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Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia

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ABSTRACT

X-linked hypophosphatemia (XLH) is characterized by lower extremity deformities that lead to bone and/or joint pain that result from decreased renal tubular reabsorption leading to hypophosphatemia caused by elevated levels of fibroblast growth factor 23 (FGF23).

Objective: Validate the use of SF-36v2 Health Survey (SF-36v2) and the Western Ontario and McMaster Osteoarthritis Index (WOMAC) to measure previously unstudied health-related quality of life (HRQoL) in XLH patients and determine the change in HRQoL before and after treatment with KRN23, a human monoclonal anti-FGF23 antibody.

Methods: Twenty-eight adult outpatients with XLH received up to four doses of KRN23 administered subcutaneously every 28 days. General HRQoL was measured with the SF-36v2 and condition-related HRQoL with the WOMAC at baseline and study endpoint as a secondary outcome of a Phase 1/2, open-label, multicenter, dose-escalation trial.

Results: Testing for scale discriminant validity and convergent-divergent validity supported the use of these scales in the assessment of HRQoL in XLH. Both instruments indicated impairment of physical function at baseline with all mean scores showing a trend to improved health at study endpoint compared to baseline. When corrected for multiple comparisons, the score for Role Limitations due to physical health on the SF-36v2 which measures the patient's perception of their own chronic functional impairments due to poor physical health remained significantly improved ($P < 0.05$), increasing to the mean score of US adults. For the WOMAC, Physical Functioning and Stiffness scores were significantly improved ($P < 0.05$).

Conclusion: KRN23 administration was associated with significantly improved patient perception of their Physical Functioning and Stiffness due to their disease. This study demonstrates that the SF-36v2 and WOMAC are valid tools for assessing HRQoL in XLH.

1. Introduction

X-linked hypophosphatemia (XLH; MIM307800) is a dominant hereditary bone disorder resulting from *PHEX* mutations and characterized by elevated levels of fibroblast growth factor 23 (FGF23) leading to a dual defect in phosphate metabolism with consequent renal phosphate wasting and impaired renal production of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (Imel & Econs, 2005; Liu & Quarles, 2007; Carpenter et al., 2011; Lee & Imel, 2013). It is the most common form of heritable rickets, usually presenting with bowing deformities of the legs in childhood (Holm et al., 2003). Adults suffer from bone pain and osteomalacia, increased risk of skeletal insufficiency fractures, joint abnormalities and pain, enthesopathy, osteoarthritis, and dental abscesses (Reid et al., 1989; Tenenhouse & Econs, 2013). Formal assessments of how this

Abbreviations: PRO, patient reported outcomes; HRQoL, health-related quality of life; WOMAC, Western Ontario and McMaster Osteoarthritis Index; MIC, Minimally Important Change.

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symptomatology affects patients' quality of life have not been previously reported. It is also not known whether treatment influences quality of life.

The main therapeutic option, oral calcitriol plus phosphate supplements, offers limited efficacy, is inconvenient to administer, and requires regular monitoring for potential toxicities (Carpenter et al., 2011; Costa et al., 1981). KRN23 is a recombinant human IgG1 monoclonal antibody directed at FGF23. In a recent Phase 1 and Phase 1/2, dose-escalation study of repeated subcutaneous doses of KRN23 in adults with XLH, we showed that KRN23 effectively increased the ratio of renal tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR), and serum inorganic phosphorus (Pi) and $1.25(OH)_2D$ concentrations (Carpenter et al., 2014; Imel et al., 2015). As a secondary objective of the dose escalation study, we sought to assess the psychometric validity of formal health-related quality of life (HRQoL) testing utilizing two well-established Patient Reported Outcome (PRO) instruments: general HRQoL was measured with the Medical Outcomes Study Short Form Health Survey version 2 (SF-36v2) (Maruish, 2011) and condition-related HRQoL with the Western Ontario and McMaster Osteoarthritis Index (WOMAC) (Bellamy et al., 1988). In addition, we also sought to evaluate the effects of KRN23 on HRQoL.

