POST-AUTHORISATION SAFETY STUDY (PASS)

First interim Study Report (data cut-off: 13 May 2021)

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age and Adolescents with X-linked Hypophosphataemia (protocol number 2019-36-EU-CRY)
Version identifier of the interim study report	1.0
Date of last version of the interim study report	Not applicable
EU PAS/ENCePP 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 paediatric subjects[1] with XLH and radiographic evidence of bone disease who are

	aged one year and older and adolescents with growing skeletons, and who are treated with burosumab, including but not limited to: 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 Secondary objective: 1. To perform a retrospective cohort study using data from the XLH Registry to compare the safety outcomes of interest in subjects exposed to burosumab to those in subjects receiving alternative treatments for XLH
Country(-ies) of study	Data from the following countries are included in this interim report: France, Italy, Netherlands, Norway, Spain, and United Kingdom.
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[1] **N.B.:** This interim report is based on version 1 of the protocol dated 15 Aug 2018, which includes children >1 year of age and adolescents (Appendix 1). Protocol amendment 1 (version 2, 12 Jan 2021, Appendix 1) includes adults in the study population.

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – post-authorisation safety studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

MARKETING AUTHORISATION HOLDER(S)

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
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1. ABSTRACT

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age and Adolescents with X-linked Hypophosphataemia (protocol number 2019-36-EU-CRY)
Keywords	X-Linked Hypophosphataemia, XLH, Adverse Events, Burosumab, Safety
Rationale and background	X-linked hypophosphataemia (XLH) is a rare, hereditary, chronic, deforming bone disease characterised by excess levels of circulating Fibroblast Growth Factor-23 (FGF23) leading to increased urinary phosphate excretion, reduced 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] synthesis, and subsequent hypophosphataemia. Crysvita® is a recombinant human Immunoglobulin G1 (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 this Category 3 Post-Authorisation Safety Study (PASS). The data source to conduct the PASS is the data collected in the XLH Registry. The purpose of the 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 and adolescents 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 **N.B.:** This interim report is based on version 1 of the protocol dated 15 Aug 2018, which includes children >1 year of age and adolescents (Appendix 1). Protocol amendment 1 (version 2, 12 Jan 2021, Appendix 1) includes adults in the study population. While version 2 has been approved by PRAC, it is not yet implemented in the sites that participate to the PASS. In several sections of this interim report, the wording of the version 2 of the protocol has been used to make the report easier to read.

Research question and objectives	**Primary objectives** 1. To evaluate the frequency and severity of safety outcomes in paediatric subjects with XLH with radiographic evidence of bone disease who are aged one year and older and adolescents with growing skeletons, and who are treated with burosumab, including but not limited to: 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 **Secondary objective** 1. To perform a retrospective cohort study using data from the XLH Registry to compare the safety outcomes of interest 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 new European disease Registry for XLH. The PASS is non-interventional, so all data is being collected during the usual clinical management of these subjects.
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 (MA). Therefore, all subjects investigated for the primary objective will comprise: Children aged one year and older and adolescents with growing skeletons, receiving burosumab for the treatment of XLH, and enrolled in the XLH Registry via one of the 18 participating European countries.
Subjects and study size	Approximately 1,200 subjects with XLH in Europe are estimated to be eligible for inclusion in the XLH Registry. Assuming that 50% of the subjects in the XLH Registry are children aged one year and older and adolescents (broadly accurate from EU centre with available demographic data) and two-thirds of them receive burosumab: 400 children aged one year and older and adolescents, and treated with burosumab, are expected to be included in the PASS (population for primary and secondary objectives).

Variables and data sources	In summary, the variables collected in the XLH Registry which are relevant for the PASS are: Demographic information; Medical history; Phosphate-Regulating Endopeptidase Homolog X-Linked (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.
Statistical analyses	Statistical analysis were only descriptive for the primary objective (frequency and severity of safety outcomes). Statistical analyses related to secondary objective were not planned for this first interim report.
Results	A total of 67 subjects that received burosumab treatment were included in this study between 12 Sep 2017 and the interim data cut-off of 13 May 2021. In total, 25 out of these 67 subjects reported an adverse event (AE) over the course of the study. The total number of AEs reported was 83. From the 25 subjects reporting AEs, 13 subjects reported 25 AEs possibly/probably related to the XLH treatment (of whom 12 reported 23 AEs possibly/probably related to burosumab specifically), 4 subjects reported 6 severe AEs in total, and 2 subjects reported 2 serious adverse events (SAEs). No deaths, no AEs leading to XLH treatment withdrawal, and no SAEs related to XLH treatment were reported in the study. Five (5) from the 67 subjects had chronic kidney disease. From these 5 subjects, 3 subjects reported at least one AE, of whom 2 reported AEs qualifying as possibly/probably related to XLH treatment (from which 1 had an AE possibly/probably related to burosumab specifically). Neither SAEs nor severe AEs were reported in subjects with chronic kidney disease in the study. There were no pregnancies reported in the study population over the course of the study.
Discussion	The primary objective of this study is to evaluate the frequency and severity of AEs in children and adolescents using burosumab for the treatment of XLH. The mean follow-up time at data cut-off was 2.2 years. The number of observed AEs reported in this interim analysis was 83 in 25 subjects, with 6 qualifying as severe AEs, and 2 as SAEs. No deaths, no AEs leading to XLH treatment withdrawal, and no SAEs related to XLH treatment were reported in the study. Upon continuation of the study, the aim is to follow the subjects for a period of up to 10 years and provide long-term safety data for medical care providers and subjects with XLH that will improve the knowledge of burosumab safety and will assist in treatment decision-making processes.
Marketing authorisation holder (MAH)	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
Name(s) and affiliation(s) of principal investigator(s)	Not Applicable.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
$1,25(OH)_2D$	1,25-dihydroxyvitamin D
AE	Adverse Event
AESI	Adverse Event of Special Interest
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organisation
DMFT	Decayed/Missing/Filled Teeth
DMP	Data Management Plan
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
FGF23	Fibroblast Growth Factor-23
GFR	Glomerular Filtration Rate
GPP	Good Pharmacoepidemiology Practice
GVP	Good pharmacovigilance practices
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IgG1	Immunoglobulin G1
ISPE	International Society for Pharmacoepidemiology
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
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
QoL	Quality of Life
RMP	Risk Management Plan
SAE	Serious Adverse Events
SAF	Safety Analysis Set
SAS	Statistical Analysis System
SD	Standard Deviation
SF	Short Form
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SC	Steering Committee
WHODD	World Health Organization Drug Dictionary
XLH	X-linked hypophosphataemia

3. INVESTIGATORS

Please view full list of Investigators in Appendix 3.

4. OTHER RESPONSIBLE PARTIES

This study is performed by IQVIA, a contract research organisation (CRO), with guidance, input, review, and approval of Kyowa Kirin International plc, including development of materials, recruitment, training and management of sites, electronic data capture (EDC), and data management and analysis.

An XLH Registry Steering Committee (SC) has been established. The XLH Registry SC composition provides a balance of expertise, by including experts from endocrinology, nephrology, rheumatology etc. who, collectively, have the scientific, medical, and subject perspective, and study management experience to design and conduct the study, and evaluate the study results appropriately. Study Sponsor's representatives, selected based on their expertise, also participated to XLH Registry SC meetings as invited observers.

The XLH Registry SC provides scientific advice and guidance with regard to the study methodology (design, data collection and analysis), including with respect to protocol revision and amendments, as well as clinical input aspects of the study. The XLH Registry SC is responsible for overseeing the conduct of the study and making recommendations if needed, discussing study results and communication plan and motivating physicians participating in the study. The composition of the XLH Registry SC can be found in Appendix 7.

The signatures of Coordinating Investigator and sponsor's relevant officer involved in the study are provided in Appendix 5.

5. MILESTONES

Table 1. Study Milestones

Milestone	Planned Dates (Children and Adolescents, i.e., paediatric)	Actual Dates (Children and Adolescents, i.e., paediatric)	Comments
Start of PASS	PRAC approval of protocol v1.0	13 Dec 2018	
Start of PASS at country level	Product availability in participating countries	Between 2018 and 2023	
Start of data collection	First ICF for PASS signed (paediatric)	24 Apr 2019	
End of data collection	10 years from start of data collection (paediatric)	18 Aug 2020	
Study progress reports	Annually or as required by the EMA as part of PBRER (one report describing all populations)	Annually in October	
First interim report of study results	To be submitted after 50 paediatric subjects have achieved at least 6 months of time in the PASS	Oct 2021	
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)	Dec 2023	
Final report of study results	To be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029)	Dec 2028	

EMA: European Medicines Agency, ICF: informed consent form, PASS: Post-Authorisation Safety Study, PRAC: Pharmacovigilance Risk Assessment Committee, PBRER: periodic benefit-risk evaluation report

6. RATIONALE AND BACKGROUND

X-Linked Hypophosphataemia (XLH) is a rare, hereditary, chronic, deforming bone disease, which affects 1 in 20,000 to 60,000 people globally (1-4). XLH is an X-linked dominant disorder which accounts for more than 80% of all familial hypophosphataemia (5). It is characterised by excess levels of circulating Fibroblast Growth Factor-23 (FGF23) leading to increased urinary phosphate excretion, reduced 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] synthesis, and subsequent hypophosphataemia (6).

Crysvita® is a recombinant human Immunoglobulin G1 (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 (7).

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, and 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 Post-Authorisation Safety Study (PASS) will be conducted using data collected in the XLH Registry. The XLH Registry will be supported by the MAH.

This is an interim study report for the Non-interventional PASS of Burosumab in the Treatment of Children with XLH, as specified in Art 36 to 38 and Art 40 of the Commission Implementing Regulation (EU) No 520/2012 covering the primary objective of the study. The currently approved version of the PASS protocol is version 2, dated 12 January 2021, approved by the Committee for Medical Products for Human Use (CHMP) on 20 May 2021. The protocol was amended to include adults in the study population along with other updates, such as inclusion of additional countries and acknowledgement of the potential impact of the COVID-19 pandemic on the study. This interim report has been based on version 1 of the protocol dated 15 Aug 2018, which includes children >1 year of age and adolescents (Appendix 1), as the data cut-off point (13 May 2021) was prior to the implementation of the version 2. However, in several sections of this interim report, the wording of the version 2 of the protocol has been used to make this report easier to read and interpret.

The safety concerns to be investigated in this long-term PASS examining children and adolescents 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 QUESTIONS AND OBJECTIVES

7.1 Primary Objectives

1. To evaluate the frequency and severity of safety outcomes in paediatric subjects with XLH with radiographic evidence of bone disease who are aged one year and older and adolescents with growing skeletons, and who are treated with burosumab, including but not limited to: 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 Objective

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

The secondary objective will not be addressed in this first interim report.

8. AMENDMENTS AND UPDATES

The currently approved version of the PASS protocol is version 2, dated 12 January 2021, approved by the CHMP on 20 May 2021. As of the date of this report (October 2021), the version of the PASS which includes children >1 year of age, adolescents, and adults, has not yet been implemented in the sites that participate in the PASS.

This interim report has been based on version 1 of the protocol which includes children >1 year of age and adolescents (15 Aug 2018, Appendix 1), because the data cut-off point (13 May 2021) was prior to the implementation of the version 2. In several sections of this interim report, the wording of the version 2 of the protocol has been used to make this report easier to read and interpret.

9. RESEARCH METHODS

9.1 Study Design

Overall, this is a 10-year prospective cohort study using data collected in a European disease Registry for subjects with 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 (1-4), 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 manner, should one arise.

The PASS is non-interventional, so all data is being collected during the usual clinical management of these subjects.

9.2 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 MA. Therefore, all subjects investigated for the primary objective will comprise:

- Children aged one year and older and adolescents with growing skeletons, receiving burosumab for the treatment of XLH and enrolled in the XLH Registry via one of the 18 participating European countries.

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

9.3 Subjects

It is projected that the European XLH Registry will contain data on around 1,200 subjects covering the duration of the 10 years' lifespan of the Registry. The number of subjects exposed to burosumab is currently uncertain and depends on respective countries' reimbursement decisions but is anticipated to be around 400 subjects at the end of 10 years, forming the sample for the primary objective.

Approximately 800 subjects who receive a drug treatment for XLH other than burosumab are anticipated to be enrolled in the XLH Registry at 10 years, and included in the PASS as the comparator group for the secondary objective.

A subset of the XLH Registry data is used to fulfil a PASS as requested by the European Medicines Agency's (EMA's) CHMP. Not all centres are expected to participate in the PASS. Study centres which agree to participate in the PASS are asked to solicit adverse events (AEs) on enrolled subjects. The PASS is designated by the EMA as a non-interventional observational study. All data collected originates from the usual clinical management of these subjects. Any investigations performed for subjects in the PASS (such as blood tests, Electrocardiogram [ECGs], renal ultrasound scans or echocardiograms [ECHOs]) are at the discretion of the physicians managing the subjects according to the subjects' medical needs. Such investigations are not mandatory under the PASS protocol.

This first interim report of study results was to be submitted after 50 subjects had achieved at least 6 months in the PASS. This population comprises the Safety Analysis Set (SAF). The actual number of subjects screened is 647, enrolled in 18 countries. Among those, 67 subjects were included in the SAF, enrolled in 6 countries.

9.3.1 Inclusion Criteria

A subject must meet the following criteria at the enrolment visit (baseline) to be eligible for inclusion into this PASS (Inclusion Criteria are as per XLH Registry Protocol, with exclusion of adults as per PASS Protocol version 1):

1. Children aged one year and older, and adolescents with growing skeletons.
2. In the opinion of the treating physician, the subject has clinical presentation, radiological, biochemical, or genetic investigation results that support the diagnosis of XLH.

9.3.2 Exclusion Criteria

A subject who meets any of the following criteria at the enrolment visit (baseline) cannot be included in the XLH 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 XLH Registry once their involvement in the trial ends (including the completion of all trial follow-up assessments). Participation in a Compassionate Use Programme, Pre-commercial Programme (i.e., Named Patient Sales, Nominative temporary authorisation for use [ATU]) or Investigator Initiated Study does not preclude a subject from participation in the XLH Registry.

9.3.3 Screening Procedures

Eligible subjects are enrolled in the study at the time of presentation for a routine clinic visit and after signing of an informed consent form (ICF). No clinic visits are required as part of participation in this study. All assessments are intended to be performed at the time of a routine clinical encounter or by referencing the medical record.

All subjects presenting during the enrolment period are assessed for eligibility according to the protocol defined inclusion and exclusion criteria (see Section 9.3.1 and 9.3.2), and all eligible subjects are consecutively proposed to be enrolled in the study.

A screening log is maintained by each site to record the disposition of consecutive subjects potentially eligible for study participation, in order to better assess the representativeness of the sampled population.

9.4 Variables

The PASS is non-interventional, so all data collected will originate from the usual clinical management of these subjects and according to the recommendations described within the Summary of Product Characteristics (SmPC). Data are collected from the time that the subject signed informed consent for participation in the XLH Registry. Table 2 gives a summarised version of the Schedule of Assessments for Data Recording and highlights those assessments to be extracted for investigation in this PASS. Full details of all the information collected in the XLH Registry at baseline and subsequent visits are given in Appendix 6, Tables A to C.

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	X*	Yes
Demographic information	X	-	-	Yes
Medical history	-	X	X	Yes
PHEX Mutation (if available)**	-	X	X**	Yes
XLH medications and drug history	X	X	X	Yes
Radiographs and imaging	X	X	X	Yes
Physical examination	X	X	X	Yes
Vital signs	X	X	X	Yes
Growth assessment	X	X	X	No
Laboratory assessments	X	X	X	Yes
Physiotherapy	X	X	X	No
ECHO	X	X	X	Yes
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

ECG: Electrocardiogram, ECHO: Echocardiogram, PASS: Post-Authorisation Safety Study, PHEX: Phosphate-regulating neutral Endopeptidase X-linked, QoL: Quality of Life, XLH: X-linked hypophosphataemia

* Reconsent to adult Registry consent when subject transitions from paediatric subject to adult

** Phosphate-Regulating Endopeptidase Homolog X-Linked (PHEX) mutation to be recorded in prospective visit if not available at baseline

*** SF-36 and Paediatric Quality of Life Inventory (PedsQL) will be collected at baseline and prospective only in the 5 countries selected (France, Italy, Spain, Sweden, and UK), *and* the country's sites and subjects who have consented to participate in the PASS

9.4.1 Outcome Definition and Measures

The safety outcomes of this study include (but are 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 outcomes
- Effects in subjects with mild to moderate chronic kidney disease

9.5 Data Sources and Measurement

The source data for the PASS is a European XLH Registry of subjects of all ages 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 captures 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 is 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 SC), the conduct of this PASS is considered to constitute secondary use of data.

