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Gathering 10 years of real-world FGF23-related hypophosphatemic rickets and osteomalacia data in GCC countries through a non-interventional registry: study protocol.

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Abstract

Background

Hypophosphatemic rickets (HR) and osteomalacia related to fibroblast growth factor 23 (FGF23) are rare, lifelong disorders characterized by phosphate wasting, resulting in defective bone mineralization, multisystem manifestations, and reduced quality of life (QoL). Excess FGF23 is central to the pathophysiology of many HR subtypes, including X-linked hypophosphatemia (XLH). Supplementation with oral phosphate and active vitamin D analogs is often ineffective and associated with side effects. Burosumab, a fully humanized monoclonal immunoglobulin G1 antibody that inhibits FGF23, has been approved in the Gulf Cooperation Council (GCC) countries for the treatment of XLH and tumor-induced osteomalacia. Epidemiological, treatment, resource utilization, and outcomes data on FGF23-related HR and osteomalacia are limited in the Middle East region.

Methods

We present a 10-year, multicenter, non-interventional registry of patients with FGF23-related HR/osteomalacia at 14 sites across the Gulf Cooperation Council (GCC) countries. Up to 200 patients of any age or sex with a confirmed diagnosis of FGF23-related HR/osteomalacia have been enrolled over five years (June 2020 to June 2025), with follow-up extending five years post-enrollment. Retrospective data include a three-year look-back period from the date of diagnosis; prospective data will be collected biannually during routine clinical visits. The study will generate up to ten years of real-world data, with the last patient follow-up concluding in 2030.

The primary study objective is to characterize the burden, progression, treatment patterns, and long-term outcomes of FGF23-related HR/osteomalacia. Secondary objectives include evaluations of treatment effectiveness, safety, and QoL, using patient-reported outcome tools – the Short Form-36 (SF-36) for adults and the Pediatric Quality of Life Inventory (PedsQL) for children <18 years – completed approximately every six months during routine visits. Exploratory analyses will focus on healthcare resource utilization. All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies.

Conclusions

This 10-year regional rare disease registry aims to fill critical knowledge gaps regarding epidemiology, real-world treatment, and outcomes of FGF23-related HR and osteomalacia in the GCC. Insights will seek to inform clinical decision-making, optimize management strategies, and improve patient outcomes. Findings will also contribute to the global understanding of FGF23-related disorders.

Background

Hypophosphatemic rickets (HR) and osteomalacia are rare metabolic bone disorders characterized by phosphate wasting, leading to impaired bone mineralization [1]. Phosphate homeostasis is regulated by

a delicate interaction between hormones, including fibroblast growth factor 23 (FGF23), parathyroid hormone, and vitamin D metabolites. FGF23 plays a central role in phosphate metabolism by reducing renal phosphate reabsorption and suppressing the production of active vitamin D, resulting in chronic hypophosphatemia.

There are both genetic and acquired causes of HR. The most common hereditary form of HR is X-linked hypophosphatemia (XLH), a rare disease with an incidence of 3.9 per 100,000 births and a prevalence of 1.7 to 4.8 per 100,000 people [2–5]. Over 88% of cases of XLH result from mutations in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene [2]. This mutation leads to excessive FGF23 production and impaired phosphate reabsorption, although the pathogenesis of XLH is not completely understood, and other genetic mutations have been implicated [6]. Other hereditary forms of HR include autosomal dominant HR (FGF23 mutation), autosomal recessive HR types 1, 2, and 3, and osteoglophonic dysplasia (fibroblast growth factor receptor 1 [FGFR1] mutation) [7]. Acquired causes of HR include tumor-induced osteomalacia, where mesenchymal tumors produce excessive FGF23, and phosphate-wasting conditions associated with certain medications [8].