2. Methods

2.1. Overall study design

The primary Phase 1/2 study was an open-label, dose-escalation trial of KRN23 in adults age ≥ 18 years with a documented clinical diagnosis of XLH conducted at six study centers. The primary results of this study have been previously published with the full methods found within that publication (Imel et al., 2015). Briefly, inclusion criteria were: intact serum FGF23 level > 30 pg/ml, TmP/GFR < 2.0 mg/dl, estimated glomerular filtration rate ≥ 60 ml/min, and serum calcium < 10.8 mg/dl. Exclusion criteria included pregnancy or lactation, major surgery, and receipt of live vaccine or monoclonal antibody products within 3 months before screening. Vitamin D (and its analogues), calcium supplements, phosphate supplements and aluminum hydroxide were not permitted within 10 days before screening nor throughout the study. The screening occurred within 30 days prior to baseline dosing day (Day 0). Patients received KRN23 0.05 mg/kg subcutaneously at baseline (Day 0) followed by step-wise dose escalation (0.1 to 0.3 to 0.6 mg/kg subcutaneously) every 4 weeks based on serum Pi levels for a total of four doses.

The clinical study was conducted according to the principles of the Declaration of Helsinki and with Institutional Review Board approval at each study center. Written informed consent was obtained from the participants prior to study inclusion. The study was conducted between 31 October 2011 and 10 April 2013, and was registered at ClinicalTrials.gov (#NCT01340482).

2.2. PRO measures

SF-36v2 (Maruish, 2011) and WOMAC (Bellamy et al., 1988; Bellamy, 2009) were completed by the patients on the day of initial KRN23 dosing (baseline, Day 0) and at study endpoint (Day 120) which occurred 36 days after the last dose of KRN23. The 36-question self-reported SF-36v2 measures eight concepts to evaluate general HRQoL: Physical Functioning, Role Limitations due to Physical Health, Bodily Pain, General Health Perceptions, Vitality, Social Functioning, Role Limitations due to Emotional Problems, and Mental Health. The Role Limitations scales are construct-based measurements that are meant to measure more abstract properties. These measures evaluate the patient's perception of their own chronic functional limitations due either to poor physical health (Role Limitations due to physical health) or poor emotional health (Role Limitations due to emotional health). Norm-based standardized scores are calculated, with scores below 50 being below the mean for the US population. The eight scales are then used to compute Physical Component Summary and Mental Component Summary scores in the same manner as the individual domains to produce standardized scores relative to the general population. The SF-36v2 is widely accepted as a valid measure of disease burden and has been frequently applied across multiple diseases.

The 24-question self-reported WOMAC was originally designed to evaluate the condition of the knee, hip, and other joints in patients with osteoarthritis using three scales: Pain, Stiffness, and Physical Functioning. This study used WOMAC version LK3.1 (Bellamy, 2004) in which responses to all questions are measured on a 5-point Likert scale: none (0), mild (1), moderate (2), severe (3) and extreme (4). Scoring is a simple sum, so Pain scores range from 0 to 20, Stiffness from 0 to 8, and Physical Functioning from 0 to 68, with higher numbers indicating worse condition. Scores are normalized to a 0–100 metric scale for Pain Scores (20 points is 100%), Stiffness (8 points is 100%) and Physical functioning (68 points is 100%), representing the percent of the maximum score. Unlike SF-36v2 scores, WOMAC scores are not norm-based, so they cannot be interpreted directly as a difference from a population mean. However, mean WOMAC scores from a large population-based sample of healthy adults have been published (Bellamy et al., 2011) giving benchmark values for comparison. These are as follows (mean ± SD): Pain 14.1 ± 19.7, Stiffness 20.1 ± 23.6 and Physical Functioning 15.4 ± 20.2.

