Post-authorisation safety study of burosumab use in paediatric, adolescent and adult patients with X-Linked hypophosphataemia : rationale and description

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Study Protocol

Post-authorisation safety study of burosumab use in paediatric, adolescent and adult patients with X-linked hypophosphataemia: rationale and description

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Abstract

Background: X-linked hypophosphataemia (XLH) is a rare, inherited, phosphate-wasting disorder that elevates fibroblast growth factor 23 (FGF23), causing renal phosphate-wasting and impaired active vitamin D (1,25$(OH)_2$D) synthesis. Disease characteristics include rickets, osteomalacia, odontomalacia, and short stature. Historically, treatment has been oral phosphate and 1,25$(OH)_2$D supplements. However, these treatments do not correct the primary pathogenic mechanism or treat all symptoms and can be associated with adverse effects. Burosumab is a recombinant human immunoglobulin G1 monoclonal antibody against FGF23, approved for treating XLH in several geographical regions, including Europe and Israel. Burosumab restores normal serum phosphate levels, minimising the clinical consequences of XLH. Safety data on long-term treatment with burosumab are lacking owing to the rarity of XLH. This post-authorisation safety study (PASS) aims to evaluate the safety outcomes in patients aged >1 year.

Methods: The PASS is a 10-year retrospective and prospective cohort study utilising data from the International XLH Registry (NCT03193476), which includes standard diagnostic and monitoring practice data at participating centres. The PASS aims to evaluate frequency and severity of safety outcomes, frequency and outcomes of pregnancies in female patients, and safety outcomes in patients with mild to moderate kidney disease at baseline, in children, adolescents and adults treated with burosumab for XLH. It is expected that there will be at least 400 patients who will be administered burosumab.

Results: Data collection started on 24 April 2019. The expected date of the final study report is 31 December 2028, with two interim reports.

Conclusion: This PASS will provide data on the long-term safety of burosumab treatment for XLH patients and describe safety outcomes for patients receiving burosumab contrasted with those patients receiving other XLH treatments, to help inform the future management of XLH patients. The PASS will be the largest real-world safety study of burosumab.

Registry identification: The International XLH Registry is registered with clinicaltrials.gov as NCT03193476 (https://clinicaltrials.gov/ct2/show/NCT03193476), and the PASS is registered with the European Union electronic Register of Post-Authorisation Studies as EUPAS32190 (http://www.encepp.eu/encepp/viewResource.htm?id=32191).

Keywords: burosumab, patient registry, phosphate, post-authorisation safety study (PASS), rare bone disease, real-world evidence, X-linked hypophosphataemia (XLH)

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Introduction

X-linked hypophosphataemia (XLH) is a rare, hereditary, chronic, deforming bone disease that affects approximately one in 20,000–60,000 people globally.[1–4] XLH is an X-linked dominant disorder that accounts for around 80% of all cases of monogenic hypophosphataemic rickets.[5] The disorder is caused by inactivating mutations in the *PHEX* gene, which encodes phosphate-regulating endopeptidase homolog, X-linked, a cell-surface–bound protein-cleavage enzyme.[5,6] XLH is characterised by excess levels of circulating fibroblast growth factor 23 (FGF23), resulting in increased renal phosphate excretion, reduced synthesis and increased degradation of active vitamin D ($1,25(OH)_2D$), leading to chronic hypophosphataemia.[5] This in turn can lead to defective bone and tooth mineralisation and formation, causing rickets, osteomalacia and odontomalacia in children, and osteomalacia and odontomalacia in adults. In addition, several other skeletal and extra-skeletal symptoms, for example, leg bowing, growth retardation, craniosynostosis, enthesopathy, insufficiency fractures, dental fistula formation, tooth abscesses in caries-free dentition and sensorineural hearing loss may occur, the pathogenesis for which is largely elusive.[5,6] A large heterogeneity of XLH phenotype exists, especially in adults and even between members of the same family.[7,8] Children with XLH typically present with impaired and disproportionate growth, rickets, gait abnormalities, lower-limb deformities and dental complications, for example, wide dental pulp chambers, globular dentine and increased propensity to dental abscesses.[9] Adults with XLH often display symptoms and signs of osteomalacia, such as excessive pain, pseudofractures, osteoarthritis and musculoskeletal complaints, including stiffness, reduced mobility, weakness and fatigue.[9] Coupled with the rarity of XLH and the fact that knowledge is often restricted to a few specialised centres, significant unmet needs and challenges exist for patients with this disorder, particularly around diagnosis and treatment.[5]

