POST-AUTHORISATION SAFETY STUDY (PASS)

Annual Progress Report

STUDY OVERVIEW

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children >1 year of age, Adolescents and Adults with X-linked Hypophosphataemia
Version of the progress report	Version 5.0
Date of last version of the progress report	05-Apr-2023
European Union electronic Register of Post-Authorisation Studies (EU PAS)/ European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) register number	EUPAS32190
Active substance	Active substance: burosumab - recombinant human IgG1 monoclonal antibody to fibroblast growth factor 23 ATC code: M05BX05: Drug for the treatment for bone diseases, 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 and 10, 20 and 30 mg/mL solution in prefilled syringe

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).

Product reference	EU/1/17/1262/001 EU/1/17/1262/002 EU/1/17/1262/003 } vials EU/1/17/1262/004 EU/1/17/1262/005 } prefilled syringes EU/1/17/1262/006
Procedure number	EMEA/H/C/004275
Joint PASS	No
Research question and objectives	**Primary objectives:** 1. To evaluate the frequency and severity of safety outcomes in children and adolescents aged 1 to 17 years with radiographic evidence of bone disease, and adults, who are treated with burosumab for X-linked Hypophosphataemia (XLH), including but not limited to: long-term safety (as evidenced by death, hospitalisations, cardiovascular disease, cancer [all sites]), hypophosphataemia 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 (CKD) at baseline treated with burosumab. **Secondary objective:** To perform a retrospective cohort analysis 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.
Author	IQVIA on behalf of the Marketing Authorisation Holder

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Kyowa Kirin Holdings B.V. Bloemlaan 2 2132NP Hoofddorp Netherlands Tel: +31 (0) 237200822 Email: medinfo@kyowakirin.com Kyowa Kirin Holdings B.V. is owned by Kyowa Kirin International plc
MAH contact person	Beatriz Mengotti European Qualified Person for Pharmacovigilance Kyowa Kirin Farmacéutica, S.L. Paseo de la Castellana 259 C, Planta 23 28046 Madrid, Spain Tel: +34 699812173 Email: Beatriz.Mengotti@kyowakirin.com

Table of Contents

PASS PROGRESS INFORMATION

Protocol version and date	Version 2.0; 12-Jan-2021 (Sub-study to the parent XLH Registry Protocol Version 4.0; 27-Oct-2021) **N.B.:** This annual progress report is based on Version 2 of the post-authorisation safety study (PASS) protocol dated 12-Jan-2021, which includes children >1 year of age, adolescents, and adults. The tables in the appendix (Table 1.1.1 and Table 2.1.1) are based on primary objectives of the PASS protocol (Version 2), which includes as the study population those patients who are on burosumab. Those patients who are on alternative XLH treatments only (not exposed to burosumab) are studied for the secondary objective of the PASS and are not included in this progress report. Protocol Version 2 approved in all countries; approval for 2 sites in progress. Moreover, adult subjects need to provide additional consent via local versions of the master Informed Consent Form Version 4.0 dated 14-Feb-2022 to participate in the PASS. At the time of data cut-off, 64 adults have consented to PASS protocol Version 2 and children and adolescents minors participating to the PASS protocol Version 1 are being reconsented to protocol Version 2. This report therefore includes children, adolescents, and adults with an expanded sample size over previous years.
Approval date/s (approved by Committee for Medicinal Products for Human Use [CHMP])	13-Dec-2018

<table>
<tr><td>Study initiated (FPI)</td><td>24-Apr-2019</td></tr>
<tr><td>Data cut-off date</td><td>16-Feb-2024</td></tr>
<tr><td>Country(-ies) of study</td><td>Planned: Belgium, Bulgaria, Czech Republic, Germany, Denmark, France, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, UK

Currently enrolling: Belgium, Bulgaria, Czech Republic, Denmark, France, Hungary, Italy, Latvia, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, UK,</td></tr>
<tr><td>Subject disposition</td><td>A total of 464 subjects were included in the safety analysis set (SAF) as of 16-Feb-2024. Because the reconsent of subjects enrolled under PASS protocol Version 1 at time of data cut-off is ongoing, the population considered for this report contains both subjects consented under PASS Version 1 and PASS Version 2. Differently from PASS protocol Version 1, subjects consented under PASS Version 2 will only be under burosumab treatment. It is to be noted that this report considers only subject under burosumab treatment.