2.3. PRO analyses

The aims of the PRO analyses were to describe baseline quality of life in XLH, interpret changes in PRO scales over time, and validate PRO analyses implementation in XLH patients. As described below, disease burden was assessed by comparing the scores to those of a cohort of patients with a disease having several similarities to XLH (osteoarthritis) while validation analysis was performed by comparing the scores to those of a cohort of patients affected with a disease having few similarities (asthma). Both PRO instruments have established algorithms for estimating scores with missing data and were used in these analyses. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

2.4. Descriptive and interpretative analyses

Patient demographics and their response frequencies to all individual PRO questions were analyzed descriptively. The paired *t*-test statistical analysis was then applied to determine whether there were any significant changes in mean PRO scales with treatment.

Significance was set at $P < 0.05$. An adjustment for multiplicity was made to control the family-wise error rate below a given α of 0.05. To adjust for multiplicity, a parallel gatekeeping approach was applied using Hommel's adjustment for the non-primary hypotheses (Hommel, 1988). The inclusion of PROs as secondary endpoints was exploratory. For this reason, both the standard *P*-values of tests (labeled *P*) as well as the multiplicity-adjusted *P*-values (labeled P^m) are presented.

Interpretative disease burden analyses were then conducted for SF-36v2 results for the XLH population compared to two age- and sex-matched SF-36v2 comparator datasets (data on file at Optum/QualityMetric, Lincoln, RI): the general United States population ($N = 4040$) and a subsample with osteoarthritis ($N = 583$), who were unselected with respect to their treatment of osteoarthritis. These samples were chosen so that disease burden analyses could be conducted for XLH relative to the population norm and to a known clinical disease that has some symptoms in common with XLH. The change in values was compared to the Minimally Important Change (MIC). MIC is the smallest change over time in an individual patient's score that represents a clinically significant change in their health status. Using a distributional approach with a U.S. general population sample, MIC scores have been established for the SF-36v2 as: Physical Functioning, 3.5; Role Limitations due to Physical Health, 3.2; Bodily Pain, 4.5; General

Health Perceptions, 5.7; Vitality, 5.5; Social Functioning, 5.0; Role Limitations due to Emotional Health, 3.8; Mental Health, 5.5; Physical Component Score, 3.1; and Mental Component Score, 3.8 (Maruish, 2011). The User's Manual for the WOMAC lists MICs as 9.7 for Pain, 10.0 for Stiffness, and 9.3 for Physical Functioning (Bellamy, 2009).

2.5. Validation analyses

Scale discriminant validity was determined by disease burden analysis for SF-36v2 results at baseline and endpoint compared to a representative reference sample (patients with asthma), for which an age- and sex-matched SF-36v2 comparator dataset is available and presents a medical condition that is clinically different from XLH. Convergent-divergent validity was assessed by calculating correlation coefficients between conceptually-related pairs from the SF-36v2 and WOMAC scales at baseline and endpoint.

3. Results

3.1. Patient demographic and baseline characteristics

PRO assessments were undertaken at baseline in the 28 patients who were enrolled in the study and in the 26 patients who completed the study. Two patients withdrew from the study due to a pre-existing condition and injection site urticaria, respectively. For the sample completing the study ($N = 26$), mean age was 41.9 (SD 14.1; range, 19–66), 17 (65.4%) were female, all but one was Caucasian (25, 96.2%), and mean bodyweight was 77.3 kg (SD 19.9, range 46.4 kg–121.9 kg)

The median duration between stopping therapy with oral calcitriol plus phosphate and initial KRN23 dosing was 44 days (range, 25 days to 50.4 years).

At baseline, median intact FGF23 measured using a validated ELISA method was 95 pg/ml (range, 36–3520). Mean serum Pi was 1.9 mg/dl (SD 0.3) and TmP/GFR was 1.6 mg/dl (SD 0.4), which were below the normal reference ranges (2.5–4.3 mg/dl and 2.5–4.2 mg/dl, respectively). Mean $1,25(OH)_2D$, 25-hydroxyvitamin D, serum calcium, parathyroid hormone, bone alkaline phosphatase, 24-hour urine calcium, 24-hour creatinine and fasting 2-hour urine calcium/creatinine ratio were within normal ranges.

