KYOWA KIRIN

X-Linked Hypophosphatemia Registry Protocol

Clinical Trials.Gov ID:	NCT03193476
Protocol Version:	3.0
Date:	15 February 2019

Registry title	X-Linked Hypophosphatemia Registry
Design	Multicentre, prospective, non-interventional observational registry
Population studied	X-linked hypophosphatemia (XLH)
Sponsor signatory	Dr Michael Smyth: Senior Vice President Medical Affairs Kyowa Kirin International Galabank Business Park, Galashiels, TD1 1OH +44 7584219256 Michael.smyth@kyowakirin.com

Statistician	Anna Compagnoni: Statistical Scientist IQVIA Via Fabio Filzi 29, 20124 Milan anna.compagnoni@IQVIA.com
Medical Adviser	Dr Michael Smyth: Senior Vice President Medical Affairs Kyowa Kirin International Galabank Business Park, Galashiels, TD1 1OH +44 7584219256 michael.smyth@kyowakirin.com
Project Manager	Christelle Da Cruz: Senior Clinical Project Manager IQVIA 151-161 Blvd. Victor Hugo 93588 Saint-Ouen Cedex, Paris, France +33 1 74 88 22 96 christelle.dacruz@IQVIA.com

Amendment No: 1	**Date of Amendment:** 22 January 2019
Amendment No: 2	**Date of Amendment:** 15 February 2019

Confidentiality Statement

Protocol Approval

Protocol Title:	An international, multicentre, prospective, non-interventional observational registry for patients with X-linked hypophosphatemia (XLH)
Protocol Version:	Version 3.0
Protocol Date:	15 February 2019

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Name: Dr Michael Smyth

Date (DD/MMM/YYYY)

Title: Senior Vice President Medical Affairs

Kyowa Kirin International

E: Michael.smyth@kyowakirin.com

Protocol Synopsis

Registry Title An international, multicentre, prospective, non-interventional observational registry for patients with X-linked hypophosphatemia (XLH)
ClinicalTrials.gov Registration NCT03193476
Participating Countries: Including, but not limited to, United Kingdom, France, Italy, Spain, Netherlands, Sweden, Finland, Denmark, Germany, Belgium, Norway, Ireland, Austria, Portugal, Czech Republic, Slovakia, Slovenia, Hungary, Croatia, Romania, Bulgaria, Serbia, Poland, Russia, Greece, Israel, Kingdom of Saudi Arabia, Kuwait, United Arab Emirates, Oman
Background XLH is characterised by renal phosphate wasting, hypophosphatemia, defective bone and teeth mineralization and/or delayed endochondral ossification caused by inactivating mutations in the PHEX gene. KKI markets burosumab, a drug to treat XLH. KKI set up a registry to collect data on treatment, burden of disease, disease progression and long-term outcomes of XLH.
Primary Objective The registry will collect data of XLH to characterise the treatment, burden of disease, disease progression and long-term outcomes of XLH.
Number of Patients Planned This registry will take place in centres across Europe and the Middle East. Total number of patients anticipated: approximately 1200
Inclusion Criteria A patient must meet the following criteria at the enrolment visit (baseline) to be eligible for inclusion into the registry 1. Patients of all ages at baseline. 2. In the opinion of the treating physician the patient has clinical presentation, radiological, biochemical or genetic investigation results that support the diagnosis of XLH.
Exclusion Criteria A patient who meets any of the following criteria at the enrolment visit (baseline) cannot be included in the registry:

1. Patient or their legally designated representative does not have the cognitive capacity to provide informed consent.
2. Patient is currently participating in an interventional clinical trial. Patients will be approached for inclusion into the registry once their involvement in the trial ends (including the completion of all trial follow-up assessments). Participation in a Compassionate Use Program, Pre-commercial Program (i.e. Named Patient Sales, Nominative ATU) or Investigator Initiated Study does not preclude a patient from participation in this registry.

Methodology

This is an international, multicentre, prospective, non-interventional observational registry of patients with XLH. The objectives of the registry are to collect natural history data of XLH to characterise the treatment, progression and long-term outcomes of XLH in both adult and paediatric patients.

The registry will include patients with XLH independent of treatment regimen (unless participating in an interventional clinical trial at the time of identification). Those patients participating in an interventional clinical trial will be approached to take part in the registry when their involvement in the clinical trial has ended.

All eligible patients at the participating clinics will be asked to participate in the registry.

- Informed consent will be obtained from adult patients.
- Parental informed consent for the inclusion of a child will be obtained from the child's legally designated representative in line with national guidance.
- Assent will also be sought from children of applicable age in line with national guidance. In all cases the health professional responsible for enrolling the patient into the registry will assess the appropriateness of gaining assent from an individual at their discretion.
- After the patient or legally designated representative has signed the informed consent, the patient data will be recorded in the registry, including baseline, retrospective and prospective data. Data will be collected using a web-based Electronic Data Capture (EDC) system. A patient identification number will be automatically generated by the system upon enrolment.

No pre-determined follow-up requirements will apply. However, physicians should update the registry EDC on a regular basis after a patient's visit with the physician, once new information is available or at a minimum on an annual basis. This is a prospective observational non-interventional registry and no additional clinical interventions other than standard clinical practice are required by the protocol. Patients will be asked to provide responses to some quality of life scales (SF-36 and EQ5D-5L and their equivalent in children). Completion of these questionnaires is optional/recommended, but not required.

A subset of the registry data will be used to fulfil a Post-Authorisation Safety Study (PASS). Study centres which agree to participate in the PASS will be asked to solicit adverse events on enrolled patients (PASS is detailed in Appendix 13.2).

Not all centres are expected to participate in the PASS.
Duration Of Patients' Involvement In The Registry Kyowa Kirin International will sponsor the XLH Registry for 10 years. Patients will provide informed consent to participate as long as the registry is active. The decision to discontinue the registry will be made by the Sponsor in agreement with applicable regulatory agencies.
Statistical Methods There is no sample size based on statistical considerations. A survey conducted with XLH clinical experts across Europe provided evidence that the recruitment target of approximately 1200 XLH patients would be eligible to take part in the registry. Descriptive statistics will be supplied in the following format: • Quantitative variables: number of observations, mean, standard deviation, median, minimum and maximum (quartiles and confidence intervals will be calculated as appropriate) • Qualitative variables: absolute and relative frequencies per class

Amendments and Updates

Number	Date	Amendment or update	Reason
1	22 January 2019	CRO was changed from Medialis to IQVIA, including updates to related processes.	Administrative
		Registry sponsor name was updated to Kyowa Kirin International.	Administrative
		List of countries to be included in Registry was updated.	Administrative
		Proposed data to be recorded by sites and recommended frequency of data collection was updated.	To align data collected with needs of the scientific community.
		PASS was added as a sub-study to the Registry.	Required by Regulatory Authority.
2	15 February 2019	Registry sponsor name signatory was updated	Administrative
		Language on proposed data to be recorded revised	Administrative

Contents

1 List of Abbreviations and Definition of Terms

The following abbreviations and special terms are used in this document.

Abbreviation or special term	Explanation
6MWT	Six-minute walk test
BMI	Body Mass Index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency Section Edition
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CT	Computed Tomography
DXA	Dual-Energy X-Ray Absorptiometry
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FGF23	Fibroblast Growth Factor 23
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
ICF	Informed Consent Form
ICH	International Council for Harmonization
IRB	Independent Review Board
Kg	Kilogram
MRI	Magnetic Resonance Imaging
PASS	Post-Authorisation Safety Study
PHEX	Phosphate-regulating gene with homologies to endopeptidases
PIS	Patient Information Sheet

Abbreviation or special term	Explanation
QoL	Quality of Life
SF	Short Form
TUG	Timed Up and Go
XLH	X- Linked Hypophosphatemia

2 Introduction

2.1 Disease background

X- Linked Hypophosphatemia (XLH) is the most common cause of inherited phosphate wasting with an incidence of 3.9/100,000 live births and a prevalence ranging from 1.7/100,000 children to 4.8/100,000 persons (Beck-Nielsen 2009; Endo 2015; Rafaelsen 2016). XLH is characterised by renal phosphate wasting, hypophosphatemia, defective bone and teeth mineralization and/or delayed endochondral ossification caused by inactivating mutations in the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome). The PHEX gene encodes a cell surface bound protein cleavage enzyme, predominantly expressed in osteoblasts, osteocytes and teeth (odontoblasts and cementoblasts) (Holm 2001; Dixon 1998; Tyynismaa 2000; Ichikawa 2008; Chesher 2018; Christie 2001; Makras 2008). In the absence of functional PHEX, the release of FGF23 by osteocytes is greatly increased (Bonewald 2013). Excess circulating FGF23 can provide a signal to the kidney tubules to decrease phosphate reabsorption by decreasing the expression of NaPi-IIa and NaPi-IIc in the tubular cells (Tiosano 2009), and to suppress 1,25(OH)2D production, resulting in decreased intestinal absorption of calcium and phosphate (Sabbagh 2008). The chronic presence of low serum phosphate levels leads to defective bone and teeth mineralization and the 2 major pathological consequences of the hypophosphatemia are rickets and osteomalacia. In addition to rickets, children have disproportional short stature, bowing of the long weight-bearing bones, as well as dental abscesses (Tenenhouse 2001). As children age and become adults, the disease evolves. Adult XLH patients may suffer from osteomalacia, bone pain, enthesopathy (calcification of ligaments or at their attachments to bone), increased risk of pseudo-fractures, arthrosis and joint pain. The development of arthrosis is suggested to be related to childhood-acquired bone deformities (Tenenhouse 2001; Reid 1989).

