KYOWA KIRIN

X-Linked Hypophosphatemia Registry Protocol

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Protocol Version:	4.0
Date:	27 October 2021

Registry title	X-Linked Hypophosphatemia Registry
Design	Multicentre, prospective, non-interventional observational registry
Population studied	X-Linked Hypophosphataemia (XLH)

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Confidentiality Statement

KYOWA KIRIN

Protocol Approval

Protocol Title:	An international, multicentre, prospective, non-interventional observational registry for patients with X-linked hypophosphatemia (XLH)
Protocol Version:	Version 4.0
Protocol Date:	27 October 2021

DocuSigned by:
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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, Austria, Belgium, Bulgaria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Latvia, Luxembourg, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom.
Background XLH is characterised by renal phosphate wasting, hypophosphataemia, defective bone and teeth mineralisation, and/or delayed endochondral ossification caused by inactivating mutations in the PHEX gene. Kyowa Kirin International (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 enable studies to characterise the treatment, burden of disease, disease progression, and long-term outcomes of XLH.
Number of Subjects Planned This Registry will take place at hospital sites across Europe and the Middle East. It is projected that the Registry will contain data on approximately 1,200 subjects spanning 10 years. The number of subjects that will be treated with burosumab is currently uncertain and depends on in-country reimbursement decisions, but it is anticipated to be approximately 400 subjects at the end of 10 years. Therefore, approximately 800 subjects are anticipated to be enrolled in the Registry at the end of 10 years who will either be receiving drug treatment for XLH other than burosumab or be untreated.

Inclusion Criteria

A subject must meet the following criteria at the enrolment visit (i.e. "baseline visit") to be eligible for inclusion into the Registry:

1. Subjects of all ages at baseline.
2. In the opinion of the treating physician, the subject has clinical presentation, radiological, biochemical, genetic or family mapping investigation results that support the diagnosis of XLH.
3. Subjects who provide written informed consent/assent after the nature of the Registry has been explained.

Exclusion Criteria

A subject who meets any of the following criteria at the enrolment visit (i.e. "baseline visit") cannot be included in the Registry:

1. Subject - or their legally-designated representative - does not have the cognitive capacity to provide informed consent.
2. Subject is currently participating in an interventional clinical trial. Subjects will be approached for inclusion into the Registry once their involvement in that interventional trial ends (including the completion of all trial follow-up assessments). Participation in a Compassionate Use Programme, Pre-commercial Programme (e.g. Named Patient Sales, Nominative Autorisation Temporaire d'Ultisation [ATU], Early Access Programme [EAP], Post-Trial Access Programme [PTAP]), Investigator Initiated Study, or an observational study does not preclude a subject from participation in this Registry.

Methodology

This is an international, multicentre, prospective, non-interventional observational Registry of subjects 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 subjects.

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

All eligible subjects at the participating hospital sites are expected to be asked by their physician to participate in the Registry.

- Informed consent will be obtained from adult subjects.
- 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 subject into the Registry will assess the appropriateness of gaining assent from an individual at their

discretion.

- After the subject - or legally-designated representative - has signed the informed consent, the subject's 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 subject identification number will be automatically generated by the system upon enrolment.

No pre-determined follow-up requirements will apply. However, physicians should ensure prompt reporting of accurate and complete data in the Registry Electronic Data Capture (EDC) after a subject'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. Subjects will be asked to provide responses to some Quality of Life scales (including, but not limited to, SF-36 and PedsQL). Completion of these questionnaires is optional/recommended, but not required.

Additionally, a subset of the Registry data will be used to fulfil a Post-Authorisation Safety Study (PASS) of burosumab treatment. Hospital sites which agree to participate in the PASS will be asked to solicit Adverse Events on enrolled subjects treated with burosumab (the PASS is detailed in Appendix 13.1).

Not all hospital sites are expected to participate in the PASS.

Duration Of Subjects' Involvement In The Registry

Kyowa Kirin International will sponsor the XLH Registry for 10 years. Subjects will provide informed consent to participate as long as the Registry is active. A subject, or their legally-designated representative, may withdraw consent at any time.

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. Based upon the scope of the participating countries and their hospital sites, it is projected that the XLH Registry will contain data on approximately 1,200 subjects spanning 10 years.

The data analysis will be in the form of descriptive statistics. 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
3	27 October 2021	The Registry protocol was updated to capture changes from the PASS protocol Version 2.0.	To align the Registry protocol with the PASS protocol version 2.0
		Details of the Sponsor signatory, statistician, medical advisor and project manager were updated	Administrative
		The list of participating countries was updated	Administrative
		The primary objective wording was updated	For clarification
		The secondary objective wording was updated to remove reference to effectiveness and safety	Safety of burosumab is addressed in the PASS protocol
		The new IQVIA Connection platform and details on the data collection process for the PRO questionnaires was included.	Administrative
		Specific time windows were added for data entry in the EDC.	To align with the SIV and SAP
		Inclusion of COVID-19 data collection in the EDC.	To capture the impact of the COVID-19 pandemic

			on subject visits and assessments
		Reference to a Registry "study" removed.	Updated for clarification since the Registry is a data collection tool
		PASS protocol Version 2.0 added to the appendix.	To replace the Version 1.0 PASS protocol
		Correction of minor typographical and grammatical errors throughout the protocol.	Administrative
		Appendix 13.1 Country coordinating investigators was removed.	The appendix is not applicable

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
AE	Adverse Event
ATU	Autorisation Temporaire d'Utilisation
BMI	Body Mass Index
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency Section Edition
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
CT	Computed Tomography
DEXA	Dual-Energy X-Ray Absorptiometry
EAP	Early Access Programme
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
ePRO	Electronic Patient Reported Outcomes
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

Abbreviation or special term	Explanation
Kg	Kilogram
KKI	Kyowa Kirin International
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PASS	Post-Authorisation Safety Study
PedsQL	Paediatric Quality of Life
PHEX	Phosphate-regulating gene with homologies to endopeptidases on the X chromosome
PTAP	Post-Trial Access Programme
QoL	Quality of Life
SAP	Statistical Analysis Plan
SF-36	Short Form 36
TUG	Timed Up and Go
WHO	World Health Organisation
XLH	X- Linked Hypophosphataemia

2 Introduction

2.1 Disease background

X-Linked Hypophosphataemia (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, hypophosphataemia, defective bone and teeth mineralisation, 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 mineralisation resulting in the two major pathological consequences of the hypophosphataemia, i.e. 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 can heal rickets, limit dental abscess formation and prevent 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). Burosumab, a fully humanised monoclonal IgG1 antibody which neutralises FGF23, has been approved by the health authorities for treatment of XLH patients in a number of countries worldwide, including a conditional marketing authorisation in the European Union by the European Medicines Agency (EMA) and in the United Kingdom by the Medicines and Healthcare products Regulatory Agency for use in children and adolescents 1 to 17 years of age and in adults (EMA 2021).

2.2 Registry background

There are 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.

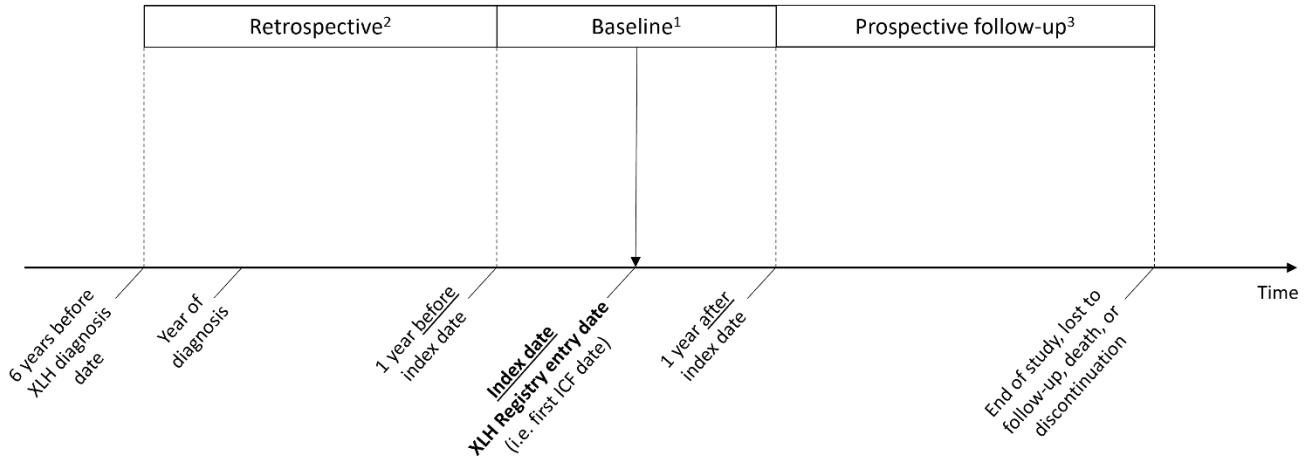
The Registry will be a multicentre, prospective, non-interventional observational Registry of subjects with XLH, sponsored by Kyowa Kirin International. Data from the Registry are intended to enhance understanding of the variability, progression, and natural history of XLH as well as the burden of disease for healthcare providers and healthcare decision-makers. Eligible hospital sites will be invited to participate in the Registry.