<table>
<tr><th></th><th>Belgium</th><th>Bulgaria</th><th>Czech Republic</th><th>Denmark</th><th>France</th><th>Hungary</th><th>Italy</th><th>Netherlands</th><th>Norway</th><th>Portugal</th><th>Slovakia</th><th>Slovenia</th><th>Spain</th><th>Sweden</th><th>United Kingdom</th><th>Latvia</th><th>Total</th></tr>
<tr><td>PASS</td><td>2</td><td>13</td><td>5</td><td>1</td><td>170</td><td>14</td><td>44</td><td>25</td><td>14</td><td>5</td><td>4</td><td>3</td><td>27</td><td>7</td><td>126</td><td>4</td><td>464</td></tr>
</table>
PASS = post-authorisation safety study

Note that, because confirmation of signed consent to participate in the PASS is a requirement for being included in the SAF analysis set, subjects who are participating in the PASS can be excluded from the SAF if they are missing a record of which ICF version was</td></tr>
</table>

	signed. This could result in some subjects who are participating in the PASS having a flag for PASS participation in the EDC but being excluded from the SAF and the current interim CSR. The overall subject disposition for all screened subjects (until data cut-off date) can be found in the end-of-text Appendix Table 1.1.1 Subject Disposition by Age group, Gender and Country (All Screened Subjects).
Recruitment	For the XLH Registry, enrolment to new subjects was closed on 10-Feb-2023. For the PASS, eligible patients participating in the XLH Registry can still be enrolled once consented for inclusion in the PASS. Additionally, enrolment will continue where there is a country specific requirement to be on XLH Registry to receive burosumab (Belgium and Switzerland for the XLH Registry and Belgium for the PASS).
Adverse event (AE)	A summary overview of all adverse events (AEs) by age group (prospective) is provided in the end-of-text Table 2.1.1 Summary Overview of All Adverse Events by Age Group (Prospective) Safety Analysis Set. Cumulatively from the start of the PASS up to the cut-off date: • Of the 464 subjects considered in this report, there were 164 subjects (35.3%) with at least 1 AE reported. There was a total of 502 AEs reported for these subjects. No AEs led to death in the study, however, AEs leading to XLH treatment withdrawal were reported in 2 subjects (0.4%). In total, 13 subjects (2.8%) reported at least one severe AE in the study and 3 subjects (0.6%) reported at least one severe event possibly related to burosumab. • There were 15 subjects (3.2%) who collectively reported 20 serious adverse events [SAEs] (033002-010, 033005-002, 033005-006, 033005-008, 033006-001, 039007-004, 039012-001, 044001-006, 044001-014, 044009-010, 044026-001, 044026-009, 047001-003, 047001-004, and 047001-005). • A total of 8 SAEs reported in 6 subjects were severe in intensity, which include nephrocalcinosis, foramen magnum decompression for Chiari malformation, intracranial hypertension, drug intoxication, femur fracture of right side, infection

	in surgical wound of left leg, knee problems requiring hospital admission, and suicide attempt. Only 2 severe SAEs were ongoing (nephrocalcinosis and femur fracture of right side), with the remaining severe SAEs having recovered at the data cut-off date. • Of the 20 SAEs reported among 15 subjects, 15 (among 11 subjects) were assessed as 'not related' or 'unlikely related' to burosumab. Three subjects (033002-010, 033005-002, 033005-008) had SAEs of intracranial hypertension, mild nephrocalcinosis Grade I, and nephrocalcinosis, respectively, which were assessed by the investigator as 'possibly related' to burosumab. The burosumab dose was not altered following the event for 2 subjects (033002-010 and 033005-002), while it was reduced for 1 subject (033005-008). Another subject (044001-014) reported a SAE of tertiary hyperparathyroidism which was assessed by the investigator as 'probably related' to burosumab. The burosumab treatment of the subject was interrupted following the event. The event of intracranial hypertension was considered as recovered, while mild nephrocalcinosis Grade I, nephrocalcinosis, and tertiary hyperparathyroidism were considered as ongoing at the data cut-off date. • Of the 20 reported SAEs, 15 SAEs (11 of the 15 subjects) had recovered, and 5 SAEs (5 of the 15 subjects) were ongoing at the data cut-off date (including 1 subject with 2 SAEs, 1 recovered and 1 ongoing). Details of ongoing SAEs are as follows: o Subject 044001-006 reported craniosynostosis and this event was assessed as 'not related' to burosumab. o Subject 047001-004 reported right side femur fracture and this event was assessed as 'unlikely related' to burosumab. o Subject 044001-014 reported tertiary hyperparathyroidism and this event was assessed as 'probably related' to burosumab.