The Gulf Cooperation Council (GCC) region faces many public health challenges in diagnosing and managing metabolic bone disorders. There is a high regional prevalence of genetic conditions resulting in HR and osteomalacia [9, 10], and acquired (nutritional) rickets due to low population serum levels of 25-(OH) vitamin D [11, 12]. This is further complicated by limited clinician awareness and suboptimal diagnosis [9, 10, 13–15], along with variation in healthcare systems and access to targeted therapies such as burosumab [9, 10, 13]. X-linked dominant conditions, including XLH, are not affected by consanguinity rates; cases may, however, cluster in communities with intermarriages and large extended families [10]. Therefore, a high index of suspicion is required to accurately diagnose the rarer forms of rickets [10] and provide effective treatment early in the disease course [6].

XLH is a phenotypically heterogeneous disease with numerous multisystem clinical manifestations, the severity of which is highly variable even among affected individuals within the same family [3, 9, 13, 16]. Impaired quality of life (QoL) is common at all ages [3]. In children, XLH commonly manifests with skeletal abnormalities such as rickets, bone pain, and lower limb deformities, including genu varum or genu valgum, growth retardation leading to disproportionate short stature, craniosynostosis, and dental morbidity [2, 6]. Radiographically, rachitic changes, widened growth plates, and flaring of the metaphyses are typically observed [7].

In adults, XLH is often associated with complications of long-standing disease, including osteomalacia, which causes bone pain, muscle weakness, pseudofractures, and stiffness [2, 3]. Enthesopathies, characterized by calcification and ossification at ligament and tendon attachment sites, are common and can limit mobility [2, 3]. Early-onset osteoarthritis, particularly in weight-bearing joints, frequently occurs, as does spinal stenosis, which can lead to neurological symptoms [17]. Adults with XLH also report chronic fatigue and reduced QoL due to persistent pain and physical limitations [18, 19]. Dental

manifestations persist into adulthood, often presenting as periodontitis and recurrent dental infections [20].

Historically, treatment for HR and osteomalacia included oral phosphate salts and active vitamin D analogs [6]. However, these treatments are often associated with limited efficacy and adverse effects such as secondary hyperparathyroidism and nephrocalcinosis [6]. Burosumab, a first-in-class fully humanized monoclonal immunoglobulin G1 antibody that inhibits FGF23, has been approved for both pediatric (including adolescents with growing skeletons) and adult patients with XLH in the GCC. Recent guidelines suggest that burosumab should be continued in adults at least into the third decade of life, until peak bone quality has been attained, and as long as the treatment is effective and tolerable [6, 21].

Burosumab has also been approved for the treatment of pediatric and adult patients with tumor-induced osteomalacia. Clinical trials have shown that burosumab significantly increases mean serum phosphorus levels and the ratio of renal tubular maximum phosphate reabsorption to glomerular filtration rate, and improves rickets severity in children and healing of fractures in adults [6, 16, 22–24]. Despite these advances, significant knowledge gaps remain regarding regional epidemiology, treatment patterns, long-term outcomes, QoL, and healthcare resource utilization (HCRU) for FGF23-related HR and osteomalacia.

Generating robust real-world evidence for rare diseases is challenging due to the wide range of genetic conditions often presenting in early childhood, phenotypic heterogeneity, small and dispersed patient populations, underdiagnosis, and limited clinical expertise outside specialized centers [25]. Real-world registries are therefore an important scientific mechanism for capturing data on rare diseases [25].

This study aims to address regional evidence gaps through a 10-year observational registry of patients diagnosed with FGF23-related HR and osteomalacia in the GCC. By systematically collecting both retrospective and prospective clinical data on these rare diseases, the registry will provide vital additions to the evidence base, including disease burden, treatment pathways, and real-world patient outcomes. The insights gained will help healthcare providers and policymakers optimize clinical decision-making and improve long-term patient care.