If left untreated, XLH can have a severe lasting negative impact on quality of life (QoL) for patients of all ages. Many complications in adults appear to be a result of sub-optimal treatment during childhood, meaning unresolved complications from childhood persist, such as lower extremity deformity and short stature.[6,10,11] The current standard of treatment for XLH, commonly referred to as 'conventional treatment', consists of a combination of oral phosphate and active vitamin D analogues, such as calcitriol or alphacalcidol.[5] While these treatments may improve clinical symptoms and rickets, they do not actually correct FGF23 excess, which is a major underlying cause of XLH skeletal manifestations.[5,10] Furthermore, these oral treatments rarely normalise growth, bone and dental health or improve patient QoL.[12–14] Attempts to bring phosphate levels into the normal range imply a considerable risk for inducing side effects, such as hypercalciuria and nephrocalcinosis, which may progress to subsequent chronic kidney disease (CKD). In addition, secondary and eventually tertiary hyperparathyroidism may contribute to nephrocalcinosis and bone disease by aggravating the renal phosphate-wasting. Moreover, oral phosphate is associated with poor patient adherence due to its unpleasant taste, frequent dosing in some patients and associated gastrointestinal side effects, such as abdominal cramping and diarrhoea.[5]

Burosumab is a fully human immunoglobulin G1 monoclonal antibody for FGF23 that was approved by the US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) in 2018. Burosumab is approved in a number of geographical regions, including the European Union and Israel, for the treatment of XLH in children and adolescents aged 1–17 years with radiographic evidence of bone disease, and in adults.[15,16] Clinical trial evidence has demonstrated the efficacy of burosumab: it restores blood phosphate levels to within the lower normal range through the reduction of renal phosphate-wasting and increase in $1,25(OH)_2D$ levels.[17–19] These studies have demonstrated that treatment can result in the amelioration of rickets in children and improve the healing of insufficiency fractures and patient-reported outcomes of stiffness, pain, physical function and total distance walked in 6 min (as assessed by the 6-Minute Walk Test) in adults, without causing hypercalciuria or elevated parathyroid hormone (PTH) levels.[17–19] Data are lacking on the use of burosumab in pregnant women. However, animal studies have shown evidence of toxicity and the use of burosumab is therefore not recommended during pregnancy or by women of childbearing potential not using

contraception.[15] Real-world evidence on the long-term efficacy, safety and drug usage is needed to confirm how burosumab performs outside of clinical trial conditions.

The International XLH Registry (NCT03193476) aims to collect data to address knowledge gaps around XLH.[9] Patient registries allow for long-term collection of patient data with fewer exclusion criteria than typical clinical studies, such as interventional clinical trials.[20] The International XLH Registry, which was established in 2017, aims to recruit 1200 patients, and is planned to run for 10 years, with the primary outcome to collect data to characterise the treatment, burden of disease, progression and long-term outcomes of XLH in patients across all age groups.[9] To be eligible for inclusion in the International XLH Registry, patients must have met all of the following criteria: male or female subjects of all ages at baseline; diagnosis of XLH with clinical, radiological, biochemical and/or genetic findings consistent with XLH. Any patient meeting any of the following exclusion criteria at baseline could not be included in the International XLH Registry: patient or their legally designated representative does not have the cognitive capacity to provide informed consent; patients who are currently participating in an interventional clinical trial (patients may be approached for inclusion in the International XLH Registry once their involvement in the clinical trial (including all trial follow-up assessments) has been completed; participating in a Compassionate Use Programme, Pre-commercial Programme (i.e. Named Patient Sales, Nominative Temporary Use Authorisation [TUA]) or Investigator-Initiated Study does not preclude a patient from participation in the International XLH Registry.[9] Data from the International XLH Registry will be published in an interim analysis in due course. In addition, a post-authorisation safety study (PASS) for burosumab is nested as a sub-study within this XLH patient registry and, therefore, meets the same patient inclusion and exclusion criteria.[9] As the PASS is also non-interventional, all data collected will arise from the usual clinical management of these subjects. The PASS, which is described in the current paper, aims to evaluate the long-term safety of burosumab treatment in XLH, and will be conducted using data that are routinely collected in the International XLH Registry. The original PASS (Version 1.0) was approved in 2019 and followed the licenced indication as stipulated by the original marketing authorisation of burosumab at the time, that is, the PASS only included the paediatric XLH population and adolescents who were still growing. However, in 2020, the EMA granted an extension to the licenced indication for burosumab to include the treatment of all adolescents and also adults.[15,16] To achieve harmonisation with this major update to the licenced indication for burosumab, the PASS Version 1.0 consequently underwent significant amendments to include these new patient populations, resulting in a PASS Version 2.0, of which has been reviewed by the EMA Pharmacovigilance Risk Assessment Committee (PRAC) and been granted a Positive Opinion by the Committee for Medicinal Products for Human Use (CHMP), of which this article describes the rationale and methodology. Real-world safety data included in the PASS will therefore provide evidence from all age groups treated, and those not treated, with burosumab, which will help improve care and outcomes for patients with XLH.