3.2. Dose and exposure

All participants received the initial KRN23 dose of 0.05 mg/kg. For dose 2, 26 (96.3%) escalated to 0.1 mg/kg, and one remained at 0.05 mg/kg, and one withdrew. For dose 3, 25 (92.6%) escalated to 0.3 mg/kg, one continued at 0.05 mg/kg and one at 0.1 mg/kg. For dose 4, 16 (61.5%) escalated to 0.6 mg/kg, eight continued at 0.3 mg/kg, one increased from 0.05 to 0.1 mg/kg, one from 0.1 to 0.3 mg/kg, and one withdrew. No patient required dose delay or reduction.

3.3. Responses to PRO questions

For the SF-36v2, where lower scores indicate worse functioning, the subjects rated all physical scales at baseline below those of the general population. Only mental health and mental composite score were higher than the mean for the U.S. population (Table 1). When evaluated for significance, mean Bodily Pain ($P < 0.0001$), Physical Functioning ($P < 0.0001$), Role Limitations due to Physical Health ($P = 0.0054$; $P^m = 0.0162$), and Physical Component Score ($P < 0.0001$) scores were far below the general U.S. population norm, while all other scales did not show a statistically significant difference. Likewise on the WOMAC, where higher scores indicate worse perceived functioning, all scales were above the established norms (Table 1).

At endpoint, mean scores for all SF-36v2 scales increased and those for WOMAC decreased (Table 1) from baseline. At endpoint, the mean Mental Health ($P = 0.03$) and Mental Component Score ($P = 0.009$) scales became significantly higher than the U.S. norm; mean Role Limitations due to Physical Health ($P = 0.95$; $P^m = 0.95$) became normal; mean Physical Component Score ($P = 0.0004$), Bodily Pain ($P = 0.01$), and Physical Functioning ($P = 0.0001$) remained significantly lower than the norm; and the other scales (Role Limitations due to Emotional Health, Social Functioning, Vitality and General Health) remained normal. Only Role Limitations due to Physical Health from the SF-36v2 retained significance ($P^m = 0.02$) after correction for multiplicity (Table 1). Additionally, Role Limitations due to Physical Health crossed the established threshold for MIC, which represents the smallest increment that represents a clinically significant change in health status

Table 1
Change in mean PRO scores and significance over time in the completer population ($N = 26$).

PRO instrument	Scale	Mean ± SD score		Change in mean*	Statistics	
		Baseline	Endpoint		P	P^m
SF-36v2	PF	41.1 ± 10.2	42.8 ± 10.4	1.77	0.1264	1.0000
	RP	45.1 ± 9.9	50.6 ± 7.8	5.53	0.0012	0.0198
	BP	42.2 ± 9.1	45.5 ± 9.1	3.27	0.0287	0.2209
	GH	48.1 ± 9.5	48.3 ± 8.5	0.17	0.8820	1.0000
	VT	46.5 ± 10.9	48.9 ± 9.6	2.40	0.1030	1.0000
	SF	48.1 ± 10.3	50.4 ± 8.8	2.31	0.1554	1.0000
	RE	48.9 ± 9.6	51.8 ± 8.8	2.81	0.0718	1.0000
	MH	51.3 ± 8.2	53.7 ± 9.8	2.42	0.0509	0.8489
	PCS	41.4 ± 10.3	44.1 ± 9.4	2.75	0.0426	0.5328
	MCS	52.3 ± 10.3	54.5 ± 10.2	2.17	0.1542	1.0000
WOMAC	Pain	30.0 ± 18.8	26.2 ± 19.7	−3.8	0.2182	1.0000
	Physical Functioning	29.3 ± 21.3	23.9 ± 17.9	−5.4	0.0077	0.0968
	Stiffness	42.8 ± 20.9	35.6 ± 19.5	−7.2	0.0405	0.5064