Early treatment with oral phosphate supplementation and active vitamin D heals rickets, limits dental abscess formation and prevents progressive growth failure, but in a significant proportion of patients it is unsuccessful and/or associated with side effects, e.g. hyperparathyroidism and nephrocalcinosis (Carpenter 2011; Linglart 2014). Up to two-thirds of children with XLH require lower limb surgery (Gizard 2017; Kocaoglu 2010; Matsubara 2008; Sharkey 2015). Conventional therapy further stimulates FGF23 levels, and thereby renal phosphate wasting resulting in a vicious circle, which may limit its efficacy (Carpenter 2010; Imel 2014; Endo 2008; Jonsson 2003). Adult patients with XLH are at risk of complications such as early osteoarthritis, enthesopathies,

spinal stenosis, fractures, and hearing loss, which may limit the quality of life (Beck-Nielsen 2010, Che 2016; Biosse Duplan 2017). Recently, burosumab, a fully humanized monoclonal IgG1 antibody neutralizing FGF23, was approved by the health authorities for treatment of XLH patients in the European Union and in the United States, based on encouraging results obtained in trials (Carpenter 2018; Carpenter 2014; Aono 2009; EMA 2018; FDA 2018; Insogna 2018).

2.2 Registry background

There is limited data available on XLH in terms of incidence, prevalence, risk factors, co-morbidity, treatment modalities and treatment pathway, treatment outcomes or mortality on an international level.

The registry will be a multicentre, prospective, non-interventional observational registry of patients with XLH sponsored by Kyowa Kirin International. Data from the registry is intended for health care providers and healthcare decision makers to optimise clinical decision making through enhanced understanding of the variability, progression, and natural history of XLH as well as the burden of disease. Expert centres will be invited to participate in the registry.

3 Study Design

The registry is an international, multicentre, prospective, non-interventional observational registry, open to individuals of both sexes and any age with a diagnosis of XLH, who are naïve to treatment, treated with conventional therapy (oral phosphate and active vitamin D analogue) or currently untreated.

This registry will capture treatment details and clinical outcome variables in patients with XLH. Patients will be followed until the end of the registry unless they withdraw informed consent. Only clinical data collected during standard routine examinations will be recorded in the registry. Patients will be asked to complete quality of life scales (SF-36 and EQ5D-5L and their equivalent in children); these are optional/recommended and not mandated as per this protocol.

A subset of the registry data will be used to fulfil a Post-Authorisation Safety Study (PASS) as requested by the European Medicines Agency's (EMA's) Committee for Medical Products for Human Use (CHMP). Study centres which agree to participate in the PASS will be asked to solicit adverse events on enrolled patients. Not all centres are expected to participate in the PASS. The PASS has been designated by the EMA as a non-interventional observational study. All data

collected will arise from the usual clinical management of these patients. Any investigations performed for patients in the PASS (such as blood tests, ECGs, renal ultrasound scans or echocardiograms) will be at the discretion of the physicians managing the patients according to the patients' medical needs. Such investigations are not mandatory under the PASS protocol.

Details on the PASS are provided in Appendix 13.2.

4 Registry Objectives

The main objectives of the registry are:

4.1 Primary objective

- The registry will collect data to characterise the treatment, burden of disease, disease progression and long-term outcomes of XLH.

4.2 Secondary objectives

- Describe the effectiveness and safety of treatments used to manage the symptoms and signs of XLH as well as the value that treatments offer in certain subpopulations.

5 Study Population

5.1 Inclusion criteria

A patient must meet the following criteria at the enrolment visit (baseline) to be eligible for inclusion into the registry

1. Patients of all ages at baseline.
2. In the opinion of the treating physician the patient has clinical presentation, radiological, biochemical or genetic investigation results that support the diagnosis of XLH.

5.2 Exclusion criteria

A patient who meets any of the following criteria at the enrolment visit (baseline) will be excluded from the registry

1. Patient or their legally designated representative does not have the cognitive

capacity to provide informed consent.

2. Patient is currently participating in an interventional clinical trial. Patients will be approached for inclusion into the registry once their involvement in the trial ends (including the completion of all trial follow-up assessments). Participation in a Compassionate Use Program, Pre-commercial Program (i.e. Named Patient Sales, Nominative ATU) or Investigator Initiated Study does not preclude a patient from participation in this registry.

6 Therapy

6.1 Therapy schedule

All drug therapy considered necessary for the patients' welfare may be given at the discretion of the treating physician. All such therapy and any changes that occur throughout participation in the registry should be entered into the study database.

7 Data Collection

7.1 Overall registry design and schedule of assessments

All eligible patients with XLH, at the participating clinics, will be asked to take part in the registry. Once patients or their legally designated representative have signed the informed consent, patients will be enrolled into the registry. A patient identification number will be generated automatically by the system. Patient data will be link-anonymised, and physicians will retain a site enrolment log detailing the patient identification number alongside patient identifiable information. This enrolment log will remain at the participating clinic and will not be transferred outside of the clinic.

No pre-determined follow-up requirements will apply. However, physicians should update patient data in the registry on a regular basis after a patient's visit with the physician, once new information is available or at a minimum on an annual basis. ***Table 1*** shows the potential data that can be captured and entered into the registry electronic data capture (EDC) system.

As part of the informed consent form (ICF), permissions will be sought from patients to include details of hospitalisations and general medical history, to further the understanding of the natural history of XLH. All data will be collected using a web-based EDC system.

All patient care and management are determined by the physician. Physicians will be prompted to enter the following available information:

Retrospective data entry (potentially as part of baseline visit)

Retrospective data entry will include the patient's medical history and may include the following data, **if available**.

1. XLH specific clinical, medical, surgical, and dental history, including
    - Diagnostic history: age at onset of symptoms, age at diagnosis, diagnosis method(s)
    - PHEX mutation and other genomic tests (if available)
    - Family history: number of known affected relatives and relationship to subject
2. General medical history, including pregnancy and foetal outcomes (including weight, length, Apgar score, mode of delivery, if applicable)
3. XLH specific medications taken in the past including pain medications and growth hormones (including dose, duration of treatment and reason for discontinuation, if available)
4. Physiotherapy reports (including the number of visits, use of a wheelchair, walking aids, medical device, and home adaptations)
5. Historical physical examinations (including dental and audiology assessment)
6. Historical vital signs (including temperature, blood pressure [sitting], pulse rate and respiratory rate)
7. Historical growth assessments (including standing and sitting height [meters], arm and leg length [meters], weight [kg], Body mass index (BMI), Z score [based on background national reference])
8. Historical examinations:
    - Electrocardiogram (ECG) reports
    - Echocardiogram (ECHO) reports

- Radiographs and imaging (including any radiological assessment of disease severity – X-ray, dual-energy X-ray absorptiometry [DXA], computed tomography [CT], Xtreme CT [new generation of CT], or magnetic resonance imaging [MRI]) – scanner type and analysis software used)
- Renal ultrasound scan

9. Historical laboratory assessments (including biochemistry, haematology, urine, endocrine and serum biochemical bone turnover markers)
10. Historical tolerance tests (ATS Statement 2002; Bruininks 2005; Kolber 2005; Podsiadlo 1991):
    - Six-minute walk test (6MWT)
    - Timed Up and Go (TUG)
    - Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2)
    - Dynamometry
11. Social impact history (including work/school days off due to XLH)

Baseline Visit

1. Site characteristics
2. Informed consent (date and type of consent)
3. Demographics (including date of birth, biological gender, and ethnicity/race)

Information to be recorded in the registry, **if available**: The registry does not mandate investigations outside of standard care as determined by the patient's physician.

4. XLH specific physical exam
5. Physical examination (including dental and audiology assessment)
6. Vital signs (temperature, blood pressure [sitting], pulse rate and respiratory rate)
7. Growth assessments (including standing and sitting height [meters], arm and leg length

[meters], weight [kg], BMI, Z score [based on background national reference])

8. XLH specific medications
    - All current XLH specific medications including pain medications and growth hormones (including dose, adherence, duration of treatment and reason for discontinuation, if applicable)
9. Concomitant medications
    - All medications used within 30 days prior to written consent (including dose, adherence, duration of treatment and reason for discontinuation, if applicable)
10. Examinations
    - ECG reports
    - ECHO reports
    - Radiographs and imaging (including any radiological assessment of disease severity – X-ray, DXA, CT, XtremeCT, or MRI – scanner type and analysis software used)
    - Renal ultrasound scan
11. Laboratory assessments (including biochemistry, haematology, urine, endocrine and serum biochemical bone turnover markers, genomic mutations)
12. Exercise tolerance tests (ATS Statement 2002; Balke 1963; Bruininks 2005; Kolber 2005; Podsiadlo 1991):
    - 6MWT
    - TUG
    - BOT-2
    - Dynamometry
13. Patient quality of life (QoL) questionnaires (Ware 1992; Herdman 2011):

- Short Form 36 (SF-36) (for adult subjects) and its equivalent in children
- Five-level version of the EuroQol five-dimensional descriptive system (EQ-5D 5L, for children ≥ 5 years of age and adult subjects) and its equivalent in children

Prospective/Routine Clinic Visit

Paediatric subjects will be asked to provide registry consent when they reach the applicable age to do so, according to national guidelines at participating centres. Physicians are asked to update the registry EDC on a regular basis after a patient's visit with the physician, once new information is available or at a minimum on an annual basis. The registry does not mandate investigations outside of standard care as determined by the patient's physician.

Centres that participate in the PASS will be asked to prospectively solicit adverse events.

In addition, all the changes since the last recorded entry will be collected in the registry, **if available**:

1. Changes to general medical history (since baseline or last recorded entry) including:
    - All incidents of hospitalisation (including duration and cause of admission)
    - Pregnancy (including the follow information relating to Sponsor products: timing of gestational exposure, duration of exposure and foetal outcomes including weight, length, Apgar score and mode of delivery)
    - Date of death (including cause of death)
2. Changes to XLH – specific medical, surgical, and dental history (since baseline or last recorded entry)
    - Relevant genetic testing (if available)
3. XLH specific medications (including dose adherence, duration of treatment and reason for discontinuation if available)
4. Concomitant medications
    - Current – All medications ongoing at the time of prospective clinic visit including dose, adherence and duration of treatment

- Previous – All medications and therapies (since baseline or last recorded entry) including dose, adherence, duration of treatment and reason for discontinuation, if available.

