Assessment of Quality of Life Data After Four Monthly Subcutaneous (SC) Doses of a Human Monoclonal Anti-FGF23 (Fibroblast Growth Factor 23) Antibody (KRN23) in Adults with X-linked Hypophosphatemia (XLH)

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Introduction

X-linked hypophosphatemia (XLH) is due to loss-of-function mutations in *PHEX*, which result in elevated circulating levels of fibroblast growth factor 23 (FGF23). Increased FGF23 limits renal tubular reabsorption of phosphate thereby reducing serum phosphorus (inorganic phosphate, Pi). Circulating 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] levels are low or inappropriately normal in relation to the hypophosphatemia. Progressive bowing, anteromedial rotational torsion of tibiae, and short stature represent the predominant skeletal outcomes in growing children (rickets). The mineralization defect (osteomalacia) may persist in adulthood leading to long-term complications in many patients (pseudofractures, dental abscesses, enthesopathy, osteophytes, and osteoarthritis). Current therapy (oral calcitriol and phosphate) aids mineralization by increasing phosphate intake and intestinal absorption; however, hypercalciuria, nephrocalcinosis, and hyperparathyroidism may occur.

Anti-FGF23-Antibody (KRN23)

KRN23 is a recombinant human IgG1 monoclonal antibody which binds to FGF23, blocking its biologic activity. Both intact and fragmented FGF23 polypeptides are immunoprecipitated with KRN23.In a *Phex*-deficient hypophosphatemic mouse model, FGF23 antibodies increased grip strength and spontaneous movement. These results suggest that the inhibition of excess FGF23 action not only ameliorates hypophosphatemia and impaired mineralization of bone in hypophosphatemic mice but also may have the potential to improve muscle weakness and daily activities of patients with FGF23-related hypophosphatemic rickets/osteomalacia. We undertook an open label Phase 1/2, dose-escalation study of 4 monthly SC doses of KRN23 in adults with XLH with a primary objective to assess efficacy and safety (**Peacock M., et al, oral session number: 0619**) and a secondary objective to evaluate pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity (**Zhang X., et al, oral session number: 0624**). We here report quality of life data following multiple-dose administrations of KRN23 to adult subjects with XLH.

Objectives

To evaluate the effects of KRN23 on health-related quality of life (HRQL) using two Patient Reported Outcome (PRO) instruments: general HRQL measured with the Medical Outcomes Study Short Form Health Survey version 2 (SF-36v2) and condition-related HRQL with the Western Ontario and McMaster Osteoarthritis Index (WOMAC).

Methods

- Up to 4 doses of KRN23 were given SC every 28 days to adults with XLH. Pre-dose Pi level guided KRN23 dose in a stepwise dose escalation algorithm. KRN23 doses were 0.05 to 0.1 to 0.3 to 0.6 mg/kg.
- The 36-question self-reported SF-36v2 evaluates general HRQL using 8 underlying scales (Table 1). The 8 scales were then used to compute Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.
- SF-36v2 and WOMAC were completed by the subjects at baseline (Day 0) and study endpoint (Day 120).

Table 1. SF-36v2 Scales

	Acronym	n[a]
Physical Functioning	PF	10
Role Limitations due to Physical Health	RP	4
Bodily Pain	BP	2
General Health Perceptions	GH	5
Vitality	VT	4
Social Functioning	SF	2
Role Limitations due to Emotional Problems	RE	3
Mental Health	MH	5

a: n = Number of questions combined into the scale score.

Table 2. WOMAC Scales

	Acronym	n[a]
Pain	None	5
Stiffness	None	2
Physical Functioning	None	17

a: n = Number of questions combined into the scale score.

- The 24-question self-reported WOMAC originally designed to evaluate the condition of the knee, hip, and other joints in patients with osteoarthritis has 3 scales (Table 2).
- Significance was set at P < 0.05 for the paired t-test. The multiplicity-adjusted *P*-values are labeled as P^m.

Demographics and Baseline Characteristics

- Twenty-eight patients were enrolled in the study and 26 patients completed the study.
- One patient withdrew from the study (pre-existing condition) after one dose, and one patient withdrew after three doses (injection site reaction).
- The enrolled population ranged in age from 19 to 66 (mean 41.9) years, approximately two-thirds were female, all but one were Caucasian (96.4%), mean body weight was 75.5 kg (range: 46.4 to 121.9 kg), and mean body mass index was 34.0 kg/m^2.
- Characteristics were similar in the completer population (*N*=26).
- Mean TmP/GFR and serum Pi were below the normal range. Mean 1,25$(OH)_2$D was within the normal range (Table 3).