Methods

Study population

This study is a non-interventional PASS, using data routinely collected in the International XLH Registry. The International XLH Registry contains data on male and female patients of all ages diagnosed with XLH, regardless of their treatment regimen; the methods and rationale for the International XLH Registry have been described previously.[9] Patients included in the PASS are expected to receive treatment with burosumab according to the EU indication; that is, children and adolescents 1–17 years of age with radiographic evidence of bone disease, and in adults,[15] all of whom will also be enrolled in the International XLH Registry. Additional patients investigated for the secondary objective will similarly be taken from the International XLH Registry, with patients having the same characteristics with the exception that they will be treated with either burosumab or with other treatments for XLH.

Study design

The PASS is a 10-year retrospective and prospective cohort study, for which data collection started on 24 April 2019. It is an international, multi-centre (Europe and Israel), non-interventional study,

meaning that all data gathered will arise from the patients' physician's usual clinical practice. Patients investigated for the primary objectives are expected to receive treatment with burosumab in accordance with its marketing authorisation.

Study objectives

The primary objectives of the PASS are to evaluate the frequency and severity of safety outcomes in children, adolescents and adults who are being treated with burosumab for XLH, including but not limited to long-term safety, as evidenced by death, hospitalisations, cardiovascular disease, cancer, hyperphosphataemia and its complications, ectopic mineralisation, nephrocalcinosis and increased PTH levels; to prospectively evaluate the frequency and outcomes of pregnancies in female patients treated with burosumab; and to prospectively evaluate the frequency and severity of safety outcomes in patients with mild to moderate CKD at baseline treated with burosumab. The secondary objective is to perform a retrospective cohort analysis using data from the International XLH Registry to compare the safety outcomes in patients treated with burosumab to those in patients receiving alternative treatments for XLH as comparators, that is, typically conventional therapy (oral phosphate and active vitamin D analogues), the use of growth hormone (for children and adolescents), and no therapy. Note that the variables collected in the PASS include collection of data related to safety outcomes only. Other outcomes (e.g. growth, QoL) will be collected in the International XLH Registry, in which the PASS is embedded, and are outside the scope of this current paper.

Study size

As this is primarily a prospective observational registry, the sample size was not based on statistical considerations. The sample size was determined based on evidence provided by XLH clinical experts across Europe, suggesting that a total recruitment target of 1200 patients with XLH would be appropriate to enable robust research to be conducted on the data contained within the registry.[9] Assuming 50% enrolment of the eligible XLH patient population, it is projected that the International XLH Registry will contain data on approximately 1200 patients spanning the 10 years of the registry's lifespan. For inclusion in the PASS, data collection will commence from the time the patient provides informed consent for participation in the International XLH Registry and PASS. Patients exposed to burosumab are estimated to number approximately 400 at the end of the 10-year life span of the PASS. The number estimated to be receiving an alternative, or no treatment, will be approximately 800, which will form the comparator cohort for the secondary objective (Figure 1).