5. Physiotherapy reports (including number of visits, use of a wheelchair, walking aids, medical device and home adaptations)
6. Physical examination (including dental and audiology assessment)
7. Growth assessment (including standing and sitting height [meters], arm and leg length [meters], weight [kg], BMI, Z score [based on background national reference])
8. Vital signs (temperature, blood pressure [sitting], pulse rate and respiratory rate)
9. Examinations
    - ECG reports
    - ECHO reports
    - Radiographs and imaging (including any radiological assessment of disease severity – X-ray, DXA, CT, XtremeCT, or MRI – scanner type and analysis software used)
    - Renal ultrasound scan
10. Laboratory assessments (including biochemistry, haematology, urine, endocrine and serum biochemical bone turnover markers, genomic mutations)
11. Exercise tolerance tests (ATS Statement 2002; Balke 1963; Bruininks 2005; Kolber 2005; Podsiadlo 1991):
    - 6MWT
    - TUG
    - BOT-2
    - Dynamometry
12. Patient QoL questionnaires (Ware 1992; Herdman 2011):

- SF-36 (for adult subjects) and its equivalent in children
- EQ-5D 5L (for children ≥ 5 years of age and adult subjects) and its equivalent in children

13. Social impact (work/school days off due to XLH)

Table 1 Schedule of Assessments for Data Recordings

	Retrospective Data Entry	**Baseline** Data Entry	**Prospective** Data Entry* (Data to be updated in the database at least annually)
Informed consent*		X	X*
Demographic information		X	
Medical history and ongoing medical conditions	X		X
Relevant mutations (if available)**	X	X	X**
XLH medications and history	X	X	X
Concomitant medications		X	X
Physiotherapy	X		X
Physical examination (including dental and audiology)	X	X	X
Vital signs	X	X	X
Growth assessment	X	X	X
Examinations (X-Rays, CT, ECG, ECHO, renal ultrasound)	X	X	X
Laboratory assessments	X	X	X
Exercise tolerance tests	X	X	X
Patient quality of life (QoL)	X	X	X
Social impact (work/school day off)	X		X

*Re-consent to adult registry consent when patient transitions from paediatric patient to adult

** PHEX and other genomic mutations to be recorded in prospective visit if not available at baseline

Reminders about updating the registry will be issued from the database to alert the clinic that new data should be entered in the EDC. The reminders will be issued based on the date of the previous visit. If no contact has been reported for a registered patient at 12 months, the system will issue a reminder asking for a report on the status of that patient.

7.2 Withdrawal of patients from registry

A patient should be withdrawn from the registry if requested by the patient or their legally designated representative. The registry should be updated with the information that the patient is withdrawn and the reason for withdrawal (if provided by the patient or legally designated representative).

An interruption of patient data collection shall be made during a patient's participation in an interventional clinical trial. Data entry will be re-initiated for the patient once their participation in the trial has ended. This is defined by the end of their participation in all trial associated follow-up assessments.

7.3 Patient confidentiality

To protect confidentiality of those enrolled into the registry, patients will be assigned a patient identification number automatically upon registration. No personal identifiable information will be entered into the EDC forms. This identification number will be used in place of identifying information throughout the study.

Patient names and identifying information will be withheld from the Contract Research Organization (CRO) and the Sponsor in all communications, nor will this information be requested. Identifiable information may be accessed during clinical site audit in line with regulatory guidelines.

7.4 Data quality assurance

7.4.1 Monitoring and auditing procedures

Physicians and institution(s) will permit registry related monitoring of the data. The registry site will be remotely monitored by the CRO or the Sponsor. Essential registry and site documents will be requested from physicians for quality check and for storage in the registry master file. Registry sites will be regularly contacted via telephone to assist with registry activities and through remote monitoring for queries.

On-site monitoring visits will take place for the sites participating in the PASS sub-study and if required by the sponsor On-site monitoring visit may take place also in sites not part of the PASS sub-study. The Monitor must be given direct access to clinical records, as far as these relate to the study and without jeopardising patient confidentiality.

Data inconsistencies or absence of follow-up assessments will be reviewed and discussed with

the sites until fully resolved.

The registry site may also be subject to quality assurance audit by the Sponsor or CRO.

7.4.2 Electronic case report forms (eCRFs)

The registry eCRF will be completed and signed electronically for each included patient. The Sponsor and the physician or his delegate should only allow individuals with the required qualifications or training in eCRF completion and data verification to take part in this task. Training to complete the eCRF will be provided by Sponsor assigned personnel.

Confirmation of this qualification or training should be available for inspection. Only authorised persons will receive a user name and password for data entry.

The physician should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs. All data requested on the eCRF must be recorded. Any missing data must be explained.

Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification. Additional requests for confirming or modifying questioned data may be generated through eCRF and obliged the investigator to respond.

7.4.3 Incorporation of data in the registry

XLH clinical trial data collected in clinical trials sponsored by Strakan International, Kyowa Hakko Kirin, Ultragenyx or Kyowa Kirin International will be used for data analysis with the registry data, if the informed consent in these studies allow for the data being used for further research purposes. The addition of previously collected XLH patient data will strengthen the ability of the registry to meet its primary objective.

7.4.4 Data extraction

Data collected in the registry may be extracted in the future to align with global XLH registries under development by Kyowa Hakko Kirin and Kyowa Kirin International. The purpose would be to create a global data resource to study the natural history of XLH. All parties are committed to ensuring patient confidentiality, data security and access to data to enable the characterisation of treatment, progression and long-term outcomes of XLH.

7.4.5 Source data

Data recorded in the eCRF should correspond to the data in the source documents, as applicable. To ensure the protection of patient confidentiality, only patient identification numbers will be used to identify all data reported in the eCRF.

7.4.6 Management and reporting of adverse events/adverse reactions

A subset of the registry data will be used to fulfil a PASS as requested by the EMA's CHMP. Study centres which agree to participate in the PASS will be asked to solicit adverse events on enrolled patients (please see Appendix 13.2).

Not all centres are expected to participate in the PASS. Centres which do not participate in the PASS will not actively solicit adverse event reports. Any adverse events reported by the patient and observed in normal clinical practice of the use of products other than burosumab (Sponsor product), will be reported to the Marketing Authorisation Holder for that product by the treating physician. Adverse events associated with exposure to Sponsor products (burosumab) will be handled and evaluated as spontaneously reported events and submitted to the Sponsor. Details of adverse event reports associated with any treatment for XLH submitted for an individual patient in the previous year will be captured in the annual registry entry for that patient. Adverse events will be coded with Medical Dictionary for Regulatory Activities (MedDRA) system and described by system organ class. Evaluation of cumulative adverse event information will be reported in the registry's interim and final analyses.

7.4.7 Training of registry staff

It is the responsibility of the physician to ensure that all site personnel involved in the registry are fully informed of all relevant aspects of the registry and have detailed knowledge of, and training in, the procedures that are to be completed by them.

All physicians and staff carrying out observations of primary or other major clinical outcome variables involved in the registry should provide curriculum vitae and where appropriate evidence of Good Clinical Practice (GCP) training. The physician will keep a list of all personnel involved in the registry, together with their function and delegated registry related duties. The physician will ensure that appropriate registry related training is given to all staff and that any new information of relevance to the performance of this registry is forwarded to all staff involved. Before the inclusion of patients, the CRO will perform a site initiation visit to inform and train relevant registry staff. All appropriate regulatory documents will be held in a registry trial

master file.

All participating clinics will be provided with instructions on which variables to enter and how to enter them into the registry. Calibration of scales used in the participating clinic will be performed according to hospital routines; it is expected that all participating clinics will have a routine established for such control. Laboratory analyses will be conducted according to hospital routines.

7.5 Scientific steering committee

An international scientific committee consisting of experts on XLH has been set up. This committee consists of Sponsor representatives and XLH physicians from across the globe.

Governance principles have been established describing committee members' responsibilities and obligations as well as the scientific oversight of the registry's publication policy (XLH Registry Access Agreement).

Physicians entering data into the registry will have ownership of their centre's aggregated data set. They or the patient will be free to withdraw their consent for their data to be used in analyses at any time.

Ownership of evidence generated from the aggregated data set will belong to the Sponsor. All evidence generated will be freely published by researchers with acknowledgment of the Sponsor and contributing investigator sites.

8 Statistical Methods and Determination of Sample Size

8.1 Analysis data set

All enrolled patients will be included in the data analysis set.

8.1.1 Analysis of registry data

MedDRA will be used to code medical history and concomitant disease. Reports will incorporate information up to and including the latest registry update for each patient. For regular reports on the registry data, all continuous variables will be described using standard statistical measures, i.e. number of observations, mean, standard deviation, median, minimum and maximum (quartiles and confidence intervals will be calculated as appropriate). All categorical variables will be summarised in frequency tables.

Disposition of patients, demographic data and other baseline characteristics will be analysed as described in the paragraph above. Laboratory measurements and other clinical data will be tabulated. Medications and medical history will be coded using the World Health Organisation Drug Dictionary before being summarised and tabulated. Patient outcome measures and QoL questionnaires will be summarised.

Additional details will be provided in the Statistical Analysis Plan.

8.2 Determination of sample size

This is a prospective observational registry study for patients with XLH. There is no sample size calculation based on statistical considerations. A survey conducted with XLH clinical experts across Europe provided evidence that the recruitment target of approximately 1200 XLH patients would be eligible to take part in the registry.