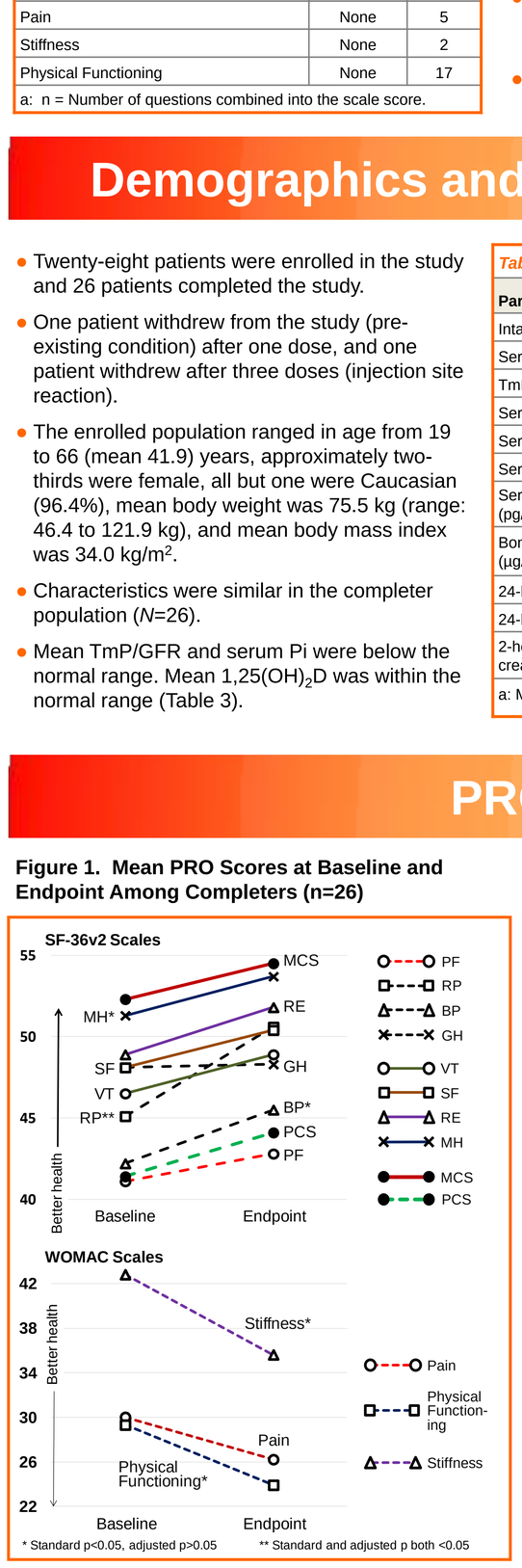
Table 3. Patient Baseline Disease Characteristics (N=28)

Paramaters	Mean ±SD (range)[a]	Reference Range
Intact FGF23 (pg/mL)[a]	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 parathyroid hormone (PTH) (pg/mL)[a]	74 (38, 143)	10–65
Bone alkaline phosphatase (BALP) (µg/L)	28.3±12.8 (8.2, 52.4)	M: 3.7–20.9 F: 2.9–22.6
24-hour urine calcium (mg/24 hour)[a]	67 (11, 253)	M: 50–300; F: 50–250
24-hour urine creatinine (g/24 hour)[a]	1.13 (0.54, 3.01)	0.63–2.50
2-hour calcium/creatinine ratio (mg/g creatinine)[a]	36 (7, 192)	M: 10–240; F: 10–320

a: Median (range) is reported for the data with a skewed normal distribution.

PRO Results

Figure 1. Mean PRO Scores at Baseline and Endpoint Among Completers (n=26)



KRN23 Dose

- All 26 subjects received an initial dose of 0.05 mg/kg. For dose 2, 25 (96.2%) escalated to 0.1 mg/kg, and 1 remained at 0.05 mg/kg. For dose 3, 24 (92.3%) escalated to 0.3 mg/kg, 1 continued at 0.05 mg/kg and 1 at 0.1 mg/kg. For dose 4, 15 (60%) escalated to 0.6 mg/kg, 9 (36%) continued at 0.3 mg/kg, 1 increased from 0.05 to 0.1 mg/kg. No subject required dose reduction