3 Registry 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/or active vitamin D analogue), treated with burosumab, or currently untreated.

This Registry will capture treatment details and clinical outcome variables in subjects with XLH. Subjects 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. Subjects will be asked to complete Quality of Life scales (including, but not limited to, Short Form 36 [SF-36] and Paediatric Quality of Life [PedsQL]); these are optional/recommended and not mandated as per this protocol. The study diagram is presented in ***Figure 1***.

Figure 1 Study Diagram



[1] Baseline period is the closest assessment date allowing a time window of +/- 1 year from index date (i.e. first ICF signature) including the ICF signing visit.
[2] Retrospective period is all the assessment dates since baseline up to 6 years before diagnosis date, except for Medical History form where sites will enter all data available. Example: a patient signed the first ICF on 20Oct2018 and was diagnosed on 11Jul2014, then retrospective will be all the visits up to 6 years before diagnosis, i.e. all visits up to 6 years before 11Jul2014. For Medical History form, all available information should be entered.
[3] Prospective period is all the assessment dates after baseline until the earliest of end of study, lost to follow-up, death, or discontinuation.

A subset of the Registry data will be used to fulfil a Post-Authorisation Safety Study (PASS) of burosumab as requested by the EMA's Committee for Medical Products for Human Use (CHMP). Details of the analysis populations for the PASS are described in the PASS protocol (Appendix 13.1). Hospital Sites which agree to participate in the PASS will be asked to solicit Adverse Events (AEs) on enrolled subjects treated with burosumab. Not all hospital sites 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 subjects. Any investigations performed for subjects in the PASS (such as blood tests, ECGs, renal ultrasound scans, or echocardiograms) will be at the discretion of the physicians managing the subjects according to the subjects' medical needs. Such investigations are not mandatory under the PASS protocol.

4 Registry Objectives

The main objectives of the Registry are:

4.1 Primary objective

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

4.2 Secondary objectives

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

5 Registry Population

5.1 Inclusion criteria

A subject must meet the following criteria at the enrolment visit (i.e. "baseline visit") to be eligible for inclusion into the Registry:

1. Subjects of all ages at baseline.
2. In the opinion of the treating physician, the subject has clinical presentation, radiological, biochemical, genetic or family mapping investigation results that support the diagnosis of XLH.
3. Subjects who provide written informed consent/assent after the nature of the Registry has been explained.

5.2 Exclusion criteria

A subject who meets any of the following criteria at the enrolment visit (i.e. "baseline visit") will be excluded from the Registry:

1. Subject - or their legally-designated representative - does not have the cognitive capacity to provide informed consent.
2. Subject is currently participating in an interventional clinical trial. Subjects will be approached for inclusion into the Registry once their involvement in that interventional trial ends (including the completion of all trial follow-up assessments). Participation in a Compassionate Use Programme, Pre-commercial Programme (e.g. Named Patient Sales, Autorisation Temporaire d'Utilisation Nominative [ATU], Early Access Programme [EAP], Post-Trial Access Programme [PTAP]), Investigator Initiated Study, or an observational study does not preclude a subject from participation in this Registry.

6 Therapy

6.1 Therapy schedule

All drug therapy considered necessary for a subject's 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 Registry database.

7 Data Collection

7.1 Overall Registry design and schedule of assessments

All eligible subjects with XLH, at the participating hospital sites, will be asked to take part in the Registry. Once subjects - or their legally-designated representative - have signed the informed consent, subjects will be enrolled into the Registry. A subject identification number will be generated automatically by the EDC system. Subject data will be pseudonymised, and physicians will retain a site enrolment log detailing the subject identification number alongside subject-identifiable information. This enrolment log will remain at the participating hospital site and will not be transferred outside of the site.

No pre-determined follow-up requirements will apply. However, physicians should update subject data into the Registry on a regular basis after a subject'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. The EDC system will allow for uploading of copies of ECGs and/or cardiac scans into the XLH Registry database, enabling this information and data to be available for further review.

As part of the Informed Consent Form (ICF), permissions will be sought from subjects to include their general medical history and details of hospitalisations, to further the understanding of the natural history of XLH. All data will be collected using the web-based EDC system.

All subject 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" in this XLH Registry is defined as "all the data available prior to the baseline visit up to six years before XLH diagnosis". Retrospective data entry will include the subject'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 genetic testing (if available)
    - Family history: number of known affected relatives, and their relationship to the subject (provided that the appropriate authorisations to process this data have been collected and that any relative involved in this activity has been informed about how their data shall be processed, if required).
2. General medical history, including pregnancy and foetal outcomes (including, if available, weight, length, Apgar score, mode of delivery) and subjects with chronic kidney disease. Note: It is suggested that sites enter all available information on general medical history as retrospective data, regardless of the time elapsed between the baseline visit and the XLH diagnosis, but the bulk of the data will be limited and justified.
3. XLH-specific medications including pain medications (including dose, adherence, duration of treatment and reason for discontinuation, if available)
4. Drug history
    - Current - All medications ongoing at the time of retrospective clinic visit including dose, adherence, duration of treatment
    - Previous – All medications and therapies including dose, adherence, duration of treatment, and reason for discontinuation, if available
5. Historical physiotherapy reports (including the number of visits, use of a wheelchair, walking aids, medical device, and home adaptations)
6. Historical physical examinations (including dental assessment, age and disease-specific

examinations)

7. Historical vital signs (including temperature, blood pressure [sitting], pulse rate and respiratory rate)

8. Historical auxological assessments (including standing and sitting height [metres], arm and leg length [metres], weight [kg], Body Mass Index (BMI), z-score [based on World Health Organisation (WHO) and Centers for Disease Control and Prevention (CDC) data])

9. Historical radiographs and imaging including:

    - Any radiological assessment of disease severity (X-ray, dual-energy X-ray absorptiometry [DEXA], computed tomography [CT], Xtreme CT [new generation CT], or Magnetic Resonance Imaging [MRI])
    - Scanner type
    - Analysis software used

10. Historical laboratory assessments (including biochemistry, haematology, urine, endocrine, and bone biomarkers)

11. Historical echocardiogram (ECHO) reports

12. Historical electrocardiogram (ECG) reports

13. Historical audiology assessments

14. Historical renal ultrasound scans

15. Historical assessment tools/outcome measure reports (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

16. Historical social history (including number of work/school dates missed due to XLH-related illness since last visit)

17. Adverse Events including, but not limited to, the following:

    - Long-term safety:
        - Death
        - Hospitalisations
        - Cardiovascular disease
        - Cancer
    - Hyperphosphataemia
    - Ectopic mineralisation
    - Increased parathyroid hormone levels
    - Effects on pregnancy and pregnancy outcomes

Baseline Visit

The "Baseline Visit" is the closest visit to the enrolment date (i.e. ICF signing date) available within one year before or after the enrolment date. The baseline visit will include the following procedures/data:

1. Informed Consent (date and type of consent)
2. Demographics (including date of birth, biological sex, and ethnicity/race, in accordance with national data protection laws)