9 Ethical Requirements

9.1 Ethical review

Necessary approvals of the Registry Protocol, the Patient Information Sheet (PIS) and Informed Consent/Assent Forms, Letter of Invitations and GP Letters (as applicable) must be obtained before enrolment of any patient into the registry.

Furthermore, it is the responsibility of the Sponsor, according to local regulations, to keep the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) informed of any substantial amendments to the protocol during the study period. The written approval from the IRB/IEC, including registry identification and the date of the review will be filed at Sponsor and at the registry sites together with a list of the IRB/IEC members, their titles or occupation, and their institutional affiliations. All correspondence with the IRB/IEC should be filed both at Sponsor and at the study sites.

Annual and final registry reports will be completed for IRB/IEC by the Sponsor.

9.2 Ethical conduct of the study

The registry will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

9.3 Patient information and consent

It is the responsibility of the physician or clinical designee to give each potential patient (or their legally designated representative) adequate verbal and written information regarding the objectives and the procedures of the registry. This includes answering any questions the patient (or their legally designated representative) may have throughout their or their child's participation and sharing in a timely manner any new information that may be relevant to their willingness to continue their own or their child's participation in the registry.

The patient (or their legally designated representative) must be informed about the right to withdraw their permission for the entry of their own or their child's data into the registry at any time with no consequences for their own or their child's future treatment options. The patient (or their legally designated representative) should be allowed sufficient time for consideration of the proposal as assessed by the physician or clinical designee.

It is the responsibility of the physician or clinical designee to obtain signed informed consent (or witnessed verbal consent, according to local regulations) from all patients (or their legally designated representative) before including them in the registry. The ICF (adult or parental) must be signed and dated before any data can be registered in the registry.

The signed ICF (adult or parental) should be filed by the physician for possible future audits and/or inspections. A copy of the completed ICF (adult or parental) will be given to the patient (or their legally designated representative) for their records. The physician will confirm the receipt of the signed ICF (adult or parental) for each patient by marking the appropriate field of the patient's eCRF.

The final version of the PIS and ICF is submitted to the IRB/IEC(s) and must not be changed without permission from Sponsor and the local IRB/IEC.

Kyowa Kirin International will sponsor the XLH Registry for 10 years. Patients will provide informed consent to participate as long as the registry is active. The decision to discontinue the registry will be made by the Sponsor in agreement with applicable regulatory agencies.

10 Record Retention

The physician must arrange for retention of the list of patients and their identifying code (enrolment log), patient files and other registry documents at the investigational site. The

archiving period must be adapted to regulations in force and should not be shorter than 5 years after the termination of the registry and the presentation of the final report.

It is the responsibility of the Sponsor to inform the physician/institution as to when these documents no longer need to be retained.

10.1 Changes to any other pertinent study documents in the approved registry protocol

Any proposed change to the approved final registry protocol (including appendices) will be documented in a written and numbered protocol amendment. All amendments including substantial changes to the protocol must be submitted to appropriate IRB/IEC for approval, according to applicable national regulations. A substantial protocol amendment should be signed and dated by the same parties who signed the final registry protocol, as applicable.

10.2 Processing of personalised data

The physician must file a patient enrolment log which includes sufficient information to link records, i.e. the eCRF and clinical records. This list should be preserved for possible future inspections/audits but should not be made available to the CRO or Sponsor except for monitoring or auditing purposes.

Data will be stored in a regulatory compliant database and processing of the data including analysis will be performed according to the Regulation on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, the General Data Protection Regulation (EU) 2016/679 ("GDPR"). Patient data collection, processing, transfer, and storage will be performed in accordance with national data protection laws, identification of individual patient data will only be possible for the site physician.

The potential registry patient should be informed, that by signing the ICF he/she approves the processing of the data, the possible use of the data for research purposes other than the registry and that authorised representatives from the Sponsor, the IRB/IEC and the Regulatory Authorities might have direct access to his/her medical records. The patient has the right to withdraw the permission to enter data into the registry at any time, however informed consent will be asked to store all the data recorded up until the date of withdrawal.

Each centre will only have access to the patients under their direct care. The only demographic information collected includes their date of birth, biological gender, ethnic origin, and social demography. A unique username and password will be generated for each

person entering the data. Once the patient is initiated into the system, he/she will be assigned a unique number, which becomes his/her identification in the registry system.

10.3 Timetable

The registry will be initiated during August 2017. This registry is planned for 10 years and will be open for inclusion of patients until the decision to discontinue the registry has been taken by the Sponsor in agreement with applicable regulatory authorities.

10.4 Final study report and publication of registry results

Registry reports are to be written according to the objectives specified for evaluating the registry data. Statistical analysis of study reports will be performed under the supervision of the XLH Registry Steering Committee to meet any regulatory requirements from Regulatory/Health Authorities.

Statistical analysis methods to be applied to registry data aimed at publications in peer-reviewed journal or presented at congresses will be reviewed by the XLH Registry Steering Committee as part of the access to data assessment undertaken by the committee (please see XLH Registry Access Agreement).

10.5 Disclosure and confidentiality

Disclosure to third parties will be limited to those undertaking a legitimate peer review of the scientific and ethical aspects of the registry and to those participating, including the recipients of treatments, so that customary medical care and informed consent can be achieved. Details of access to data are outlined in the XLH Registry Access Agreement.

11 Site Agreements

The responsible physician at the investigational site must comply with all the terms, conditions, and obligations of the Site Agreement/Contract for this registry. In the event of any inconsistencies between the Registry Protocol and the Site Agreement, the Site Agreement shall prevail. Financial compensation given to the participating centres will be in relation to the time spent conducting registry related activities. Financial compensation will be documented in the agreement between Sponsor and the physician and/or institution and will be filed by both the physician and/or institution and the Sponsor.

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13 Appendices

13.1 Country coordinating investigators

This information will be provided in a separate document.

13.2 PASS protocol

Summary of differences between PASS protocol Version 1.0 and XLH Registry protocol Version 3.0

Crysvita (burosumab) was approved in Europe for the treatment of X-linked hypophosphataemia with radiographic evidence of bone disease in children 1 year of age and older and adolescents with growing skeletons, on 19 February 2018.

During assessment of the Crysvita marketing authorisation application, the Committee for Medicinal Products for Human Use (CHMP) stated that the company must perform a Post-Authorisation Safety Study (PASS) to investigate the long-term safety of burosumab. The CHMP requested that a full protocol for a PASS should be submitted by the company post-approval. The company therefore submitted a draft PASS protocol to the regulatory authorities in March 2018 and, following some revisions, the final PASS protocol was approved by the CHMP on 13 December 2018.

The approved PASS protocol describes a study to be conducted using an XLH disease registry as its data source and it is based upon information in the initial version of the XLH disease registry protocol (Version 1.0, dated 31 July 2017). However, the need for some important changes has led to the production of Version 3.0 of the registry protocol, dated 15 February 2019.

As a result, there are now some discrepancies between the information in the recently approved PASS protocol and the second version of the registry protocol.

The following table summarizes the differences between Version 1.0 of the PASS protocol and Version 3.0 of the registry protocol. It is anticipated that an application will be made to EU regulatory authorities to update the PASS protocol in line with Version 3.0 of the registry protocol in due course.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
1	Throughout the approved PASS protocol reference is made to a total of 11 participating EU countries (Belgium, Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom). The relevant sections of the protocol where this is mentioned are: **Section 1, PASS information, country(ies) of study – page 5** **Section 3, abstract, population – page 8** **Section 8.5, study size – page 13**	The registry protocol states that participating countries include, but are not limited to, United Kingdom, France, Italy, Spain, Netherlands, Sweden, Finland, Denmark, Germany, Belgium, Norway, Ireland, Austria, Portugal, Czech Republic, Slovakia, Slovenia, Hungary, Croatia, Romania, Bulgaria, Serbia, Poland, Russia, Greece, Israel, Kingdom of Saudi Arabia, Kuwait, United Arab Emirates and Oman. The relevant section where this is mentioned is: **Protocol synopsis, participating countries – page 5**	Since submission of the draft PASS protocol for EMA approval, the registry has been expanded as described in the registry protocol. The PASS will examine long-term safety in patients in European countries only.
2	The PASS protocol refers to a 'European registry of patients aged 1 year and older and adolescents with growing skeletons diagnosed with XLH'. **Section 3, abstract, data sources – page 8**	The disease registry will collect data on patients of all ages with XLH. **Protocol synopsis, inclusion criteria – page 5**	The PASS will only examine use of burosumab in those populations included in the European marketing authorisation.
3	Throughout the approved PASS protocol reference is made to a 'European (XLH/disease) registry'. The relevant sections of the protocol where this is mentioned are: **Section 3, abstract, study design – page 8** **Section 3, abstract, data sources – page 8**	The full registry title is 'An international, multicentre, prospective, non-interventional observational registry for patients with X-linked hypophophataemia'. **Protocol approval, protocol title – page 4** **Protocol synopsis, registry title – page 5**	Since the development of the first version of the registry protocol (dated 31 July 2017), the number of participating countries has been expanded from EU-only territories to include, but not be limited to, the 29 countries listed under comment no. 1 above. Hence the registry is described as international and not restricted to Europe.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
	Section 3, abstract, study size – page 8 **Section 6, rationale and background – page 10** **Section 8.1, study design – page 11** **Section 8.2, setting – page 11** **Section 8.4, data sources – page 12** **Section 8.7, data analysis – page 14** **Section 8.9, limitations of the research methods – page 15**		
4	The table listing the schedule of assessments has been updated in the registry protocol relative to the approved PASS protocol. **Section 8.3, variables, table 2 'Schedule of Assessments'**	The differences in this table in the two protocols are: - 'Medical history' in the PASS protocol table has been updated to 'Medical history and ongoing medical conditions' in the registry protocol - 'PHEX Mutation' in the PASS protocol has been updated to 'Relevant mutations' in the registry protocol and the schedule changed from retrospective/prospective to all data entry points - In the registry protocol 'Concomitant medications' has been deleted - In the registry protocol the 'Physiotherapy' schedule has been amended from	Since the submission of the draft PASS protocol for regulatory approval and the development of the first version of the registry protocol, the nature and schedule of assessments in the registry protocol have been reviewed. These changes will be applied to the PASS and will have minimal impact on the volume or nature of data to be analysed for the PASS.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
		retrospective/prospective to all data entry points - 'Physical examination (inc dental and audiology) in the PASS protocol has been amended in the registry protocol to separately specify 'physical examination' and 'audiology' – schedules unchanged; 'dental' has been deleted - In the registry protocol 'Examinations' has been separated into the categories of 'Radiographs and imaging', 'Echocardiogram', 'Electrocardiogram' and 'Renal ultrasound' – schedules unchanged - 'Exercise tolerance tests' in the PASS protocol has been deleted in the registry protocol - 'Patient quality of life' in the PASS protocol has been amended in the registry protocol to 'Patient QoL questionnaires' - 'Social impact' in the PASS protocol has been amended to 'Social history' in the	