	○ Subject 033005-002 reported mild nephrocalcinosis Grade I and this event was assessed as 'possibly related' to burosumab. ○ Subject 033005-008 reported nephrocalcinosis and this event was assessed as 'possibly related' to burosumab. • There were 153 ongoing AEs among 88 subjects at the data cut-off date. • Out of the 88 subjects with ongoing AEs, 11 subjects (031001-009, 032006-002, 033002-014, 033005-001, 034002-002, 034007-001, 034007-003, 034007-004, 044001-014, 044016-006, 044028-006) had 13 AEs which were assessed by the investigator as 'probably related' to burosumab. Among these 11 subjects, burosumab treatment was altered following the event for 3 subjects (dose increased for 031001-009, dose reduced for 034002-002, and treatment interrupted for 044001-014). Among these same 11 subjects: ○ Subject 044016-006 reported localised reaction around both injection sites, the size of a 20p coin (mild AE), itchy injection sites, the size of a 20p coin, lasting around 24 hours (mild AE) and sore around both injection sites, the size of a 20p coin, lasting around 24 hours (mild AE). ○ Subject 034002-002 reported hypercalciuria (mild AE). ○ Subject 044001-014 reported tertiary hyperparathyroidism (moderate AE). ○ Subject 031001-009 reported sometimes pain in the legs (mild AE). ○ Subject 032006-002 reported intermittent increased pain in legs 1 and a half week after each burosumab injection (mild AE). ○ Subject 034007-001 reported hyperparathyroidism (mild AE). ○ Subject 034007-003 reported hyperparathyroidism (mild AE).

	○ Subject 034007-004 reported hyperparathyroidism (mild AE). ○ Subject 033002-014 reported painful injection (severity not reported). ○ Subject 033005-001 reported nephrocalcinosis (moderate AE). ○ Subject 044028-006 reported fatigue (moderate AE).
Protocol deviations	There were 86 protocol deviations reported for subjects participating in the PASS and exposed to burosumab, cumulatively up to the data cut-off date: • Of the 86 total deviations, 53 were assessed as 'major' severity, meaning a deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects – 42 of the 53 were related to the informed consent forms (ICFs) and informed consent process, 9 were related to safety and 2 were related to study-related procedures criteria. • Of the 86 total deviations, 20 were assessed as 'critical' severity, meaning a deviation from protocol-related procedures that threatens integrity of data, adversely affects subjects and/or could invalidate acceptability of a project (or part of it): ○ Subject 044025-008 – On the 09-Apr-2021, it was noted by the monitor that the study coordinator (SC) had taken an informed consent form (ICF) from the subject and entered this subject into the electronic data capture (EDC) (providing XLH family history details – retrospective data), not realising that the SC was not on the delegation log to take an informed consent and to obtain medical/concomitant medication history. The principal investigator (PI) noted the error and informed the Contract Research Organization (CRO) site manager (SM) about this event by email on 09-Apr-2021. The SM of the CRO discussed the deviation with the PI and reminded the PI of the importance of following the informed consent process. Subject 044025-008 was reconsented to ICF (Version 2.0 dated 14-Jan-2019) on 20-May-2021. A comment was added to the new ICF and source data (SD) explaining that