Ethics

The International XLH Registry is run in accordance with the Declaration of Helsinki (1964). It has received ethical, regulatory and institutional approvals at all required levels for each participating site with the EMA Ethics Submission Procedure Number assigned as: EMEA/H/C/004275/MEA/004.2, approval date: 20 May 2021. Patient information and consent will be obtained locally for each potential patient (or their legally designated guardian) before their inclusion and participation in the International XLH Registry and the PASS. The institutional review board/independent ethics committee will be informed of any substantial amendments to the protocol during the study period, and annual and final International XLH Registry reports will be completed for the institutional review board/independent ethics committee. Each potential patient (or their legally designated guardian) will be given adequate verbal and written information regarding the objectives and the procedures of the International XLH Registry and the PASS, and will also be informed about their right to withdraw their permission for entry of their (or their child's) data into the International XLH Registry and the PASS at any time. The written informed consent forms (parental or adult), and adolescent assent forms if applicable, must be signed and dated before any data can be registered in the International XLH Registry and included in the PASS analysis.

Data collection and management

The PASS will investigate diagnostic and monitoring practice data collected in the International XLH Registry. Patients will be followed for as long as informed consent exists, and only data collected during standard routine clinical examinations will be recorded (Tables 1 and 2).

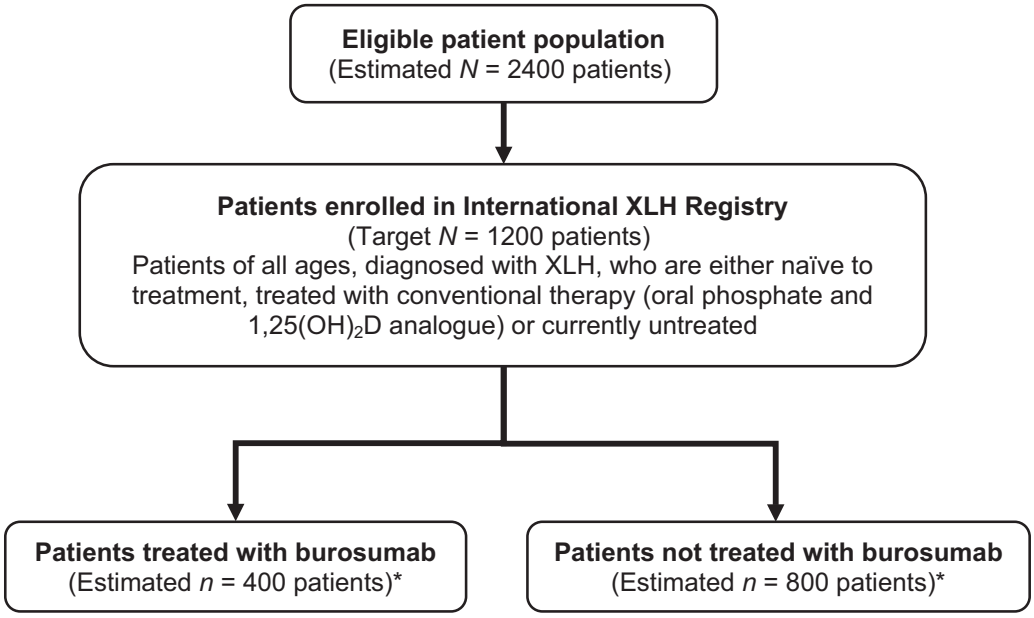

Figure 1. Flow chart of patient inclusion/selection.
*Total number of patients to be enrolled in the International XLH Registry during the 10-year lifespan of the registry is projected to be approximately 1200. Based on the assumption that 50% of these patients in the International XLH Registry are children and adolescents 1–17 years of age or adults who may be considered suitable for burosumab treatment, the number of burosumab-*eligible* patients within this group of 1200 patients is projected to be approximately 600. Assuming then that two-thirds of these 600 patients receive burosumab, based on numerous factors, such as in-country reimbursement decisions, individual patients' factors/choice, and personal consent to their inclusion for participation in the PASS, the number of burosumab-*treated* patients included in the PASS for the primary objectives is estimated to be approximately 400. Assuming the other patients *not* exposed to burosumab receive alternative treatments (i.e. other than burosumab), this cohort will amount to approximately 800 patients and will act as the comparator group for the secondary objective in the PASS. $1,25(OH)_2D$, active vitamin D; PASS, post-authorisation safety study; XLH, X-linked hypophosphataemia.