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
		registry protocol with the schedule amended to include all data entry points **Section 7.1, overall registry design and schedule of assessments, table 1 'Schedule of assessment for data recordings'**	
5	The approved PASS protocol states that 'Data storage for the registry is being conducted by the contractor Castor EDC, with secure servers located in the Netherlands at Overamstel, Amsterdam, with backups located in Keienbergweg, Amsterdam, to ensure maximum security and continuity, in line with the EU Data Protection Directive. **Section 8.6, data management – page 13** **Section 8.8, quality control - page 14**	In the registry protocol all information relating to CASTOR EDC has been removed. **Section 7.4.2, electronic case report forms (eCRFs) – page 24**	Since the first version of the registry protocol the Contract Research Organisation has changed from Medialis to IQVIA and, thus, the EDC system has changed from Castor EDC to IBM CD.
6	The approved PASS protocol states that 'Medical history and drug details will be captured in the registry via use of ICD10 codes and the World Health Organisation Drug Dictionary'. **Section 8.7, data analysis – page 13**	The registry has been amended to state that MedDRA will be used to code medical history and concomitant disease, while the World Health Organisation Drug Dictionary will be used to code medications and medical history. **Section 7.4.6, management and reporting of adverse events/adverse reactions –**	Since the first version of the registry protocol these details have changed.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
		page 25 **Section 8.1.1, analysis of registry data – page 27**	
7	The approved PASS protocol states that 'the EDC tool used by the XLH disease registry will allow uploading of copies of ECGs or cardiac ultrasound scans into the registry database'. **Section 8.7, data analysis - page 14**	The new EDC tool described in the registry protocol version 3, does not allow for uploading of this information.	A new process for capturing ECG/cardiac ultrasound information is being implemented by the Sponsor. This information is a requirement of the PASS as stipulated by the PRAC.
8	The approved PASS protocol states that 'if any missing data are detected, an edit report will be generated. The edit reports will be sent electronically to the registry sites. When clarification has been obtained, the edit reports will be returned electronically to the registry. Electronic edit checks will be prepared in the system so that the data inconsistencies will be tested periodically.' **Section 8.8, quality control - page 14**	The registry protocol now states that missing data will be addressed via use of queries and not edit reports. **Section 7.4.1, monitoring and auditing procedures – page 23**	The registry protocol version 3 (section 7.4.1) now describes how missing data will be managed in the PASS.
9	The approved PASS protocol states that 'Funding is in place for 5 years. Further funding decisions will be made by the Sponsor after 5 years'. **Section 9, protection of human subjects, patient information and consent – page 16**	The registry protocol states that 'Kyowa Kirin International will sponsor the XLH Registry for 10 years'. **Section 9.3, patient information and consent – page 28**	Following comments from the PRAC, during assessment of the PASS protocol, that the study duration should be 10 years, the registry protocol was amended to reflect this.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
10	The data to be collected at the baseline data entry visit has been updated in the registry protocol relative to the approved PASS protocol. **Appendix 1, Table A, Details of data to be collected in XLH disease registry – baseline data entry visit – page 19**	The main differences in the two protocols are: - 'Site characteristics' has been added to the registry protocol - 'XLH-specific physical examination' has been added to the registry protocol - From the PASS protocol 'physical examination (inc age and disease specific examinations)' has been amended in the registry protocol to 'physical examination (inc dental and audiology)' - In the registry protocol 'genomic mutations' has been added to the list of laboratory assessments - In the registry protocol the following information has been deleted: 'physiotherapy reports', 'audiology assessment', most of the examples of 'patient quality of life questionnaires or assessment reports', 'social history' **Section 7.1, overall registry design and schedule of assessments, baseline visit - page 17**	Since the submission of the draft PASS protocol for regulatory approval and the development of the first version of the registry protocol, the nature and schedule of assessments in the registry protocol have been reviewed. These changes will be applied to the PASS and will have minimal impact on the volume or nature of data to be analysed for the PASS.

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
11	The data to be collected at the retrospective data entry visit has been updated in the registry protocol relative to the approved PASS protocol. **Appendix 1, Table B, Details of data to be collected in XLH disease registry – retrospective data entry visit – page 20**	The main differences in the two protocols are: - In the registry protocol 'PHEX mutation' has been augmented to 'PHEX mutation…and other genomic tests' - In the registry protocol 'XLH-specific medications inc pain medications' has been augmented to also specify growth hormones - In the registry protocol 'historical physical examinations' has been augmented to include dental and audiology assessments - In the registry protocol 'historical audiology assessment' and 'historical patients quality of life questionnaires or assessment reports' have been deleted **Section 7.1, overall registry design and schedule of assessments, retrospective visit - page 16**	Since the submission of the draft PASS protocol for regulatory approval and the development of the first version of the registry protocol, the nature and schedule of assessments in the registry protocol have been reviewed. These changes will be applied to the PASS and will have minimal impact on the volume or nature of data to be analysed for the PASS.
12	The data to be collected at the prospective data entry visit has been updated in the registry protocol relative to the approved PASS protocol. **Appendix 1, Table C, Details**	The main differences in the two protocols are: - In the registry protocol 'physical examination' has been augmented to include dental and	Since the submission of the draft PASS protocol for regulatory approval and the development of the first version of the registry protocol, the nature and schedule of assessments in

Comment no.	PASS protocol statement and location in protocol	XLH registry protocol statement and location in protocol	Explanation of discrepancy / proposal for future revision in PASS protocol
	of data to be collected in XLH disease registry – prospective/routine clinic visit – page 22	audiology assessments - In the registry protocol, 'laboratory assessments' has been augmented to specify genomic mutations - In the registry protocol 'audiology assessment' has been deleted - In the registry protocol most of the examples of 'patient quality of life questionnaires or assessment reports' have been deleted **Section 7.1, overall registry design and schedule of assessments, prospective/routine clinic visit - page 19**	the registry protocol have been reviewed. These changes will be applied to the PASS and will have minimal impact on the volume or nature of data to be analysed for the PASS.

Kyowa Kirin International plc

Post-Authorisation Safety Study - Burosumab

Final Protocol

Version 1.0

15 August 2018

Table of contents

List of abbreviations

Abbreviation	Definition
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU PAS register	European Union Electronic Register of Post-Authorisation Studies
FGF23	Fibroblast Growth Factor-23
GP	General Practitioner
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IgG1	Immunoglobulin G1
IRB	Institutional Review Board
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PHEX	Phosphate-regulating neutral Endopeptidase, X-linked
QoL	Quality of Life
RMP	Risk Management Plan
XLH	X-linked hypophosphataemia

1. PASS information

Title	**Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-linked Hypophosphataemia**
Protocol version identifier	Version 1.0
Date of last version of protocol	15 August 2018
EU PAS register number	Study will be registered in the EU PAS Register following PRAC approval of the final protocol, and prior to study initiation
Active substance	Active substance: burosumab - recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 ATC code: M05BX, other drugs affecting bone structure and mineralization
Medicinal product	Invented name: Crysvita Pharmaceutical form and strength: 10, 20 and 30 mg/mL solution for injection in vials
Product reference	To be confirmed
Procedure number	EMEA/H/C/4275
Marketing authorisation holder(s)	Kyowa Kirin Ltd Galabank Business Park Galashiels UK, TD1 1QH Tel +44 (0)1896 6640001 Email medinfo@kyowakirin.com
Joint PASS	No
MAH(s) contact	Charlotte Barrett European Qualified Person for Pharmacovigilance Address as above Email charlotte.barrett@kyowakirin.com
Research question and objectives	Primary objectives: 1. To evaluate the frequency and severity of safety outcomes in paediatric patients with XLH and radiographic evidence of bone disease who are aged 1 year of age and older and adolescents with growing skeletons, treated with

Title	**Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-linked Hypophosphataemia**
	burosumab, including but not limited to: death, hospitalizations, cardiovascular disease, cancer [all sites], hyperphosphataemia and its complications, ectopic mineralization and increased parathyroid hormone levels 2. To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab 3. To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at baseline treated with burosumab Secondary objective: 1. To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH
Country(-ies) of study	Belgium, Denmark, Finland, France, Germany, Italy, , Netherlands, Norway, Spain, Sweden and United Kingdom

2. Responsible parties

Main protocol authors	Kyowa Kirin International plc
Principal investigator	To be confirmed
Coordinating investigator for each participating country	To be confirmed