Since the XLH Registry is new, it will not be possible to validate the data source. Data linkage is not a feature of the PASS.

Table 2 below gives a summarised version of data collection and highlights those assessments to be extracted for investigation in the PASS.

Full details of all the information collected in the XLH Registry at baseline and subsequent visits are given in Appendix 6, Tables A to C.

9.5.1 Enrolment/Baseline

All data elements are collected from information routinely recorded in the medical record, or are prospectively recorded by the investigator for the purposes of the study. No visits or examinations, laboratory tests, or procedures are mandated as part of this study.

Please view Table 2 for details regarding data collected at Enrolment/Baseline.

9.5.2 Follow-up

No pre-determined follow-up requirements apply. However, physicians should update subject data in the XLH 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 2 shows the potential data that can be captured and entered into the XLH Registry EDC system.

For this first interim report, the end of data collection was set at 13 May 2021, i.e., after 50 subjects had achieved at least 6 months treatment with burosumab in the PASS.

9.5.3 Discontinuation

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

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

9.6 Bias

Selection Bias was addressed as follows:

- Site selection - a comprehensive programme was conducted by the MAH in order to identify XLH-treating health centres in Europe. All identified XLH treatment sites were approached and invited to participate in the XLH Registry. All sites participating in the XLH Registry will be invited to participate in the PASS. Hence the MAH has attempted to minimise the possibility of selection bias in the approach taken to site recruitment.

- Subject selection - all investigators have been encouraged to enrol subjects who are representative of the general XLH population in Europe.

- Statistical analysis - an approach to overcome selection bias is the use of case-control matching. However, this type of analysis requires a population sufficiently large to identify cases of interest and randomly-selected controls. As part of the statistical analysis for the final study report for the PASS, the MAH will undertake case-control matching based on burosumab exposure/non-exposure.

Information Bias was addressed as follows:

- The use of the same EDC system by every XLH Registry site standardises the nature of the information collected. Source data verification of a representative portion of raw data at participating centres have been 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 of care as determined by the treating physicians.

Confounding was addressed as follows:

- The EDC system allows the collection of detailed information on multiple variables relevant to the objectives being explored in the PASS. This will reduce potential residual confounding subject to the completeness of the data entry by the sites.

9.7 Study Size

Approximately 1,200 subjects with XLH in Europe are estimated to be eligible for inclusion in the XLH Registry. Assuming that 50% of the subjects in the XLH Registry are children aged one year and older and adolescents (broadly accurate from EU centre with available demographic data) and two-thirds of them receive burosumab:

- 400 children aged one year and older and adolescents, and treated with burosumab are expected to be included in the PASS (population for primary and secondary objectives)

Furthermore, assuming that two-thirds of the children aged one year and older, and adolescents, in the XLH Registry receive alternative XLH treatment (note that subjects can receive burosumab and/or alternative XLH treatments over the 10 years), 400 children aged one year and older and adolescents, and treated with alternative XLH treatments are expected to be included in the PASS (population for primary and secondary objectives).

9.8 Data Transformation

Data collection within the European XLH Registry is taking place via an EDC tool, with its core data specification approved by the XLH Registry SC. The specific subset of information to be recorded to support the conduct of the PASS is reflected in Table 2 above and in Appendix 6 Tables A to C.

Data storage for the XLH Registry is being conducted by a third-party contractor, IBM Clinical Development, 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 was conducted.

9.9 Statistical Methods

9.9.1 Main Summary Measures

All study data was summarised using descriptive statistics. For continuous variables, the number of non-missing values and number of missing values (i.e., n [missing], arithmetic mean, standard deviation [SD], median, 1st and 3rd quartile, minimum and maximum) was presented. N (number of subjects studied) and n (number of non-missing data points) were presented as whole numbers. The minimum and maximum statistics were presented to the same number of decimal places as the original data. The arithmetic mean, median and quartiles were presented to one more decimal place than the original data. The SD was presented to 2 more decimal places than the original data. If there was only one observation (i.e., n=1), the SD was displayed as a hyphen ("-"). If there were no observations, summary statistics were displayed with a hyphen ("-").

Categorical variables were summarised by frequency counts (n) and percentages (%) of subjects in each category, unless otherwise specified. Counts of missing data were provided in all tables. Percentages did not include the missing category and were calculated over the number of subjects with available (non-missing) data. Percentages were rounded to one decimal place except for cases where 100% was presented. In cases of an absolute frequency of 0, the relative frequency (percentage) will not be presented.

All analyses and generation of tables, listings, and data for figures were performed using Statistical Analysis System (SAS®) version 9.4 or higher (SAS Institute, Cary, NC, USA) (for more details, see Appendix 2).

9.9.1.1 Exposure Definition and Analysis Sets

Exposure definition

Exposure to study medication is presented for the SAF for each type of medication independently (Burosumab, Phosphate, Active Vitamin D, Growth hormone, Other XLH treatment).

The dates of first and last XLH medication administration were taken from the Electronic Case Report Form (eCRF) "XLH Treatments Details" form. In the case of missing data on the eCRF, the

rules described in Section 9.9.3 were applied in order to implement the first and last date of XLH medication. Interruptions, compliance, and dose changes are not considered for the duration of cumulative exposure.

In addition, the number and percentage of subjects taking each type of medication at least once, is presented together with the dose, compliance with the medication, prescribed pain medications, and reason for treatment discontinuation.

Analysis sets

- All Screened: All subjects who were included and assigned a seven-digit E-code enrolment number (i.e., Exxxxxxx) in the EDC
- Safety Analysis Set (SAF) includes all screened subjects enrolled in the XLH Registry, where:
    - That subject's hospital site has accepted to participate in the PASS (subjects will be flagged in the EDC if they are a participant in the PASS), AND
    - The subject's reported age at the signing date of the earliest ICF date (i.e., the "Index Date") is ≥1 year and <18 years, AND
    - The subject (or their parent or their legal guardian) has signed the appropriate ICF document for enrolment in the XLH Registry and participation in the PASS, AND
    - If the response in the EDC to the question "has the subject re-consented?" is "Yes", the subject (or their parent or their legal guardian) must have signed the (most recent and currently approved) ICF document for enrolment in the XLH Registry and participation in the PASS. Note that if the response to the question "has the subject re-consented?" is "No", the subject will be excluded, and if the response is "Not applicable", the subject will be included, AND
    - The subject has received burosumab treatment between 30 days prior to the signing date of the first ICF and the data cut-off date of the first Interim Analysis in PASS (13 May 2021).

Examination of subgroups

All analyses were performed over the entire SAF population, and also by:

- Age group at first informed consent date: toddler (1 to < 5 years), children (5 to < 12 years), adolescents (12 to < 18 years)
- Burosumab treatment on or after 30 days prior to first informed consent date until the end of the study. This includes the following subgroups:
    - Burosumab only
    - Burosumab + alternative XLH treatment

A study flow diagram is provided in Figure 1.

Primary safety analyses such as analyses of AEs, serious adverse events (SAEs), deaths, hospitalisations, and pregnancies, were performed over the entire study population, and by:

- Stage of chronic kidney disease at baseline (normal, mild, moderate, severe, very severe)

9.9.2 Main Statistical Methods

Given the orphan indication and therefore the 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 is in the form of descriptive statistics as the sample size is not sufficiently large for formal comparative analysis.

Medical history and drug details are captured in the XLH Registry via use of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary (WHODD). AEs are coded using the MedDRA and are described by System Organ Class (SOC) and Preferred Term (PT).

For the primary objectives, relevant code lists were developed to identify cardiovascular disease, cancers, hyperphosphataemia and its complications, and increased parathyroid hormone levels. Deaths and hospitalisations were identified using structured data fields in the XLH Registry. Ectopic mineralisation was identified from results of various investigations, such as ECG. The EDC tool used by the XLH Registry allowed the upload of copies of ECGs or cardiac ultrasound scans into the XLH Registry database, which highlighted the availability of this information and made the data

available for independent review. Results of all ECGs, or ad hoc cardiac investigations such as echocardiography, may have been subject to central specialist review.

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

Information on renal status was assessed from data captured in the XLH Registry and from the results of laboratory tests. This enabled stratification of the cohort by renal status and performance of descriptive comparisons of safety outcomes.

Statistical analyses related to secondary objective were not planned for this first interim report (see Section 9.9.5).

9.9.3 Missing Values

As a general rule, no imputation of missing data was performed. Descriptive analyses were performed using available data. The number of subjects with missing data was reported for each measured variable in the study. In descriptive analyses, missing data were described separately and not included in the denominator for the calculation of the percentage for each category of a variable.

At the time of data cut any incomplete dates of therapies and AEs were handled as described in Appendix 9 and Appendix 10. Imputed dates were not presented in the listings.

9.9.4 Sensitivity Analyses

No sensitivity analyses were performed.

9.9.5 Amendments to the Statistical Analysis Plan

There were changes to the definition of the SAF on 19 April 2021. Please refer to Appendix 2 and Section 9.9.1.1 for more details.

Furthermore, the SAP includes the following definition of adverse events of special interest (AESI):

"AESI are those events recorded as "Hyperphosphataemia", "Ectopic mineralisation", "Pregnancy", "Increased parathyroid hormone levels", "Cardiovascular disease", "Cancer", "Death", "Hospitalisation", or "Renal" on the AEs Details page of the eCRF."

However, at this phase of the study all the AEs are considered of scientific and medical interest due to the exploratory nature of the study, and therefore no AESI are included in the statistical analyses.

Finally, the comparison of the safety outcomes of interest in subjects exposed to burosumab to those in subjects receiving alternative treatments for XLH (secondary objective) was not planned for this first interim report. The report focused solely on subjects exposed to burosumab.

9.10 Quality Control

Data entered into the XLH Registry was checked automatically using logical checks - limits set within the database programme. Additional controls were performed by the CRO managing the XLH Registry to detect inconsistencies or absence of follow-up assessments. If any missing data were detected, an edit report was generated. The edit reports were sent electronically to the XLH Registry sites. When clarification was obtained, the edit reports were returned electronically to the XLH Registry. Electronic edit checks were prepared in the system so that the data inconsistencies were tested periodically.

To ensure the quality and integrity of research, this study was conducted under the guideline on good pharmacovigilance practices (GVPs) (Module VIII – post-authorisation safety studies) issued by the EMA, guidelines for good pharmacoepidemiology practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the principles outlined in the Declaration of Helsinki, and any applicable national guidelines (1, 8-10).

A data management plan (DMP) was created before data collection began, which described all functions, processes, and specifications for data collection, cleaning, and validation. The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical, or potentially erroneous. Concurrent manual data review was performed based on parameters dictated by the DMP. Ad hoc queries were generated within the EDC system and followed up for resolution.

High data quality standards were maintained, and processes and procedures utilised, to repeatedly ensure that the data were as clean and accurate as possible when presented for analysis. Data quality was enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

To enable evaluations and/or audits from regulatory authorities or the Client, the investigator agreed to keep records, including the identity of all participating subjects, all original signed ICFs, copies of all eCRFs, source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls, or reports). The records were to be retained by the investigator according to local regulations, or as specified in the study contract, whichever was longer.

Each site received a study site file at study initiation that contained all documents necessary for the conduct of the XLH Registry and was updated throughout the study. This file was available for review in the event the site was selected for monitoring, audits, or inspections, and was safely archived after subjects completed participation in the study. Archived documents included the subject enrolment log and the signed ICFs. In the event that archiving of the file was no longer possible at the site, the site was instructed to notify the Client.

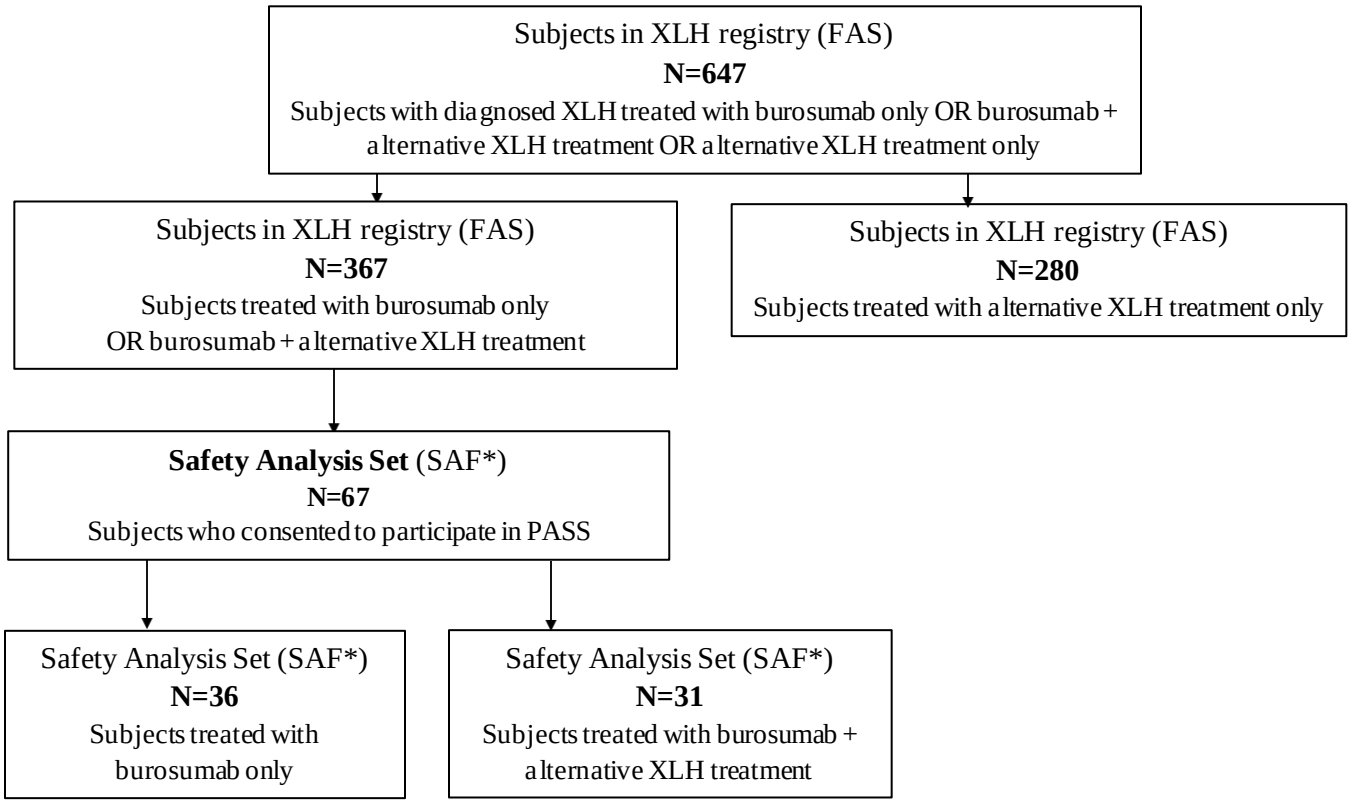
During the site initiation visit, the monitor provided training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. Site monitoring was performed by IQVIA Clinical Research Associates to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents were being properly maintained for the duration of the study. The monitor performed targeted source data verification by review of original subject records. All monitoring procedures and frequency of monitoring visits were described in the Clinical Operations Plan.

10. RESULTS

10.1 Participants

For this interim report, a total of 647 subjects were screened in the XLH Registry at the date of data cut-off of 13th May 2021, with 367 subjects receiving burosumab only or in addition to alternative XLH treatment. Out of the above 367 subjects, there were 67 subjects included the SAF (refer to Section 9.9.1.1 for definition of the SAF). In the SAF population, 36 subjects received burosumab as the only treatment for XLH, and 31 subjects also received an alternative XLH treatment at some point in the course of their treatment period, either sequentially or concomitantly with burosumab. The mean (SD) follow-up time was 2.2 (0.96) years overall. At the time of this report only one subject discontinued the study. The reason for discontinuation was transition to adult care. Subject disposition by XLH treatment can be found in Table 3. A study flow diagram is provided in Figure 1.

