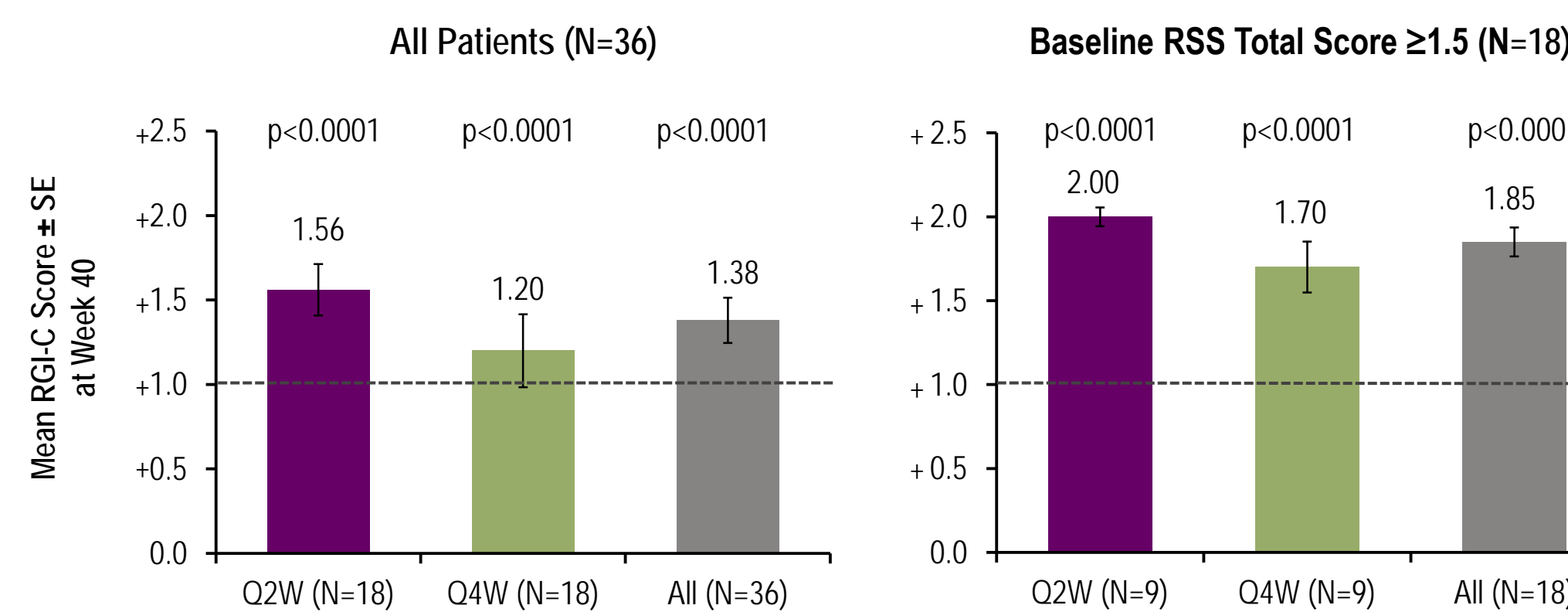
|  | Baseline Characteristics |                    |                        |
|--|--------------------------|--------------------|------------------------|
|  | KRN23 Q2W (N = 18)       | KRN23 Q4W (N = 18) | KRN23 Overall (N = 36) |
| Age, yrs   | 8.3 (1.6)                | 8.1 (2.1)          | 8.2 (1.8)              |
| Male   | 9 (50%)                  | 9 (50%)            | 18 (50%)               |
| White  | 16 (89%)                 | 16 (89%)           | 32 (89%)               |
| Weight, kg                                       | 31.5 (17.6, 47.2)        | 24.4 (14.7, 55.2)  | 28.8 (14.7, 55.2)      |
| Height Z score                                   | -1.6 (1.0)               | -2.2 (1.0)         | -1.9 (1.0)             |
| RSS total score                                  | 1.53 (1.05)              | 1.33 (1.02)        | 1.43 (1.02)            |
| Range  | 0, 3.5                   | 0, 3.0             | 0, 3.5                 |
| Received Prior Oral P / Active Vitamin D         | 17 (94%)                 | 18 (100%)          | 35 (97%)               |
| Duration of Prior Oral P / Active Vitamin D, yrs | 6.9 (1.9)                | 6.3 (3.1)          | 6.6 (2.6)              |

Values as mean (SD), median (min, max), or n (%). Q2W, biweekly; Q4W, monthly; P, phosphate; RSS, Thacher Rickets Severity Score; SD, standard deviation

### Rickets

- KRN23 significantly improved rickets at Week 40
- Subjects in the Q2W group with higher rickets severity score (RSS) at baseline had substantial healing of rickets (RGI-C score of +2.0) after 40 weeks of KRN23 treatment.