When patients are enrolled into the International XLH Registry, both retrospective data (past medical history) and data available at the time of consent (baseline visit) will be collected.[9] Prospective data collected at subsequent routine clinical visits will be added periodically (at least annually) to the database. No investigations outside of routine clinical practice are required. Baseline and prospective data will utilise normal ranges specific to the laboratory, hospital and/or country and will be age- and sex-adjusted.

International XLH Registry data collection is via an electronic data capture (EDC) tool, its core data specification approved by the International XLH Registry Steering Committee, a group comprised of expert physicians from Europe and Israel who are experienced in treating XLH. Data storage is via a third-party contractor, in line with the EU Directive on data protection, with the patient data pseudo-anonymised. The source data for the PASS are taken from the International XLH Registry, and data for the PASS provided by the International XLH Registry owners will follow the same rules for data use from the International XLH Registry.

Data analysis

Given the relatively small projected number of patients who will be treated with burosumab, the sample size in the PASS may not be sufficient for formal comparative analyses. Data analyses will therefore be in the form of descriptive statistics, although the aim of course is to conduct formal statistical analyses wherever final numbers can provide sufficient power for such analyses.

For the primary objectives, code lists will be developed in the database and datasets, to identify cardiovascular diseases, cancers, hyperphosphataemia and its complications, and increased PTH levels. Deaths and hospitalisations will be identified using structured data fields in the

Table 1. Data fields to be investigated in the PASS (if collected and recorded) for each patient enrolled into the International XLH Registry.

Variable group heading	Variables	
Informed consent	Date	Assent
	Type	
Demographics	Date of birth	Ethnicity
	Sex	
XLH-specific medication (all XLH-specific medications, including pain medication)	Dose	Duration
	Compliance	Reason for discontinuation
Drug history	Dose	Duration
	Compliance	Reason for discontinuation
Radiography and imaging	Any radiological assessment of disease severity Type of assessment	Scanner type Analysis software used
Physical examination	Age	Disease-specific examinations
Vital signs	Temperature	Pulse rate
	Blood pressure (sitting)	Respiratory rate
Growth assessments	Standing height (metres)	Weight (kg)
	Sitting height (metres)	Body mass index
	Arm length (metres)	*Z* scores (based on national reference)
	Leg length (metres)	
Biochemistry*	$1,25(OH)_2D$	Creatinine
	25(OH)D	Gamma-glutamyl transpeptidase
	Alanine aminotransferase	FGF23
	Aspartate aminotransferase	Intact PTH
	Amylase	Lactate dehydrogenase
	Bilirubin (direct and total)	Phosphate
	Blood urea nitrogen	Potassium
	Calcium (total)	Protein (albumin and total)
	Chloride	Sodium
	Carbon dioxide	Alkaline phosphatase
	Cholesterol (total)	
Haematology*	Haematocrit	Red blood cell count
	Haemoglobin	Mean corpuscular volume

(Continued)

Table 1. (Continued)

Variable group heading	Variables	
	Platelet count	Mean cell haematocrit
Urine*	pH	Phosphate
	Specific gravity	Phosphate/creatinine ratio
	Protein	Ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate (TmP/GFR)
	Calcium	Tubular reabsorption of phosphate (TRP)
	Calcium/creatinine ratio	Pregnancy test (if applicable)
	Glucose	
Bone biomarkers*		
Physiotherapy reports	Number of visits	Use of medical devices
	Use of a wheelchair	Home adaptations
	Use of walking aids	
Echocardiogram reports		
Electrocardiogram reports		
Audiology assessment		
Renal ultrasound scans		
Social history	Number of work/school dates missed due to XLH-related illness since last visit	
XLH-specific medical, surgical and dental history	Age of onset of symptoms	*PHEX* mutation (if available)
	Age at diagnosis	Number of known affected relatives and relationship to patient
	Diagnosis method	
General medical history	Pregnancy and foetal outcome	Incidence of hospital admission
	Pregnancy information relating to burosumab: timing and duration of gestational exposure, duration of exposure, foetal outcomes (including weight, length, Apgar score, mode of delivery)	Duration of hospital admission
		Cause of hospital admission