Figure 1. Study Flow Diagram



Source: Table 3 and Appendix 1 – Table 1.1.1: Subject Disposition by Gender and Country
FAS: Full Analysis Set, PASS: Post-Authorisation Safety Study, SAF: Safety Analysis Set, XLH: X-linked hypophosphataemia,
*Refer to Section 9.9.1.1 for definition

Table 3. Subject Disposition by XLH Treatment – All Screened Subjects

	burosumab (N=367)	burosumab only (N=169)	burosumab + alternative XLH treatment (N=198)	Alternative XLH treatment only (N=280)	Total (N=647)
Subjects screened, n	367	169	198	280	647
Subjects included in SAF, n (%)[a]	67 (18.3)	36 (21.3)	31 (15.7)	0	67 (10.4)
Follow-up time (years)[b]					
n	67	36	31	0	67
Mean (SD)	2.2 (0.96)	2.1 (0.92)	2.3 (1.02)	-	2.2 (0.96)
Median	2.5	2.4	2.6	-	2.5
Min : Max	0.5 : 3.6	0.5 : 3.2	0.6 : 3.6	-	0.5 : 3.6
Missing	0	0	0	0	0
Study ongoing, n (%)	66 (98.5)	36 (100)	30 (96.8)	0	66 (98.5)
Study discontinued, n (%)	1 (1.5)	0	1 (3.2)	0	1 (1.5)
Reason[c], n (%)					
n	1	0	1	0	1
Adverse event	0	0	0	0	0
Death	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Physician decision	0	0	0	0	0
Study terminated by sponsor	0	0	0	0	0
Withdrawal by subject	0	0	0	0	0
Other	1 (100)	0	1 (100)	0	1 (100)
Missing	0	0	0	0	0
XLH treatments[d], n (%)					
burosumab	67 (100)	36 (100)	31 (100)	0	67 (100)
Phosphate	28 (41.8)	0	28 (90.3)	0	28 (41.8)
Active Vitamin D	24 (35.8)	0	24 (77.4)	0	24 (35.8)
Growth hormone	0	0	0	0	0
Adcal (Calcium Carbonate)	0	0	0	0	0
Adcal D3 (Calcium Carbonate & Cholecalciferol)	1 (1.5)	0	1 (3.2)	0	1 (1.5)
Stexerol (Cholecalciferol)	3 (4.5)	0	3 (9.7)	0	3 (4.5)
Other	8 (11.9)	0	8 (25.8)	0	8 (11.9)

Source: Appendix 1 – Table 1.1.1: Subject Disposition by Gender and Country
Min: Minimum, Max: Maximum, SAF: Safety Analysis Set, SD: Standard deviation, XLH: X-linked hypophosphataemia
Screened subjects: All subjects who were included and assigned a seven-digit E-code enrolment number (i.e., Exxxxxxx) in the Electronic Data Capture.
SAF: All screened subjects with age ≥1 and <18 years who signed informed consent form and reconsent document if applicable before 28 November 2020 and received burosumab treatment on or after 30 days prior to first informed consent date (irrespective of whether they meet all eligibility criteria or not).
[a] Percentages are calculated using the number of subjects screened as denominator.

[b] The follow-up time is calculated as the time from the date of informed consent to the date of study discontinuation or date of cut-off analysis. Follow-up time = (date of discontinuation/cut-off - date of informed consent+1) / 365.25.
[c] Percentages are calculated using the number of subjects who discontinued the study as denominator.
[d] Percentages are calculated using the number of subjects in the SAF as denominator.

10.2 Descriptive Data

10.2.1 Demographic Data

The demographic characteristics by age group can be found in Table 4. The mean (SD) age of the subjects was 7.3 (4.3) years, the minimum age was 1.0 years and the maximum 17.5 years.

There were 31 male (46.3%) and 36 (53.7%) female subjects in the study population. Only one female was of child-bearing potential, belonging to the adolescent subgroup. Most subjects were in the 'not Hispanic or Latino' (51 subjects [76.1%]) ethnicity group, followed by 'Unknown' (10 subjects [14.9%]). The primary race was 'Caucasian' (48 subjects [71.6%]), followed by 'Other' (9 subjects [13.4%]).

There were in total 56 children (1 to <12years) in the study population, with 22 children in the toddler subgroup of 1 to 5 years of age, and 34 children in the subgroup of children between 5 and 12 years of age. The mean (SD) age of the toddlers was 2.6 (1.1) years, with minimum age of 1.0 year and maximum age of 4.2 years. The mean (SD) age of the children between 5 and 12 years of age, was 8.0 (2.0) years, with the minimum age of 5.0 years and the maximum age of 11.8 years. There were 11 male (50%) and 11 female (50%) subjects among the toddlers, and 15 male (44.1%) and 19 female (55.9%) subjects among children between 5 and 12 years of age. Most children were in the 'not Hispanic or Latino' ethnicity group (20 toddlers [90.9%] and 25 children between 5 and 12 years of age [73.5%]).

There were 11 adolescent subjects (12 to <18years) in the SAF. The mean (SD) age of the adolescent subjects was 14.3 (2.0) years, with the minimum age of 12.3 years and the maximum age

of 17.5 years. There were 5 male (45.5%) and 6 female (54.5%) subjects among the adolescents. Most adolescents were in the 'not Hispanic or Latino' (6 subjects [54.5%]) ethnicity group. Additional demographic characteristics such as level of education, current employment status, and annual household income are available in Appendix 1 – Table 1.3.1: Demographic Characteristics by Age Group (Baseline).

Table 4. Demographic Characteristics by Age Group (Baseline) - Safety Analysis Set

TOTAL (N)	Burosumab (N=67)
Age at IC[a] (years)	
n	67
Mean (SD)	7.28 (4.311)
Median	6.78
Min : Max	1.0:17.5
Missing	0
Gender, n (%)	
n	67
Male	31 (46.3)
Female	36 (53.7)
Missing	0
If Female: Child-bearing Potential, n (%)	
n	34
Yes	1 (2.9)
No	33 (97.1)
Missing	2
Ethnicity, n (%)	
n	67
Hispanic or Latino	2 (3.0)
Not Hispanic or Latino	51 (76.1)
Unknown	10 (14.9)
Not Applicable/Not collected per local regulations	4 (6.0)
Missing	0
Primary race, n (%)	
n	67
Caucasian	48 (71.6)
Black or African	3 (4.5)
Asian	2 (3.0)
Other	9 (13.4)
Not Applicable/Not collected per local regulations	2 (3.0)
Unknown	3 (4.5)
Missing	0

TOTAL (N)	Burosumab (N=67)
TODDLER (1 to <5years) (N)	**22**
Age at IC[a] (years)	
n	22
Mean (SD)	2.64 (1.051)
Median	2.41
Min : Max	1.0:4.2
Missing	0
Gender, n (%)	
n	22
Male	11 (50.0)
Female	11 (50.0)
Missing	0
If Female: Child-bearing Potential, n (%)	
n	11
Yes	0
No	11 (100)
Missing	0
Ethnicity, n (%)	
n	22
Hispanic or Latino	0
Not Hispanic or Latino	20 (90.9)
Unknown	2 (9.1)
Not Applicable/Not collected per local regulations	0
Missing	0
Primary race, n (%)	
n	22
Caucasian	17 (77.3)
Black or African	1 (4.5)
Asian	0
Other	2 (9.1)
Not Applicable/Not collected per local regulations	0
Unknown	2 (9.1)
Missing	0
CHILDREN (5 to <12years) (N)	**34**
Age at IC[a] (years)	
n	34
Mean (SD)	8.02 (2.017)
Median	7.28
Min : Max	5.0:11.8
Missing	0
Gender, n (%)	

TOTAL (N)	Burosumab (N=67)
n	34
Male	15 (44.1)
Female	19 (55.9)
Missing	0
If Female: Child-bearing Potential, n (%)	
n	18
Yes	0
No	18 (100)
Missing	1
Ethnicity, n (%)	
n	34
Hispanic or Latino	1 (2.9)
Not Hispanic or Latino	25 (73.5)
Unknown	6 (17.6)
Not Applicable/Not collected per local regulations	2 (5.9)
Missing	0
Primary race, n (%)	
n	34
Caucasian	23 (67.6)
Black or African	2 (5.9)
Asian	2 (5.9)
Other	6 (17.6)
Not Applicable/Not collected per local regulations	0
Unknown	1 (2.9)
Missing	0
ADOLESCENTS (12 to <18years) (N)	**11**
Age at IC[a] (years)	
N	11
Mean (SD)	14.27 (1.961)
Median	13.32
Min : Max	12.3:17.5
Missing	0
Gender, n (%)	
N	11
Male	5 (45.5)
Female	6 (54.5)
Missing	0
If Female: Child-bearing Potential, n (%)	
N	5
Yes	1 (20.0)

TOTAL (N)	Burosumab (N=67)
No	4 (80.0)
Missing	1
Ethnicity, n (%)	
n	11
Hispanic or Latino	1 (9.1)
Not Hispanic or Latino	6 (54.5)
Unknown	2 (18.2)
Not Applicable/Not collected per local regulations	2 (18.2)
Missing	0
Primary race, n (%)	
n	11
Caucasian	8 (72.7)
Black or African	0
Asian	0
Other	1 (9.1)
Not Applicable/Not collected per local regulations	2 (18.2)
Unknown	0
Missing	0

Source: Appendix 1- Table 1.3.1: Demographic Characteristics by Age Group [Baseline]
IC: Informed Consent, Min: Minimum, Max: Maximum, SD: Standard deviation, XLH: X-linked hypophosphataemia
[a]Age at informed consent (years) = [(date of IC signature – date of birth+1) / 365.25].
Note: If only year of birth is available, missing day and month will be imputed as 30 June; if month and year are available, the missing day will be imputed as 15th.
Note: Percentages are calculated using the 'n' indicated for each variable as the denominator.

10.2.2 Medical History

Medical history of subjects (retrospective) is provided in Table 5. A total of 33 subjects (49.3%) had at least one medical condition.

In the study population, 13 subjects (19.4%) had musculoskeletal and connective tissue disorders, with the most frequent musculoskeletal and connective tissue condition being knee deformity, which was reported by 5 subjects (7.5%), followed by hypophosphataemic osteomalacia and pain in extremity which was reported by 4 subjects (6.0%), each.

The second most frequently reported medical conditions was from the category infections and infestations, reported by 11 subjects (16.4%). The most frequently reported condition in this

category was tooth abscess, reported by 3 subjects (4.5%), followed by pneumonia and urinary tract infection, reported by 2 subjects (3.0%), each.

Congenital, familial and genetic disorders were reported by 9 subjects (13.4%). The most frequent condition in this category was Arnold-Chiari malformation and hereditary hypophosphataemic rickets which were reported by 2 subjects (3.0%) each.

Medical History by Age Group (retrospective) is presented in Appendix 1 – Table 1.9.1: Medical History by Age Group (Retrospective).

Table 5. Medical History (Retrospective) – Safety Analysis Set

	Burosumab (N=67)
Subjects with at least one medical condition, n (%)	33 (49.3)
Medical condition[a]	
Cardiac disorders	2 (3.0)
Pulmonary valve stenosis	2 (3.0)
Congenital, familial and genetic disorders	9 (13.4)
Arnold-Chiari malformation	2 (3.0)
Hereditary hypophosphataemic rickets	2 (3.0)
Cerebral palsy	1 (1.5)
Craniosynostosis	1 (1.5)
Gene mutation	1 (1.5)
Kidney duplex	1 (1.5)
Macrocephaly	1 (1.5)
Plagiocephaly	1 (1.5)
Porencephaly	1 (1.5)
Scaphocephaly	1 (1.5)
Tibial torsion	1 (1.5)
Ear and labyrinth disorders	2 (3.0)
Deafness neurosensory	1 (1.5)
Tinnitus	1 (1.5)
Endocrine disorders	1 (1.5)
Hypothyroidism	1 (1.5)
Eye disorders	2 (3.0)
Hypermetropia	1 (1.5)
Refraction disorder	1 (1.5)
Gastrointestinal disorders	2 (3.0)
Abdominal discomfort	1 (1.5)
Ascites	1 (1.5)
Diarrhoea	1 (1.5)
Tooth loss	1 (1.5)
General disorders and administration site conditions	1 (1.5)
Adverse drug reaction	1 (1.5)
Gait disturbance	1 (1.5)
Hepatobiliary disorders	1 (1.5)
Hepatic fibrosis	1 (1.5)
Hepatomegaly	1 (1.5)
Immune system disorders	2 (3.0)
Seasonal allergy	2 (3.0)
Drug hypersensitivity	1 (1.5)
Infections and infestations	11 (16.4)
Tooth abscess	3 (4.5)
Pneumonia	2 (3.0)
Urinary tract infection	2 (3.0)
Abscess	1 (1.5)
Bronchiolitis	1 (1.5)

	Burosumab (N=67)
Ear infection	1 (1.5)
Otitis media	1 (1.5)
Pharyngitis	1 (1.5)
Rhinitis	1 (1.5)
Tooth infection	1 (1.5)
Investigations	3 (4.5)
Cardiac murmur	2 (3.0)
Blood parathyroid hormone increased	1 (1.5)
Musculoskeletal and connective tissue disorders	13 (19.4)
Knee deformity	5 (7.5)
Hypophosphataemic osteomalacia	4 (6.0)
Pain in extremity	4 (6.0)
Growth failure	2 (3.0)
Aneurysmal bone cyst	1 (1.5)
Arthralgia	1 (1.5)
Bone pain	1 (1.5)
Growth retardation	1 (1.5)
Hypermobility syndrome	1 (1.5)
Joint swelling	1 (1.5)
Limb asymmetry	1 (1.5)
Limb deformity	1 (1.5)
Muscular weakness	1 (1.5)
Musculoskeletal discomfort	1 (1.5)
Patellofemoral pain syndrome	1 (1.5)
Short stature	1 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.5)
Hair follicle tumour benign	1 (1.5)
Nervous system disorders	4 (6.0)
Headache	2 (3.0)
Cognitive disorder	1 (1.5)
Epilepsy	1 (1.5)
Hemiparesis	1 (1.5)
Language disorder	1 (1.5)
Petit mal epilepsy	1 (1.5)
Sensory processing disorder	1 (1.5)
Psychiatric disorders	2 (3.0)
Anxiety disorder	1 (1.5)
Behaviour disorder	1 (1.5)
Renal and urinary disorders	3 (4.5)
Nephrocalcinosis	1 (1.5)
Nephrolithiasis	1 (1.5)
Vesicoureteric reflux	1 (1.5)
Respiratory, thoracic and mediastinal disorders	4 (6.0)
Asthma	2 (3.0)
Pulmonary artery stenosis	1 (1.5)
Sleep apnoea syndrome	1 (1.5)
Skin and subcutaneous tissue disorders	2 (3.0)

	Burosumab (N=67)
Dry skin	1 (1.5)
Eczema	1 (1.5)
Social circumstances	1 (1.5)
Corrective lens user	1 (1.5)
Surgical and medical procedures	4 (6.0)
Endodontic procedure	1 (1.5)
Internal fixation of fracture	1 (1.5)
Limb operation	1 (1.5)
Tooth extraction	1 (1.5)
Uncoded	3 (4.5)
Uncoded	3 (4.5)

Source: Appendix 1– Table 1.9.1: Medical History by Age Group (Retrospective)
HEENT: head, eyes, ears, nose, and throat, Max: Maximum, MedDRA: Medical Dictionary for Regulatory Activities, Min: Minimum, PT: Preferred Term, SAF: Safety Analysis Set, SD: Standard deviation, SOC: System Organ Class, XLH: X-linked hypophosphataemia
MedDRA <dictionary version 23.1>.
[a]Percentages are calculated using the number of subjects in SAF as denominator.
Source Data: ADSL ADMH.

10.2.3 Diagnosis History

The details of XLH diagnosis history are provided in Table 6. The mean (SD) time since first XLH symptoms was 6.3 (3.7) years, and the mean (SD) time since XLH diagnosis was 4.8 (3.8) years. The mean (SD) time since first XLH symptoms until the date of XLH diagnosis was 1.1 (2.0) years. Three subjects were diagnosed prenatally, all 3 based on family history, and additionally 2 were also diagnosed based on genetic testing. Diagnosis history by age group is presented in Appendix 1 – Table 1.4.1: XLH Diagnosis History by Age Group (Retrospective).