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

3. Medical history including pregnancies and outcomes of pregnancy, and subjects with chronic kidney disease.
4. Physical examination (including dental assessment, age and disease-specific

examinations)

5. Vital signs (temperature, blood pressure [sitting], pulse rate, and respiratory rate)
6. Auxological assessments (including standing and sitting height [metres], arm and leg length [metres], weight [kg], BMI, z-score [based on WHO and CDC data])
7. XLH-specific medication
    - All current XLH-specific medications prescribed within 30 days prior to informed consent (including dose, adherence, duration of treatment, and reason for discontinuation, if applicable)
8. Drug history
    - All current medications prescribed within 30 days prior to informed consent (including dose, adherence, duration of treatment, and reason for discontinuation, if applicable)
9. Radiographs and imaging including:
    - Any radiological assessment of disease severity (X-ray, DEXA, CT, XtremeCT, or MRI)
    - Scanner type
    - Analysis software used
10. Laboratory assessments (including biochemistry, haematology, urine, endocrine, and bone biomarkers)
11. Physiotherapy reports (including use of a wheelchair, walking aids, medical device, home adaptations)
12. ECHO reports
13. ECG reports
14. Audiology assessments
15. Renal ultrasound scans

16. Assessment tools/outcome measure reports (ATS Statement 2002; Balke 1963; Bruininks 2005; Kolber 2005; Podsiadlo 1991):
    - 6MWT
    - TUG
    - BOT-2
    - Dynamometry
17. Subject's Quality of Life (QoL) questionnaires (Ware 1992; Herdman 2011), including, but not limited, to:
    - PedsQL (for paediatric subjects), in applicable countries
    - SF-36 (for adult subjects), in applicable countries
18. Social history (including number of work/school dates missed due to XLH-related illness since last visit)

Prospective/Routine Clinic Visit

"Prospective data" is considered to be all the available data after the baseline visit until: the end of Registry, subject discontinuation, lost to follow-up, or death, whichever occurs first. Paediatric subjects will be asked to provide Registry consent when they reach the applicable age to do so, according to the respective national guidelines at the participating hospital sites. The Registry does not mandate investigations outside of standard care as determined by the subject's physician. Physicians are asked to update the Registry EDC on a regular basis after a subject's visit with the physician, once new information is available or, at a minimum, on an annual basis. If there is new information on auxological, dental or main laboratory parameters, a new prospective visit should be created in the EDC. Once the visit is created, at a minimum the parameters in the core dataset will either be entered or marked as "unknown/unavailable" in the EDC. This process should be repeated for all prospective visits available in the clinical records of the subject.

Data for the PASS will be collected once consent has been given as documented by the signing of the ICF, which allows participation in the PASS by the subject. Hospital sites that participate in the PASS will be asked to prospectively and actively solicit Adverse Events for enrolled subjects treated with burosumab.

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 visit or last recorded entry) including:
    - All incidents of hospitalisation (including duration and cause of admission)
    - Pregnancy (including the following 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 visit or last recorded entry)
    - PHEX genetic testing (if available)
3. XLH-specific medications including pain medications (including dose adherence, duration of treatment, and reason for discontinuation if available)
4. Drug history
    - 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 visit 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. ECHO reports

7. ECG reports
8. Audiology assessments
9. Renal ultrasound scans
10. Physical examination (including dental assessment, age and disease-specific examinations)
11. Auxological assessment (including standing and sitting height [metres], arm and leg length [metres], weight [kg], BMI, z-score [based on WHO and CDC data])
12. Vital signs (temperature, blood pressure [sitting], pulse rate, and respiratory rate)
13. Radiographs and imaging including:
    - Any radiological assessment of disease severity (X-ray, DEXA, CT, XtremeCT, and/or MRI)
    - Scanner type
    - Analysis software used
14. Laboratory assessments (including biochemistry, haematology, urine, endocrine, and bone biomarkers)
15. Assessment tools/outcome measure reports (ATS Statement 2002; Balke 1963; Bruininks 2005; Kolber 2005; Podsiadlo 1991):
    - 6MWT
    - TUG
    - BOT-2
    - Dynamometry
    - Subject's QoL questionnaires (Ware 1992; Herdman 2011), including:
    - PedsQL (for paediatric subjects), in applicable countries
    - SF-36 (for adult subjects)

16. Social history (including number of work/school dates missed due to XLH-related illness since baseline or last recorded entry)

17. Adverse Events including, but not limited to, the following:

    - Long-term safety:
        - Death
        - Hospitalisations
        - Cardiovascular disease
        - Cancer
    - Hyperphosphataemia
    - Ectopic mineralisation
    - Increased parathyroid hormone levels
    - Effects on pregnancy and pregnancy outcomes

18. COVID-19 impact data (impact on subject visits and assessments, and relationship of missed information due to the COVID-19 pandemic).

Table 1 Schedule of Assessments for Data Recordings

	Retrospective Data Entry[a]	**Baseline** Data Entry[b]	**Prospective** Data Entry[c,d] (Data to be updated in the database at least annually)
Informed Consent[d]	X	X	X[d]
Demographic information	-	X	-
Medical history including pregnancy history and outcomes, any chronic kidney disease status, and other safety outcomes	X[e]	X	X
PHEX mutations (if available)[f]	X	-	X[f]
XLH medications and drug history	X	X	X
Concomitant medications	-	X	X
Radiographs and imaging	X	X	X
Physical examination (including dental)	X	X	X
Vital signs	X	X	X
Auxological assessment	X	X	X
Laboratory assessments	X	X	X
Physiotherapy	X	X	X
Echocardiogram (ECHO)	X	X	X
Electrocardiogram (ECG)	X	X	X
Audiology	X	X	X
Renal ultrasound	X	X	X
Subject assessment tools/outcome measures	X	X	X
Subject Quality of Life (QoL) questionnaires	-	X	X
Social history	X	X	X
Adverse Events	X	X	X
COVID-19 impact data	-	-	X

A "-" denotes when an assessment was not performed

[a] Retrospective data is defined as all data available prior to the baseline visit up to six years before XLH diagnosis

[b] Baseline visit is the closest visit to the enrolment date (i.e. ICF signing date) available within one year before or after enrolment date

[c] Prospective data is considered to be all the available data after the baseline visit until: the end of Registry, subject discontinuation, lost to follow-up, or death, whichever occurs first

[d] Re-consent to adult Registry consent when subject transitions from paediatric subject to adult subject

[e] It is suggested that sites enter all available information on general medical history as retrospective data, regardless of the time elapsed between the baseline visit and the XLH diagnosis, but the bulk of the data will be limited and justified.

[f] PHEX and other genomic mutations to be recorded in p rospective visit if not available at baseline

Reminders about updating the Registry database will be issued to alert the physician's team 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 subject at 12 months, the system will issue a reminder asking for a report on the status of that subject.

COVID-19 impact data: As a consequence of the COVID-19 pandemic and its consequent restrictions and some de-prioritisation of non-essential hospital-based activities, there may have been changes to routine clinical visit schedules, missed visits, or subject discontinuations to treatment which may lead to some missing information. The EDC system will enable capture of information regarding the relationship of missed information due to the COVID-19 pandemic. This information will be summarised in the final XLH Registry report.

7.2 Withdrawal of subjects from Registry

A subject will be withdrawn from the Registry if requested by the subject or their legally-designated representative. The Registry will be updated with the information that the subject is withdrawn and the reason for their withdrawal if provided by the subject or legally-designated representative.

If the subject starts a clinical trial during the participation of this XLH Registry, an interruption of subject data collection and data process shall be made during the subject's participation in the interventional clinical trial. Data entry will be re-initiated for the subject once their participation in the trial has ended. The subject will be informed about such interruption as well as when the collection and processing of their data restarts again. This is defined by the end of their participation in all trial-associated follow-up assessments.

7.3 Subject confidentiality

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

Subject names and identifying information will be withheld from the Contract Research Organisation (CRO) and the Sponsor in all communications, and this information will not 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 visits may also take place also in sites not part of the PASS sub-study. The Monitor , i.e. represented by the CRO, must be given direct access to clinical records, as far as these relate to the study and without jeopardising subject confidentiality and privacy.