BP, Bodily Pain; GH, General Health Perceptions; MH, Mental Health; MCS, Mental Component Summary; P, standard P-value; P^m, multiplicity-adjusted P-value; PCS, Physical Component Summary; PF, Physical Functioning; PRO, Patient Reported Outcome; RE, Role Limitations due to Emotional Problems; RP, Role of Limitations due to Physical Health; SF, Social Functioning; SF-36v2, Medical Outcomes Study Short Form Health Survey, version 2; VT, Vitality; WOMAC, Western Ontario and McMaster Osteoarthritis Index.

* Positive change indicates improved health on SF-36v2 scale and negative change indicates improved health on WOMAC scale.

3.4. 3.3 disease burden analyses

At baseline, disease burden for the XLH patients was different from patients with osteoarthritis (Fig. 1). General Health ($P = 0.009$), Bodily Pain ($P = 0.03$), and Social Functioning ($P = 0.01$) scores for XLH patients were significantly higher than those of the osteoarthritis sample at baseline, indicating better health in the XLH group, and all other scores were no different. At endpoint, all mean SF-23v2 scale scores for XLH patients except Physical Functioning and Role Limitations due to Emotional Health were improved relative to the baseline osteoarthritis scores: Role Limitations due to Physical Health ($P < 0.0001$; $P^m < 0.0001$), Bodily Pain ($P = 0.0003$), General Health ($P = 0.004$), Vitality ($P = 0.006$), Social Functioning ($P = 0.0002$), Mental Health ($P = 0.008$), Physical Component Score ($P = 0.007$), and Mental Component Score ($P = 0.01$).

3.5. Validation analyses

For scale discriminant validity of the use of SF-36v2, the XLH scores were compared to those of a population with asthma ($N = 343$, data on file at Optum/QualityMetric). Fig. 2 shows the difference between mean SF-36v2 scale scores for XLH patients and the means for asthma patients. For the SF-36v2, the subjects rated all scales at or above those of the asthma patients at baseline.

Convergent-divergent validity was assessed from correlations between SF-36v2 and WOMAC scales for all PRO measurements at baseline ($N = 28$) and endpoint ($N = 26$). The correlation coefficient

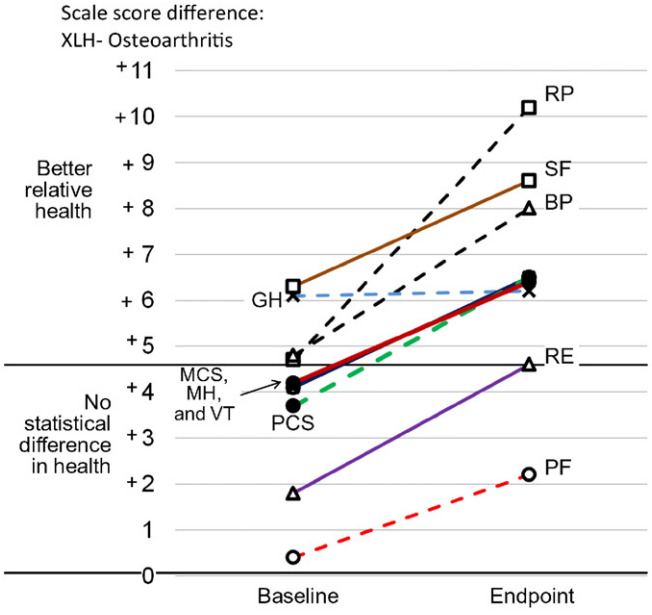

Fig. 1. Mean scale score difference between XLH patients and an age- and sex-matched osteoarthritis sample at baseline and endpoint (Day 120) on SF-36v2 scales. Horizontal dotted line shows threshold for statistically significant difference ($P < 0.05$, better relative health above upper horizontal dotted line and worse relative health below lower horizontal dotted line) or no significant difference ($P > 0.05$, between the two horizontal dotted lines) of scale scores between the trial population and osteoarthritis patients. Abbreviations: BP, Bodily Pain; GH, General Health Perceptions; MH, Mental Health; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Limitations due to Emotional Problems; RP, role of limitations due to Physical Health; SF, Social Functioning; VT, Vitality.