Table 6. XLH Diagnosis History (Retrospective) – Safety Analysis Set

TOTAL (N)	Burosumab (N=67)
Time since first XLH symptoms[a] (years)	
N	38
Mean (SD)	6.33 (3.709)
Median	5.90
Min : Max	0.4:16.2
Missing	29
Time since XLH diagnosis[b] (years)	
N	53
Mean (SD)	4.78 (3.841)
Median	4.12

TOTAL (N)	Burosumab (N=67)
Min : Max	0.1:16.2
Missing	14
Time since first XLH symptoms until date of XLH diagnosis[c] (years)	
N	37
Mean (SD)	1.14 (1.973)
Median	0.16
Min : Max	0.0:8.9
Missing	30
Diagnosed prenatally? n (%)	
N	67
Yes	3 (4.5)
No	64 (95.5)
Missing	0
If Yes:	
Method of diagnosis[d], n (%)	
N	3
Genetic testing	2 (66.7)
Family history	3 (100)
Biochemical/clinical profile	0
Other	0
Missing	0

Source: Appendix 1– Table 1.4.1 XLH Diagnosis History by Age Group (Retrospective)
Min: Minimum, Max: Maximum, SD: Standard deviation, XLH: X-linked Hypophosphataemia.
[a] Time since first XLH symptoms (years) = [(date of ICF signature – date of first XLH symptoms+1) / 365.25].
[b] Time since XLH diagnosis (years) = [(date of ICF signature – date of XLH diagnosis+1) / 365.25].
[c] Time since first XLH symptoms until date of XLH diagnosis(years) = [(date of XLH diagnosis – date of first XLH symptoms+1) / 365.25].
[d] Several procedures could be used in the diagnosis for the same subject. So, the total could be more than 100%.
Note: Percentages are calculated using the "n" indicated for each variable as the denominator.

10.2.4 Co-morbidities at Baseline

Co-morbidities at baseline are provided in Table 7. The most frequent co-morbidities for which subjects were diagnosed or treated were bone conditions (23 subjects, 92.0%), followed by dental/oral conditions, diagnosed or treated in 5 subjects (20.0%). One subject (4.0%) suffered from renal conditions. Data for 42 subjects were missing.

Genu varum was the most common bone condition, reported in 12 subjects (52.2%), followed by genu valgum which was reported in 9 subjects (39.1%). The intercondylar distance was measured in 3 subjects with genu varum, and the mean (SD) was 4.7 (1.3) cm.

Tooth abscess was the most common dental condition, and was observed in 4 out of 5 subjects with dental/oral conditions. One subject had renal condition at baseline which was reported as nephrocalcinosis.

Co-morbidities by age group at baseline are presented in Appendix 1 – Table1.7.1: XLH Clinical Data Details by Age Group (Baseline).

Table 7. Co-morbidities (Baseline) – Safety Analysis Set

TOTAL (N)	Burosumab (N=67)
Has the subject been diagnosed or treated for conditions affecting any of the following?[a] n(%)	
n	25
Bone	23 (92.0)
Joint	0
Renal	1 (4.0)
Dental/oral	5 (20.0)
Missing	42
If Bone:	
Bone conditions[b], n (%)	
n	23
Craniosynostosis/Abnormally shaped head (skull)	2 (8.7)
Widened/Thickened wrists	1 (4.3)
Rachitic rosary/Abnormally shaped chest (rib cage abnormalities)	2 (8.7)
Genu varum/Bowing (ankles touch but knees do not when standing upright)	12 (52.2)
Genu valgum/Knock knees (knees touch but ankles do not when standing upright)	9 (39.1)
Windswept deformity	1 (4.3)
Tibial torsion	1 (4.3)
Club foot deformity	0
Intoeing	1 (4.3)
Spinal stenosis	0
Bone spur(s)/Osteophyte(s)	0
Enthesopathy (calcification of the tendons or ligaments)	0
Waddling	2 (8.7)
Chiari malformation symptoms	0
Bowing of the forearms	0
Missing	0
Intercondylar distance measured? n (%)	
n	23
Yes	3 (13.0)
No	20 (87.0)
Missing	0
If Yes:	

TOTAL (N)	Burosumab (N=67)
Intercondylar distance (cm)	
n	3
Mean (SD)	4.7 (1.26)
Median	4.5
Min : Max	4:6
Missing	0
Intermalleolar distance measured? n (%)	
n	23
Yes	3 (13.0)
No	20 (87.0)
Missing	0
Intermalleolar distance (cm)	
n	3
Mean (SD)	4.7 (3.21)
Median	6.0
Min : Max	1:7
Missing	0
If Genu varum/Bowing: Intercondylar distance (cm)	
n	3
Mean (SD)	4.7 (1.26)
Median	4.5
Min : Max	4:6
Missing	0
If Renal: Renal conditions[d], n (%)	
n	1
Nephrolithiasis (kidney stones)	0
Nephrocalcinosis (calcium deposits in the kidneys)	1 (100)
Missing	0
If Dental/oral: Dental/oral conditions[e], n (%)	
n	5
Tooth abscess	4 (80.0)
Excessive cavities (caries)	1 (20.0)
Extractions of adult teeth	0

TOTAL (N)	Burosumab (N=67)
Dental implant surgery (to replace missing teeth)	0
Root canal surgery	0
Orthodontic treatment	0
Poor oral health DMFT	0
Enlargement of pulp chamber evocating taurodontism	1 (20.0)
Prominent pulp horns	1 (20.0)
Presence radiolucent alveolar bone images	0
Radiolucent dentine, dentino-enamel junction	0
Gingivitis	0
Periodontitis	0
Osteoarthritis	0
Oral implants failure	0
12-12 Surgery count	0
Recurred surgical outcomes	1 (20.0)
Missing	0

Source: Appendix 1– Table 1.7.1: XLH Clinical Data Details by Age Group (Baseline)
DMFT: Decayed/Missing/Filled Teeth, Min: Minimum, Max: Maximum, SD: Standard deviation, XLH: X-linked Hypophosphataemia.
[a] Several conditions could be diagnosed or treated for the same subject. So, the total could be more than 100%.
[b] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the bones as denominator.
[c] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the joint as denominator.
[d] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the renal as denominator.
[e] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the dental/oral as denominator.
Note: Percentages are calculated using the 'n' indicated for each variable as the denominator

10.2.5 Co-morbidities during the follow-up

Co-morbidities during the follow-up (prospective) can be found in Table 8. During the course of the study, 23 subjects were diagnosed or treated for various medical conditions. The majority of the subjects (17 subjects [73.9%]) were diagnosed or treated for conditions affecting the bones, followed by dental/oral conditions diagnosed or treated in 12 subjects (52.2%). One subject was diagnosed or treated for a renal condition (Nephrocalcinosis). Data on 44 subjects was missing.

The majority of the subjects diagnosed or treated for a bone condition had either genu varum, or genu valgum. Furthermore, there were 2 subjects with intoeing and 2 subjects with waddling and 1

case each of: more than 1 suture affected by craniosynostosis; rib cage abnormality; windswept deformity; and tibial torsion.

The main dental/oral condition in the study population was tooth abscess diagnosed or treated in 9 subjects (75.0%), followed by excessive cavities (caries) abscess diagnosed or treated in 5 subjects (41.7%), and extractions of adult teeth in 4 subjects (33.3%). Furthermore, there were 2 subjects with orthodontic treatment, 1 subject with dental implant surgery, 1 subject with root canal surgery, and 1 subject with gingivitis.

Co-morbidities during the follow-up by age group are presented in Appendix 1 – Table 1.7.2: XLH Clinical Data Details by Age Group (Prospective).

Table 8. Co-morbidities (Prospective) – Safety Analysis Set

TOTAL (N)	Burosumab (N=67)
Has the subject been diagnosed or treated for conditions affecting any of the following?[a] n(%)	
n	23
Bone	17 (73.9)
Joint	0
Renal	1 (4.3)
Dental/oral	12 (52.2)
Missing	44
If Bone:	
Bone conditions[b], n (%)	
n	17
Craniosynostosis/Abnormally shaped head (skull)	1 (5.9)
Number of sutures affected by craniosynostosis	
n	1
Absent	0
1 Suture	0
>1 Suture	1 (100)
Missing	0
Widened/Thickened wrists	0
Rachitic rosary/Abnormally shaped chest (rib cage abnormalities)	1 (5.9)
Genu varum/Bowing (ankles touch but knees do not when standing upright)	9 (52.9)
Genu valgum/Knock knees (knees touch but ankles do not when standing upright)	9 (52.9)
Windswept deformity	1 (5.9)
Tibial torsion	1 (5.9)
Club foot deformity	0
Intoeing	2 (11.8)
Spinal stenosis	0
Bone spur(s)/Osteophyte(s)	0
Enthesopathy (calcification of the tendons or ligaments)	0
Waddling	2 (11.8)
Chiari malformation symptoms	0
Bowing of the forearms	0
Missing	0
Intercondylar distance measured? n (%)	

TOTAL (N)	Burosumab (N=67)
n	17
Yes	4 (23.5)
No	13 (76.5)
Missing	0
If Yes: Intercondylar distance (cm)	
n	4
Mean (SD)	3.1 (1.55)
Median	3.5
Min : Max	1:5
Missing	0
If Genu varum/Bowing: Intercondylar distance (cm)	
n	2
Mean (SD)	2.5 (2.12)
Median	2.5
Min : Max	1:4
Missing	0
If Genu valgum/Knock knees: Intercondylar distance (cm)	
n	2
Mean (SD)	2.8 (2.47)
Median	2.8
Min : Max	1:5
Missing	0
Intermalleolar distance measured? n (%)	
n	17
Yes	5 (29.4)
No	12 (70.6)
Missing	0
If Yes: Intermalleolar distance (cm)	
n	5
Mean (SD)	5.9 (3.36)
Median	7.0
Min : Max	0:8
Missing	0
If Genu varum/Bowing: Intermalleolar distance (cm)	

TOTAL (N)	Burosumab (N=67)
n	1
Mean (SD)	7.0 (-)
Median	7.0
Min : Max	7:7
Missing	0
If Genu valgum/Knock knees: Intermalleolar distance (cm)	
n	4
Mean (SD)	7.4 (0.75)
Median	7.5
Min : Max	7:8
Missing	0
If Renal: Renal conditions[d], n (%)	
n	1
Nephrolithiasis (kidney stones)	0
Nephrocalcinosis (calcium deposits in the kidneys)	1 (100)
Missing	0
If Dental/oral: Dental/oral conditions[e], n (%)	
n	12
Tooth abscess	9 (75.0)
Excessive cavities (caries)	5 (41.7)
Extractions of adult teeth	4 (33.3)
Dental implant surgery (to replace missing teeth)	1 (8.3)
Root canal surgery	1 (8.3)
Orthodontic treatment	2 (16.7)
Poor oral health DMFT	0
Enlargement of pulp chamber evocating taurodontism	0
Prominent pulp horns	0
Presence radiolucent alveolar bone images	0
Radiolucent dentine, dentino-enamel junction	0
Gingivitis	1 (8.3)
Periodontitis	0
Osteoarthritis	0
Oral implants failure	0
12-12 Surgery count	0
Recurred surgical outcomes	0
Missing	0

Source: Appendix 1– Table 1.7.2: XLH Clinical Data Details by Age Group (Prospective)
DMFT: Decayed/Missing/Filled Teeth, Min: Minimum, Max: Maximum, SD: Standard deviation, XLH: X-linked Hypophosphataemia.

[a] Several conditions could be diagnosed or treated for the same subject. So, the total could be more than 100%.
[b] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the bones as denominator.
[c] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the joint as denominator.
[d] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the renal as denominator.
[e] Percentages are calculated using the number of subjects diagnosed or treated for conditions affecting the dental/oral as denominator.
Note: Percentages are calculated using the 'n' indicated for each variable as the denominator.

10.2.6 Study Medication Exposure

Study medication exposure (prospective) can be found in Table 9. The drug history was collected for all subjects included in the SAF.

During the study period, the majority of the subjects that received burosumab and an alternative XLH treatment, used phosphate (28 subjects [41.8%]) and/or active vitamin D (24 subjects [35.8%]) either sequentially or concomitantly to burosumab. One subject used calcium carbonate + vitamin D3 (1.5%) apart from burosumab, and 3 subjects used vitamin D (Stexerol [colecalciferol]) (4.5%) apart from burosumab. Eight subjects used ‘other’ treatment apart from burosumab. Growth hormone and calcium carbonate were not used as treatment for XLH in this study population.

The mean duration of exposure to burosumab was 29.7 (25.0) months. The mean (SD) drug dose was 32.9 (20.5) mg. Compliance with medication data was missing for the majority of the subjects (64 out of 67). Only one subject had pain medication prescribed.

The main reason for discontinuation of treatment was physician decision in 34 subjects (75.6%). For 13 subjects (28.9%), the reason for discontinuation was ‘other’.

For those subjects that used phosphate apart from burosumab, the mean (SD) duration of exposure to phosphate was approximately 20.7 (19.9) months, with the mean (SD) dose of 178.5 (184.9) mg. The main reason for discontinuation of phosphate treatment was physician decision (17 subjects [63.0%]). One subject discontinued the treatment because of lack of effectiveness. For 11 subjects the reason for discontinuation was ‘other’.

For those subjects that received treatment with active vitamin D apart from burosumab treatment, the mean (SD) duration of exposure to active vitamin D was 23.4 (21.3) months, with the mean (SD) dose of 223.1 (326.2) mg. The main reason for discontinuation of active vitamin D treatment in these subjects, was physician decision (13 subjects [59.1%]). One subject discontinued the treatment because of lack of effectiveness. For 11 subjects the reason for discontinuation was 'other'. Six subjects have not discontinued the treatment with active vitamin D, and are therefore flagged as taking contraindicated combination of treatment according to the SmPC of Crysvita (11), i.e., a concomitant use of burosumab and active vitamin D (please refer to Appendix 1– Listing 1.11: XLH Treatment Details).

For those subjects that used other XLH treatment than phosphate or active vitamin D apart from burosumab, the mean duration of exposure to such was 66.6 (62.4) months, with the mean (SD) dose of 206.7 (262.0) mg. The main reason for discontinuation of other XLH treatment than phosphate or active vitamin D was physician decision (4 subjects). One subject discontinued the treatment because of an AE.

Exposure to study medication by age group is presented in Appendix 1 – Table 1.8.1: Study Medication Exposure by Age Group (Prospective).

Table 9. Study Medication Exposure (Prospective) – Safety Analysis Set

	Burosumab (N=67)
Has the drug history been collected? n (%)	
n	67
Yes	67 (100)
No	0
Missing	0
If Yes:	
Treatment[a], n (%)	
n	67
burosumab	67 (100)
Phosphate	28 (41.8)
Active Vitamin D	24 (35.8)
Growth hormone	0
Adcal (Calcium Carbonate)	0
Adcal D3 (Calcium Carbonate & Colecalciferol)	1 (1.5)
Stexerol (Colecalciferol)	3 (4.5)
Other	8 (11.9)
Missing	0
If burosumab:	
Duration of exposure[b](months)	
n	67
Mean (SD)	29.73 (24.963)
Median	29.63
Min : Max	1:198
Missing	0
Dose(mg)[c]	
n	66
Mean (SD)	32.88 (20.533)
Median	30.00
Min : Max	10:90
Missing	1
Compliance with the medication[c,d], n (%)	
n	3
No	0
Yes	3 (100)
Missing	64
If pain medication was prescribed, treatment regime type[d,e], n (%)	
n	67
Step 1(non Opioid ± adjuvant)	0
Step 2(weak Opioid ± step 1)	0
Step 3(strong Opioid ± step 1)	1 (1.5)
Not applicable	66 (98.5)
Missing	0

	Burosumab (N=67)
Reason for discontinuation[d,e], n (%)	
n	45
Physician decision	34 (75.6)
Subject decision	0
Lack of effectiveness	0
Side effect	0
Adverse Event	0
Other	13 (28.9)
Missing	22
If Phosphate:	
Duration of exposure[b](months)	
N	22
Mean (SD)	20.69 (19.929)
Median	14.88
Min : Max	3:84
Missing	6
Dose(mg)[c]	
N	28
Mean (SD)	178.54 (184.868)
Median	125.00
Min : Max	3:552
Missing	0
If pain medication was prescribed, treatment regime type[d,e], n (%)	
n	28
Step 1 (non Opioid ± adjuvant)	0
Step 2 (weak Opioid ± step 1)	0
Step 3 (strong Opioid ± step 1)	1 (3.6)
Not applicable	26 (92.9)
Missing	0
Reason for discontinuation[d,e], n (%)	
n	27
Physician decision	17 (63.0)
Subject decision	0
Lack of effectiveness	1 (3.7)
Side effect	0
Adverse Event	0
Other	11 (40.7)
Missing	1
If Active Vitamin D:	
Duration of exposure[b](months)	
n	21
Mean (SD)	23.38 (21.284)
Median	16.26
Min : Max	1:81

	Burosumab (N=67)
Missing	3
Dose(mg)[c]	
n	23
Mean (SD)	223.11 (326.194)
Median	2.25
Min : Max	0:1000
Missing	1
If pain medication was prescribed, treatment regime type[d,e], n (%)	
n	24
Step 1 (non Opioid ± adjuvant)	0
Step 2 (weak Opioid ± step 1)	0
Step 3 (strong Opioid ± step 1)	1 (4.2)
Not applicable	23 (95.8)
Missing	0
Reason for discontinuation[d,e], n (%)	
n	22
Physician decision	13 (59.1)
Subject decision	0
Lack of effectiveness	1 (4.5)
Side effect	0
Adverse Event	0
Other	11 (50.0)
Missing	2
If other XLH treatment:	
Duration of exposure[b](months)	
N	6
Mean (SD)	66.63 (62.382)
Median	46.67
Min : Max	8:166
Missing	2
Dose(mg)[c]	
N	8
Mean (SD)	206.72 (262.037)
Median	100.00
Min : Max	1:700
Missing	0
If pain medication was prescribed, treatment regime type[d,e], n (%)	
N	8
Step 1 (non Opioid ± adjuvant)	0
Step 2 (weak Opioid ± step 1)	0
Step 3 (strong Opioid ± step 1)	0
Not applicable	8 (100)
Missing	0

	Burosumab (N=67)
Reason for discontinuation[d,e], n (%)	
N	5
Physician decision	4 (80.0)
Subject decision	0
Lack of effectiveness	0
Side effect	0
Adverse Event	1 (20.0)
Other	0
Missing	3

Source: Appendix 1– Table 1.8.1: Study Medication Exposure by Age Group (Prospective)
Min: Minimum, Max: Maximum, SD: Standard deviation, XLH: X-linked Hypophosphataemia.
[a] Several treatments could be taken for the same subject. So, the total could be more than 100%.
[b] Duration of exposure (months) = (date of last XLH medication – date of first XLH medication+1) / 30.4375. Note: If a subject received a medication for 2 or more non-consecutive periods, the duration of exposure was calculated as the sum of the exposures to each period. If end date of last XLH medication was missing (medication ongoing), date of study discontinuation or date of cut-off analysis, whichever comes first, will be used as date of last XLH medication.
[c] If more than one value was reported for one XLH medication (if a subject received a medication for 2 or more non-consecutive periods), the last reported value was used in the summary table.
[d] Percentages are calculated using the number of subjects taking each treatment as denominator.
[e] Several values could be reported for the same subject. So the total could be more than 100%.
Note: Percentages are calculated using the "n" indicated for each variable as the denominator.