	due to the issues identified a new ICF needed to be completed. The delegation and training logs were updated on 29-Apr-2021 following re-training of the SC on the ICF Management Process. o Subject 044025-002 - During an on-site monitoring visit on 14-Oct-2022, it was noted by the monitor that the parent of the subject had not initialled the boxes of the ICF at the time of consent. The monitor discussed the deviation with the PI and study nurse (SN) and requested that the parent of the subject should add the initials to the ICF at the next clinic visit. The monitor documented the deviation and re-trained the PI and SN on the ICF process. Subject reconsented to the ICF for PV4 on 20-Oct-2023. o Subject 044025-004 - During an on-site monitoring visit on 14-Oct-2022, it was noted by the monitor that the parent of the subject had not initialled the boxes of the ICF at the time of consent. The monitor discussed the deviation with the PI and SN and requested that the parent of the subject should add the initials to the ICF at the next clinic visit. The monitor documented the deviation and re-trained the PI and SN on the ICF process. The subject was reconsented to the ICF for PV4 on 03-Aug-2023. o Subject 034005-004 - On the 27-Mar-2020, it was noted by the monitor that the original ICF was missing from the site records. The PI was retrained on the ICF procedures on 15-Jul-2020. The subject was reconsented on 01-Sep-2020 and the source data was completed appropriately. A copy of the training log was collected and filed on 23-Dec-2020. A Quality Incident (RI#: 510920) was raised on 17-Apr-2020 and was completed on 31-Aug-2021. o Subject 044012-005 - On the 29-Jul-2021, during a review of the ICF (Version 2.0 dated 14-Jan-2019), the monitor noted that the parent of the subject did not sign the ICF due to an error in the formatting of the ICF. Also, the ICF was not printed on the site letter headed paper. The study team were informed of the error and re-trained on the completion of ICFs and the ICF process. The formatting of the template ICF (Version 2.0 dated 14-Jan-2019) was updated to confirm that the letter header is now present, and it is clear where the subject should sign. The study team were reminded to review the completed ICFs at the subject visit to confirm that no information is missing. The parent of the subject completed a new ICF at their next clinic visit on 24-Aug-2021.

	○ Subject 044026-006 – On the 25-May-2021, it was noted by the monitor that the parent of the subject had not signed the ICF (Version 2.0 dated 14-Jan-2019). The Monitor re-trained the PI on the ICF completion and collected a completed copy of the training log to document this process. The Monitor requested the PI to ask the parent to reconsent using a new ICF (Version 2.0 dated 14-Jan-2019) and ensure that all the data are correctly added to the ICF, and that a note to be added to the ICF to explain why a new ICF is being completed. Additionally, the monitor requested the study team to document this in the subject's medical records. Site confirmed that the actions were completed at patient visit on 08-Feb-2022. ○ Subject 044026-005 - On the 25-May-2021, it was noted by the monitor that the parent of the subject had not signed the ICF (Version 2.0 dated 14-Jan-2019) in error. The monitor re-trained the PI on the ICF completion and collected a completed copy of the training log to document this process. The monitor requested the PI to ask the parent to reconsent using a new ICF (Version 2.0 dated 14-Jan-2019) to ensure all the data are correctly added to the ICF, and that a note be added to the ICF to explain why a new ICF is being completed. Additionally, the monitor requested the study team to document this in the subject's medical records. Site confirmed that the actions were completed at the patient visit on 24-Mar-2022. ○ Subject 044026-004 - On the 25-May-2021, it was noted by the monitor that the parent of the subject had not signed the ICF (Version 2.0 dated 14-Jan-2019). The monitor re-trained the PI on the ICF completion and collected a completed copy of the training log to document this process. The monitor requested the PI to ask the parent to reconsent using a new ICF (Version 2.0 dated 14-Jan-2019) to ensure all the data is correctly added to the ICF, and that a note to be added to the ICF to explain why a new ICF is being completed. Additionally, the monitor requested the study team to document this in the subject's medical records. Site confirmed that the actions were completed at patient visit on 28-Oct-2021. ○ Subject 044005-005 - After the on-site monitoring visit on 26-Sep-2022 it was noted by the monitor that the ICF (Version 2.0 dated 14-Jan-2019) was available in the site file for the subject, signed on 16-Nov-2021. While