between conceptually-related pairs of scales was high: Bodily Pain and Pain (−0.79) and Physical Functioning from the SF-36v2 and Physical Functioning from the WOMAC (−0.81) were highly correlated (the negative sign reflects the opposing direction of the two PRO instrument scales). All other correlations were smaller, although some were nearly as high, e.g., Bodily Pain and Physical Functioning (−0.76), Physical Functioning and Pain (−0.73). Other less conceptually related scales, such as Mental Health and Stiffness, were far less correlated (−0.07).

4. Discussion

It has long been recognized that patients with XLH report muscle weakness and bone pain (Reid et al., 1989; Nunnally, 1978; Sullivan et al., 1992; Bergwitz et al., 2006; Schott & Wills, 1976). It has been assumed that patients with XLH have an impaired quality of life due to bone pain, fractures, enthesopathies, osteoarthritis, joint pain and dental abscesses; however, HRQoL has not been systematically evaluated in this disease. With an improving understanding of the disease pathophysiology and particularly with new treatments under development, it is important to establish methods to assess HRQoL in XLH. In this study, the use of the SF-36v2 and WOMAC as instruments for PRO analysis in adults with XLH was validated before and after the intervention with KRN23, a drug developed to block FGF23 action.

Both PRO instruments (SF-36v2 and WOMAC) appear to be appropriate and valid measures of HRQoL in XLH patients. SF-36v2 was selected as a candidate PRO instrument as it has been extensively used to evaluate general HRQoL across a broad range of diseases and clinical conditions. WOMAC, however, was specifically developed to measure HRQoL in patients with osteoarthritis (Bellamy, 2002), but has also been used in other painful musculoskeletal disorders such as back pain, rheumatoid arthritis, and fibromyalgia (Wolfe, 1999). Given the major symptom overlap between osteoarthritis and XLH, it was hypothesized that WOMAC would also be applicable as a PRO instrument in adults with XLH for HRQoL assessment.

Using these instruments, we demonstrate the significant burden of XLH on HRQoL. Compared to the general US population, the XLH trial patients showed lower physical HRQoL with deficits in baseline Bodily Pain, Physical Functioning, Role Limitations due to Physical Health, and Physical Component Score scales, and normal to high levels of mental HRQoL (Mental Health and Mental Component Score) of the SF-36v2 instrument.

Additionally, using the two PRO instruments (SF-36v2 and WOMAC), we show HRQoL improved in patients with XLH after four months of KRN23 treatment. At the end of the study, the Role Limitations due to Physical Health deficit was eliminated; Physical Component Score, Bodily Pain, and Physical Functioning deficits were lessened but remained below the US norm; Mental Health and Mental Component Score became higher than the norm; and other scales showed increased scores but were not different from the norm. In particular the area with the most significant change, the Role Limitations due to Physical Health concept scale represents the patient's perception of their own chronic functional physical limitations due to poor health with this scale felt to be one of the best measures to detect the impact of interventions that affect physical health (Ware & Kosinski, 2001). Importantly, the improvement in Role Limitations due to Physical Health was greater than the minimally significant change for this parameter following the therapy.

The validation analysis, using an asthma population for the comparator group, showed expected associations with the pattern of change observed in our comparison to the general US population. In that the asthma population is a subset of the general U.S. population (with at least one medical condition), this overall pattern is expected, and supports the discriminant validity of SF-36v2 used in an XLH population.