Data inconsistencies or absence of follow-up assessments will be reviewed and discussed with the sites until fully resolved as feasibly possible.

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 study is performed using electronic data capture. The Registry eCRFs will be completed and signed electronically within the EDC system for each included subject. The Sponsor and the physician or his/her 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 should be recorded. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

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

7.4.3 Incorporation of data in the Registry

Data on Patient Reported Outcomes (PROs) will be collected in a validated electronic Patient Reported Outcomes (ePRO) database management system. In addition to the XLH 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 if the informed consent provided by the subjects in these studies allows for the data being used for further research purposes. The addition of previously-collected XLH subject data will strengthen the ability of the Registry to meet its primary objective.

In participating countries, eligible subjects may be invited to complete PRO questionnaires. The completion of these questionnaires is not mandated. It is the responsibility of the physician (or delegate) to register eligible subjects in the EDC system to be able to complete subject QoL questionnaires in a validated ePRO database management system. Subject QoL questionnaires will be completed electronically by the subject (and/or their parent/legally-designated representative) on a smartphone or other personal electronical device (in a non-clinical setting) via a validated ePRO database management system, which will also ensure the confidentiality for the subject (and/or their parent/legally-designated representative completing, when applicable. Each subject (and/or their parent/legally-designated-representative) will receive login credentials to access this online portal. The subject name will not be used or entered. Subjects will only be identified with the same identification number used in the XLH Registry eCRF. Only the data that are directly entered by the subject (and/or their parent/legally-designated representative) will be processed. Subjects (and/or their parent/legally-designated representative) will be sent an email reminder (to their registered email account) during the

Follow-up period to complete the online subject QoL questionnaires at the required time-points.

Once a subject reaches 18 years of age, the QoL questionnaires will not be available for completion until the subject has been re-consented as an adult and have provided their own email address for the subject QoL questionnaire online portal. Once the subject has completed the re-consent process, future questionnaires will be sent directly to the subject's email address rather than to the parent's/legally-designated representative's email address. The parent/legally-designated representative will be informed of this process via a reminder email when a subject reaches 18 years of age. The physician will also be informed through regular reports from a validated ePRO database management system when they have subjects close to reaching 18 years of age. It is the responsibility of the physician (or delegate) to ensure that the reconsent is documented in the EDC system and that the subject is registered via the PRO page in the EDC system.

If the subject, or their parent/legally-designated representative, does want to withdraw their consent and also to delete their personal data, they will need to contact to their physician in writing. The physician will then inform the Sponsor so that the subject's data will be deleted from the Registry.

7.4.4 Data extraction

Data collected in the Registry may be extracted in the future to align with other global XLH registries under development by the Sponsor and its affiliates, licensors, licensees, and partner(s), and the companies who provide the Sponsor services related to studies. The purpose would be to create a global data resource to study the natural history of XLH. All parties are committed to ensuring subject 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 subject confidentiality, only subject identification numbers will be used to identify all data reported in the eCRF. Personal data will be collected in the first instance by the physicians and directly from subjects.

7.4.6 Management and reporting of adverse events/adverse reactions

The XLH Registry will collect AEs for all subjects (regardless of burosumab treatment) based on spontaneous reporting by the subject. AEs associated with exposure to Sponsor products (e.g. burosumab) will be submitted to the Sponsor. All Serious Adverse Events (SAEs) must be reported within 24 hours from the time of site awareness, and all non-serious AEs must be reported within 4 days from the time of site awareness via the EDC system. Details of AE reports associated with any treatment for XLH submitted for an individual subject in the previous year will be captured in the annual Registry entry for that subject. AEs will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) system and described by system organ class. Evaluation of cumulative AE information will be reported in the Registry's interim and final analyses.

A subset of the Registry data will be used to fulfil a PASS as requested by the EMA's CHMP. Hospital sites which agree to participate in the PASS will be asked to solicit AEs on enrolled subjects treated with burosumab (please see Appendix 13.1).

7.4.6.1 Definitions and classification of adverse events

Adverse Event (AE):

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Pre-existing conditions that worsen during a study are to be reported as AEs as well.

If, according to the physician, there is a worsening of a medical condition that was present prior to administration of the intervention, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the treatment that remains unchanged or improved should not be recorded as an AE at subsequent visits.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, seriousness, relationship to product, actions(s) taken, and outcome of any sign or symptom observed by the physician or reported by the subject upon questioning.

Serious Adverse Event (SAE):

An SAE is any experience that suggests a significant hazard, contraindication, side-effect or precaution. An SAE must fulfil at least one of the following criteria at any dose level:

- Results in death
- Is life-threatening, i.e. subject was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it was more severe
- Requires subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity; defined as a substantial disruption of a subject's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Constitutes an important medical event, e.g. based upon appropriate medical judgement, the event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Relationship to treatment:

For all events reported in subjects treated with burosumab, the treating physician or other reporting healthcare provider must be asked to assess the relationship of the AEs/SAEs to burosumab using the following definitions:

- Probably related: An AE that is likely related to burosumab
- Possibly related: An AE that may be related to burosumab
- Unlikely related: An AE that is doubtfully related to burosumab
- Not related: An AE that is clearly not related to burosumab, beyond a reasonable doubt

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, including how to register subjects on to the ePRO platform.

All physicians and staff carrying out observations of primary or other major clinical outcome variables involved in the Registry should provide their Curriculum Vitae and, where appropriate, their 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 any subjects, 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 hospital sites 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 hospital site will be performed according to hospital routines; it is expected that all participating hospital sites 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 Steering Committee consisting of experts on XLH has been set up. This C ommittee consists of Sponsor representatives and XLH physicians from across Europe and the Middle East.

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

Physicians entering data into the Registry will have accountability of their hospital site's aggregated data set. They, and/or the subject, will be free to withdraw the consent for the subject's data to be used in any 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 physician sites.

8 Statistical Methods and Determination of Registry Size

8.1 Analysis data set

All enrolled subjects will be eligible for analysis through an appropriate Statistical Analysis Plan (SAP).

8.1.1 Analysis of Registry data

Medical history and drug details will be captured in the XLH Registry via use of the World Health Organisation Drug Dictionary before being summarised and tabulated. AEs will be coded using the latest version of MedDRA. Reports will incorporate information up to and including the latest Registry update for each subject. 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 subjects, demographic data, and other baseline characteristics will be analysed as described in the paragraph above. Laboratory measurements and other clinical data will be tabulated. Subject outcome measures and QoL questionnaires will be summarised.

Additional details will be provided in the SAP.

Interim analyses and specified cohorts analyses may be performed as appropriate.

8.2 Determination of sample size

This is a prospective observational Registry for subjects with XLH. There is no sample size calculation based on statistical considerations. Based upon the scope of the participating countries and their hospital sites, it is projected that the Registry will contain data on approximately 1,200 subjects spanning 10 years. The number of subjects that will be exposed to burosumab is currently uncertain and depends on in-country reimbursement decisions, but it is anticipated to be approximately 400 subjects at the end of 10 years. Therefore, approximately 800 subjects who will either be receiving drug treatment for XLH other than burosumab, or be untreated, are anticipated to be enrolled in the Registry at the end of 10 years.

9 Ethical Requirements

9.1 Ethical review

Necessary approvals of the Registry Protocol, the Subject Information Sheet and Informed Consent/Assent Forms, Letter of Invitations, General Practitioner/Primary Care Physician Letters (as applicable), and PROs (e.g. QoL questionnaires) must be obtained before enrolment of any subject 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 the 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 Registry sites.

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

9.2 Ethical conduct of the Registry

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 Subject information and consent

It is the responsibility of the physician or clinical designee to give each potential subject (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 subject (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 subject (or their legally-designated representative) must be informed about their 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 subject (or their legally-designated representative) should be allowed sufficient time for consideration

of the proposal as assessed by the physician or clinical designee. In addition, the physician or clinical designee will be responsible to respond to any data protection right requests from subjects to exercise their rights under the applicable data protection legislation within the time limits imposed by the data protection legislation. The Sponsor may provide assistance as is reasonably required to enable the physician or clinical designee (hospital/site) to comply with requests from data subjects.