10.2.7 Laboratory tests and ECG results

Baseline and prospective data related to ECG, biochemistry, haematology, and urinalysis are presented in Appendix 1 – Table 1.21.1: Electrocardiogram Data by Age Group (Baseline), Appendix 1 – Table 1.21.2: Electrocardiogram Data by Age Group (Prospective), Appendix 1 – Table 1.25.1: Biochemistry Data by Age Group (Baseline), Appendix 1 – Table 1.25.2: Biochemistry Data by Age Group (Prospective), Appendix 1 – Table 1.26.1: Haematology Data by Age Group (Baseline), Appendix 1 – Table 1.26.2: Haematology Data by Age Group (Prospective), Appendix 1 – Table 1.27.1: Urinalysis Data by Age Group (Baseline), Appendix 1 – Table 1.27.2: Urinalysis Data by Age Group (Prospective), respectively.

10.3 Outcome Data

10.3.1 Summary of all AEs by age group

A summary of all AEs by age group is presented in Table 10. A total of 25 subjects (37.3%) reported at least one AE over the course of the study. The total number of AEs reported was 83 (for details, see Appendix 1 – Table 1.29.1: Adverse Events by Age Group (Prospective). The most common AEs reported by SOC and PT are highlighted below.

Sixteen subjects reported 30 AEs in the SOC of 'Musculoskeletal and connective tissue disorders', with the main PTs being 'Pain in extremity', reported 18 times in 12 subjects, and 'Arthralgia' reported 4 times in 4 subjects. Eleven subjects reported 12 AEs in the SOC of 'Infections and infestations', with the main PT being 'Tooth abscess', reported 7 times in 7 subjects. Seven subjects reported 11 AEs in the SOC of 'General disorders and administration site conditions', with the main PTs being 'Pain', reported 4 times in 3 subjects, and with 'Fatigue' and 'Injection site erythema' reported 2 times in 2 subjects, each. Six subjects reported 8 AEs in the SOC of 'Gastrointestinal disorders', with the main PT being 'Toothache', reported 3 times in 2 subjects. Additionally there were 6 subjects with 6 uncoded AEs (for details, see Appendix 1 – Table 1.29.1: Adverse Events by Age Group (Prospective).

From the 25 subjects that reported at least one AE over the course of the study, 13 subjects (19.4%) had AEs possibly/probably related to XLH treatment as reported by the investigator, with a total of 25 AEs. From these 13 subjects, 12 subjects had AEs possibly/probably related to burosumab specifically, with a total of 23 AEs (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). Highlighting the most common SOC and PTs, 7 subjects reported 9 AEs in the SOC of 'Musculoskeletal and connective tissue disorders', with the main PT being 'Pain in extremity', reported 7 times in 6 subjects. Five subjects reported 5 AEs in the SOC of 'Infections and infestations', with the main and only PT being 'Tooth abscess'.

Four subjects reported 5 AEs in the SOC of 'General disorders and administration site conditions', with the main PT being 'Injection site erythema' reported 2 times in 2 subjects. For further details, see Appendix 1 – Table 1.29.2: Adverse Events Possibly/Probably Related to XLH Treatment by Age Group (Prospective).

Four subjects (6.0%) reported severe AEs, with 6 severe AEs in total. When broken down by SOC and PT, 4 subjects reported 5 severe AEs in the SOC of 'Musculoskeletal and connective tissue disorders', with the main PT being 'Pain in extremity', reported 4 times in 4 subjects. One subject reported a severe AE in the SOC 'Injury, poisoning and procedural complications' with the PT being 'Procedural pain'. For further details, see Appendix 1 – Table 1.29.7: Severe Adverse Events by Age Group (Prospective).

Two subjects (3.0%) reported SAEs, with 2 SAEs in total; 1 SAE falling into the SOC category of Congenital, familial and genetic disorders' with PT being 'Craniosynostosis' and 1 SAE falling into the SOC category of Musculoskeletal and connective tissue disorders with PT being 'Knee deformity'. For further details, see Appendix 1 – Table 1.29.10: Serious Adverse Events by Age Group (Prospective). No deaths, no AEs leading to XLH treatment withdrawal, and no SAEs related to XLH treatment were reported in the study (for details, see Appendix 1 – Table 1.29.5: Adverse Events Leading to XLH Treatment Withdrawn by Age Group [Prospective], Appendix 1 – Table 1.29.11: Serious Adverse Events Possibly/Probably Related to XLH Treatment by Age Group (Prospective), and Appendix 1 – Table 1.31.1: Deaths by Age Group [Prospective]). There were also no pregnancies reported in the study population over the course of the study (for details, see Appendix 1 – Table 1.33.1: Pregnancy by Age Group [Prospective]).

From the 6 subjects that were flagged as taking contraindicated combination of treatment (for details, see Section 10.2.6), 2 subjects reported 2 AEs each, all mild in severity. The first subject reported an AE classified in the SOC of 'Ear and labyrinth disorders', with the PT being 'Ear pain',

and an AE that was not classified in any SOC category and reported as 'Low chest pain'. The second subject reported an AE classified in the SOC of 'Infections and infestations', with the PT being 'Tooth abscess', and an AE classified in the SOC of 'General disorders and administration site conditions', with the PT being 'Injection site erythema', with both AEs reported by the investigator as possibly/probably related to XLH treatment (burosumab) (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]).

In the sub-population of toddlers, 7 subjects (31.8%) reported AEs, with the total number of AEs being 22. From these, 4 (18.2%) subjects had 8 AEs that were possibly/probably related to XLH treatment, as reported by the investigator, of whom 3 had 6 AEs that were possibly/probably related to burosumab specifically (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). For details on the SOC and PT categories, please refer to Table 10 and Appendix 1 – Table 1.29.2: Adverse Events Possibly/Probably Related to XLH Treatment by Age Group (Prospective). No SAEs, deaths, severe AEs and AEs leading to XLH treatment withdrawal were reported in toddlers (for details, see Appendix 1 – Table 1.29.5: Adverse Events Leading to XLH Treatment Withdrawn by Age Group (Prospective), Appendix 1 – Table 1.29.7: Severe Adverse Events by Age Group (Prospective), Appendix 1 – Table 1.29.10: Serious Adverse Events by Age Group (Prospective), and Appendix 1 – Table 1.31.1: Deaths by Age Group (Prospective)).

In the sub-population of children, 13 subjects (38.2%) had at least one AE reported, with the total number of reported AEs being 53. From these 13 subjects, 7 subjects (20.6%) had AEs that were possibly/probably related to XLH treatment (burosumab), as reported by the investigator (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). For details on the SOC and PT categories, please refer to Appendix 1 – Table 1.29.2: Adverse Events Possibly/Probably Related to XLH Treatment by Age Group

(Prospective). Three subjects (8.8%) had 4 severe AEs, 3 in the SOC of 'Musculoskeletal and connective tissue disorders', with the main and only PT being 'Pain in extremity', and additionally 1 subject reported a severe AE in the SOC of 'Injury, poisoning and procedural complication' with the PT being 'Procedural pain' (for details, see Appendix 1 – Table1.29.7: Severe Adverse Events by Age Group (Prospective)). Two subjects had 2 SAEs in total, one in the SOC of 'Congenital, familial and genetic disorders' with PT being 'Craniosynostosis', and one in the SOC of 'Musculoskeletal and connective tissue disorders' with PT being 'Knee deformity' (for details, see Appendix 1 – Table 1.29.10: Serious Adverse Events by Age Group (Prospective)). No deaths or AEs leading to XLH treatment withdrawn were reported in children (for details, see Appendix 1 – Table 1.29.5: Adverse Events Leading to XLH Treatment Withdrawn by Age Group (Prospective), and Appendix 1 – Table 1.31.1: Deaths by Age Group (Prospective)).

In the sub-population of adolescents, 5 subjects (45.5%) had at least one AE reported, with 8 AEs reported in total. From these 5 subjects (45.5%), 2 subjects (18.2%) had in total 4 AEs that were reported as possibly/probably related to XLH treatment (burosumab) by the investigator (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). For details on the SOC and PT categories, please refer to Appendix 1 – Table 1.29.2: Adverse Events Possibly/Probably Related to XLH Treatment by Age Group (Prospective). One adolescent subject (9.1%) reported 2 severe AEs, both in the SOC of 'Musculoskeletal and connective tissue disorders', with PTs being 'Limb discomfort' and 'Pain in extremity' (for details, see Appendix 1 – Table 1.29.7: Severe Adverse Events by Age Group (Prospective)). No SAEs, deaths, and AEs leading to XLH treatment withdrawal were reported in adolescents (for details, see Appendix 1 – Table 1.29.5: Adverse Events Leading to XLH Treatment Withdrawn by Age Group (Prospective), Appendix 1 – Table 1.29.10: Serious Adverse Events by Age Group (Prospective), and Appendix 1 – Table 1.31.1: Deaths by Age Group (Prospective)).

Table 10. Summary Overview of All Adverse Events by Age Group (Prospective) – Safety Analysis Set

	Burosumab (N=67)
Any AE, n (%)	25 (37.3)
Any AE possibly/probably related to XLH treatment*, n (%)	13 (19.4)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	4 (6.0)
Any SAE, n (%)	2 (3.0)
Any SAE possibly/probably related to XLH treatment*, n (%)	0
TODDLER(1 to <5years)(N)	22
Any AE, n (%)	7 (31.8)
Any AE possibly/probably related to XLH treatment*, n (%)	4 (18.2)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
CHILDREN(5 to <12years)(N)	34
Any AE, n (%)	13 (38.2)
Any AE possibly/probably related to XLH treatment*, n (%)	7 (20.6)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	3 (8.8)
Any SAE, n (%)	2 (5.9)
Any SAE possibly/probably related to XLH treatment*, n (%)	0
ADOLESCENTS(12 to <18years)(N)	11
Any AE, n (%)	5 (45.5)
Any AE possibly/probably related to XLH treatment*, n (%)	2 (18.2)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	1 (9.1)

	Burosumab (N=67)
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0

Source: Appendix 1 – Table 1.28.1: Summary Overview of All Adverse Events by Age Group (Prospective)
AE: Adverse Event, SAE: Serious Adverse Event, SAF: Safety Analysis Set, XLH: X-linked hypophosphataemia
*The relationship of the AE with XLH treatment as reported by the investigator.
Note: Percentages are calculated using the number of subjects in the SAF as denominator.

10.3.2 Summary of all AEs by chronic kidney disease

A summary of all AEs reported in subjects with medical history/co-morbidity of chronic kidney disease is presented in Table 11. In total 5 subjects had chronic kidney disease. From these 5 subjects, 3 subjects (60.0%) had at least one AE reported, with a total of 9 AEs. For details on the SOC and PT categories, please refer to Appendix 1 – Table 1.29.12: Adverse Events by Chronic Kidney Disease (Prospective). From these 3 subjects, 2 subjects (40.0%) had AEs that were reported as possibly/probably related to XLH treatment by the investigator (see Table 11), of whom 1 had an AE possibly/probably related to burosumab (for details, see Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). No SAEs, severe AEs, deaths or AEs leading to XLH treatment withdrawal, were reported in subjects with chronic kidney disease in the study (see Table 11).

From the 5 subjects with chronic kidney disease, 4 subjects had a normal stage of chronic kidney disease (normal stage: glomerular filtration rate (GFR) = 90 ml/min/1.73m^2). From these 4 subjects, 2 reported at least one AE, with the total number of AEs being 5. For details on the SOC and PT categories, please refer to Appendix 1 – Table 1.29.12: Adverse Events by Chronic Kidney Disease (Prospective). One subject had AEs that were possibly/probably related to XLH treatment (phosphate and calcitriol), as reported by the investigator (Table 11, Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]).

From the 5 subjects with chronic kidney disease, 1 subject had a mild stage of chronic kidney disease (mild stage: GFR = 60 and < 90 ml/min/1.73m^2). This subject reported in total 4 AEs with 1 AE possibly/probably related to XLH treatment (burosumab), as reported by the investigator (see

Table 11, Appendix 1– Listing 1.41: Adverse Events [Part 1] and Appendix 1 – Listing 1.42: Adverse Events [Part 2]). For details on the SOC and PT categories of the AEs, please refer to Appendix 1 – Table 1.29.12: Adverse Events by Chronic Kidney Disease (Prospective).
There were no subjects with moderate, severe, or very severe stage of chronic kidney disease (moderate stage: GFR = 30 and < 60 ml/min/1.73m^2, severe stage: GFR = 15 and < 30 ml/min/1.73m^2, very severe stage: GFR < 15 ml/min/1.73m^2) in the SAF population (see Table 11).

Table 11. Summary Overview of All Adverse Events by Chronic Kidney Disease (Prospective) – Safety Analysis Set

	Burosumab (N=67)
Total (N)	**5**
Any AE, n (%)	3 (60.0)
Any AE possibly/probably related to XLH treatment*, n (%)	2 (40.0)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
	4
Normal stage (N)**	
Any AE, n (%)	2 (50.0)
Any AE possibly/probably related to XLH treatment*, n (%)	1 (25.0)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
Mild stage (N)**	**1**
Any AE, n (%)	1 (100)
Any AE possibly/probably related to XLH treatment*, n (%)	1 (100)
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
Moderate stage (N)**	**0**
Any AE, n (%)	0
Any AE possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0

	Burosumab (N=67)
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
Severe stage (N)**	**0**
Any AE, n (%)	0
Any AE possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0
Very Severe stage (N)**	**0**
Any AE, n (%)	0
Any AE possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to death, n (%)	0
Any AE leading to death and possibly/probably related to XLH treatment*, n (%)	0
Any AE leading to XLH treatment withdrawn, n (%)	0
Any AE leading to XLH treatment withdrawn and possibly/probably related to XLH treatment*, n (%)	0
Any severe AE, n (%)	0
Any SAE, n (%)	0
Any SAE possibly/probably related to XLH treatment*, n (%)	0

Source: Appendix 1 – Table 1.28.2: Summary Overview of All Adverse Events by Chronic Kidney Disease (Prospective)
AE: Adverse Event, SAE: Serious Adverse Event, SAF: Safety Analysis Set, XLH: X-linked hypophosphataemia
Note: Percentages are calculated using the number of subjects in the SAF as denominator.
*The relationship of the AE with XLH treatment as reported by the investigator.
**Stage of chronic kidney disease: Normal: GFR = 90 ml/min/1.73m2, Mild: GFR = 60 and < 90 ml/min/1.73m2, Moderate: GFR = 30 and < 60 ml/min/1.73m2, Severe: GFR = 15 and < 30 ml/min/1.73m2, Very severe: GFR < 15 ml/min/1.73m2.
GFR: glomerular filtration rate

10.4 Main Results

In total, 25 out of 67 subjects in the SAF reported at least one AE over the course of the study. The total number of AEs reported was 83. The most commonly reported AEs were in the SOC of 'Musculoskeletal and connective tissue disorders', with the main PT being 'Pain in extremity', and in the SOC of 'Infections and infestations', with the main PT being 'Tooth abscess'. From these 25 subjects, 13 subjects had AEs possibly/probably related to XLH treatment, of whom 12 had AEs

possibly/probably related to burosumab specifically, as reported by the investigator, with the most common SOCs and PTs corresponding to the description above: 'Musculoskeletal and connective tissue disorders' with 'Pain in extremity' as the main PT, and 'Infections and infestations' with 'Tooth abscess' as the main PT. Four subjects reported severe AEs with the majority of the severe AEs falling into the SOC of 'Musculoskeletal and connective tissue disorders', with the main PT being 'Pain in extremity', and 2 subjects reported SAEs; 1 SAE falling into the SOC category of 'Congenital, familial and genetic disorders' with PT being 'Craniosynostosis', and 1 SAE falling into the SOC category of 'Musculoskeletal and connective tissue disorders' with PT being 'Knee deformity'. No deaths, no AEs leading to XLH treatment withdrawal, and no SAEs related to XLH treatment were reported in the study. There were also no pregnancies reported in the study population over the course of the study.