### Improvement in Rickets at Week 40

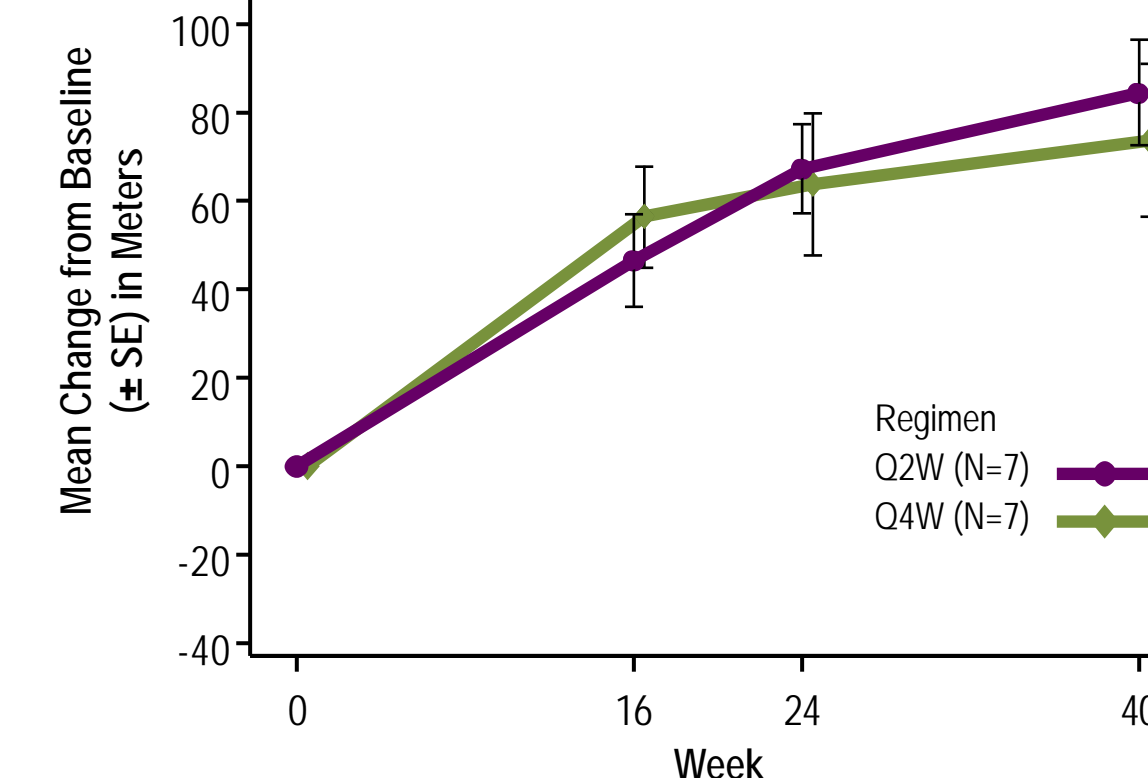


p value is based on one-sample t test  
RGI-C Scores: +1.0 = minimal healing; +2.0 = substantial healing; +3.0 = complete or near complete healing