Methods/Design

This is a multi-center, non-interventional observational rare disease registry, open to patients of any age or sex with a diagnosis of FGF23-related HR and/or osteomalacia, who are either receiving treatment, currently untreated, or naïve to treatment (Table 1). Exclusion criteria include a lack of capacity to provide informed consent and current participation in an interventional clinical trial. Participation is permitted under compassionate use, pre-commercial programs, or investigator-initiated studies. The registry is being conducted in all six countries across the GCC region. All eligible patients at participating sites will be invited to take part in the study.

Table 1
Inclusion and exclusion criteria

Inclusion criteria
Patients of all ages at baseline
Provision of informed consent by the patient or legal guardian (if applicable) and/or assent (if applicable)
In the treating investigator's opinion, the patient presents clinical features, radiological findings, biochemical results, or genetic investigation results that support a diagnosis of FGF23-related HR/osteomalacia, with one of the following: Hereditary FGF23-mediated: • X-linked dominant (PHEX mutation) • Autosomal dominant (FGF23 mutation) • Autosomal recessive type 1 (DMP1 mutation) • Autosomal recessive type 2 (ENPP1 mutation) • Autosomal recessive type 3 (FAM20C mutation) (Raine Syndrome) • Osteoglophonic dysplasia (FGFR1 mutation) Other FGF23-mediated conditions: • Tumor-induced osteomalacia • Linear nevus sebaceous syndrome/epidermal nevus syndrome (FGFR3/PIK3CA/HRAS/KRAS/NRAS mutations) • Fibrous dysplasia / McCune-Albright syndrome (GNAS mutation)
Exclusion criteria
• The patient or their representative cannot provide informed consent. • The patient is participating in an interventional clinical trial and will be approached for registry inclusion after all trial follow-up is completed. • Participation in a compassionate use program, pre-commercial program, or investigator-initiated study does not exclude a patient from this registry.
DMP1, dentin matrix protein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FGF23, fibroblast growth factor 23; FGFR, fibroblast growth factor receptor; GNAS, guanine nucleotide-binding protein, alpha stimulating; HR, hypophosphatemic rickets; HRAS, Harvey rat sarcoma viral oncogene homolog; KRAS, Kirsten rat sarcoma viral oncogene homolog; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PHEX, phosphate-regulating endopeptidase homolog X-linked.

(Insert Table 1 *here)*

Patients (or their legal representatives) are asked to provide informed consent for the duration of the registry's activity, unless they decide to withdraw their consent. Patients are enrolled over a five-year

period, from June 2020 to June 2025. Follow-up for each patient will take place for five years following enrollment, with the first patient's follow-up concluding in 2026 and the last ending in 2030. For the retrospective component, data will be collected over a look-back period of up to three years from the date of diagnosis of FGF23-related HR and osteomalacia. Prospective data will be gathered during the enrollment and follow-up periods. The registry may extend beyond this date. Kyowa Kirin Pharma Free Zone – Limited Liability Company (FZ-LLC), Dubai, United Arab Emirates, which manufactures burosumab (Crysvita ®), has sponsored the registry for a period of ten years. Figure 1 provides an overview of the study design.

Outcomes and Measures

The primary outcomes are disease burden, progression, treatment patterns, and long-term outcomes. Secondary outcomes are treatment efficacy and safety, and QoL metrics using the Short Form-36 (SF-36; adults) and Pediatric Quality of Life Inventory (PedsQL; children < 18 years) under real-world standards of care. An exploratory outcome is HCRU data.

Since this is a real-world observational registry, all visits and interactions will follow routine clinical practices and will be scheduled at the discretion of the treating investigator. Enrolled patients will not face any additional tests or invasive procedures. The study protocol does not recommend the use of any specific treatments, nor is study medication provided as part of participation. Data will be collected from existing patient medical records following each patient’s standard of care visit (or once new information becomes available) and from patient questionnaires.