Response to PRO Questions

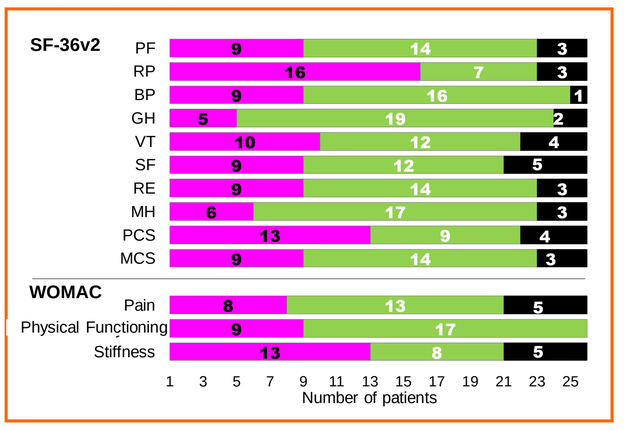
- The two PROs used in this study are scaled in opposite directions. A higher score indicates better health with SF-36v2, whereas a higher score indicates worse health in WOMAC.
- At the end of KRN23 treatment, mean scores for all SF-36v2 domains increased and those for WOMAC decreased, suggest improvement in health status for all domains of both PRO scales.
- Five of these PRO scores were significant at endpoint: RP, BP, and PCS for SF-36v2 and Physical Functioning and Stiffness for WOMAC.
- Only RP retained significance after correction for multiplicity. (Figure 1).

PRO Results (Continued)

Responder Analysis

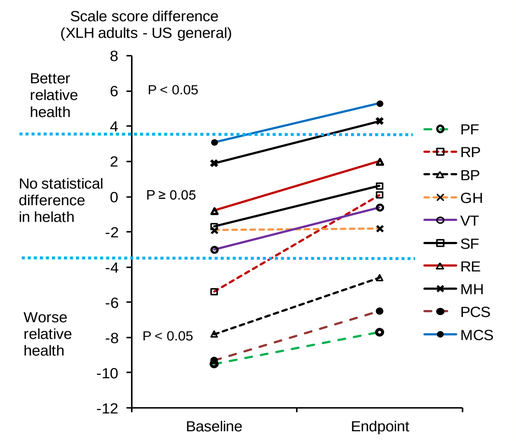
- Figure 2 displays the number of patients who were classified as “better”, “same”, or “worse” according to the established MIC (Minimally Important Change) for each PRO scale.
- For each scale, at least some of the patients were qualified as “better”, (range from five cases [19%] for GH to 16 cases [62%] for RP).
- For nearly all the scales, a few patients did “worse” (one case [4%] for BP to five cases [19%] for SF, pain, and stiffness).
- The WOMAC Physical Functioning scale was the only one to register no “worse” cases.
- For many scales, the ratio of “better” to “worse” may suggest a treatment benefit. The SF-36v2 PF scale, for example, has a 3:1 ratio of “better” patients to "worse“.
- The WOMAC Physical Functioning categorized 9 patients as “better” and none as “worse,” whereas the SF-36v2 PF, with its higher level of functioning, also categorized 9 patients as “better” but also identified 3 cases as “worse”. This suggests that in the XLH population, the items of the WOMAC scale are better targeted to the level of functioning of XLH patients, where treatment appeared to have its greatest impact.

Figure 2. Number of Patients Better, Same or Worse by Endpoint (n=26)



Disease Burden Analysis

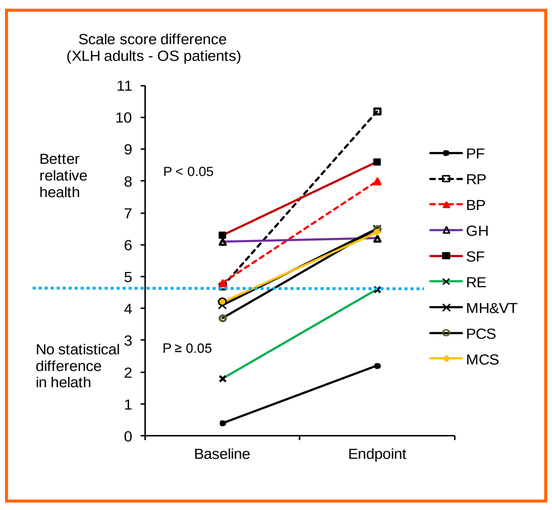
Figure 3. Burden of Disease Compared to a General Population in United States (US)



Compare with Asthma Population

- Figure 4 shows mean SF-36v2 scale scores for XLH patients at baseline and endpoint relative to patients with asthma (N=343).
- Results mirror those from the general US population, although at a generally higher level of magnitude. Although asthma patients are on the whole less healthy than the general population, their condition does not resemble XLH.
- Their burden relative to XLH follows the same pattern as that of the US population.
- Results support the discriminant validity of SF-36v2 used in an XLH population.