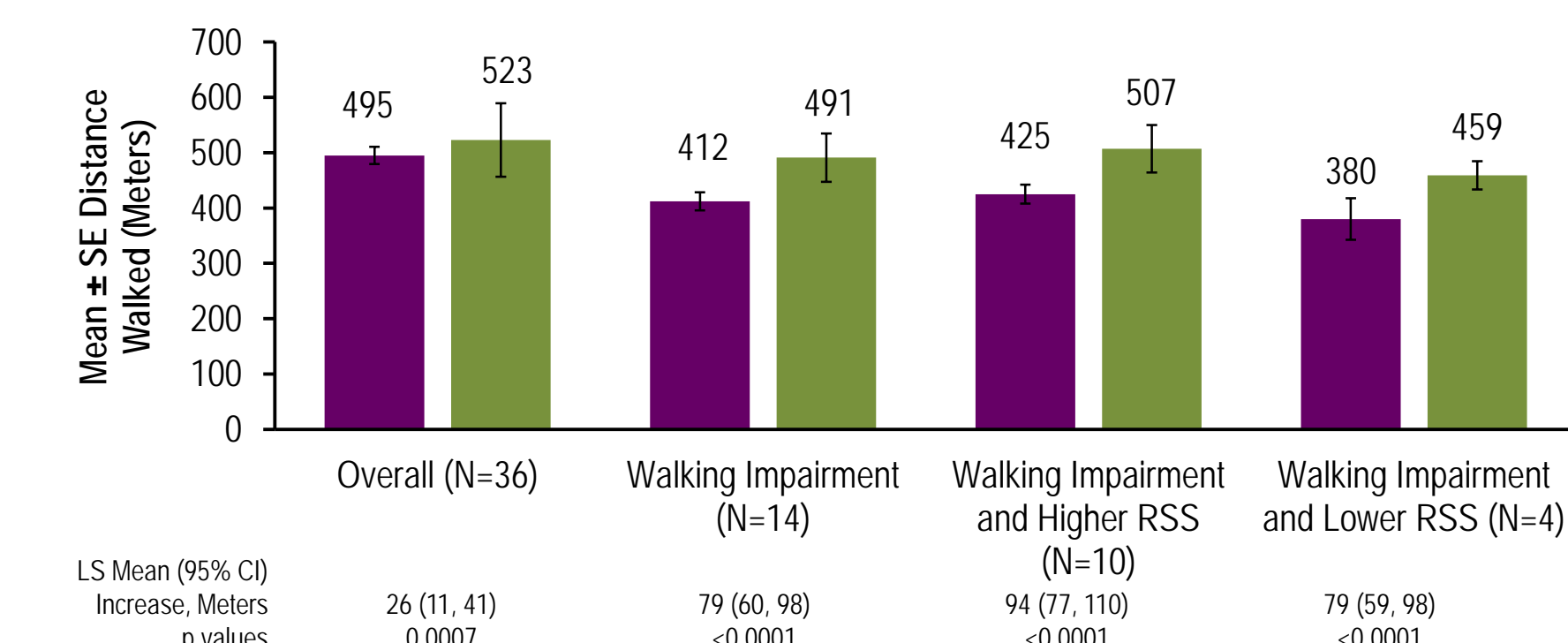
### 6MWT

#### 6MWT in Subjects With Impaired Walking Ability at Baseline (<80% Predicted)

- At baseline, 14 of the 36 (39%) subjects had walking impairment, defined as 6MWT distance <80% predicted for age
  - 10/14 had Higher rickets severity score (RSS) at baseline
  - 4/14 had Lower RSS at baseline
- At Week 40:
  - Subjects with walking impairment improved by 19% from baseline (Least Squares [LS] mean of 79 meters [p<0.0001])
  - Subjects with walking impairment and higher RSS improved by 22% from baseline (LS mean of 94 meters [p<0.0001])
  - Subjects with walking impairment and lower RSS improved 21% from baseline (LS mean of 79 meters [p<0.0001])