(Insert Table 2 *here)*

Table 2
Data collection schedule

	Retrospective[l]	Baseline	Prospective[m]
Informed consent[a]		X	X
Demographic information[b]		X	
Medical history[c]	X		
Comorbidities	X	X	X
Relevant genetic mutations (if available)[d]	X	X	X
FGF23-related HR/osteomalacia medications and history[e]	X	X	X
Concomitant medications[f]		X	X
AEs related to treatment for FGF23-related HR and osteomalacia[g]		X	X
Physiotherapy	X		X
Physical examination (including dental and audiology assessment)	X	X	X
Vital signs (temperature, sitting blood pressure, pulse rate, respiratory rate)	X	X	X
Growth assessment[h]	X	X	X
X-rays	X	X	X
Laboratory assessments[i]	X	X	X
Hospitalizations (including ER visits), visits to general practitioner, physiotherapist, specialists, and other healthcare professionals	X	X	X
Patient QoL[j]	X	X	X
Social impact (work/school days off due to FGF23-related HR and osteomalacia)	X		X
Site characteristics[k]		X	

	Retrospective[l]	Baseline	Prospective[m]
[a] Re-consent to adult registry: consent obtained again when patient transitions from pediatric patient to adult (per national guidelines); assent patients when patient transitions from infant to child.			
[b] Includes age, gender, ethnicity, highest level of education, employment status, time since first FGF23-related symptoms and diagnosis, prenatal diagnosis, method of diagnosis, and FGF23 level.			
[c] General medical history, including comorbidities, pregnancy and fetal outcomes (including weight, length, Apgar score, mode of delivery, if applicable).			
[d] PHEX and other genomic mutations to be recorded in prospective visit if not available at baseline.			
[e] Includes age at onset of symptoms, age at diagnosis, diagnosis method, FGF23 level (if available), and family history (number of known affected relatives and relationship to patient).			
[f] Includes indication, dose, duration of treatment and reason for discontinuation, and possible AEs.			
[g] AE reporting period begins when the patient is included in the study (date of first signature of informed consent) and continues until 30 days after the end of the observational period.			
[h] Includes standing and sitting height (meters) for children and final height (meters) for adults, arm and leg length (meters), weight (kg), BMI, Z score (based on background national reference – if available).			
[i] Information collected from all laboratory assessments performed including biochemistry, urine, endocrine and serum biochemical bone turnover markers, e.g., 1,25-dihydroxyvitamin D3 (1,25[OH]2D), 25-hyroxyvitamin D (25[OH]2D), alkaline phosphatase, urea nitrogen, calcium, chloride, carbon dioxide (CO2), creatinine, FGF23, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, uric acid, parathyroid hormone (PTH), magnesium, procollagen type 1 N-terminal propeptide (P1NP), C-terminal telopeptide (Ctx), bone alkaline phosphatase (BALP); for urine analysis: potential of hydrogen (pH), protein, glucose, magnesium citrate, uric acid (potassium), calcium, phosphorous, creatinine, TmP/GFR, tubular reabsorption phosphate (TRP) (without using phosphate supplementation).			
[j] QoL questionnaires – SF-36 for adult patients and PedsQL for pediatric patients – to be completed approximately every 6 months at routine standard of care visits.			
[k] Includes geographic location, specialty or area of primary practice, practice type, practice size, patient volume, referral (if the patient was referred from another hospital/specialty).			
[l] Data to be collected over a look-back period of up to 3 years from the date of diagnosis of FGF23-related HR and osteomalacia. Data to be collected at one timepoint per year; last standard of care visit per year to be collected only.			
[m] Database to be updated twice per year, at 6-monthly intervals; data from all standard of care visits occurring over each respective 6-month period will be recorded in the registry.			
AE, adverse event; BMI, body mass index; ER, emergency room; FGF23, fibroblast growth factor receptor 3; HR, hypophosphatemic rickets; PedsQL, Pediatric Quality of Life Inventory; PHEX, phosphate-regulating endopeptidase homolog X-linked; QoL, quality of life; SF-36, Short Form-36; TmP/GFR, ratio of renal tubular maximum phosphate reabsorption to glomerular filtration rate.			