Data are grouped under headings, followed by a listing of all individual data variables collected. Paediatric patients will be asked to provide adult consent for the International XLH Registry when they reach the applicable age to do so per national guidelines at participating centres. The International XLH Registry does not mandate investigations outside of standard care as determined by the patient's physician. Normal ranges will be specific to the laboratory, hospital, and/or country, and will be age- and sex-adjusted. The EDC system notifies any data entry that falls outside the normal range to the CRO, which is then checked, and the source data verified to either confirm or correct the data entry.
$1,25(OH)_2D$, active vitamin D (calcitriol); $25(OH)_2D$, 25 hydroxy vitamin D; CRO, contract research organisation; EDC, electronic data capture; FGF23, fibroblast growth factor 23; PASS, post-authorisation safety study; PTH, parathyroid hormone; XLH, X-linked hypophosphataemia.
*Assays can vary, depending on the local practice at the laboratory, hospital site and/or country

Table 2. Schedule of assessment for data recording.

	Baseline data entry	Retrospective data entry	Prospective*	Assessment to be investigated in PASS
Informed consent*	X	X	X†	X
Demographic information	X	–	–	X
Medical history, including pregnancy history and outcomes	–	X	X	X
PHEX mutation (if available)‡	–	X	X‡	X
XLH medications and drug history	X	X	X	X
Radiographs and imaging	X	X	X	X
Physical examination	X	X	X	X
Vital signs	X	X	X	X
Growth assessment	X	X	X	–
Laboratory assessments	X	X	X	X
Physiotherapy	X	X	X	–
Echocardiogram	X	X	X	X
Electrocardiogram	X	X	X	X
Audiology	X	X	X	X
Renal ultrasound	X	X	X	X
Patient assessment tools/ outcome measures	X	X	X	–
Patient QoL questionnaires	X	X	X	–
Social history	X	X	X	X
AEs	–	X	X	X

AE, adverse event; PASS, post-authorisation safety study; QoL, quality of life; XLH, X-linked hypophosphataemia.
X, data to be collected.
–, data not to be collected (PASS data collected for safety outcomes only).
*Data prompted to be updated in the database annually.
†Re-consent to International XLH Registry adult consent form when patient transitions from paediatric age to adult age.
‡*PHEX* mutation to be recorded in prospective visit if not available at baseline.

International XLH Registry. Ectopic mineralisation will be identified from results of various investigations, including echocardiography. The EDC tool used by the International XLH Registry will help to make the data available for independent review. Pregnancy will be captured by relevant structured data fields, and the outcome of any pregnancies will be followed up. Information on renal function will be assessed from data captured in the International XLH Registry and from the results of laboratory tests to enable stratification of the cohort by renal characteristics in addition to stratification of PASS data by *PHEX* mutations (where available) and the burosumab dose/kg body weight in children, adolescents and adults.

For the secondary objective, the International XLH Registry will provide the basis for a contextual cohort of patients with XLH not treated with burosumab. Data from these patients will be used for a retrospective cohort analysis to contrast the safety outcomes of patients treated with burosumab; although, due to the relatively small number of patients, this analysis may possibly not be statistically powered for anything other than for very high relative risks. A retrospective cohort analysis will be performed to account for potential selection bias, based on burosumab exposure and burosumab non-exposure.

Quality control

Data entered into the International XLH Registry will be automatically checked using limits set within the database programme. Additional controls will be carried out by the contract research organisation (CRO) managing the International XLH Registry to detect inconsistencies, such as erroneous value entries or the absence of any follow-up assessments. For example, if an entry is made that falls outside the normal range of that particular variable, the EDC system highlights that specific entry/non-entry to the CRO. The queried entry/non-entry is then checked, and the source data are verified to either confirm or correct the data entry.

Management and reporting of adverse events/adverse reactions

Patients enrolled in the PASS will be subject to solicited adverse event (AE) reporting by their investigator physician to the PASS sponsor. Healthcare professionals and other site staff submitting data via the EDC to the International XLH Registry will receive appropriate training. The EDC tool used by the International XLH Registry will prompt users to enter data on any AEs to ensure appropriate data collection. Reports of AEs/drug reactions as defined by the study endpoints will be summarised as part of any interim safety analyses for the PASS and also in the final study report for the PASS.