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

Not applicable as AEs are the primary outcome.

11. DISCUSSION

11.1 Key Results

The present study is a PASS that is conducted using data collected in the XLH Registry. The primary objective of this PASS is to evaluate the frequency and severity of AEs in children and adolescents using burosumab for the treatment of XLH.

The secondary objective of this study was to perform a retrospective cohort study using data from the XLH Registry to compare the safety outcomes of interest in subjects exposed to burosumab to those

in subjects receiving alternative treatments for XLH. However, such comparison was not planned for this first interim report. The report focused solely on subjects exposed to burosumab.

Sixty seven (67) subjects receiving at least one dose of burosumab were included in this study between 12th Sep 2017 and the interim data cut-off 13th May 2021. Of these, 25 subjects experienced at least one AE during the reporting period. The total number of AEs reported was 83, with 25 AEs reported as possibly/probably related to XLH treatment by the investigator, of which 23 were reported as possibly/probably related to burosumab specifically. The most frequently reported AEs were classified in the SOC of 'Musculoskeletal and connective tissue disorders' with 'Pain in extremity' as the most common PT, followed by 'Infections and infestations', with 'Tooth abscess' being the most reported PT.

From the 83 AEs reported, 6 qualified as severe AEs. Five out of these 6 severe AEs were classified in the SOC of 'Musculoskeletal and connective tissue disorders'. One severe AE was classified in the SOC of 'Injury, poisoning and procedural complications'.

The number of reported SAEs in the study population was 2,with 1 SAE classified in the SOC of 'Congenital, familial and genetic disorders', and 1 SAE classified in the SOC of 'Musculoskeletal and connective tissue disorders'.

Two of the 6 flagged subjects on the contraindicated combination of treatments, i.e., a concomitant use of burosumab and active vitamin D, reported 2 AEs each, all of mild severity. Two of the 4 AEs were reported by the investigator as possibly/probably related to XLH treatment (burosumab): 1 classified in the SOC of 'Infections and infestations', with the PT being 'Tooth abscess', and 1 classified in the SOC of 'General disorders and administration site conditions', with the PT being 'Injection site erythema'. For these 6 flagged subjects, data will be further investigated to understand the full context. As this is an observational study, treatment decisions are solely influenced by the treating physicians.

11.2 Limitations

The study relies on use of data from the XLH Registry.

Despite several steps taken to limit the effect of bias and confounding in the study (Section 9.6), several points need to be kept in mind when considering the results:

- Selection bias: To minimise selection bias, the eligibility criteria in the study were selected to be as broad as possible for this study population.
- Generalisability of results: Since the study is based on XLH Registry, the results of this study can only be generalised to population with access to health care in the participating countries. The participating countries were identified based on market authorisation of burosumab.
- Information bias is a distortion in the estimate of association between risk factor and disease that is due to systematic measurement error or misclassification of subjects on one or more variables, either risk factor or outcome. To minimise this type of bias in the current study, instructions were provided to all physicians in the centres participating in the XLH Registry. Therefore, special consideration was taken during the design of the PASS, to align the study variables with data available in the XLH Registry.
- Confounding by indication: Selective prescribing of a specific medication to subjects with a different clinical profile (e.g., more severe disease) is expected. This will influence drug prescription and, if related to the outcome, act as a confounding factor.
- Channelling bias: burosumab was a new drug on the market at the start of this study. Thus, subjects newly initiating burosumab at the very beginning of the study might differ from subjects starting the treatment later. This effect will tend to decrease upon study progression. In this interim report, as the study population size was still relatively small, subgroup analysis, adjusting for confounding or propensity adjustment was not carried out. However, such analysis is planned for future reports.
- Limitation related to missing data: no imputation of missing data was performed. The missingness in this study has only been reported in descriptive data, leading to less accurate precision of the

study population characteristics. It is however plausible that there is unreported missingness in the main results, i.e., the frequency and severity of AEs, which would result in underestimation of such in this study.

11.3 Interpretation

This PASS study is conducted using data collected in an XLH Registry and its primary objective is to evaluate the frequency and severity of AEs in children and adolescents using burosumab for the treatment of XLH. Going forward, the PASS study aims to include approximately 400 subjects aged 1 year and above by the end of the enrolment period (10 years after the initiation of the study). However, in adherence to the first version of the protocol, this interim analysis focuses only on children and adolescents, i.e., a population aged between 1 and 18 years. At the time of the data-cut for this interim analysis, 67 subjects were enrolled in the PASS. Since the use of burosumab is an inclusion criterion for participation in the PASS, all 67 subjects use burosumab as treatment of XLH. From this total, 31 subjects additionally used an alternative XLH treatment that they combined with burosumab either sequentially or concomitantly.
There are 2 planned interim analyses; the current interim analysis, another one 4 years after, and a final analysis after study completion.

The mean follow-up time at data cut-off was 2.2 years (range: 0.5 to 3.6). The number of observed AEs reported in this interim analysis was 83, with 6 qualifying as severe AEs, and 2 as SAEs. No deaths, no AEs leading to XLH treatment withdrawal, and no SAEs related to XLH treatment were reported in the study.

To our knowledge, this is the first large scale international observational study on XLH in children and adolescents that assesses the safety of burosumab. However, several paediatric clinical studies have reported the frequency and severity of AEs during the clinical trials. One clinical trial (UX023-CL201) investigating burosumab therapy in 52 children between 5 and 12 years of age,

reported AEs in all participating subjects (12). The most frequent AEs were injection site reaction, headache and cough; one of the AEs was qualified as SAE (hospitalisation for fever and myalgia). In another clinical trial (UX023-CL301) evaluating the differences in efficacy and safety of continuing conventional therapy versus switching to burosumab in paediatric cohort of children between 1 and 12 years of age , all of the 29 subjects that were treated with burosumab reported AEs during the course of the study, with 3 subjects reporting treatment-emergent SAEs; craniosynostosis, a viral infection, and a migraine (13). In a third study (UX023-CL205) on the efficacy and safety of burosumab in children aged 1 to 5 years, all 13 subjects reported at least one AE, with the total number of AEs being 278, of which 14 were related to burosumab. Cough and pyrexia were the most frequent AEs. One SAE considered unrelated to treatment (tooth abscess) occurred in a child with a history of tooth abscess (14). The study population of the current PASS appears to report the same type of AEs as those reported in these clinical trials. Injection site reaction and cough appear to be the most frequent reported AEs. However, such direct comparisons cannot be made as the current study has fewer exclusion criteria than typical clinical studies and the monitoring of subjects is less frequent and intense than in clinical trials.

11.4 Generalisability

The study population is presumed to be representative of the broader population of children and adolescents using burosumab as treatment of XLH due to few exclusion criteria. However, as the study is based on XLH Registry, the results of this study can only be generalised to population with access to health care in the participating countries.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

The safety profile of burosumab observed in this PASS interim analysis is consistent with previously reported safety data for burosumab. The most commonly reported AEs were typical of a paediatric population or frequent manifestations of XLH (majority of AEs classified in the SOCs of 'Musculoskeletal and connective tissue disorders' and 'Infections and infestations'). Upon continuation of the study, the aim is to follow the subjects for a period of up to 10 years and provide long-term safety data for medical care providers and subjects with XLH that will improve the knowledge of burosumab safety.

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15. APPENDICES

Appendix 1. Tables and listings referred to but not included in the text

Appendix 2. List of stand-alone documents

Number	Document type	Date	Version	Title
1	Post-Authorisation Safety Study – Burosumab Final Protocol	15 Aug 2018	1.0	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-Linked Hypophosphataemia
2	Post-Authorisation Safety Study – Burosumab Final Protocol	12 Jan 2021	2.0	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-Linked Hypophosphataemia
3	Statistical Analysis Plan for the Post-Authorisation Safety Study – Burosumab	22 Oct 2020	1.0	Statistical Analysis Plan for Post-Authorisation Safety Study - Crysvita®
4	Biostatistics File Note	29 Apr 2021	N/A	Update of Safety Analysis Set (SAF) definition for the first Interim Analysis in the Post-Authorisation Safety Study for Burosumab
5	Blank Case Report Forms	07 Jun 2021	10.0	IBM Clinical Development Blank Case Report Forms

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Dr.	Arango Sancho, Pedro	Hospital Sant Joan de Deu	Passeig Sant Joan de Deu 2 Pediatria Esplugues de Llobregat Barcelona	Spain
Dr.	Ariceta Iraola, Gema	Hospital Universitari Vall d'Hebron	Passeig Vall d Hebron119-129 Servicio de Pediatria Barcelona	Spain
Dr.	Cabrera Sevilla, Jose Eugenio	Hospital General Universitario Santa Lucía	C/ Mezquita s/n. Paraje Los Arcos Cartagena Murcia	Spain
Dr.	Calderón, Carmen Vicente	Hospital Universitario Virgen de la Arrixaca	Ctra. Madrid-Cartagena, s/n UCI Pediatrica El Palmar Murcia	Spain
Dr.	Gómez Alonso, Carlos	Hospital Universitario Central de Asturias	C/ Julian Claveria s/n Secretaria Servicio de Neurologia Oviedo Asturias	Spain
Dr.	Luis Yanes, Maria Isabel	Hospital Universitario Nuestra Señora de la Candelaria	Ctra. del Rosario 145 Sª Cruz de Tenerife Tenerife	Spain
Dr.	Madariaga Dominguez, Leire	Hospital de Cruces	Plaza de Cruces, s/n Nefrologia Pediatrica Barakaldo Vizcaya	Spain
Dr.	Munoz Torres, Manuel	Hospital Universitario San Cecilio	Avenida Doctor Oloriz 16 Endocrinologia Granada Granada	Spain
Dr.	Peris, Pilar	Hospital Clinic de Barcelona	c/ Villarroel, nº170 Reumatology Barcelona	Spain

Title	Surname, Name	Site	Address	Country
			Barcelona	
Dr.	Santos Rodriguez, Fernando	Hospital Central de Asturias	Av. Roma, s/n Oviedo Asturias	Spain
Dr.	Valenciano, Blanca	Complejo Hospitalario Universitario Insular Materno-Infantil	Av. Maritima del Sur, s/n Oncologia - 3ª Planta, Ala Oeste Las Palmas de Gran Canaria Las Palmas	Spain
Dr.	de Lucas Collantes, Maria del Carmen	Hospital Infantil Universitario Niño Jesus	Avenida Menendez Pelayo, 65 Neurologia Madrid	Spain
Dr.	de la Cerda Ojeda, Francisco	Hospital Universitario Virgen del Rocio	Avda. Manuel Siurot s/n Nefrologia Sevilla	Spain
Dr.	Björnsdottir, Sigridur	Karolinska Institute	Vlrdvagen 1 Plan 1 Stockholm	Sweden
Dr.	Fors, Hans	Queen Silvia Children's Hospital	SW Goteborg	Sweden
Dr.	Gustafsson, Jan	Uppsala University Hospital	Uppsala Clinical Research Centre Dept. of Cardiology Uppsala	Sweden
Prof.	Nilsson, Ola	Karolinska Institute - Paedeatric	Karolinska Institutet, Stockholm	Sweden
Dr.	Olsson, Karin	Lund University	Universitetssjukhuset Lund	Sweden
Dr.	Svensson, Johan	Skånes Universitetssjukhus, Malmö	Inga Marie Nilssons gata 46 Malmö	Sweden
Prof.	Baumgartner, Matthias	Kinderspital Zürich	Steinwiesstrasse 75 Zürich	Switzerland
Dr.	Bilz, Stefan	Kantonsspital St. Gallen	Rorschacher Strasse 95 St. Gallen	Switzerland
Dr.	Fischli, Stefan	Luzerner Kantonsspital	Spitalstrasse 16 Luzern	Switzerland
Prof.	Haeberle, Johannes	Kinderspital Zuerich	Steinwiesstrasse 75 Zuerich	Switzerland
Prof.	Meier, Christian	Universitaetsspital Basel	Petersgraben 4 Basel	Switzerland
Prof.	Parvex, Paloma	Hôpitaux Universitaires de Genève - HUG	Rue Gabrielle-Perret Gentil 4 Genève 14	Switzerland
Prof.	Serra, Andreas	Klinik Hirslanden Zuerich	Witellikerstrasse 40 Zuerich	Switzerland
Dr.	Trombetti, Andrea	Hopitaux Universitaires de Geneve (HUG)	Rue Gabrielle-Perret-Gentil 4 Genève 14	Switzerland

Title	Surname, Name	Site	Address	Country
Dr.	Abid, Noina	Royal Belfast Hospital for Sick Children	180 Falls Road Belfast	United Kingdom
Dr.	Ahmed, Syed	NHS Greater Glasgow & Clyde - South Glasgow University Hosp Division	1055 Great Western Road Glasgow Strathclyde	United Kingdom
Dr.	Arundel, Paul	Sheffield Children's Hospital	Western Bank Sheffield South Yorkshire	United Kingdom
Dr.	Bath, Louise	Royal Hospital for Children and Young People	Sciennes Road Edinburgh Lothian Region	United Kingdom
Dr.	Burren, Christine	University Hospitals Bristol	Level 6, UH Bristol Research & Education Centre Upper Maudlin Street Bristol Avon	United Kingdom
Dr.	Cheung, Moira	Evelina Childrens Hospital	1st floor, North Wing Westminster Bridge Road London Greater London	United Kingdom
Dr.	Daroszewska, Anna	Royal Liverpool University Hospital	Prescot Street, Liverpool Merseyside	United Kingdom
Dr.	Davies, Justin	Southampton General Hospital	Tremona Road, Level E, Laboratory & Pathology Block, SCBR - MP 138 Southampton Hampshire	United Kingdom
Dr.	Dharmaraj, Poonam	Alder Hey Children's Hospital	Eaton Road Liverpool Merseyside	United Kingdom
Dr.	Gevers, Evelien	Royal London Hospital	Whitechapel London Greater London	United Kingdom
Dr.	Gittoes, Neil	University Hospitals Birmingham NHS Foundation Trust	Bordesley Green East Birmingham West Midlands	United Kingdom
Dr.	Hayes, Wesley	Great Ormond Street Hospital for Children	Great Ormond Street Bloomsbury London Greater London	United Kingdom
Dr.	Henderson, Stuart	Raigmore Hospital	Old Perth Road Inverness Highland Region	United Kingdom