For the prospective section of the registry, data from all standard routine visits will be entered into the registry (see Table 2). Investigators will update the registry every six months; all data from visits within each six-month period will be documented. Moreover, adult and pediatric patients may optionally complete the QoL questionnaires SF-36 and PedsQL, respectively, approximately every six months during routine visits. Table 3 shows the variables to be derived for statistical analysis; these will be used to describe disease status and treatment effectiveness at baseline and during follow-up.

Table 3
Variables for statistical analysis

Weight for height Z score	**Based on background national reference, if available.**
Rickets Severity Score (RSS)	Quantitative assessment of rickets severity in wrists and knees based on metaphyseal fraying, concavity, and growth plate involvement. A 10-point scale is used, where 10 indicates the highest severity and 0 denotes no radiographic changes. Scores are assigned separately for wrists (up to 4 points) and knees (up to 6 points) [26].
Radiographic Global Impression of Change (RGI-C)	Scale used to assess changes in the skeletal burden of pediatric disease. Radiographic scoring uses a 7-point ordinal scale to assess changes between two time-point radiographs. RGI-C reflects perceived differences, with clinical significance indicated. Scores of -3, -2, and − 1 signify severe, moderate, and minimal worsening, respectively; +1, + 2, and + 3 denote minimal, substantial, or complete healing. The global score is based on the overall impression of changes in wrist and knee images [27, 28].
Short Form-36 (SF-36) – quality of life score for adult patients	The SF-36 is a standardized 36-item questionnaire used to measure health-related quality of life in adults. Summary SF-36 scores will be calculated for the health domains: physical functioning, bodily pain, role limitations due to physical and emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. Each domain is scored from 0 to 100, and a lower score indicates limitations in physical and social activities and worse health quality life [29].
Pediatric Quality of Life Inventory (PedsQL) – quality of life score for pediatric patients	A 23-item questionnaire used to measure health-related quality of life in children and adolescents. Four domains (physical, emotional, social, and school functioning) are scored on a 0–100 scale. Mean psychosocial and physical health summary scores will be calculated using the PedsQL algorithm. Lower scores indicate health problems and reduced quality of life [30].

PedsQL, Pediatric Quality of Life Inventory; SF-36, Short Form-36; RGI-C, Radiographic Global Impression of Change.

(Insert Table 3 *here; includes references* [26–30]*)*

If a patient becomes pregnant, relevant information will be submitted to the sponsor's drug safety department. The site investigator will discuss with the patient the potential benefits and risks regarding treatment continuation during pregnancy. All adverse events (AEs) from FGF23-related HR and osteomalacia treatments are monitored throughout the study, regardless of causal relationship to treatment. The data partner will notify the study sponsor of all non-serious AEs assessed as being

related to burosumab, and any serious AEs regardless of treatment. AE reporting starts with informed consent and continues for 30 days after the observational period ends. AEs will be coded using the MedDRA system and categorized by organ class, severity, treatment relationship, and outcome. Cumulative AE data will be included in the registry's interim and final analyses.

Data quality standards are in line with Good Clinical Practices (GCP) and Good Pharmacoepidemiology Practices (GPP) guidelines, alongside processes and procedures to optimize data cleanliness and accuracy. Data quality will be improved through a series of programmed checks that automatically identify out-of-range or anomalous data, as well as concurrent manual data reviews.

Statistical Methods

As this study is a 10-year observational registry, there is no pre-defined hypothesis to test; therefore, no sample size has been calculated for statistical considerations. Based on clinical experience, approximately 200 patients are expected to be eligible to participate in the registry. Pooled analyses (for all countries) will be conducted for each of the objectives. Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected. Summary statistics for patient demographics, treatment patterns, clinical outcomes, safety, HCRU, and QoL will be performed. Continuous variables will be reported as mean (standard deviation) or median and range, where appropriate. Categorical variables will be summarized as numbers and proportions of the total study population, and by subgroups where appropriate.