Plans for disseminating and communicating study results

Progress reports will be prepared annually and as required by the EMA as part of the periodic benefit–risk evaluation report (PBRER). Interim analysis reports and final reports will be prepared at pre-determined milestones (Table 3).

Discussion

Multi-centre international patient registries can provide important information about rare diseases on a scale that would not be possible by traditional means, such as registrational clinical trials, because the limited number of patients in such registrational trials may not be able to provide strong enough conclusions to be made from the limited dataset available.[9,20–22] Real-world and observational studies that include patient populations treated in a less-controlled environment and usually for a longer duration, can often better identify less common AEs, especially those potentially occurring in rare diseases, thus improving burosumab safety data.[23] Long-term data collected in these registries can also help determine longer-term benefits of treatments, providing additional insights to inform future clinical practice.[24]

The PASS (Version 1.0 and Version 2.0) for burosumab was required by the EMA as part of the initial marketing authorisation for burosumab to enable the collection of long-term real-world data which can then be analysed to inform about the safety of treatment with burosumab. This specific study is designated as a 'Category 3 PASS' meaning it is required as part of the risk management plan to investigate safety concerns; this is as opposed to being designated a 'Category 1 PASS' or a 'Category 2 PASS', which are imposed in accordance with regulations, or as a specific obligation in the framework of a marketing authorisation granted under exceptional circumstances, respectively. Variables to be collected in the International XLH Registry, which are relevant for the PASS include demographic information, medical history, *PHEX* mutation (if available), medication history, radiographs and bone imaging, physical examination, vital signs, laboratory assessments, echocardiogram, electrocardiogram, audiology, renal ultrasound and social history. Safety concerns to be investigated in the PASS include long-term safety, hyperphosphataemia, ectopic mineralisation, pregnancy outcomes, increased PTH and effects in patients with mild to moderate CKD at baseline.

Recently, the first evidence-based guidelines for XLH were developed,[5] which also identified key

Table 3. Study milestones.

Milestone	Planned timings (children and adolescents, i.e. paediatric)	Planned timings (adults)
Start of PASS	PRAC approval of protocol V.1.0	PRAC approval of protocol V.2.0
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 patients have achieved at least 6 months of time in the PASS	To be submitted after approximately 50 adult patients 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	To be prepared 10 years from the start of data collection in the adult population

EMA, European Medicines Agency; ICF, informed consent form; PASS, post-authorisation safety study; PBRER, periodic benefit–risk evaluation report; PRAC, Pharmacovigilance Risk Assessment Committee.

areas for the generation of further knowledge. Two of these areas were the increased understanding of the natural history of XLH and additional data on burosumab, with the guidelines acknowledging these would be crucial for generating improved guidelines and, ultimately, better patient care in the future.[5] The International XLH Registry and this PASS will contribute strongly to this evidence generation by collecting natural history data for XLH, and data to characterise treatment progression and long-term outcomes in XLH.

As well as generating real-world evidence on the natural history of XLH and patient demographics, the International XLH Registry and this PASS will provide data on the real-world effectiveness and safety of both burosumab and conventional therapy, which may help to inform best clinical practice and ultimately improve the QoL of many patients with XLH.[9]

The International XLH Registry protocol was submitted for ethical approval in all participating countries in August 2017, and the first patient was recruited in October 2017. Subsequently, in May 2021, the EMA CHMP approved the PASS protocol (Amendment 1.0, Version 2.0), which covers the extended licenced population of adult and adolescent patients with XLH following the approval of the full indication for burosumab in XLH. The updated wording and syntax in this new amendment of the PASS protocol aims to provide greater clarity and conciseness for physicians and their teams at participating sites. As of February 2022, across 81 hospital sites from 16 countries, 1059 patients have been recruited into the International XLH Registry. Of these 1059 patients, 384 patients on burosumab have been enrolled into the PASS, correlating to ~96% of the final target for the primary objectives of the PASS. Publication of the interim analysis data is planned once the milestone criteria are met. Current projections indicate that the target of 1200 patients with XLH, which will be the largest single registry dataset of patients with XLH in the world, will be reached by 2023.