Title	Surname, Name	Site	Address	Country
Dr.	Jacobs, Benjamin	Stanmore Royal Orthopaedic Hospital	Brockley Hill Stanmore Middlesex	United Kingdom
Prof	Javaid, Kassim	Oxford University Hospital NHS Trust	Windmill Road, Headington Oxford OX3 7LD Oxford Oxfordshire	United Kingdom
Dr.	Keen, Richard	Royal National Orthopaedic Hospital	Brockley Hill Stanmore Middlesex	United Kingdom
Dr.	Murphy, Elaine	University College London Hospitals	250 Euston Road 1st Floor east London Greater London	United Kingdom
Dr.	Mushtaq, Talat	Leeds General Infirmary	Great George Street Leeds West Yorkshire	United Kingdom
Dr.	Owen, Catherine	Royal Victoria Infirmary	Queen Victoria Road Newcastle upon Tyne Tyne & Wear	United Kingdom
Dr.	Padidela, Raja	Royal Manchester Children's Hospital	Oxford Road Campus 29 Grafton Street Manchester, Greater Manchester	United Kingdom
Dr.	Pryce, Rebekah	University Hospital of Wales	Heath Park Way Cardiff West Glamorgan	United Kingdom
Prof.	Ralston, Stuart	Western General Hospital	Crewe Road South Edinburgh Lothian Region	United Kingdom
Dr.	Randell, Tabitha	Nottingham University Hospitals Queen's Medical Centre	Derby Road Queens Medical Centre Nottingham Nottinghamshire	United Kingdom
Dr.	Saraff, Vrinda	Birmingham Children's Hospital	Steelhouse Lane Birmingham West Midlands	United Kingdom
	Schini, Marian	Sheffield Teaching Hospital NHS Foundation Trust	Herries Road Sheffield South Yorkshire	United Kingdom
Dr.	Srivastava, Rajeev	Queen Elizabeth University Hospital	1053 Great Western Road Glasgow Strathclyde	United Kingdom
Dr.	Stone, Mike	University Hospital Llandough	Penlan Road Penarth Llandough Vale of Glamorgen	United Kingdom

Title	Surname, Name	Site	Address	Country
Prof.	Fuster, Daniel	Inselspital Bern	Freiburgstrasse 15 Bern	Switzerland

Appendix 4. List of all Independent Ethics Committee (IEC)/Institutional Review Board (IRB) Study Approvals by Country

*Initial Protocol=Registry Protocol V3.0 dated 15Feb2019 with embedded PASS protocol V1.0 dated 15Aug2018

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Belgium	UZ Leuven	CEC	UZ Leuven4	Central Ethics Committee	Approved (Closed)	26/Nov/2019	01/Apr/2020
Belgium	UZ Leuven	Ethics/Central IRB Submission	UZ Leuven	Central Ethics Committee	Approved	26/Nov/2019	01/Apr/2020
Belgium	Hopital Universitaire des Enfants Reine Fabiola	CEC	UZ Leuven	Central Ethics Committee	Approved (Closed)	26/Nov/2019	01/Apr/2020
Belgium	Hopital Universitaire des Enfants Reine Fabiola	Ethics/Central IRB Submission	Commission d'Ethique Médicale de l'Hôpital Universitaire des Enfants Reine Fabiola	Local Ethics Committee	Approved	26/Nov/2019	01/Apr/2020
Belgium	Cliniques Universitaires Saint-Luc	CEC	UZ Leuven	Central Ethics Committee	Approved (Closed)	26/Nov/2019	01/Apr/2020
Belgium	Cliniques Universitaires Saint-Luc	Ethics/Central IRB Submission	Comite Ethique Local Clinique universitaire Saint-Luc	Local Ethics Committee	Approved	26/Nov/2019	01/Apr/2020
Belgium	UZA	CEC	UZ Leuven	Central Ethics Committee	Approved (Closed)	26/Nov/2019	01/Apr/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Belgium	UZA	Ethics/Central IRB Submission	UZA	Local Ethics Committee	Approved	26/Nov/2019	01/Apr/2020
Bulgaria	UMHAT "SofiaMed", OOD	CEC	Ethics Committee for Clinical Trials	Central Ethics Committee	Approved (Closed)	24/Mar/2020	22/Apr/2020
Bulgaria	UMHAT "SofiaMed", OOD	RA	Bulgarian Drug Agency	Regulatory Authority (Country)	Approved (Closed)	24/Mar/2020	22/Jun/2020
Bulgaria	SHATPD "Prof. Ivan Mitev" EAD	CEC	Ethics Committee for Clinical Trials	Central Ethics Committee	Approved (Closed)	24/Mar/2020	22/Apr/2020
Bulgaria	SHATPD "Prof. Ivan Mitev" EAD	RA	Bulgarian Drug Agency	Regulatory Authority (Country)	Approved (Closed)	24/Mar/2020	22/Jun/2020
Czech Republic	Fakultni nemocnice v Motole	Ethics/Central IRB Submission	Eticka komise pro multicentricke klinicke hodnoceni Fakultni nemocnice v Motole	Local Ethics Committee	Approved	31/Oct/2019	04/Dec/2019
Czech Republic	Children Hospital	Ethics/Central IRB Submission	Eticka komise Fakultni Nemocnice Brno	Central Ethics Committee	Approved	31/Oct/2019	11/Dec/2019
Denmark	Aalborg University Hospital	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Denmark	Rigshospitalet	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
Denmark	Rigshospitalet	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
Denmark	OUH	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
Denmark	Århus Universitetshospital	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
Denmark	Hospital South West Jutland	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
Denmark	Aarhus Universitetshospital - Århus sygehus	RA	Danish Medicines Agency	Regulatory Authority (Country)	Notified	22/May/2020	
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020
France	CHU de Lyon - Hôpital Femme Mere Enfant	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020
France	Hôpital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020
France	CHU Paris Sud - Hopital Bicêtre	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020
France	Hôpital Cochin	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	Hopital Purpan	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	24/Jan/2018	18/May/2018
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	20/Nov/2018	
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Submitted for Approval	28/Aug/2019	
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	(More) Questions - Response Due	20/Feb/2019	
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
France	CHRU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
France	Hopital Roger Salengro - CHU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	31/Aug/2020	14/Sep/2020
France	Hopital Roger Salengro - CHU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approval Pending	16/Oct/2020	
France	Hopital Roger Salengro - CHU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	26/May/2020	12/Jun/2020
France	Hopital Roger Salengro - CHU Lille	CEC	Comité de Protection des Personnes Sud-Est I	Central Ethics Committee	Approved (Closed)	29/Nov/2020	28/Aug/2020
Hungary	Semmelweis Egyetem	Ethics/Central IRB Submission	National Institte of Pharmacy and Nutrition	Central Ethics Committee	Approved	11/Sep/2019	27/Sep/2019
Hungary	Semmelweis Egyetem	Ethics/Central IRB Submission	Orszagos Gyogyszereszeti es Elelmezes-egeszsegugyi Intezet	Central IRB	Approved	11/Sep/2019	07/Oct/2019
Hungary	Semmelweis Egyetem	Ethics/Central IRB Submission	Orszagos Gyogyszereszeti es Elelmezes-egeszsegugyi Intezet	Regulatory Authority (Country)	Approved	22/Jan/2020	31/Jan/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Ireland	The Children's University Hospital	CEC	Research Ethics Committee	Central Ethics Committee	Approved (Closed)	11/Dec/2018	20/Dec/2018
Israel	Sheba Medical Center	Ethics/Central IRB Submission	Chaim Sheba MC Ethics Committee	Local Ethics Committee	Approved	08/Nov/2020	26/Nov/2020
Israel	Schneider Medical Center	Ethics/Central IRB Submission	Rabin MC EC Committee	Local Ethics Committee	Approved	16/Nov/2020	03/Jan/2021
Israel	Rambam Health Care Center	Ethics/Central IRB Submission	Rambam Health Care Campus Ethics Committee	Local Ethics Committee	Approved	29/Oct/2020	30/Dec/2020
Italy	Azienda Ospedaliera Universitaria Careggi	Ethics/Central IRB Submission	Comitato Etico di Area Vasta Centro-CEC	Central Ethics Committee	Approved	28/Feb/2019	29/Mar/2019
Italy	Azienda Ospedaliera Universitaria Careggi	Ethics/Central IRB Submission	Comitato Etico di Area Vasta Centro-CEC	Central Ethics Committee	Approved	26/Jun/2020	21/Jul/2020
Italy	Azienda Ospedaliera Universitaria Careggi	Ethics/Central IRB Submission	Comitato Etico di Area Vasta Centro-CEC	Central Ethics Committee	Approved	02/Oct/2020	27/Oct/2020
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	02/Oct/2020	02/Oct/2020
Italy	Azienda Ospedaliera Universitaria Careggi	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Ospedale San Raffaele	Ethics/Central IRB Submission	Comitato Etico IRCCS Ospedale S. Raffaele di Milano	Local Ethics Committee	Approved	07/May/2019	20/Jun/2019
Italy	Ospedale San Raffaele	Ethics/Central IRB Submission	Comitato Etico IRCCS Ospedale S. Raffaele di Milano	Local Ethics Committee	Approved	03/Jul/2020	14/Oct/2020
Italy	Ospedale San Raffaele	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Ospedale San Raffaele	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Ospedale San Raffaele	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Ospedale San Raffaele	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Ospedale San Raffaele	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Ospedale Pediatrico Bambino Gesù	Ethics/Central IRB Submission	Ospedale Pediatrico Bambino Gesù	Local Ethics Committee	Approved	07/Oct/2019	11/Dec/2019
Italy	Ospedale Pediatrico Bambino Gesù	Ethics/Central IRB Submission	Ospedale Pediatrico Bambino Gesù	Local Ethics Committee	Approved	16/Sep/2020	30/Sep/2020
Italy	Ospedale Pediatrico Bambino Gesù	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Ospedale Pediatrico Bambino Gesù	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Ospedale Pediatrico Bambino Gesù	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Ospedale Pediatrico Bambino Gesù	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Ospedale Pediatrico Bambino Gesù	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	Ethics/Central IRB Submission	Comitato Etico Centrale IRCSS Lombardia	Local Ethics Committee	Approved	06/May/2019	21/May/2019
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	Ethics/Central IRB Submission	Comitato Etico Centrale IRCSS Lombardia	Local Ethics Committee	Approved	22/Dec/2020	20/Apr/2021
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	Ethics/Central IRB Submission	Comitato Etico Centrale IRCSS Lombardia	Local Ethics Committee	Approved	22/Dec/2020	20/Apr/2021
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	02/Oct/2020	02/Oct/2020
Italy	Istituto Auxologico Italiano-I.R.C.C.S.	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	Ethics/Central IRB Submission	Comitato Etico Interaziendale AOU Città della Salute e della Scienza di Torino	Local Ethics Committee	Approved	17/Jul/2019	13/Jan/2020
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	Ethics/Central IRB Submission	Comitato Etico Interaziendale AOU Città della Salute e della Scienza di Torino	Local Ethics Committee	Approved	03/Jul/2020	22/Feb/2021
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
	(Presidio Sant'Anna)						
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino (Presidio Sant'Anna)	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi	Ethics/Central IRB Submission	Comitato Etico Indipendente di Area Vasta Emilia Centro (CE-AVEC)	Local Ethics Committee	Approved	12/Jun/2019	23/Aug/2019

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
	IRCCS						
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	Ethics/Central IRB Submission	Comitato Etico Indipendente di Area Vasta Emilia Centro (CE-AVEC)	Local Ethics Committee	Approved	16/Sep/2020	18/Nov/2020
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Ethics/Central IRB Submission	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Local Ethics Committee	Approved	12/Jun/2019	03/Feb/2020
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Ethics/Central IRB Submission	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Local Ethics Committee	Approved	22/Jan/2020	03/Feb/2020
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Ethics/Central IRB Submission	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Local Ethics Committee	Approved	07/Jul/2020	13/Jul/2020
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Ethics/Central IRB Submission	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	Local Ethics Committee	Approved	17/Sep/2020	21/Sep/2020
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Istituto Giannina Gaslini-Ospedale	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority	Submission Created	22/Dec/2020	22/Dec/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
	Pediatrico IRCCS			(Country)			
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Istituto Giannina Gaslini-Ospedale Pediatrico IRCCS	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari	Ethics/Central IRB Submission	Comitato Etico Indipendente Locale	Local Ethics Committee	Approved	12/Jun/2019	12/May/2020
Italy	Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari	Ethics/Central IRB Submission	Comitato Etico Indipendente Locale	Local Ethics Committee	Approved	24/Feb/2020	12/May/2020
Italy	Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari	Ethics/Central IRB Submission	Comitato Etico Indipendente Locale	Local Ethics Committee	Approved	03/Jul/2020	22/Jul/2020
Italy	Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Azienda Ospedaliero Universitaria Consorziale	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority	Submission Created	15/Mar/2021	15/Mar/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
	Policlinico di Bari			(Country)			
Italy	Azienda Ospedaliero Universitaria Consorziale Policlinico di Bari	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Stabilimento Ospedaliero Santa Chiara	Ethics/Central IRB Submission	Comitato Etico Area Vasta Nord Ovest	Local Ethics Committee	Approved	22/Jan/2020	26/Mar/2020
Italy	Stabilimento Ospedaliero Santa Chiara	Ethics/Central IRB Submission	Comitato Etico Area Vasta Nord Ovest	Local Ethics Committee	Approved	03/Jul/2020	24/Sep/2020
Italy	Stabilimento Ospedaliero Santa Chiara	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Stabilimento Ospedaliero Santa Chiara	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Stabilimento Ospedaliero Santa Chiara	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Stabilimento Ospedaliero Santa Chiara	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	Ethics/Central IRB Submission	Policlinico G Martino University Hospital Trust Messina	Local Ethics Committee	Approved	25/Sep/2019	29/Oct/2019
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	Ethics/Central IRB Submission	Policlinico G Martino University Hospital Trust Messina	Local Ethics Committee	Approved	16/Sep/2020	16/Mar/2021
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	Azienda Ospedaliera Universitaria Policlinico G. Martino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	I.R.C.C.S. Burlo Garofolo	Ethics/Central IRB Submission	Comitato Etico Regionale (CER)	Local Ethics Committee	Approved	10/Mar/2020	17/Jun/2020
Italy	I.R.C.C.S. Burlo Garofolo	Ethics/Central IRB Submission	Comitato Etico Regionale (CER)	Local Ethics Committee	Approved	16/Jun/2020	17/Jun/2020
Italy	I.R.C.C.S. Burlo Garofolo	Ethics/Central IRB Submission	Comitato Etico Regionale (CER)	Local Ethics Committee	Approved	16/Sep/2020	01/Dec/2020
Italy	I.R.C.C.S. Burlo Garofolo	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	I.R.C.C.S. Burlo Garofolo	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	I.R.C.C.S. Burlo Garofolo	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	22/Dec/2020	22/Dec/2020
Italy	I.R.C.C.S. Burlo Garofolo	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Italy	I.R.C.C.S. Burlo Garofolo	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	Ethics/Central IRB Submission	Azienda Sanitaria Locale BR	Local Ethics Committee	Approved	03/Jun/2020	24/Jun/2020
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	Ethics/Central IRB Submission	Azienda Sanitaria Locale BR	Local Ethics Committee	Approved	14/Oct/2020	18/Nov/2020
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	26/Jun/2020	26/Jun/2020
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2020	15/Mar/2020
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	15/Mar/2021	15/Mar/2021
Italy	Presidio Ospedaliero Di Summa Antonio Perrino	RA	AIFA - Agenzia Italiana del Farmaco	Regulatory Authority (Country)	Submission Created	29/Apr/2021	29/Apr/2021
Netherlands	Universitair Medisch Centrum Groningen	Ethics/Central IRB Submission	University Medical Centre Groningen	Local Ethics Committee			

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Norway	Oslo Universitetssykehus HF, Aker Sykehus	Ethics/Central IRB Submission	REK Sør-øst	Central Ethics Committee	Approved	19/Mar/2019	29/May/2019
Norway	Oslo Universitetssykehus HF, Aker Sykehus	RA	Statens legemiddelverk	Regulatory Authority (Country)	Notified Acknowledged (Closed)	05/Aug/2020	
Norway	Oslo University Hospital	RA	Statens legemiddelverk	Regulatory Authority (Country)	Notified Acknowledged (Closed)	05/Aug/2020	
Norway	St. Olav's University Hospital	RA	Statens legemiddelverk	Regulatory Authority (Country)	Notified Acknowledged (Closed)	05/Aug/2020	
Portugal	Centro Hospitalar de Lisboa Central, E.P.E. - Hospital Dona Estefânia	Ethics/Central IRB Submission	Comissão de Ética do Centro Hospitalar Lisboa Central - Hospital Santo António dos Capuchos	Local Ethics Committee	Approved	13/Dec/2019	16/Jan/2020
Portugal	Centro Hospitalar de Lisboa Norte, E.P.E. - Hospital de Santa Maria	Ethics/Central IRB Submission	Comissão de Ética para a Saúde do Centro Hospitalar Lisboa Norte, EPE	Local Ethics Committee	Approved	24/Jun/2019	03/Dec/2019
Portugal	Hospital Pediatrico de Coimbra	Ethics/Central IRB Submission	Centro Hospitalar e Universitário de Coimbra E.P.E	Local Ethics Committee	Approved	24/Sep/2019	26/Aug/2020
Portugal	Centro Hospitalar do Porto, E.P.E. - Hospital de Santo	Ethics/Central IRB	Comissão de Ética do Centro Hospitalar do Porto -	Local Ethics	Approved	18/Sep/2019	10/Mar/2020