Statistical comparisons between subgroups will be provided when relevant. Typically, comparisons will be made using the Wilcoxon signed rank test, Student's paired t-test, or McNemar's test for dependent subgroups. If there are fewer than five observations per time point, Fisher's exact test will compare categorical variables. Statistical significance will be set at 0.05, and 95% confidence intervals may be reported. Missing values will be imputed using Last Observation Carried Forward, and patients with no post-baseline data will be assumed to show no change. Sensitivity analyses may be conducted without imputation.

Ethical Considerations

To ensure the quality and integrity of research, this study is conducted under GCP and GPP guidelines issued by the International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and relevant national guidelines. Institutional Review Board approval was obtained from King Saud Bin Abdulaziz University for Health Sciences,

Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia (Study No: CT20/033/R). An informed consent form must be signed by the patient (or the patient's legally authorized representative) before their participation in the study.

Dissemination and Publication Plan

Interim analyses have been planned for 2022, 2024, and 2028, with the final study results expected in 2030. All reporting will be consistent with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) Initiative checklist for cohort studies. Findings will be published in peer-reviewed journals and presented at conferences. Interim findings have been presented at the American Association of Clinical Endocrinology Communities Middle East 2022 Conference, Dubai, November 11–13, 2022 [31]; the World Congress on Osteoporosis – International Osteoporosis Foundation – European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, Barcelona, May 4–7, 2023; and the European Society for Paediatric Endocrinology, Liverpool, UK, November 16–18, 2024.

Anticipated Study Limitations

As routine clinical practice patterns may differ at both national and site levels, variations in patient selection, treatment and reporting practices, as well as the timing and completeness of clinical measures are anticipated. The relatively flexible inclusion and exclusion criteria for the study will result in a heterogeneous population for analysis, but we anticipate that it will provide a representative sample of the FGF23-related HR/osteomalacia patient population in the GCC region. Because of its observational nature, data collected from routine medical practice are vulnerable to bias and confounding. This is especially evident in effectiveness assessments, where no adjustments will be made for confounding factors.

Participants will be categorized by age group at baseline. As follow-up will last for several years, children and adolescents may transition to a different age group over time. Therefore, the final descriptive results must be interpreted carefully, as older patients will also contribute to the outcomes of child and adolescent age groups.

Conclusions

This 10-year, multi-center, non-interventional registry will provide valuable real-world GCC data on the burden, progression, and treatment patterns of the rare diseases FGF23-related HR and osteomalacia in a high-prevalence region. These data will enhance regional public health by bridging existing knowledge gaps in epidemiology, treatment efficacy, safety, and HCRU. Insights from this registry study will inform clinical decision-making, optimize patient management strategies, enhance long-term outcomes for affected individuals, and contribute to a deeper understanding of FGF23-related disorders globally.

Abbreviations

AE
adverse event
FGF23

fibroblast growth factor 23
GCC
Gulf Cooperation Council
GCP
Good Clinical Practices
GPP
Good Pharmacoepidemiology Practices
HCRU
healthcare resource utilization
HR
hypophosphatemic rickets
PedsQL
Pediatric Quality of Life Inventory
PHEX
phosphate-regulating endopeptidase homolog X-linked
QoL
quality of life
SF-36
Short Form-36
STROBE
STrengthening the Reporting of OBservational studies in Epidemiology
XLH
X-linked hypophosphatemia

Declarations

Ethics approval and consent to participate

This study is being run under the Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology, the Declaration of Helsinki and its amendments, and any applicable national guidelines. The study has received ethical, regulatory, and institutional approvals at national, regional, and site level for each participating country, as required. All participants or their legal representative will provide informed consent before their enrollment in the registry.

Consent for publication

Not applicable.

Competing interests

MA, EE, and FM are employees of Kyowa Kirin FZ-LLC, Dubai, UAE. All other authors declare that they have no competing interests.