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 subjects (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 subject (or their legally-designated representative) for their records. The physician will confirm the receipt of the signed ICF (adult or parental) for each subject by marking the appropriate field of the subject's eCRF.

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

Kyowa Kirin International will sponsor the XLH Registry for 10 years. Subjects will provide informed consent to participate as long as the Registry is active. A subject, or their legally-designated representative, may withdraw consent at any time. 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 subjects and their identifying code (enrolment log), subject 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 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 subject 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"). Subject data collection, processing, transfer, and storage will be performed in accordance with national data protection laws, identification of individual subject data will only be possible for the site physician.

The potential Registry subject 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 subject 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. In any case, if the subject or their parent/legally-designated representative wants not only to withdraw their consent but also to delete their personal data, that subject or their parent/legally-designated representative can contact their physician in writing, and the physician will inform the Sponsor so that the subject's data will be deleted from the Registry.

Each hospital site will only have access to the subjects under their direct care. The only demographic information collected includes their date of birth (in accordance with local national regulations), biological sex, ethnic origin, and social demography. A unique username and password will be generated for each person entering the data. Once the subject is initiated into the system, he/she will be assigned a unique number, which becomes his/her

identification in the Registry system.

In participating countries, eligible subjects may be invited to complete PRO questionnaires. It is the responsibility of the physician (or delegate) to register eligible subjects in the EDC system, in order to complete the patient questionnaires within the ePRO platform. Confidentiality will be ensured and subjects will only be identified with the same identification number as used in the eCRF. Only data that are entered by the subject (and/or their parent/legally-designated representative) will be processed. See Section 7.4.3 for further details.

10.3 Timetable

The Registry will be initiated during August 2017 (Note: first patient enrolment was 12 September 2017). This Registry is planned to span 10 years and will be open for inclusion of subjects until the decision to discontinue the Registry has been taken by the Sponsor in agreement with applicable regulatory authorities.

10.4 Final XLH Registry 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 Scientific Steering Committee to meet any regulatory requirements from Regulatory/Health Authorities.

The statistical analysis methods to be applied to Registry data aimed at publications in peer-reviewed journals or presentations at congresses will be reviewed by the XLH Registry Scientific 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 hospital sites 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's institution, and will be filed by both the physician's institution and the Sponsor.

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13 Appendices

13.1 PASS protocol

Note: there is a discrepancy in the text in Section 8.3. The reference to Appendix 1, Tables A to C should instead be to Appendix 1, Tables 3 to 5.

Kyowa Kirin International plc

Post-Authorisation Safety Study - Burosumab

Final

Protocol

Version

2.0

12th January, 2021

Contents

Table of Tables

List of abbreviations

Abbreviation	Definition
1,25(OH)2D	1,25-dihydroxyvitamin D
AE	Adverse Event
ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
COVID-19	Corona Virus Disease 2019
CRO	Contract Research Organisation
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EU PAS register	European Union Electronic Register of Post-Authorisation Studies
EU RMP	European Union Risk Management Plan
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
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PHEX	Phosphate-regulating neutral Endopeptidase, X-linked
PRAC	Pharmacovigilance Risk Assessment Committee
QoL	Quality of Life
SAE	Serious Adverse Event
WHODD	World Health Organization Drug Dictionary
XLH	X-Linked Hypophosphataemia

1. PASS information

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-linked Hypophosphataemia.
Protocol version identifier	Version 2.0
Date of last version of protocol	15 August 2018
EU PAS register number	EUPAS32190
Active substance	Active substance: burosumab - recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23. ATC code: M05BX, other drugs affecting bone structure and mineralisation.
Medicinal product	Invented name: Crysvita Pharmaceutical form and strength: 10, 20, and 30 mg/mL solution for injection in vials.
Product reference	EU/1/17/1262/001 EU/1/17/1262/002 EU/1/17/1262/003
Procedure number	EMEA/H/C/4275
Marketing authorisation holder(s)	Kyowa Kirin Holdings B.V. Bloemlaan 2 2132NP Hoofddorp Netherlands Tel: +31 23 720 0822 Email: medinfo@kyowakirin.com Kyowa Kirin Holdings B.V. is owned by Kyowa Kirin International plc
Joint PASS	No
Research question and objectives	Primary objectives: 1. To evaluate the frequency and severity of safety outcomes in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and adults, and who are treated with burosumab, and including but not limited to: long-term safety (as evidenced by death, hospitalisations, cardiovascular disease, and cancer [all sites]), hyperphosphataemia and its complications, ectopic mineralisation and increased parathyroid hormone levels.

	2. To prospectively evaluate the frequency and outcomes of pregnancies in female subjects treated with burosumab. 3. To prospectively evaluate the frequency and severity of safety outcomes in subjects with mild to moderate chronic kidney disease at baseline treated with burosumab. Secondary objective: 1. To perform a retrospective cohort analysis using data from the XLH Registry to compare the safety outcomes in subjects treated with burosumab to those in subjects treated with alternative treatments for XLH.
Country(-ies) of study	The following countries are involved: - Belgium, France, Ireland, Italy, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, and United Kingdom. - Additional countries may be added at a future date.
Author	Dr Danie du Plessis Executive Vice-President International Medical Affairs Kyowa Kirin International plc 2 Globeside, Fieldhouse Lane Marlow Buckinghamshire SL7 1HZ United Kingdom Tel: +44 1896 664000 Signature: .....  Date: 15 FEB 2021 .....

Marketing Authorisation Holder

Marketing Authorisation Holder	Kyowa Kirin Holdings B.V Bloemlaan 2 2132NP Hoofddorp Netherlands Tel: +31 23 720 0822 Kyowa Kirin Holdings B.V. is owned by Kyowa Kirin International plc

MAH contact person	Charlotte Barrett European Qualified Person for Pharmacovigilance [Address as above] Email: charlotte.barrett@kyowakirin.com

2. Responsible parties

The XLH Registry, and all associated studies including the PASS, is governed by a Steering Committee which includes investigators and the Sponsor. A list of the Steering Committee members and a list of investigators are kept on file with the Sponsor.

3. Abstract

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-linked Hypophosphataemia.
Rationale and background	X-linked hypophosphataemia (XLH) is a rare, chronic, deforming bone disease characterised 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 minimising the clinical consequences of XLH by restoring normal serum phosphate levels. As part of the Risk Management Plan (RMP), the majority of the safety concerns are being investigated in a Category 3 Post Authorisation Safety Study (PASS) which uses an XLH Registry. The data source to conduct the PASS is the data collected in the XLH Registry. The purpose of this XLH Registry is to collect natural history data for XLH, and to characterise the treatment progression, and long-term outcomes of XLH in subjects of all age groups. The safety concerns to be investigated in this long-term PASS examining children, adolescents and adults exposed to burosumab for the treatment of XLH are: 1. Long-term safety 2. Hyperphosphataemia 3. Ectopic mineralisation 4. Effects on pregnancy outcomes 5. Increased parathyroid hormone levels 6. Effects in subjects 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 children and adolescents aged 1 to 17 years with radiographic evidence of bone disease and adults, and who are treated with burosumab for XLH, including but not limited to: long term safety (as evidenced by death, hospitalisations, cardiovascular disease, cancer [all sites]), hyperphosphataemia and its complications, ectopic mineralisation, increased parathyroid hormone levels. 2. To prospectively evaluate the frequency and outcomes of pregnancies in female subjects treated with burosumab. 3. To prospectively evaluate the frequency and severity of safety outcomes in subjects with mild to moderate chronic kidney disease at baseline treated with burosumab. Secondary objective: 1. To perform a retrospective cohort analysis using data from the XLH Registry to compare the safety outcomes in subjects exposed to burosumab to those in subjects receiving alternative treatments for XLH.
Study design	This is a 10-year prospective cohort study using data collected in a disease Registry for XLH. The PASS is non-interventional so all data collected will arise from the usual clinical management of these subjects.
Population	This study is presented as a non-interventional PASS, with all subjects investigated for the primary objective expected to receive treatment with burosumab in accordance with the Marketing Authorisation. Therefore, all subjects investigated for the primary objective will comprise of: • Children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and adults, and who are receiving burosumab for the treatment of XLH and enrolled in the XLH Registry via one of the participating centres, and who have provided informed consent to be enrolled into the XLH Registry and the PASS. Subjects 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, and who have provided informed consent to be enrolled into the XLH Registry.
Variables	In summary, the variables to be collected in XLH 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

<table>
<tr><td>Data sources</td><td>The data source for the PASS is a disease registry for children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and in adults, with XLH.</td></tr>
<tr><td>Study size</td><td>It is projected that the XLH Registry will contain data on approximately 1,200 subjects over 10 years. The number of subjects that will be treated with burosumab is currently uncertain and depends on in-country reimbursement decisions but it is anticipated to be approximately 400 subjects at the end of 10 years, forming the sample for the primary objective.