It has recently been demonstrated that lower limb muscle density, and peak force and power are significantly reduced in XLH patients (Veilleux et al., 2012; Veilleux et al., 2013), with depletion of ATP

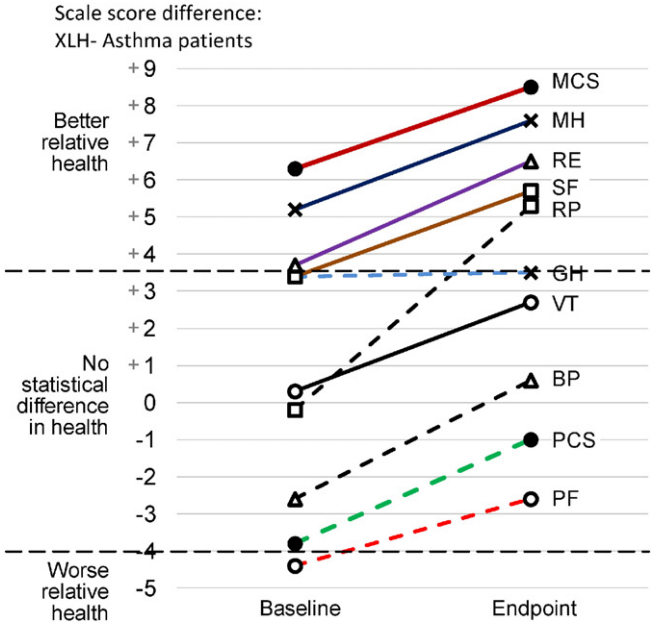

Fig. 2. Mean scale score difference between XLH patients and an age- and sex-matched asthma population at baseline and endpoint (Day 120) on SF-36v2 scales. Horizontal dotted lines show thresholds for statistically significant difference ($P < 0.05$ with better relative health above upper horizontal line and worse relative health below lower horizontal dotted line) or no significant difference ($P > 0.05$, between the two dotted horizontal lines) of scale scores between the trial population and asthma patients. Abbreviations: BP, Bodily Pain; GH, general health perceptions; MH, Mental Health; MCS, Mental Component Summary; PCS, Physical Component Summary; PF, Physical Functioning; RE, Role Limitations due to Emotional Problems; RP, role of limitations due to Physical Health; SF, Social Functioning, VT, Vitality.

(Knochel, 1982; Land et al., 1993) and phosphodiesters (Ambühl et al., 1999) being proposed as mechanism for muscle weakness associated with chronic hypophosphatemia. It could be speculated that increased muscle strength as noted by Role Limitations due to Physical Health ($P^m = 0.0198$) might contribute to the improved HRQoL observed during the administration of KRN23 among XLH patients in the current study.

The major strength of our study is that to our knowledge, this is the first time HRQoL has been formally evaluated in XLH patients. In addition, we validated two readily available instruments that can be used by others for evaluation of subjects with XLH. There are some limitations to our study. One consideration when interpreting these HRQoL results is that the patients only received four KRN23 doses. Furthermore, therapy was titrated from a relatively low starting dose (0.05 mg/kg) to a maximum of 0.6 mg/kg. Thus, potentially sub-therapeutic doses were administered for the initial portions of a relatively short overall study duration which may have affected the ability to detect significant improvement for domains apart from Role Limitations due to Physical Health. Furthermore, the results should also be interpreted cautiously due to small sample size ($N = 26$) and the open-label study design.

5. Conclusion

In conclusion, SF-36v2 and WOMAC were validated for use in XLH. The instruments show decreased HRQoL scores in XLH patients, and significant improvement in patient perception of their Physical Functioning following four doses of KRN23 given every 28 days. These PRO instruments (SF-36v2 and WOMAC) should provide a valuable addition to clinical, biochemical, and radiologic criteria in evaluating new treatment options in adults with XLH.

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Conflict of interest

TOC, MDR, EAI, TJW, KI, AAP, FHG, and MP received research grant funds from Kyowa Hakko Kirin Pharma, Inc. during the conduct of the study. XZ, MK, TI, MV, and JH are employed by Kyowa Hakko Kirin Pharma, Inc.

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