	completing the monitoring report, the monitor noted that an ICF (Version 2.0 dated 14-Jan-2019) had previously been reviewed that was signed on 12-Mar-2020 and was no longer available in the site file for review. The Monitor discussed the issue noted with the SN and PI. Upon review of the electronic medical records, the SN confirmed that the original ICF (dated 14-Jan-2019) had not been scanned and was not available. A file note was drafted to document that the ICF signed on 12-Mar-2020 was misplaced. The subject had already been reconsented using the ICF (Version 2.0 dated 14-Jan-2019) signed on 16-Nov-2021. The CRA provided re-training on ICF process to the study team on 26-Jan-2023 and this was documented on the study specific training log. o Subject 044005-007 - After the on-site monitoring visit on 26-Sep-2022, it was noted by the monitor that an adult ICF (Version 2.0 dated 14-Jan-2019) was available in the site file for the subject, signed on 24-Nov-2021. While completing the monitoring report, the monitor noted that an ICF (Version 2.0 dated 14-Jan-2019) had previously been reviewed that was signed on 12-Mar-2020 and was no longer available in the site file for review. The monitor discussed the issue noted with the SN and PI. Upon review of the electronic medical records, the SN confirmed that the original ICF (dated 14-Jan-2019) had not been scanned and was not available. A file note was drafted to document the ICF signed on 12-Mar-2020 as misplaced. The subject had already been reconsented using the ICF (Version 2.0 dated 14-Jan-2019) signed on 24-Nov-2021. The CRA provided re-training on ICF process to the study team on 26-Jan-2023 and this was documented on the study specific training log. o Subject 044025-009 – On the 12-Dec-2023, it was noted by the monitor that the parent of the subject did not add their initials on the parental ICF (Version 6.0 dated 24-Oct-2022) page 2 of 6 (first 10 statements) during reconsent on 24-Nov-2023. The monitor asked the PI and SC to make sure that the parent completes the ICF correctly during the next site visit, that the site staff add a comment on the original version of the ICF explaining the issue and that a new copy of the ICF is provided to the subject. The original ICF will be filed in the investigator site file. o Subject 039007-004 – On the 06-Apr-2023, it was noted by the monitor that the subject was hospitalised from 18-Dec-2020 to 22-Dec-2020 due to headache and flush. Due to a lack of oversight, PI did not report the SAE in the

	EDC within 1 day from acknowledgement. The monitor re-trained the PI on safety reporting procedures for subjects enrolled into the PASS sub-study, requested the PI to report the SAE to the Marketing Authorisation Holder, ethics committee, and regulatory authority as per the country requirements, and to enter the SAE into the EDC as per protocol. The site entered the SAE in the EDC on the 06-Apr-2023. o Subject 039016-014 – During the on-site monitoring visit on 11-Sep-2023, it was noted by the monitor that the site staff prefilled the subject name and date, and the subject signed in the impartial witness field on the site specific ICF adult Version 1.0 dated 11-Jan-2022 (based on country ICF adult Version 3.0 dated 06-Feb-2019). Additionally, page 16 of the ICF was not in the original (copy). In the investigator's field, the investigator's printed name and investigator's date were not written by the site staff, and it was not possible to determine who conducted the informed consent process as there was no description of the process in the source documents. The monitor discussed with the site that pre-filling of site staff was not allowed and only the delegated personnel conducting the ICF process were allowed to fill the investigator's details during the interview with the subject present. The monitor re-trained all site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain the original ICF from the subject and that the subject should also write a statement on the signature date stating that this is the correct date of signature. The monitor advised the site not to make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting. o Subject 039016-011 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that on the site specific ICF adult Version 4.0 dated 01-Mar-2022, the subject name and date were written by site staff (not personally dated by subject). The monitor re-trained all site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain a statement on signature date confirming that this is the correct date of signature. The monitor advised the site not to make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting.

	○ Subject 039016-011 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that site staff prefilled the subject name and date of signature of the main ICF site specific ICF adult Version 1.0 dated 11-Jan-2022 (based country ICF Adult Version 3.0 dated 06-Feb-2019). Additionally, the subject signed in the impartial witness field and site staff wrote an "x" in the ICF to indicate the signature location to the subject. The Monitor re-trained all site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to ask the subject to write, sign, and date a statement on signature date stating that this is the correct date of signature. The monitor advised the site not to make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting. ○ Subject 039016-013 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that the site staff prefilled the subject name, date, and the subject signed in impartial witness field on the site specific ICF adult Version 1.0 dated 11-Jan-2022 (based on country ICF Adult Version 3.0 dated 06-Feb-2019). Additionally, page 16 of the ICF was not an original (copy). In the investigator's field, the investigator's printed name and investigator's date were not written by site staff, and it was not possible to determine who conducted the informed consent process as there was no description of the process in source documents. The monitor discussed with the site that pre-filling of the site staff was not allowed and only the delegated personnel conducting the ICF process were allowed to fill the investigator's details during the interview with the subject present. The monitor re-trained all the site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain the original ICF from the subject and that the subject should also write a statement on the signature date stating that this is the correct date of the signature. The monitor advised the site not to make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting. ○ Subject 039016-006 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that the signature was copied, and the date was pre-compiled by site staff instead of the subject on the site specific ICF adult Version 1.0 dated 11-Jan-2022 (based on country ICF Adult Version 3.0 dated 06-Feb-2019). The original ICF version was