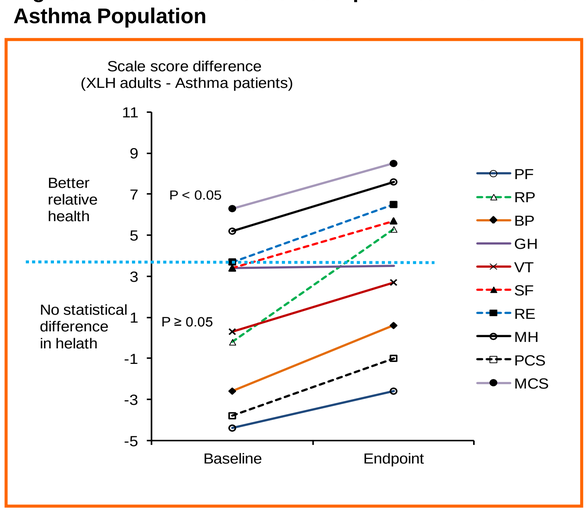
Figure 5. Burden of Disease Compared to a General Osteoarthritis Population



Comparison with General US Population

- This series of analyses compared the SF-36v2 scores of the completer XLH patient population to an age- and gender-matched general US population (N=4,040). (Figure 3)
- At baseline, mean BP (P<0.0001), PF (P<0.0001), RP (P=0.0054; Pm=0.0162), and PCS (P<0.0001) scores were far below the general US population norm, while all other scales did not show a statistically significant difference.
- Changes in disease burden from baseline to endpoint with KRN23 treatment were positive for all SF-36v2 domains, suggesting alleviation of disease burden over time.
- At endpoint, the MH (P=0.0253) and MCS (P=0.006) scale became significantly higher than the US norm; RP (P=0.9457; Pm=0.9457) became indistinguishable from the norm; mean PCS (P=0.0004), BP (P=0.0102), and PF (P=0.0001) remained significantly below the norm; and the other domains remained without statistically significant difference from the norm.

Figure 4. Burden of Disease Compared to a General Asthma Population



Compare with Osteoarthritis Population

- This series of analyses compared the SF-36v2 scores of the completer XLH subject population to an age- and gender-matched osteoarthritis population (N=583). (Figure 5).
- At baseline, the disease burden for the XLH patients when compared to the general US population (Figure 3) showed a different profile relative to that for patients with osteoarthritis.
- GH (P=0.0093), BP (P=0.0327), and SF (P=0.0136) scores for XLH patients were significantly higher than those of the osteoarthritis population at baseline, indicating better health; all other scores did not show statistically significant differences.
- All mean SF-36v2 scale scores for XLH patients were increased (improved) relative to those for osteoarthritis patients at end point, showing significance for all scales except PF and RE: RP (P<0.0001; P^m<0.0001), BP (P=0.0003), GH (P=0.0044), VT (P=0.0058), SF (P=0.0002), MH (P=0.0081), PCS (P=0.0072), and MCS (P=0.015).

Summary

- All 10 SF-36v2 scales showed higher mean scores at the end of treatment compared to baseline, with statistically significant improvements observed for 3 measures (RP, BP, and PCS). When corrected for multiplicity, RP remained statistically significant.
- All 3 WOMAC scales showed lower mean scores (indicating HRQL improvement) at the end of treatment compared to baseline, with statistically significant improvements observed for 2 measures (Physical Functioning and Stiffness).
- SF-36v2 and WOMAC appear to be appropriate measures of HRQL in XLH patients and therefore applicable for use in future clinical trials with XLH patients.
- Results should be interpreted cautiously due to the open-label study design without placebo or active comparator control.
- In conclusion, treatment with KRN23 for 4 months resulted in significantly improved patient physical functioning using SF36v2 and WOMAC as HRQL instruments.

Acknowledgements

We are grateful to the dedicated patients who participated in the study, sub-investigators, clinical study coordinators, and research nursing staff at the 6 study sites. We thank Dr. Kate Miller for the statistical analysis (Optum/QualityMetric. 24 Albion Road, Building 400, Lincoln, RI, USA), and Ms. Dana Maslowski for support of poster preparation (Kyowa Hakko Kirin Pharma, Inc.)