Approximately 800 subjects are anticipated to be enrolled in the XLH Registry at 10 years who will be receiving drug treatment for XLH other than burosumab or be untreated. Those included in the XLH Registry and receiving other treatments will be used as the group for analysis for the secondary objective. Those receiving no drug treatment for XLH will not be included in the population used for the analysis of the secondary objective.</td></tr>
<tr><td>Data analysis</td><td>As the sample size will not be sufficient for formal comparative analysis, the data analysis will be in the form of descriptive statistics</td></tr>
<tr><td>Milestones</td><td>
<table>
<tr><th>Milestone</th><th>Planned Dates (Children and Adolescents, i.e. paediatric)</th><th>Planned Dates (Adults)</th></tr>
<tr><td>Start of PASS</td><td>PRAC approval of protocol v.1.0</td><td>PRAC approval of protocol v.2.0</td></tr>
<tr><td>Start of PASS at country level</td><td>Product availability in participating countries</td><td>Product availability in participating countries</td></tr>
<tr><td>Start of data collection</td><td>First ICF for PASS signed (paediatric)</td><td>First ICF for PASS signed (adult)</td></tr>
<tr><td>End of data collection</td><td>10 years from start of data collection (paediatric)</td><td>10 years from start of data collection (adult)</td></tr>
<tr><td>Study progress reports</td><td>Annually or as required by EMA as part of PBRER (one report describing all populations)</td><td>Annually or as required by EMA as part of PBRER (one report describing all populations)</td></tr>
<tr><td>First interim report of study results</td><td>To be submitted after 50 paediatric subjects have achieved at least 6 months of time in the PASS</td><td>To be submitted after approximately 50 adult subjects have achieved at least 6 months of time in the PASS.</td></tr>
<tr><td>Second interim report of study results</td><td>To be submitted 5 years after initiation of the PASS in paediatric populations (i.e. a report</td><td>To be submitted 5 years after initiation of the PASS in paediatric populations (i.e. a report</td></tr>
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		covering use in all populations)	covering use in all populations)
	Final report of study results	To be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029)	To be prepared 10 years from the start of data collection in the adult population (estimated submission 2031)

4. Amendments and updates

Number	Date	Section of the protocol	Amendment or update	Reason
1	12th January, 2021	All sections	Update	Reformat to be consistent with 'Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies'.
2	12th January, 2021	All sections	Amendment	Correction of typographical errors and to increase clarity of text.
3	12th January, 2021	All sections	Amendment	To include the expanded population given approval of use in treatment of adults and adolescents.
4	12th January, 2021	Section 6: Rationale and background	Update	Modification of text given that the conditional MA has been granted.
5	12th January, 2021	All sections	Update	Remove reference to Europe given the UK's exit from the EU, and the inclusion of study sites in the UK.
6	12th January, 2021	PASS information: MAH details and countries of the study	Amendment	Change of MA Holder to Kyowa Kirin Holdings BV (owned by Kyowa Kirin International). Countries updated to include those countries currently included in the PASS study. Other countries may be added in the future.
7	12th January, 2021	Abstract and Section 5: Milestones	Amendment	Clarification of milestones relating to PASS reports for populations where data collection commenced (children and adolescents). Addition of milestones regarding reports for adult population.
8	12th January, 2021	Section 8.9: Limitations of research methods	Update	Correction to section describing the analysis of secondary objectives to be consistent with all other sections. Addition of text regarding impact of COVID-19 pandemic.
9	12th January, 2021	Section 10: Definitions for adverse event reporting	Update	Addition of detail to clarify definitions and procedures.
10	12th January,	Section 11	Update	Clarification of milestones relating to PASS reports for populations where

	2021			data collection commenced (children and adolescents). Addition of milestones regarding reports for adult population.
11	12th January, 2021	Table 2 and tables in appendix	Update	Addition of detail to clarify definitions and procedures, including addition of Adverse Events.

5. Milestones

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

Table 1. Study milestones

Milestone	**Planned Dates (Children and Adolescents, i.e. paediatric)**	**Planned Dates (Adults)**
Start of PASS	PRAC approval of protocol v1.0	PRAC approval of protocol v2.0
Start of PASS at country level	Product availability in participating countries	Product availability in participating countries
Start of data collection	First ICF for PASS signed (paediatric)	First ICF for PASS signed (adult)
End of data collection	10 years from start of data collection (paediatric)	10 years from start of data collection (adult)
Study progress reports	Annually or as required by the EMA as part of PBRER (one report describing all populations)	Annually or as required by the EMA as part of PBRER (one report describing all populations)
First interim report of study results	To be submitted after 50 paediatric subjects have achieved at least 6 months of time in the PASS	To be submitted after approximately 50 adult subjects have achieved at least 6 months of time in the PASS
Second interim report of study results	To be submitted 5 years after initiation of the PASS in paediatric populations (i.e. a report covering use in all populations)	To be submitted 5 years after initiation of the PASS in paediatric populations (i.e. a report covering use in all populations)
Final report of study results	To be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029)	To be prepared 10 years from the start of data collection in the adult population (estimated submission 2031)

6. Rationale and background

X-Linked Hypophosphataemia (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 hypophosphataemia. It is characterised 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) has been granted for burosumab based on submitted data in paediatric, adolescent and adult subjects with XLH.

The Marketing Authorisation Holder (MAH) for burosumab has established an XLH Registry. The purpose of this XLH Registry is to collect natural history data for XLH, to characterise the treatment, progression, and long-term outcomes of XLH in subjects of all age groups. This is a disease Registry - not a *burosumab* Registry - and the PASS will be conducted using data collected in the XLH Registry. The XLH Registry will be supported by the MAH.

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

1. Long-term safety (categorised as missing information in European Union Risk Management Plan [EU RMP])
2. Hyperphosphataemia (categorised as an important potential risk in EU RMP)
3. Ectopic mineralisation (categorised as an important potential risk in EU RMP)
4. Effects on pregnancy outcomes (categorised as an important potential risk in EU RMP)
5. Increased parathyroid hormone levels (categorised as an important potential risk in the EU RMP)
6. Effects in subjects with mild to moderate chronic kidney disease at baseline (categorised as missing information in EU RMP)

7. Research question and objectives

7.1 Primary objectives

1. To evaluate the frequency and severity of safety outcomes in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and adults and who are being treated with burosumab for XLH, including but not limited to: long term safety (death, hospitalisations, cardiovascular disease, cancer [all sites]), hyperphosphataemia and its complications, ectopic mineralisation and increased parathyroid hormone levels
2. To prospectively evaluate the frequency and outcomes of pregnancies in female subjects treated with burosumab
3. To prospectively evaluate the frequency and severity of safety outcomes in subjects with mild to moderate chronic kidney disease at baseline treated with burosumab

7.2 Secondary objectives

1. To perform a retrospective cohort analysis using data from the XLH Registry to compare the safety outcomes in subjects treated with burosumab to those outcomes in subjects 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 disease Registry for XLH. Given the very rare incidence of the disease, the fact that subjects are affected from birth 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 subjects.

8.2 Setting

This study is presented as a non-interventional PASS, with all subjects investigated for the primary objective expected to receive treatment with burosumab in line with the

stipulations of the Marketing Authorisation. Therefore, all subjects investigated for the primary objective will comprise:

Children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and adults, receiving burosumab for the treatment of XLH and enrolled in the XLH Registry and who have provided informed consent to participate in the PASS.