3. Abstract

Title	**Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-linked Hypophosphataemia**
Rationale and background	X-linked hypophosphataemia (XLH) is a rare, chronic deforming bone disease characterized by excess levels of circulating Fibroblast Growth Factor-23 (FGF23) leading to increased urinary phosphate excretion, reduced $1,25(OH)_2D$ synthesis, and subsequent hypophosphataemia. Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the excess biological activity of FGF23 thereby minimizing the clinical consequences of XLH by restoring normal serum phosphate levels. The CHMP has requested that the Company conduct a Post-Authorisation Safety Study (PASS) and recommended the use of a registry for this, if possible. The Marketing Authorisation Holder (MAH) for burosumab is working with Key Opinion Leaders specializing in the treatment of XLH to establish a European XLH registry. The purpose of the registry is to characterise the treatment, progression and long-term outcomes of XLH in the paediatric setting, expanding to later include use in adult patients pending marketing approval. It is proposed that the PASS is conducted using data collected in the new registry. The safety concerns to be investigated in this long-term PASS examining children and adults exposed to burosumab for the treatment of XLH are: 1. Long-term safety 2. Hyperphosphataemia 3. Ectopic mineralization 4. Effects on pregnancy outcomes 5. Increased parathyroid hormone levels 6. Effects in patients with mild to moderate chronic kidney disease at baseline
Research question and objectives	**Primary objectives** 1. To evaluate the frequency and severity of safety outcomes in patients with XLH with radiographic evidence of bone disease who are aged 1 year and older and adolescents with growing skeletons, and who are treated with burosumab, including but not limited to: death, hospitalizations, cardiovascular disease, cancer [all sites], hyperphosphataemia and its complications, ectopic mineralization, increased parathyroid hormone levels 2. To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab

	3. To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at baseline treated with burosumab **Secondary objective** 1. To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH
Study design	This is a 10-year prospective cohort study using data collected in a European disease registry for XLH. The PASS is non-interventional so all data collected will arise from the usual clinical management of these patients.
Population	This study is presented as a non-interventional PASS, with all patients investigated for the primary objective expected to receive treatment with burosumab in line with the stipulations of the Marketing Authorisation. Therefore, all patients investigated for the primary objective will comprise: • Children aged 1 year and older and adolescents with growing skeletons receiving burosumab for the treatment of XLH and enrolled in the registry via one of the 11 participating European centres Patients investigated for the secondary objective will be defined in the same way except that they may be treated with either burosumab or alternative pharmacotherapy for XLH.
Variables	In summary, the variables to be collected in registry which are relevant for the PASS are: • Demographic information; Medical history; PHEX Mutation (if available); XLH Medications and Drug History; Radiographs and imaging; Physical examination; Vital Signs; Laboratory assessments; Echocardiogram (ECHO); Electrocardiogram (ECG); Audiology; Renal Ultrasound; Social History
Data sources	The data source for the PASS is a European registry of patients aged 1 year and older and adolescents with growing skeletons diagnosed with XLH.
Study size	It is projected that the European XLH registry will contain data on around 1200 patients over 10 years. The number of patients exposed to burosumab is currently uncertain and depends on reimbursement decisions, but is anticipated to be around 400 patients at the end of 10 years, forming the sample for the primary objective. Approximately 800 patients are anticipated to be enrolled in the registry at 10 years, receive drug treatment for XLH other than burosumab, and be included in the PASS as the comparator group for the secondary objective.

Data analysis	The data analysis will be in the form of descriptive statistics as the sample size will not be sufficient for formal comparative analysis.
Milestones	See nested table below

Milestone	**Planned Date**
Start of data collection	Product launch (date to be confirmed)
End of data collection	2028
Study progress reports	Annually
First interim report of study results	To be submitted after 50 patients have achieved at least 6 months of time in the PASS
Second interim report of study results	To be submitted after 5 years, ie December 2023
Final report of study results	December 2028

4. Amendments and updates

Not applicable.

5. Milestones

Data from patients exposed to burosumab who have been enrolled in the registry will be presented at 6-monthly intervals initially, and thereafter, to synchronize with the data lock points of the Periodic Benefit-Risk Evaluation Reports (PBRERs). The PBRERs will describe the numbers of patients treated to date and the total patient-time. Annual progress reports will be provided as an annex to the PBRER.

Table 1. Study milestones

Milestone	**Planned Date**
Start of data collection	Product launch (date to be confirmed)
End of data collection	2028
Study progress reports	Annually
First interim report of study results	To be submitted after 50 patients have achieved at least 6 months of time in the PASS
Second interim report of study results	To be submitted after 5 years, ie December 2023
Final report of study results	December 2028

6. Rationale and background

XLH is a rare (estimated incidence 1/20,000 newborns), chronic, deforming bone disease. XLH is an X-linked dominant disorder which accounts for more than 80% of all familial hypophosphatemia. It is characterized by excess levels of circulating Fibroblast Growth Factor-23 (FGF23) leading to increased urinary phosphate excretion, reduced $1,25(OH)_2D$ synthesis, and subsequent hypophosphataemia.

Burosumab is a recombinant human IgG1 monoclonal antibody that binds to and inhibits the excess biological activity of FGF23. The aim of burosumab therapy is to minimise the clinical consequences of XLH by restoring normal serum phosphate levels.

A conditional marketing authorisation (MA) is being sought for burosumab based on submitted data from phase I and II clinical trials in paediatric subjects with XLH, with confirmatory data expected from ongoing phase III clinical trials. XLH has been acknowledged by the CHMP to be an area of unmet medical need justifying a conditional marketing authorisation application.

As part of the conditional MA approval, the CHMP requested that the majority of the safety concerns specified in the Risk Management Plan (RMP) be investigated in a Post-Authorisation Safety Study (PASS) and recommended the use of a registry for this if possible. The Marketing Authorisation Holder for burosumab is working with Key Opinion Leaders specializing in the treatment of XLH to establish a European XLH registry. The purpose of this registry is to collect natural history data for XLH, to characterize the treatment, progression and long-term outcomes of XLH in patients of all age groups. This will be a disease registry not a burosumab registry and it is proposed that the PASS is conducted using data collected in the new registry. The registry will be supported by the MAH.

The safety concerns to be investigated in this long-term PASS examining children exposed to burosumab for the treatment of XLH are:

1. Long-term safety (categorized as missing information in RMP)
2. Hyperphosphataemia (categorized as an important potential risk in RMP)
3. Ectopic mineralization (categorized as an important potential risk in RMP)
4. Effects on pregnancy outcomes (categorized as an important potential risk in RMP)
5. Increased parathyroid hormone levels (categorized as an important potential risk in the RMP)
6. Effects in patients with mild to moderate chronic kidney disease at baseline (categorized as missing information in RMP)

7. Research question and objectives

7.1 Primary objectives

1. To evaluate the frequency and severity of safety outcomes in patients with XLH aged 1 year of age and older and adolescents with growing skeletons and treated with burosumab, including but not limited to: death, hospitalizations, cardiovascular disease, cancer [all sites], hyperphosphataemia and its complications, ectopic mineralization and increased parathyroid hormone levels

2. To prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab
3. To prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate chronic kidney disease at baseline treated with burosumab

7.2 Secondary objectives

1. To perform a retrospective cohort study using data from the registry to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH

8. Research methods

8.1 Study design

Overall, this is a 10-year prospective cohort study using data collected in a new European disease registry for XLH. Given the very rare incidence of the disease, the fact that children are affected and the potential seriousness of the safety concerns, this approach is considered the most practical option for collecting detailed information over a long period of time on the disease and available treatments, and for identifying the need for regulatory action in a timely way, should one arise.

The PASS is non-interventional so all data collected will arise from the usual clinical management of these patients.

8.2 Setting

This study is presented as a non-interventional PASS, with all patients investigated for the primary objective expected to receive treatment with burosumab in line with the stipulations of the Marketing Authorisation. Therefore, all patients investigated for the primary objective will comprise:

> Children aged 1 year of age and older and adolescents with growing skeletons, receiving burosumab for the treatment of XLH and enrolled in the registry via one of the 11 participating European countries

Patients investigated for the secondary objective will be defined in the same way except that they may be treated with either burosumab or alternative pharmacotherapy for XLH.

8.3 Variables

Full details of all the information to be collected in the registry at baseline and subsequent visits are given in **Appendix 1, Tables A to C.**

Table 2 below gives a summarized version of this information and highlights those assessments to be extracted for investigation in the PASS.

Table 2. Schedule of Assessments for Data Recordings

	Baseline Data Entry	**Retrospective** Data Entry	**Prospective** (Data prompted to be updated in the database annually)	**Assessment to be investigated in PASS?**
Informed consent*	X		X*	No
Demographic information	X			Yes
Medical history		X	X	Yes
PHEX Mutation (if available)**		X	X**	Yes
XLH medications and drug history	X	X	X	Yes
Radiographs and imaging	X	X	X	Yes
Physical examination	X	X	X	Yes
Vital signs	X	X	X	Yes
Growth assessment	X	X	X	No
Laboratory assessments	X	X	X	Yes
Physiotherapy	X	X	X	No
Echocardiogram (ECHO)	X	X	X	Yes
Electrocardiogram (ECG)	X	X	X	Yes
Audiology	X	X	X	Yes
Renal ultrasound	X	X	X	Yes
Patient Assessment Tools/Outcome Measures	X	X	X	No
Patient QoL Questionnaires	X	X	X	No
Social history	X	X	X	Yes

*Re-consent to adult registry consent when patient transitions from paediatric patient to adult
** PHEX mutation to be recorded in prospective visit if not available at baseline

8.4 Data sources

The source data for the PASS is a European registry of patients of all ages and diagnosed with XLH, who are either naïve to treatment, treated with conventional therapy (oral phosphate and active vitamin D analogue) or currently untreated.

The registry will capture treatment details and clinical outcome variables in patients with XLH. Patients will be followed as long as informed consent exists. Only data collected during standard routine examinations will be recorded in the registry.

Since data from the registry can be made available to other external researchers in addition to the MAH for burosumab (subject to the agreement of the registry's Steering Committee), the conduct of this PASS is considered to constitute secondary use of data.