Limitations of this PASS

Fundamental limitations of the International XLH Registry study were discussed by Padidela

et al.[9] Even though the International XLH Registry and PASS are the largest datasets of XLH subjects in the world to date (targets of 1200 and 400 patients, respectively), the sample size may still result in limited statistical analyses; this will not be known until the first interim analysis. In addition, despite patients being under the care of a physician for their condition, data capture on intervening events may be incomplete if data are not entered meticulously and/or if appointments are infrequent, especially during the restrictions associated with the coronavirus disease 2019 (COVID-19) pandemic.

To minimise selection bias, a comprehensive screening process was conducted to identify XLH-treating hospital sites, which were then subsequently approached and invited to participate in the International XLH Registry. All sites that were successful in the screening process and provided consent to participate in the International XLH Registry were then also invited to participate in this embedded PASS. As the patient population may not be large enough to utilise precise case–control matching, a retrospective cohort analysis based on burosumab exposure and burosumab non-exposure will be undertaken.

Finally, to standardise the nature of the information collected, every International XLH Registry hospital site will use the same EDC system and undergo the same training for their staff. Source data verification of a representative portion of raw data at participating centres will be implemented to verify the quality of the data collection, although it should be noted that the International XLH Registry does not mandate investigations outside of standard care as determined by the treating physicians.

Conclusion

This PASS will enable the collection of data relating to the long-term safety of burosumab treatment for children, adolescents, and adult patients with XLH. It will allow the description of safety outcomes of patients on burosumab. It will also complement other data generated from the International XLH Registry, which will provide comprehensive information on multiple groups of patients with XLH, allowing us to further evaluate the natural history of the disease to ultimately help towards improving multidisciplinary care for all patients with XLH.

Abbreviations

$1,25(OH)_2D$, active vitamin D (calcitriol); 25(OH)D, 25 hydroxy vitamin D; AE, adverse event; CKD, chronic kidney disease; CRO, contract research organisation; EDC, electronic data capture; EMA, European Medicines Agency; FGF23, fibroblast growth factor 23; PASS, post-authorisation safety study; PBRER, periodic benefit–risk evaluation report; PTH, parathyroid hormone; QoL, quality of life; XLH, X-linked hypophosphataemia.

Declarations

Ethics approval and consent to participate

The International XLH Registry is run in accordance with the Declaration of Helsinki (1964). It has received ethical, regulatory, and institutional approvals at all required levels for each participating site. Patient information and consent will be obtained locally for each potential patient (or their legally designated guardian) before their inclusion and participation in the International XLH Registry and the PASS.

Consent for publication

Consent for publication was not required because the study did not involve patient data or personal health information.

Author contributions

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Competing interests
AB has received research grants and received honoraria as a consultant and speaker, paid to her institution, from Kyowa Kirin and Ultragenyx. CLC has received honoraria as a consultant for Kyowa Kirin. MCZ reports that her institution has received a research grant from Kyowa Kirin. DH has received a research grant or honoraria as a consultant and speaker from Amgen, Chiesi and Kyowa Kirin. DS has received honoraria as a consultant from BioMarin, Kyowa Kirin, Novo Nordisk and Sandoz. EL has received honoraria as a consultant from Advicenne, Chiesi, Kyowa Kirin, Novartis and Recordati. FE declares competing interests with Avrobio, Chiesi, Kyowa Kirin, Otsuka and Recordati Rare Diseases. GA has received personal fees and non-financial support from Advicenne, Alexion, Kyowa Kirin, Recordati Rare Diseases and received personal fees from Alnylam and Dicerna, and received personal fees and other from Chiesi. KB has received honoraria as a consultant from Amgen, Kyowa Kirin, Theramex and UCB. LTS has received honoraria as a consultant from Amgen and Kyowa Kirin. MB has received research grants or honoraria as a consultant or speaker from Abiogen, Alexion, Amgen, Bruno Farmaceutici, Calilytix, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex and UCB. ON has received honoraria as a consultant from BioMarin and Kyowa Kirin. OM has received honoraria as a consultant from BridgeBio, Kyowa Kirin and Ultragenyx. RK has received honoraria as a consultant or for advisory boards from Kyowa Kirin. SBN and ZM have received honoraria as a consultant or speaker from Inozyme Pharma and Kyowa Kirin. JL and AT are employees of Kyowa Kirin International plc. SG declares no conflict of interests.

Availability of data and materials
All relevant materials are included within the paper.

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