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
	António	Submission	Hospital de Santo António	Committee			
Portugal	Hospital de Sao Joao	Ethics/Central IRB Submission	Comissão de Ética do Centro Hospitalar do Porto - Hospital de Santo António	Local Ethics Committee	Approved	24/Jun/2019	19/Jul/2019
Slovakia	National Institute of Childrenś Health NUDCH	Ethics/Central IRB Submission	EK-Detska fakultna nemocnica s poliklinikou v Bratislave	Local Ethics Committee	Approved	31/Oct/2019	20/Nov/2019
Slovenia	University Clinical Centre Ljubljana	CEC	The Republic of Slovenia National Medical Ethics Committee	Central Ethics Committee	Approved (Closed)	10/Jan/2020	27/Feb/2020
Slovenia	University Clinical Centre Ljubljana	RA	AZMP - Public Agency of the Republic of Slovenia for Medicinal Products and Medical Devices	Regulatory Authority (Country)	Notified Acknowledged (Closed)	10/Mar/2020	
Spain	Hospital Universitari Vall d'Hebron	RA	Comunidad de Cataluña	Regulatory Authority (Region)	Submission Created	07/May/2019	14/Jun/2019
Spain	Hospital Universitari Vall d'Hebron	Ethics/Central IRB Submission	Hospital Universitari Vall d'Hebron	Central Ethics Committee	Approved	28/Feb/2019	26/Apr/2019
Spain	Hospital Sant Joan de Deu	RA	Comunidad de Cataluña	Regulatory Authority (Region)	Submission Created	07/May/2019	14/Jun/2019

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Spain	Hospital Sant Joan de Deu	Ethics/Central IRB Submission	RA Cataluna	Local Ethics Committee	Approved	13/May/2019	28/Feb/2020
Spain	Hospital Central de Asturias	Ethics/Central IRB Submission	CEIC de Asturias	Local Ethics Committee	Approved	09/May/2019	13/May/2019
Spain	Hospital Universitario Central de Asturias	Ethics/Central IRB Submission	Comité de Ética de la Investigación del Principado de Asturias	Local Ethics Committee	Approved	09/May/2019	09/May/2019
Spain	Hospital Universitario Virgen de la Arrixaca	Ethics/Central IRB Submission	RA Murcia	Central Ethics Committee	Approved	03/Jun/2019	02/Jul/2019
Spain	Hospital Universitario Virgen de la Arrixaca	Ethics/Central IRB Submission	CEIC Hospital Virgen de la Arrixaca	Local Ethics Committee	Approved	25/Apr/2019	27/May/2019
Spain	Hospital General Universitario Santa Lucía	Ethics/Central IRB Submission	CEIC Hospital General Universitario Santa Lucia	Local Ethics Committee	Approved	10/May/2019	13/Jun/2019
Spain	Hospital Infantil Universitario Niño Jesus	Ethics/Central IRB Submission	CEIC Hospital Infantil Universitario Niño Jesús	Central Ethics Committee	Approved	13/May/2019	24/Jan/2020
Spain	Hospital Clinic de Barcelona	RA	Comunidad de Cataluña	Regulatory Authority (Region)	Submission Created	07/May/2019	14/Jun/2019

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Spain	Hospital Clinic de Barcelona	Ethics/Central IRB Submission	Hospital Clinic de Barcelona	Local Ethics Committee	Approved	04/Jun/2019	14/Oct/2019
Spain	Complejo Hospitalario Universitario Insular Materno-Infantil	Ethics/Central IRB Submission	CEIC Hospital de Gran Canaria Doctot Negrín	Local Ethics Committee	Approved	23/Apr/2019	23/May/2019
Spain	Hospital Universitario Nuestra Señora de la Candelaria	Ethics/Central IRB Submission	Servicio Canario de la Salud	Central Ethics Committee	Approved	13/May/2019	11/Jul/2019
Spain	Hospital Universitario Nuestra Señora de la Candelaria	Ethics/Central IRB Submission	CEIC Hospital Universitario Nuestra Señora de la Candelaria	Local Ethics Committee	Approved	17/Jul/2019	10/Dec/2019
Spain	Hospital de Cruces	Ethics/Central IRB Submission	CEIC de Euskadi	Local Ethics Committee	Approved	30/May/2019	22/Nov/2019
Sweden	Queen Silvia Children's Hospital	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Approved (Closed)	18/Mar/2019	03/May/2019
Sweden	Queen Silvia Children's Hospital	RA	Regionala etikprövningsnämnden i Uppsala	Central Ethics Committee	Notified Acknowledged (Closed)	22/May/2020	

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Sweden	Queen Silvia Children's Hospital	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Conditional Approval	02/Jul/2020	02/Nov/2020
Sweden	Lund University	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Approved (Closed)	18/Mar/2019	03/May/2019
Sweden	Lund University	RA	Regionala etikprövningsnämnden i Uppsala	Central Ethics Committee	Notified Acknowledged (Closed)	22/May/2020	
Sweden	Lund University	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Conditional Approval	02/Jul/2020	02/Nov/2020
Sweden	Karolinska Institute	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Approved (Closed)	18/Mar/2019	03/May/2019
Sweden	Karolinska Institute	RA	Regionala etikprövningsnämnden i Uppsala	Central Ethics Committee	Notified Acknowledged (Closed)	22/May/2020	14/Aug/2020
Sweden	Karolinska Institute	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Conditional Approval	02/Jul/2020	02/Nov/2020
Sweden	Karolinska Institute - Paedeatric	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Approved (Closed)	18/Mar/2019	03/May/2019

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Sweden	Karolinska Institute - Paedeatric	RA	Regionala etikprövningsnämnden i Uppsala	Central Ethics Committee	Notified Acknowledged (Closed)	22/May/2020	
Sweden	Karolinska Institute - Paedeatric	CEC	Etikprövningsmyndigheten	Central Ethics Committee	Conditional Approval	02/Jul/2020	02/Nov/2020
Switzerland	Inselspital Bern	Ethics/Central IRB Submission	Kantonale Ethikkommission Bern (KEK-Bern)	Local Ethics Committee	Approved with Comments	17/Nov/2020	
Switzerland	Inselspital Bern	Ethics/Central IRB Submission	Kantonale Ethikkommission Bern (KEK-Bern)	Local Ethics Committee	Approved	04/Feb/2021	15/Mar/2021
Switzerland	Klinik Hirslanden Zuerich	Ethics/Central IRB Submission	Kantonale Ethikkommission Zürich (KEK-Zürich)	Central Ethics Committee	Approved with Comments	17/Nov/2020	
Switzerland	Klinik Hirslanden Zuerich	Ethics/Central IRB Submission	Kantonale Ethikkommission Zürich (KEK-Zürich)	Central Ethics Committee	Approved	04/Feb/2021	15/Mar/2021
Switzerland	Hopitaux Universitaires de Geneve (HUG)	Ethics/Central IRB Submission	CCER Commission cantonale d'éthique de la recherche	Central Ethics Committee	Approved with Comments	17/Nov/2020	
Switzerland	Hopitaux Universitaires de Geneve (HUG)	Ethics/Central IRB Submission	CCER Commission cantonale d'éthique de la recherche	Central Ethics Committee	Approved with Comments	04/Feb/2021	15/Mar/2021

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
Switzerland	Hopitaux Universitaires de Geneve (HUG)	Ethics/Central IRB Submission	CCER Commission cantonale d'éthique de la recherche	Central Ethics Committee	Approved	29/Apr/2021	06/May/2021
Switzerland	Kantonsspital St. Gallen	Ethics/Central IRB Submission	Ethikkomission Ostschweiz	Central Ethics Committee	Approved with Comments	17/Nov/2020	
Switzerland	Kantonsspital St. Gallen	Ethics/Central IRB Submission	Ethikkomission Ostschweiz	Central Ethics Committee	Approved	04/Feb/2021	15/Mar/2021
United Kingdom	Royal Manchester Children's Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Sheffield Teaching Hospital NHS Foundation Trust	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Evelina Childrens Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Royal Liverpool University Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Birmingham Children's Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
United Kingdom	NHS Greater Glasgow & Clyde - South Glasgow University Hosp Division	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Great Ormond Street Hospital for Children	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Southampton General Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Sheffield Children's Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Alder Hey Children's Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Royal Hospital for Children and Young People	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Western General Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	University Hospitals Bristol	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics	Submission Created	21/Aug/2017	08/Sep/2017

Country	Site Name	Submission Requirement	Authority/Committee Name	Protocol Account Type	Regulatory Submission Status	Date of Submission	Date of Approval
				Committee			
United Kingdom	Stanmore Royal Orthopaedic Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Leeds General Infirmary	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Oxford University Hospital NHS Trust	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	University College London Hospitals	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Queen Elizabeth University Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Royal Belfast Hospital for Sick Children	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017
United Kingdom	Addenbrooke's Hospital	CEC	North West - Liverpool East Research Ethics Committee	Central Ethics Committee	Submission Created	21/Aug/2017	08/Sep/2017

Appendix 5. Signatures of Coordinating Investigators and Sponsor's Relevant Signatures

Appendix 6. Details of Data Collected in the XLH Registry

Table A. Details of Data to be Collected in XLH Disease Registry[1] – Baseline Data Entry Visit

Information / assessment - mandatory	**Data to be investigated in PASS?**
1. Informed Consent (date and type of consent)	No
2. Demographics • Date of Birth • Biological Gender • Ethnicity	Yes
Information / assessment – data to be recorded if available; the Registry does not mandate investigations outside of standard care as determined by the subject's physician	**Data to be investigated in PASS?**
3. XLH-specific medication • all XLH-specific medications prescribed within 30 days prior to written consent (including dose, compliance, duration of treatment and reason for discontinuation if applicable)	Yes
4. Drug history • all current medications prescribed within 30 days prior to written consent (including dose, compliance, duration of treatment and reason for discontinuation if applicable)	Yes
5. Radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
6. Physical examination (including age and disease specific examinations)	Yes
7. Vital signs (temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes

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

Information / assessment - mandatory	**Data to be investigated in PASS?**
8. Growth Assessment including: • standing and sitting height (meters) • arm and leg length (meters) • weight (Kg) • Body Mass Index (BMI) • Z score (based on background national reference)	No
9. Laboratory Assessments including: • Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
10. Physiotherapy reports including: • use of a wheelchair • walking aids • medical device • home adaptations	No
11. Echocardiogram (ECHO) reports	Yes
12. Electrocardiogram (ECG) reports	Yes
13. Audiology assessment	Yes
14. Renal ultrasound scan	Yes
15. Assessment Tools/Outcome Measure reports: • Six-minute walk test (6MWT) • Timed Up and Go (TUG) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	No
16. Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age) • Pain: Faces Pain Scale-Revised (FPS-R) (for children ≥ 5 years of age)	No

Information / assessment - mandatory	**Data to be investigated in PASS?**
• 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	
17. Social History • Number of work/school dates missed due to XLH-related illness since last visit	Yes

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

Information / assessment - retrospective data entry will include the subject's medical history and may include the following data sets <u>if available</u>	**Data to be investigated in PASS?**
1. XLH-specific medical, surgical and dental history: • Diagnostic history: age of onset of symptoms, age at diagnosis, diagnosis method(s) • PHEX mutation (if available) • Family history: number of known affected relatives and relationship to subject	Yes
2. General medical history: • Pregnancy and foetal outcomes including weight, length, Apgar score, mode of delivery (if applicable)	Yes
3. XLH-specific medications including pain medications (including dose compliance, duration of treatment and reason for discontinuation if available)	Yes
4. Historical radiographs and imaging including: • Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	Yes
5. Historical physical examinations (including age and disease specific examinations)	Yes
6. Historical vital signs (including temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
7. Historical growth assessment including: • standing and sitting height (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:	Yes

Information / assessment - retrospective data entry will include the subject's medical history and may include the following data sets <u>if available</u>	**Data to be investigated in PASS?**
• Biochemistry, haematology, urine, endocrine and bone biomarkers	
9. Historical physiotherapy reports including: • number of visits • use of a wheelchair • walking aids • medical device • home adaptations	Yes
10. Historical echocardiogram (ECHO) reports	Yes
11. Historical electrocardiogram (ECG) reports	Yes
12. Historical audiology assessment	Yes
13. Historical renal ultrasound scan	Yes
14. Historical Assessment Tools/Outcome Measure reports: • Six-minute walk test (6MWT) • Timed Up and Go (TUG) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	No
15. Historical Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age) • 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	No

Information / assessment - retrospective data entry will include the subject's medical history and may include the following data sets <u>if available</u>	**Data to be investigated in PASS?**
• 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

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

Information / assessment – data to be recorded if available • **if a subject attends more regularly data will be entered in the Registry to reflect these visits at the 12 month interval, with an option to add multiple dates** • **the Registry does not mandate investigations outside of standard care as determined by the 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:	Yes

Information / assessment – data to be recorded if available • **if a subject attends more regularly data will be entered in the Registry to reflect these visits at the 12 month interval, with an option to add multiple dates** • **the Registry does not mandate investigations outside of standard care as determined by the subject's physician**	**Data to be investigated in PASS?**
• Any radiological assessment of disease severity (X-ray, DEXA, XtremeCT, CT or MRI) • Scanner type • Analysis software used	
6. Physical examination (including age and disease specific examinations)	Yes
7. Vital signs (temperature, blood pressure (sitting), pulse rate and respiratory rate)	Yes
8. Growth Assessment including: • standing and sitting height (meters) • arm and leg length (meters) • weight (Kg) • Body Mass Index (BMI) • Z score (based on background national reference)	No
9. Laboratory Assessments including: • Biochemistry, haematology, urine, endocrine and bone biomarkers	Yes
10. Physiotherapy reports including: • number of visits • use of a wheelchair • 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:	No

Information / assessment – data to be recorded if available • **if a subject attends more regularly data will be entered in the Registry to reflect these visits at the 12 month interval, with an option to add multiple dates** • **the Registry does not mandate investigations outside of standard care as determined by the subject's physician**	**Data to be investigated in PASS?**
• Six-minute walk test (6MWT) • Timed Up and Go (TUG) • Bruininks-Oseretsky Test of Motor Proficiency Section Edition (BOT-2) • Dynamometry	
16. Patient Quality of Life Questionnaires or Assessment Reports – may include the following but not exclusively: • Patient-Reported Outcomes Measurement Information System (PROMIS) (for children ≥ 5 years of age) • Short Form 10 (SF-10) (for children≥ 5 years of age) • Pain: Faces Pain Scale-Revised (FPS-R) (for children ≥ 5 years of age) • Brief Pain Inventory – Short Form (SF) (for adult subjects) • Brief Fatigue Inventory – SF (for adult subjects) • Short Form 36 (SF-36) (for adult subjects) • Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (for adult subjects) • Abbreviated XLH Resource 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

Information / assessment – data to be recorded if available	**Data to be investigated in PASS?**
• **if a subject attends more regularly data will be entered in the Registry to reflect these visits at the 12 month interval, with an option to add multiple dates** • **the Registry does not mandate investigations outside of standard care as determined by the subject's physician**	
17. Social History • Number of work/school dates missed due to XLH-related illness (since baseline or last recorded entry)	Yes

Appendix 7. XLH Registry Steering Committee members

Paediatric-treating physicians

- Dr Signe Beck-Nielsen, Consultant Paediatrician, Denmark
- Dr Annemieke Boot, Paediatric Endocrinology, The Netherlands
- Professor Francesco Emma, Paediatric Nephrology, Italy
- Professor Dieter Haffner, Paediatric Kidney, Liver and Metabolic Diseases, Germany
- Professor Gema Ariceta Iraola, Paediatric Nephrology, Spain
- Professor Elena Levtchenko, Paediatric Nephrology, Belgium
- Dr Carmen de Lucas Collantes, Paediatric Nephrology, Spain
- Professor Outimaija Mäkitie, Professor of Paediatric Endocrinology, Finland
- Professor Zulf Mughal, Consultant in Paediatric Bone Disorders, UK
- Professor Ola Nilsson, Professor of Paediatrics, Sweden
- Dr Dirk Schnabel, Paediatric Endocrinology and Diabetology, Germany

Adult-treating physicians

- Professor Maria Luisa Brandi, Endocrinology, Italy
- Professor Karine Briot, Rheumatology, France
- Professor Sandro Giannini, Professor of Internal Medicine, Italy
- Professor Richard Keen, Consultant in Metabolic Bone Diseases, UK
- Dr Liana Tripto-Shkolnik, Endocrinologist, Israel
- Professor Carola Zillikens, Endocrinology, The Netherlands

Appendix 8. Audit Certificates

No audits have been performed up to data cut-off for first interim report.