Since the registry will be new it will not be possible to validate the data source. Data linkage will not be a feature of the PASS.

8.5 Study size

Approximately 1,200 patients with XLH in Europe are estimated to be eligible for inclusion in the registry. Assuming 50% enrolment of the eligible patient population, it is projected that the European XLH registry will contain data on around 1200 patients over 10 years. The number of patients to be exposed to burosomab is currently uncertain and depends on reimbursement decisions, but is anticipated to be around 400 patients at the end of 10 years.

The sample size of 400 has been estimated as follows:

- Total number of patients to be enrolled in the registry over 10 years = 1200 (achievable if all 11 planned European centres recruit as anticipated)
- Number of burosumab-eligible patients within this group of 1200 = 600 (an assumption that 50% of patients in the registry are children aged one year or over – broadly accurate from the EU centres with available demographic data)
- Number of burosumab-treated patients enrolled in the registry over 10 years and included in the PASS = 400 (assuming that 2/3rds of eligible patients will receive burosumab, acknowledging the issues of reimbursement and individual patient factors/choice, and assuming that all exposed patients consent to inclusion in the PASS)
- Number of patients not exposed to burosumab and assumed to be receiving alternative treatments = 800 (assuming that all patients receive drug treatment)

Overall, it is anticipated that approximately 400 patients will be enrolled in the registry, receive burosumab treatment and be included in the PASS, forming the sample for the primary objective. Approximately 800 patients are anticipated to be enrolled in the registry, receive drug treatment for XLH other than burosumab, and be included in the PASS as the comparator group for the secondary objective.

8.6 Data management

Data collection within the European XLH registry will take place via an Electronic Data Capture (EDC) tool, with its core data specification approved by the registry's Steering Committee. The specific subset of information to be recorded to support the conduct of the PASS is reflected in **Table 2** above and in **Appendix 1, Tables A to C.**

Data storage for the registry is being conducted by the contractor Castor EDC, with secure servers located in the Netherlands at Overamstel, Amsterdam, with backups located in Keienbergweg, Amsterdam, to ensure maximum security and continuity, in line with the EU Data Protection Directive. Data for the PASS provided by the European XLH registry owners will follow the rules for data use from the registry.

Source data verification of a representative portion of raw data at participating centres will be conducted.

8.7 Data analysis

Given the orphan indication and likely relatively small number of burosumab patients (estimated to be around 400 patients in the registry at the end of 10 years) the data analysis will be in the form of descriptive statistics as the sample size will not be sufficient for formal comparative analysis.

Medical history and drug details will be captured in the registry via use of ICD10 codes and the World Health Organisation Drug Dictionary.

For the primary objectives, relevant code lists will be developed to identify cardiovascular disease, cancers, hyperphosphataemia and its complications and increased parathyroid hormone levels. Deaths and hospitalisations will be identified using structured data fields in the registry. Ectopic mineralisation will be identified from results of various investigations such as ECG. The EDC tool used by the XLH disease registry will allow uploading of copies of ECGs or cardiac ultrasound scans into the registry database, which will highlight the availability of this information and make the data available for independent review. Results of all ECGs, or ad hoc cardiac investigations such as echocardiography, will be subject to central specialist review.

Pregnancy will be captured by relevant structured data fields and the outcome of any pregnancies will be followed up.

Information on renal status will be assessed from data captured in the registry and from the results of laboratory tests. This will enable stratification of the cohort by renal status and for descriptive comparisons of safety outcomes to be made.

For the secondary objective:

- The European XLH registry will provide the basis for a contextual cohort of XLH patients not treated with burosumab.
- Data from these patients will be used for a retrospective cohort study to compare the safety outcomes of interest in patients exposed to burosumab to those in patients receiving alternative treatments for XLH.
- Given the small number of patients this analysis will not be statistically powered for other than very high relative risks.
- However, the descriptive analyses will provide useful information on long term outcomes for both burosumab treated and non-treated patients.
- In addition, a case-control analysis will be performed to account for potential selection bias, based on burosumab exposure/non-exposure.

8.8 Quality control

Data entered into the registry will be checked automatically using logical checks - limits set within the database program. Additional controls will be performed by the Contract Research Organisation (CRO) managing the registry (Castor EDC) to detect inconsistencies or absence of follow-up assessments. If any missing data are detected, an edit report will be generated. The edit reports will be sent electronically to the registry sites. When clarification has been obtained, the edit reports will be

returned electronically to the registry. Electronic edit checks will be prepared in the system so that the data inconsistencies will be tested periodically.

8.9 Limitations of the research methods

- Sample size: the registry and the PASS will collect clinical practice data on XLH patients. However the sample size is likely to mean that formal comparative analyses are not possible or results may not reach statistical significance.
- Missing data: patients with XLH will be under the care of a consultant for their condition but may not have frequent appointments. Therefore data capture on intervening events may be incomplete.
- Selection bias:
    - Site selection - a comprehensive program was conducted by the MAH in order to identify XLH-treating health centres in Europe. All identified XLH treatment sites were approached and invited to participate in the Registry. All sites participating in the Registry will be invited to participate in the PASS. Hence the MAH has attempted to minimize the possibility of selection bias in the approach taken to site recruitment.
    - Patient selection – all investigators will be strongly encouraged to enrol subjects who are representative of the general XLH population.
    - Statistical analysis - an approach to overcoming selection bias is the use of case-control matching, however, this type of analysis requires a population sufficiently large to identify cases of interest and randomly selected controls. As part of the statistical analysis for the final study report for the PASS, the MAH will undertake case-control matching based on burosumab exposure/non-exposure.
- Information bias: the use of the same EDC system by every Registry site will standardize the nature of the information collected. Source data verification of a representative portion of raw data at participating centres will be implemented to verify the quality of the data collection. It must be reiterated, however, that some information will only be entered by the sites if available, since the Registry does not mandate investigations outside of standard care as determined by the treating physicians.
- Confounding: the EDC system allows the collection of detailed information on multiple variables relevant to the objectives being explored in the PASS. This will reduce the potential for residual confounding subject to the completeness of the data entry by the contributors.

9. Protection of human subjects

The conduct of this PASS is considered to constitute secondary use of data. Informed consent will be required for patients to be enrolled in the registry. Patient data utilized in the PASS will be de-individualized. There will be no additional procedures relevant to the PASS.

The provisions for protection of human subjects enrolled in the registry comprise:

Ethical review

- Approvals required for the Registry Protocol, the Patient Information Sheet, Informed Consent/Assent Forms, Letter of Invitations and GP Letters will be obtained before enrolment of any patient into the registry.
- Furthermore, it is the responsibility of the Sponsor, according to local regulations, to keep the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) informed of any substantial amendments to the protocol during the study period. The written approval from the IRB/IEC, including registry identification and the date of review will be filed at Sponsor and at the registry sites together with a list of the IRB/IEC members, their titles or occupation, and their institutional affiliations. All correspondence with the IRB/IEC will be filed both at Sponsor and at the study sites.
- Annual and final registry reports will be completed for IRB/IEC by CRO or Sponsor.

Ethical conduct of the study

- The registry will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects that were adopted in 1964 by the 18th World Medical Assembly, in Helsinki, Finland, with later revisions.

Patient information and consent

- It will be the responsibility of the physician or clinical designated to give each potential patient (or their guardian) adequate verbal and written information regarding the objectives and the procedures of the registry.
- The patient (or their guardian) will be informed about the right to withdraw their permission for entry of their own or their child's data into the registry at any time.
- It will be the responsibility of the physician or clinical designate to obtain signed informed consent (or witnessed verbal consent, according to local regulations) from all patients (or their guardian) before including them in the registry. The Informed Consent form (adult or parental) must be signed and dated before any data can be registered in the registry.
- The Final version of the Patient Information sheet and Informed Consent form is submitted to the IRB/IEC(s) and must not be changed without permission from Sponsor and the local IRB/IEC.
- Funding is in place for 5 years. Further funding decisions will be made by the Sponsor after 5 years. Patients (or their guardian) will provide informed consent to participate as long as the registry is active.

Data protection

- The physician must file a patient enrolment log which includes sufficient information to link records, i.e. the eCRF and clinical records. This list should be preserved for possible future inspections/audits but will not be made available to the CRO or sponsor except for monitoring or auditing purposes.
- Data will be stored in a regulatory compliant database and processing of the data including analysis will be according to the European Directive on the processing of personal data and the protection of privacy in the electronic communication sector (2002/58/EC). All patient information

will be handled in accordance with national data protection standards, identification of individual patient data will only be possible for the site physician.

- A potential registry patient will be informed that by signing the Informed Consent Form he/she approves the processing of the data and that authorised representatives from the Sponsor, the IRB/IEC and the Regulatory Authorities to have direct access to his/her medical records.
- The patient will have the right at any time to withdraw the permission to enter data into the registry, however informed consent will be obtained to store all the data recorded up until the date of withdrawal.
- Each centre will only have access to the patients under their direct care. The only demographic information collected is the date of birth, gender and ethnic origin. A unique user name and password will be generated for each person entering the database. Once the patient is initiated into the system, he/she will be assigned a unique number, which becomes his/her identification in the Registry system. All centre information is maintained in regulatory compliant database.

10. Management and reporting of adverse events/adverse reactions

Patients enrolled in the PASS will be subject to solicited adverse event reporting. .This will take place as follows:

Staff training:

- The training provided to healthcare professionals and other staff submitting data to the registry for patients enrolled in the PASS will include a specific request for adverse event information to be solicited during interactions with patients
- The request for adverse event information from the patient will be by means of an open question which is not limited to specific adverse events of interest or to any specific XLH treatment
- This training will also remind the healthcare professional and other staff submitting data to the registry for PASS patients to report adverse events in real time to the Sponsor of the PASS (if burosumab is the suspect medication) or otherwise to the Marketing Authorisation Holder of the suspect medication (if not burosumab)

Data entry:

- The EDC tool used by the XLH disease registry will ensure that, during every episode of data entry, the person uploading information for a PASS patient will be prompted to enter data on any adverse events solicited and recorded during interactions with the patient
- The prompt will require the data entry person to report any adverse events disclosed by the patient to the PASS Sponsor via spontaneous reporting mechanisms, if this has not already been done, or to the Marketing Authorisation Holder of any other suspect medication

Any adverse events reported by the patient and arising in normal clinical practice with the use of products other than burosumab will be reported to the Marketing Authorisation Holder for that product by the treating physician.