### Improvement in 6MWT at Week 40

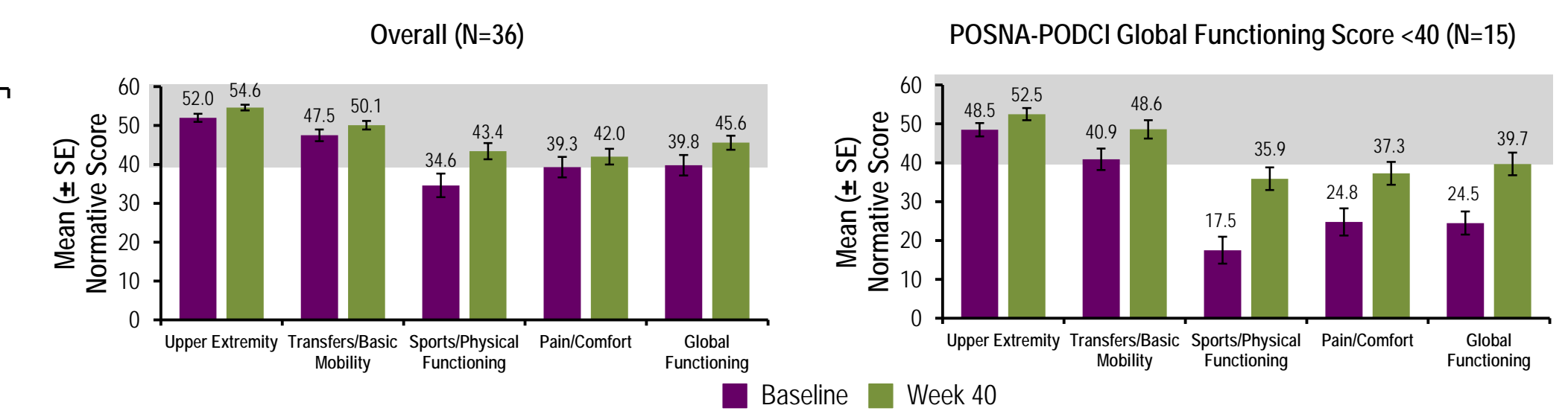


LS = least squares using the Generalized Estimating Equation

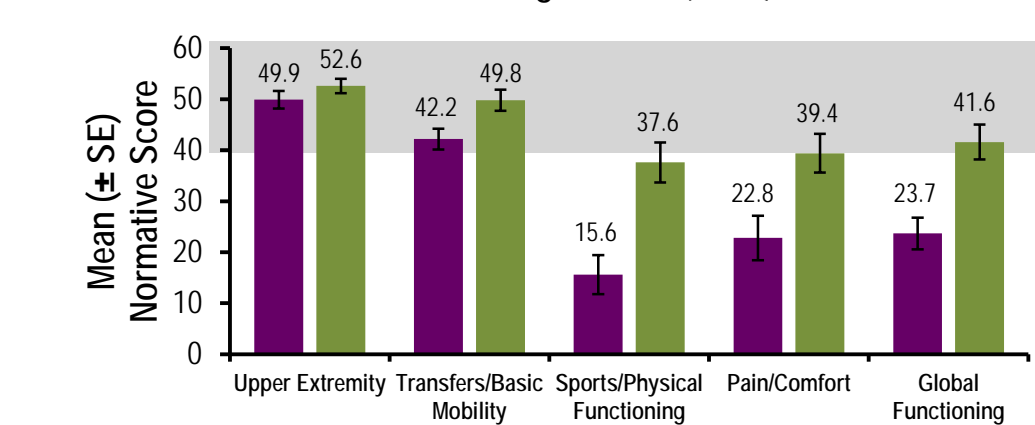
### POSNA-PODCI

- At baseline, 15 of the 36 (42%) subjects had substantial functional impairment, defined as the POSNA-PODCI Global Functioning score <40
  - 10/15 had Higher Rickets Severity Score (RSS) at baseline
  - 5/15 had Lower RSS at baseline
- The mean baseline POSNA-PODCI Global Functioning score among those with functional impairment at baseline was 24.5, or >2 standard deviations (SD) below the normal mean of 50 (1 SD = 10 points).
- Subjects' scores showed particular functional impairments in the Sports/Physical Functioning and Pain/Comfort domains (baseline means of 17.5 and 24.8, respectively).
- At Week 40:
  - Subjects with functional impairment had LS mean score increases of +15.3, +18.4, and +12.6 for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively (p < 0.0001 for all three domains)
  - Subjects with functional impairment and higher RSS had LS mean score increases of +17.9, +22.0, and +16.6 for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively (p < 0.0001 for all three domains)
  - Subjects with functional impairment and lower RSS had LS mean score increases of +10.2 (p < 0.05), +11.9 (p = 0.004), and +4.4 (p = 0.4) for Global Functioning, the Sports/Physical Functioning domain, and the Pain/Comfort domain, respectively

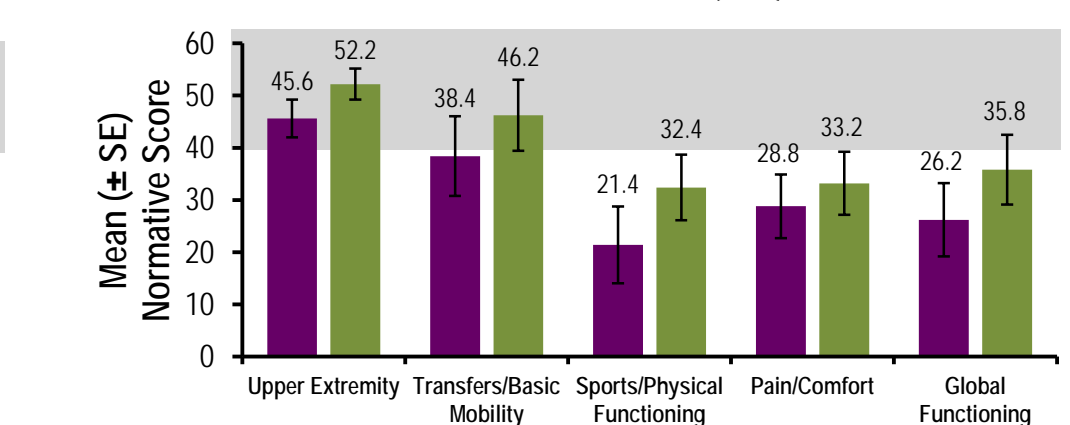
### Improvement in POSNA-PODCI



#### POSNA-PODCI Global Functioning Score <40 and Higher RSS (N=10)



#### POSNA-PODCI Global Functioning Score <40 and Lower RSS (N=5)



## CONCLUSIONS

- In this Phase 2 trial, baseline walking ability, pain, and function are impaired in a substantial number of children with XLH despite current treatment with oral phosphate and active vitamin D for a mean of 6.6 years.
- Treatment with KRN23 for 40 weeks improved walking distance and functional outcomes in patients with impairment at baseline regardless of baseline rickets score.
- KRN23 treatment also resulted in substantial healing of rickets in children with XLH.