Subjects 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

This is a 10-year prospective cohort study using data collected in a disease Registry for XLH. The PASS is non-interventional, so all data collected will arise from the usual clinical management of these subjects and according to the recommendations described within the Summary of Product Characteristics (SmPC). Data will be collected from the time that the subject signs informed consent for participation in the XLH Registry. For inclusion in the PASS, data will be collected from when the subject signs a separate informed consent for participation in the PASS.

The safety outcomes of this study will include (but not be limited to) the following:

- Long term safety:
    - Death
    - Hospitalisations
    - Cardiovascular disease
    - Cancer (all sites)
- Hyperphosphataemia
- Ectopic mineralisation
- Increased parathyroid hormone levels
- Effects on pregnancy and pregnancy outcomes
- Outcomes in subjects with mild to moderate chronic kidney disease

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

Table 2 below gives a summarised 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*	Yes
Demographic information	X	-	-	Yes
Medical history including pregnancy history and outcomes	-	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
Subject Assessment Tools/Outcome Measures	X	X	X	No
Subject QoL Questionnaires	X	X	X	No
Social history	X	X	X	Yes
Adverse events	-	X	X	Yes

*Re-consent to XLH Registry adult consent when subject transitions from paediatric subject 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 an XLH Registry of subjects 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 XLH Registry will capture treatment details and clinical outcome variables in subjects with XLH. Subjects will be followed as long as informed consent exists. Only data collected during standard routine examinations will be recorded in the XLH Registry.

Since data from the XLH Registry can be made available to other external researchers in

addition to the MAH for burosumab (subject to the agreement of the XLH Registry's Steering Committee), the conduct of this PASS is considered to constitute secondary use of data.

Since the XLH Registry will be new it will not be possible to validate the data sources. Data linkage will not be a feature of the PASS. Data contained in the XLH Registry will undergo source data verification.

8.5 Study size

Assuming 50% enrolment of the eligible subject population, it is projected that the XLH Registry will contain data on approximately 1,200 subjects over 10 years. The number of subjects that will be exposed to burosumab is currently uncertain and depends on in-country reimbursement decisions, but it is anticipated to be approximately 400 subjects at the end of 10 years.

This particular sample size of 400 subjects has been estimated as follows:

- The total number of subjects to be enrolled in the XLH Registry over the 10 years is projected to be approximately 1,200 subjects (achievable if all centres recruit subjects as anticipated).
- The number of *burosumab-eligible* subjects within this group of 1,200 subjects is projected to be approximately 600 subjects (follows an assumption that 50% of the 1,200 subjects in the XLH Registry are children and adolescents aged 1 to 17 years and adults who are *eligible* for burosumab treatment; This is broadly accurate from the EU centres with available demographic data).
- The number of burosumab-*treated* subjects is estimated to be approximately 400 subjects – this is assuming that two-thirds of the 600 burosumab-*eligible* subjects do actually receive burosumab - acknowledging the issues of individual in-country reimbursement and individual subjects' factors/choice, and further assuming that all exposed subjects consent to their inclusion in the PASS. This cohort of 400 subjects are therefore the cohort included in the PASS for the primary objective.
- Therefore, the number of subjects *not* exposed to burosumab and therefore assumed to be receiving alternative treatments (assuming that all subjects receive drug treatment) will be approximately 800 subjects.

In short, it is anticipated that approximately 400 subjects will be enrolled in the XLH Registry *and* receive burosumab treatment *and* be included in the PASS - This forms the sample for the primary objective. It follows then, that approximately 800 subjects are anticipated to be enrolled in the XLH Registry *and* receive drug treatment other than burosumab for the treatment of their XLH, and so this cohort is to act as the comparator group for the secondary objective in the PASS.

8.6 Data management

Data collection within the XLH Registry will take place via an Electronic Data Capture (EDC) tool, with its core data specification approved by the XLH 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 XLH Registry is being conducted by a third-party contractor, with secure servers ensuring maximum security and continuity, in line with the EU Data Protection Directive. Data for the PASS provided by the XLH Registry owners will follow the rules for data use from the XLH 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 subjects (estimated to be approximately 400 subjects in the XLH 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 XLH Registry via use of ICD10 codes and the World Health Organization Drug Dictionary (WHODD). Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

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 XLH Registry. Ectopic mineralisation will be identified from results of various investigations such as ECG. The EDC tool used by the XLH Registry will allow uploading of copies of ECGs or cardiac ultrasound scans into the XLH 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, may 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 XLH 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 XLH Registry will provide the basis for a contextual cohort of XLH subjects not treated with burosumab.
- Data from these subjects will be used for a retrospective cohort analysis to compare the safety outcomes of interest in subjects treated with burosumab to those in subjects receiving alternative treatments for XLH.
- Given the small number of subjects 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 subjects.
- In addition, a retrospective cohort analysis will be performed to account for potential selection bias, based on burosumab exposure/non-exposure.

8.8 Quality control

Data entered into the XLH 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 XLH Registry 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 XLH Registry sites. When clarification has been obtained, the edit reports will be returned electronically to the XLH 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 XLH Registry and the PASS will collect clinical practice data on XLH subjects. However, the sample size is likely to mean that formal comparative analyses are not possible, or results may not reach statistical significance.
Missing data:	Subjects with XLH will be under the care of a physician for their condition but may not have frequent appointments. Therefore, data capture on intervening events may be incomplete.
Selection bias:	The MAH has attempted to minimise the possibility of selection bias by the following actions: • Site selection – a comprehensive programme was conducted by the MAH in order to identify XLH-treating health centres. All identified XLH treatment sites were approached and invited to participate in the XLH Registry. All sites participating in the XLH Registry will be invited to participate in the PASS.

- Subject selection – all investigators will be strongly encouraged to enroll 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 secondary objective within the PASS, the MAH will undertake retrospective cohort analysis based on burosumab exposure/non-exposure.

Information bias:	The use of the same EDC system by every XLH Registry site will standardise 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 XLH 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.
COVID-19 pandemic:	As a consequence of the COVID-19 pandemic and its consequent restrictions and some de-prioritisation of non-essential hospital-based activities, there may have been changes to routine clinical visit schedules, missed visits, or subject discontinuations to treatment which may lead to missing information. The EDC system will enable capture of information regarding the relationship of missed information to the COVID-19 pandemic. This information will be summarised in the final clinical study report.

9. Protection of human subjects

The conduct of this PASS is considered to constitute secondary use of data. Informed consent

will be required for subjects to be enrolled in the XLH Registry and PASS. Subject data utilised in the PASS will be de-individualised. There will be no additional procedures relevant to the PASS.

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

9.1 Ethical review

- Approvals required for the XLH Registry Protocol, the Subject Information Sheet, Informed Consent/Assent Forms, Letter of Invitations and General Practitioner (GP) Letters will be obtained from the Ethics Committees before enrolment of any subject into the XLH Registry and PASS.

- 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 XLH Registry identification and the date of review will be filed by the Sponsor and at the XLH 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 XLH Registry reports will be completed for the IRB/IEC by the CRO or the Sponsor.

9.2 Ethical conduct of the study

- The XLH 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 Subject information and consent

- It will be the responsibility of the physician or clinical designate to give each potential subject (or their guardian) adequate verbal and written information regarding the objectives and the procedures of the XLH Registry and PASS.

- The subject (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 XLH Registry and PASS 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 subjects (or their guardian) before including them in the XLH Registry and PASS. The Informed Consent forms (adult or parental) must be signed and dated before any data can be registered in the XLH Registry and included in the PASS analysis.

- The final versions of the Subject Information sheet and Informed Consent forms are submitted to the IRB/IEC(s) for approval and must not be changed without

permission and approval 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. Subjects (or their guardian) will provide Informed Consent to participate as long as the XLH Registry is active.

9.4 Data protection

- The physician must file a subject enrolment log which includes sufficient information to link records, i.e. the electronic Case Report Form (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 subject information will be handled in accordance with national data protection standards, identification of individual subject data will only be possible for the site physician.