Since the PASS will be using data that are captured in the disease registry, this is therefore deemed to be secondary use of data. Individual Case Safety Reports (ICSRs) will therefore not be submitted and reports of adverse events/reactions as defined by the study endpoints will be summarised as part of any interim safety analysis for the PASS and in the final study report for the PASS.

11. Plans for disseminating and communicating study results

The sponsor will prepare progress reports annually or as required by the European Medicines Agency. In addition these may be summarised periodically for presentation at professional conferences or academic meetings as appropriate.

A first interim analysis is planned after 50 patients have at least 6 months of time in the PASS, and a second interim analysis is planned for 5 years from the date of initiation of the PASS (ie in December 2023).

This study will be entered into the European Union Electronic Register of Post-Authorisation Studies.

None of the parties involved in the management/conduct/analysis of the PASS may publish any PASS-related results without the written permission of Kyowa Kirin International plc.

12. References

APPENDIX 1

Table A. Details of data to be collected in XLH disease registry[1] – baseline data entry visit

Information / assessment - mandatory	**Data to be investigated in PASS?**
1. Informed Consent (date and type of consent)	No
2. Demographics • Date of Birth • Biological Gender • Ethnicity	Yes
Information / assessment – data to be recorded if available; the registry does not mandate investigations outside of standard care as determined by the patient's physician	**Data to be investigated in PASS?**
3. XLH-specific medication • all XLH specific medications prescribed within 30 days prior to written consent (including dose, compliance, duration of treatment and reason for discontinuation if applicable)	Yes
4. Drug history • all current medications prescribed within 30 days prior to written consent (including dose, compliance, duration of treatment and reason for discontinuation if applicable)	Yes
5. Radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
6. Physical examination (including age and disease specific examinations)	Yes
7. Vital signs (temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
8. Growth Assessment including: • standing and sitting height (meters) • arm and leg length (meters) • weight (Kg) • Body Mass Index (BMI) • Z score (based on background national reference)	No
9. Laboratory Assessments including: • Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
10. Physiotherapy reports including: • use of a wheelchair • walking aids • medical device • home adaptations	No
11. Echocardiogram (ECHO) reports	Yes
12. Electrocardiogram (ECG) reports	Yes
13. Audiology assessment	Yes
14. Renal ultrasound scan	Yes
15. Assessment Tools/Outcome Measure reports: • Six-minute walk test (6MWT) • Timed Up and Go (TUG)	No

[1] 'X-linked hypophosphataemia registry protocol', Protocol Version 1.0, 31 July 2017, clinicaltrials.gov ID no. NCT03193476

• Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	
16. Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age) • Pain: Faces Pain Scale-Revised (FPS-R) (for children ≥ 5 years of age) • Brief Pain Inventory –Short Form (SF) (for adult subjects) • Brief Fatigue Inventory – SF (for adult subjects) • Short Form 36 (SF-36) (for adult subjects) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (for adult subjects) • Abbreviated XLH Resource Utilization Survey • Five-level version of the EuroQol five-dimensional descriptive system (EQ-5D 5L) (for children ≥ 5 years of age and adult subjects) • EQ-5D 5L Proxy (for children < 5 years of age) • Paediatric Musculoskeletal Functional Health Questionnaire (PODCI- POSNA) • General Function Score (GFS) • Health Assessment Questionnaire (HAQ) • Patient Index Data 3 (RAPID3) • Patient Pain Diary	No
17. Social History • Number of work/school dates missed due to XLH-related illness since last visit	Yes

Table B. Details of data to be collected in XLH disease registry – retrospective data entry visit

Information / assessment - retrospective data entry will include the patient's medical history and may include the following data sets <u>if available</u>	**Data to be investigated in PASS?**
1. XLH-specific medical, surgical and dental history: • Diagnostic history: age of onset of symptoms, age at diagnosis, diagnosis method(s) • PHEX mutation (if available) • Family history: number of known affected relatives and relationship to subject	Yes
2. General medical history: • Pregnancy and foetal outcomes including weight, length, Apgar score, mode of delivery (if applicable)	Yes
3. XLH-specific medications including pain medications (including dose compliance, duration of treatment and reason for discontinuation if available)	Yes
4. Historical radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
5. Historical physical examinations (including age and disease specific examinations)	Yes
6. Historical vital signs (including temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
7. Historical growth assessment including: • standing and sitting height (meters) • arm and leg length (meters) • weight (Kg) • Body Mass Index (BMI) • Z score (based on background national reference)	Yes
8. Historical laboratory assessments including: • Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
9. Historical physiotherapy reports including: • Number of visits • use of a wheelchair • walking aids • medical device • home adaptations	Yes
10. Historical echocardiogram (ECHO) reports	Yes
11. Historical electrocardiogram (ECG) reports	Yes
12. Historical audiology assessment	Yes
13. Historical renal ultrasound scan	Yes
14. Historical Assessment Tools/Outcome Measure reports: • Six-minute walk test (6MWT) • Timed Up and Go (TUG) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	No
15. Historical Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age)	No

• Pain: Faces Pain Scale-Revised (FPS-R) (for children ≥ 5 years of age) • Brief Pain Inventory –Short Form (SF) (for adult subjects) • Brief Fatigue Inventory – SF (for adult subjects) • Short Form 36 (SF-36) (for adult subjects) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (for adult subjects) • Abbreviated XLH Resource Utilization Survey • Five-level version of the EuroQol five-dimensional descriptive system (EQ-5D 5L) (for children ≥ 5 years of age and adult subjects) • EQ-5D 5L Proxy (for children < 5 years of age) • Paediatric Musculoskeletal Functional Health Questionnaire (PODCI- POSNA) • General Function Score (GFS) • Health Assessment Questionnaire (HAQ) • Patient Index Data 3 (RAPID3) • Patient Pain Diary	
16. Historical social history: • Number of work/school dates missed due to XLH-related illness since last visit	Yes

Table C. Details of data to be collected in XLH disease registry – prospective/routine clinic visit

Paediatric subjects will be asked to provide registry consent when they reach the applicable age to do so per national guidelines at participating centres.

Information / assessment – data to be recorded if available • **if a patient attends more regularly data will be entered in the registry to reflect these visits at the 12 month interval, with an option to add multiple dates** • **the registry does not mandate investigations outside of standard care as determined by the patient's physician**	**Data to be investigated in PASS?**
1. Changes to general medical history (since baseline or last recorded entry) including: • All incidents of hospitalisation (including duration and cause of admission) • Pregnancy including the following information relating to Sponsor products: i. Timing of gestational exposure ii. Duration of exposure iii. Foetal outcomes including weight, length, Apgar score and mode of delivery • Date of death (including cause of death)	Yes
2. Changes to XLH – specific medical, surgical and dental history (since baseline or last recorded entry) • PHEX genetic testing (if available)	Yes
3. XLH-specific medications including pain medications (including dose compliance, duration of treatment and reason for discontinuation if available)	Yes
4. Drug history • Current - all medications ongoing at the time of prospective clinic visit including dose, compliance and duration of treatment • Previous – all medications and therapies (since baseline or last recorded entry) including dose, compliance, duration of treatment and reason for discontinuation if available	Yes
5. Radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
6. Physical examination (including age and disease specific examinations)	Yes
7. Vital signs (temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
8. Growth Assessment including: • standing and sitting height (meters) • arm and leg length (meters) • weight (Kg) • Body Mass Index (BMI) • Z score (based on background national reference)	No
9. Laboratory Assessments including: • Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
10. Physiotherapy reports including: • Number of visits • use of a wheelchair	No

• walking aids • medical device • home adaptations	
11. Echocardiogram (ECHO) reports	Yes
12. Electrocardiogram (ECG) reports	Yes
13. Audiology assessment	Yes
14. Renal ultrasound scan	Yes
15. Assessment Tools/Outcome Measure reports: • Six-minute walk test (6MWT) • Timed Up and Go (TUG) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	No
16. Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age) • Pain: Faces Pain Scale-Revised (FPS-R) (for children ≥ 5 years of age) • Brief Pain Inventory –Short Form (SF) (for adult subjects) • Brief Fatigue Inventory – SF (for adult subjects) • Short Form 36 (SF-36) (for adult subjects) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (for adult subjects) • Abbreviated XLH Resource Utilization Survey • Five-level version of the EuroQol five-dimensional descriptive system (EQ-5D 5L) (for children ≥ 5 years of age and adult subjects) • EQ-5D 5L Proxy (for children < 5 years of age) • Paediatric Musculoskeletal Functional Health Questionnaire (PODCI- POSNA) • General Function Score (GFS) • Health Assessment Questionnaire (HAQ) • Patient Index Data 3 (RAPID3) • Patient Pain Diary	No
17. Social History • Number of work/school dates missed due to XLH-related illness (since baseline or last recorded entry)	Yes

13.3 Signature page

I have read the X- linked Hypophosphatemia Registry protocol and agree to conduct the registry as outlined. I confirm that I will conduct the registry in accordance with International Council for Harmonization (ICH) GCP guidelines. I will ensure that any Sub-Investigator(s) and other relevant members of my staff have access to copies of this protocol and ICH GCP guidelines to enable them to work in accordance with the provisions of these documents. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date (DD/MMM/YYYY)