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Kyowa Kirin Pharma Free Zone Limited Liability Company is the sponsor of the registry with IQVIA as the data partner. The authors are members of the steering committee for their respective countries. The authors did not receive payment for their contribution to the manuscript. The sponsor funded editorial and medical writing support provided by Highfield Communication Consultancy, Oxford, United Kingdom.

Authors' contributions

All authors participated in reviewing, revising, and approving the manuscript.

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Availability of data and materials

All data supporting the findings of this study are available within the article or by contacting the corresponding author upon reasonable request.

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Figures

Figure 1. Study design

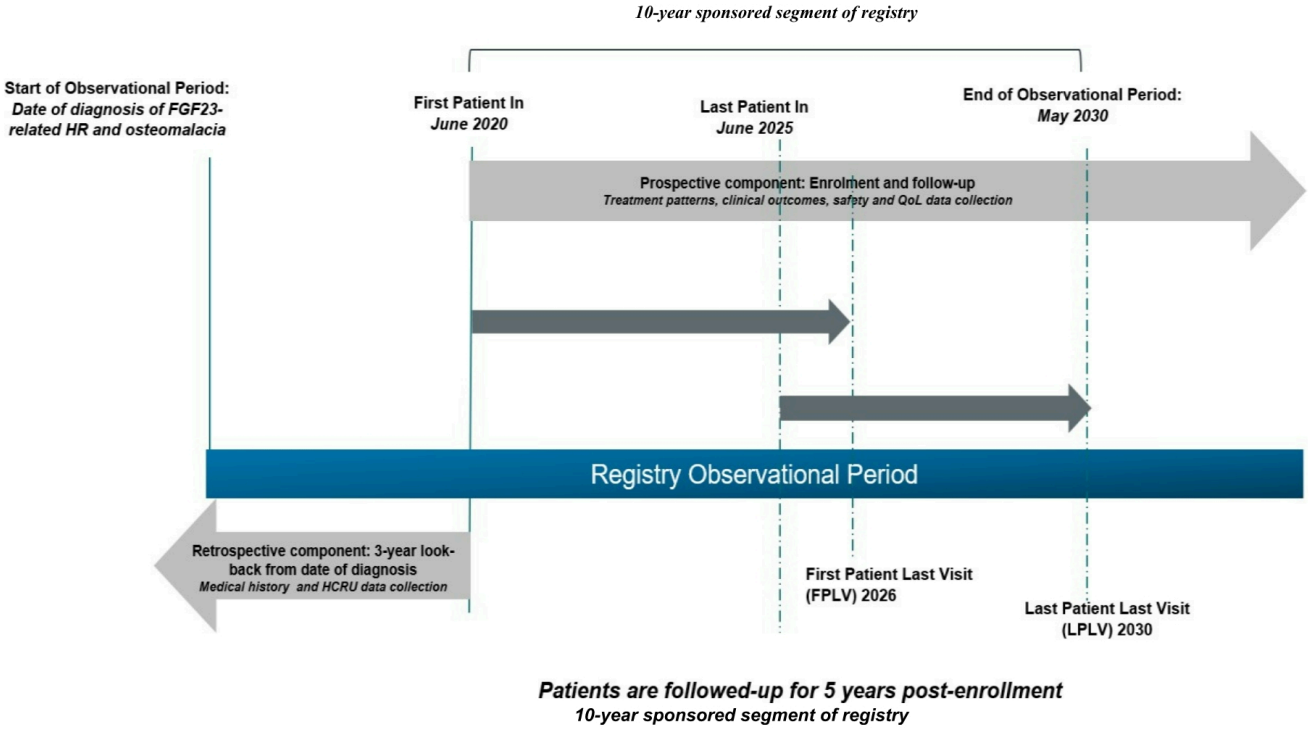


Figure 1

FGF23, fibroblast growth factor 23; HCRU, healthcare resource utilization; HR, hypophosphatemic rickets; QoL, quality of life.