- A potential XLH Registry subject 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 may have direct access to his/her medical records.

- The subject will have the right at any time to withdraw the permission to enter data into the XLH Registry and PASS, 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 subjects under their direct care. The only demographic information collected is the date of birth, gender, and ethnic origin (dependent upon local regulations and laws). A unique username and password will be generated for each subject entering the database. Once the subject is initiated into the EDC, he/she will be assigned a unique number, which becomes his/her identification in the XLH Registry and PASS. All centre information is maintained in regulatory compliant database.

10. Management and reporting of adverse events/adverse reactions

Subjects enrolled in the PASS will be subject to solicited adverse event reporting by the Investigators to the PASS sponsor. This will take place as follows:

Staff training:

- The training provided to healthcare professionals and other staff submitting data to the XLH Registry for subjects enrolled in the PASS will include a specific request for adverse event information to be solicited during interactions with subjects

- The request for adverse event information from the subject 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 entering data into the XLH Registry for PASS subjects 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 Registry will ensure that, during every episode of data entry, the person uploading information for a PASS subject will be prompted to enter data on any adverse events solicited and recorded during interactions with the subject

- The prompt will require the data entry person to report any adverse events disclosed by the subject to the Sponsor of the PASS via an eCRF alert, if this has not already been done, or to the Marketing Authorisation Holder of any other suspect medication

Any adverse events reported by the subject 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 originally captured in the XLH Registry, this is therefore deemed to be secondary use of data. Individual Case Safety Reports (ICSRs) will therefore not be submitted to the regulatory authorities by the Sponsor of this PASS for PASS-reporting purposes, 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 also in the final study report for the PASS.

Definitions

Adverse Event (AE):

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Pre-existing conditions that worsen during a study are to be reported as AEs.

If, according to the investigator, there is a worsening of a medical condition that was present prior to the administration of the intervention, this should also be considered a new AE and reported. Any medical condition present prior to the administration of the treatment that remains unchanged or improved should not be recorded as an AE at subsequent visits.

Documentation regarding the AE should be made as to the nature, date of onset, end date, severity, seriousness, relationship to product, action(s) taken, and outcome of any sign or symptom observed by the physician or reported by the subject upon questioning.

Serious Adverse Event (SAE):

An SAE is any experience that suggests a significant hazard, contraindication, side effect or precaution. An SAE must fulfil at least one of the following criteria at any dose level:

- Results in death
- Is life-threatening: Subject was at risk of death at the time of the event. This does not refer to an event which hypothetically might have caused death if it was more severe
- Requires subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity: Defined as a substantial disruption of a subject's ability to conduct normal life functions
- Results in a congenital anomaly or birth defect
- Constitutes an important medical event: Based upon appropriate medical judgement, event may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Adverse Drug Reaction (ADR):

An ADR is defined as a response to a study treatment that is noxious and unintended and that occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease, or for the restoration, correction, or modification of physiological functions.

Event severity:

Event severity is defined as a qualitative assessment of the degree of intensity as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of intervention relationship or seriousness of the event and should be evaluated according of the following scale:

- Mild: The event is noticeable to the subject, but is easily tolerated, and does not interfere with the subject’s daily activities.
- Moderate: The event is bothersome, possibly requiring additional therapy, and may interfere with the subject’s daily activities.
- Severe: The event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject’s daily activities.

Note: The terms “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE (as in mild, moderate, or severe pain); the event itself may be of relatively minor medical significance (such as severe headache).

“Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or vital functions.

Relationship to treatment:

For all events reported in subjects treated with burosumab, the treating physician or other reporting health care provider will be asked to assess the relationship of the AE/SAEs to burosumab using the following definitions:

- Related: A causal relationship is either clinically/biologically highly plausible or plausible, and there is a correlation between the onset of the AE/SAE and administration of the treatment, or between withdrawal of treatment and resolution of the AE/SAE. Or a causal relationship is improbable but cannot be definitively excluded, and another documented cause of the AE/SAE is most plausible.
- Not related: A causal relationship can be definitively excluded, and another documented cause of the AE/SAE is most plausible.

11. Plans for disseminating and communicating study results

The Sponsor will prepare progress reports annually or as required by the EMA as part of PBRERs. In addition, these may be summarised periodically for presentation at professional conferences or academic meetings as appropriate.

A first interim analysis and report for the paediatric population is planned after 50 paediatric subjects have achieved at least 6 months of time in the PASS.

A first interim analysis and report for the adult population is planned after 50 adult subjects have achieved at least 6 months of time in the PASS.

A second interim analysis and report for *both* the paediatric and adult population (i.e. a report covering use of burosumab in all populations) is planned to be submitted 5 years after initiation of the PASS in the original paediatric population.

A final report of the paediatric population will be prepared 10 years from the start of the data collection in the paediatric population, with an estimated submission date of 2029.

A final report of the adult population will be prepared 10 years from the start of the data collection in the adult population, with an estimated submission date of 2031.

This study is 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

None.

APPENDIX 1

Table 3. Details of data to be collected in XLH Registry* – baseline data entry visit

Information / assessment – Mandatory	**Data to be investigated in PASS?**
1. Informed Consent (date and type of consent)	Yes - PASS ICF
2. Demographics (dependent on local regulations and laws) • Date of Birth • Biological Gender • Ethnicity	Yes
Information / assessment – data to be recorded if available; the XLH Registry does not mandate investigations outside of standard care as determined by the subject's physician	Data to be investigated in PASS?
3. Medical history including pregnancies and outcomes of pregnancy	Yes
4. 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
5. 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
6. Radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
7. Physical examination (including age and disease specific examinations)	Yes
8. Vital signs (temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
10. Growth Assessment including: • Standing and sitting height (metres) • Arm and leg length (metres) • Weight (kg) • Body Mass Index (BMI) • Z score (based on background national reference)	No
11. Laboratory Assessments including: Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
12. Physiotherapy reports including: • Use of a wheelchair • Walking aids • Medical device • Home adaptations	No
13. Echocardiogram (ECHO) reports	Yes
14. Electrocardiogram (ECG) reports	Yes
15. Audiology assessment	Yes
16. Renal ultrasound scan	Yes

17. 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
18. Subject Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Subject-Reported Outcomes Measurement Information System • Short Form 10 (SF-10) (for children ≥5 years of age) • PROMIS (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 Utilisation 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) • Subject Index Data 3 (RAPID3) • Subject Pain Diary	No
19. Social History • Number of work/school dates missed due to XLH-related illness since last visit	Yes

*'X-linked hypophosphataemia Registry protocol', Protocol Version 1.0, 31 July 2017, clinicaltrials.gov ID no. CT03193476

Table 4. Details of data to be collected in XLH Registry – retrospective data entry visit

Information / assessment - Retrospective data entry will include the subject's medical history and may include the following data sets if available	**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 (metres) • Arm and leg length (metres) • 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 Subject Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Subject-Reported Outcomes Measurement Information System • Short Form 10 (SF-10) (for children ≥5 years of age) • PROMIS (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)	No

• Short Form 36 (SF-36) (for adult subjects) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (for adult subjects) • Abbreviated XLH Resource Utilisation 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) • Subject Index Data 3 (RAPID3) • Subject Pain Diary	
16. Historical social history: • Number of work/school dates missed due to XLH-related illness since last visit	Yes
17. Adverse events	Yes

Table 5. Details of data to be collected in XLH Registry – prospective/routine clinic visit

Paediatric subjects will be asked to provide XLH 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 subject attends more regularly, data will be entered in the XLH Registry to reflect these visits at the 12-month interval, with an option to add multiple dates.** **The XLH Registry does not mandate investigations outside of standard care as determined by the subject'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 (metres) • Arm and leg length (metres) • 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 • 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) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	No
16. Subject Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Subject-Reported Outcomes Measurement Information System • Short Form 10 (SF-10) (for children ≥5 years of age) • PROMIS (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 Utilisation 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) • Subject Index Data 3 (RAPID3) • Subject Pain Diary	No
17. Social History • Number of work/school dates missed due to XLH-related illness (since baseline or last recorded entry)	Yes
18. Adverse events	Yes