	not present at the site. The monitor re-trained all the site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain the original ICF from the subject and that the subject should also write a statement on the signature date stating that this is the correct date of the signature. o Subject 039016-012 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that the subject name and date were written by site staff (not personally dated by the subject) on the site specific ICF adult Version 4.0 dated 01-Mar-2022 . The monitor re-trained all the site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain a statement on the signature date confirming that this is the correct date of signature. The monitor advised the site to not make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting. o Subject 039016-012 – During the on-site monitoring visit on 11-Sep-2023, the monitor noted that on the site specific ICF adult Version 1.0 dated 11-Jan-2022 (based on country ICF Adult Version 3.0 dated 06-Feb-2019), the site staff prefilled the subject name and date, the subject signed in impartial witness field, and the site staff wrote an "x" in the ICF to indicate the subject where to sign. Additionally, in the investigator's field, the investigator's printed name and investigator's date were not written by the site staff, and it was not possible to determine who conducted the informed consent process as there was no description of the process in the source documents. The monitor re-trained all site staff on the ICF consenting and reconsenting procedures according to the ICH-GCP and requested the site to obtain a statement from the subject on the signature date, confirming that this is the correct date of signature. The monitor advised the site to not make any markings on the ICF's signature placeholders in order to comply with the ICH-GCP consenting process and discussed with the site that pre-filling of site staff was not allowed, and only the delegated personnel conducting the ICF process was allowed to fill the investigator's details during the interview with the subject present. o Subject 036001-003 – On the 16-Dec-2021, it was noted by the monitor that the subject's Country Minors 14-17 PIS_Hungary (HUN) Version 1.0 dated 07-Aug-2019 and Country Minors 14-17 Consent_HUN_Version 1.0

	dated 07-Aug-2019 had not been signed by the parent. However, the Parental PIS_HUN_Version 1.0 dated 26-Aug-2019 and Country Parental Consent_HUN_Version 1.0 dated 26-Aug-2019 were signed and completed correctly. The sub-investigator was re-trained on the correct ICF procedure on 16-Dec-2021 and this was noted on the training log as well.
Problems/ bottlenecks encountered	• Since the summer of 2021, most of the COVID-19 restrictions have been lifted in Europe, nevertheless, subjects only attend clinical sites when it is strictly necessary (clinical visits). Ethics approval of the XLH Registry Protocol Amendment 3 with the embedded PASS protocol (Version 4.0 dated 27-Oct-2021) and the associated additional consenting process has taken considerable time. There are about 100 adult subjects that still require additional consenting to participate in the PASS (UK, France, Italy and Germany). The option of remote consenting for the PASS has been proposed and some sites in the UK are using this process, however many sites prefer face-to-face clinic visits with their subject(s) to consent them. • Zero (0) pregnancies in female subjects treated with burosumab, currently measured via the AE page of the CRF, have been detected up to the data cut-off date. • To prospectively evaluate the frequency and severity of safety outcomes in subjects with mild to moderate CKD at baseline treated with burosumab, a middle study update of the electronic case report form (eCRF) to include the CKD variables was implemented on 26-Jul-2023. No subjects participating in the PASS study marked with CKD have been detected up to data cut-off date.
Planned interim/ final analysis report	Paediatrics: The first interim clinical study report (CSR) of study results was submitted ‘after 50 paediatric subjects on burosumab have achieved at least 6 months of time in the PASS’. This milestone was achieved on 28-Feb-2020, but due to the impact of the COVID-19

	pandemic, the analysis was delayed by 6 months to allow sites additional time to review their subjects and record the reported AEs appropriately. The first PASS interim CSR of paediatric results was submitted on 04-Oct-2021. The second PASS interim CSR of paediatric results is 'to be submitted 5 years after initiation of the PASS in the paediatric population'; this is now in progress, and it is estimated to be submitted in April 2024. The final CSR of paediatric results is to be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029). Adults: The first interim CSR of adult results is to be submitted after 50 adult subjects under burosumab have achieved at least 6 months of time in the PASS. It is estimated that this first interim CSR for adults will be submitted late 2024. The second interim CSR of adult results is to be submitted 5 years after initiation of the PASS in the adult population (estimated submission 2028). The final report of adult results is to be prepared 10 years from the start of data collection in the adult population (estimated submission 2033)

APPENDIX: END-OF-TEXT TABLES

Table 1.1.1: Subject Disposition by Age Group, Gender and Country (All Screened Subjects)

Table 2.1.1: Summary Overview of All Adverse Events by Age Group (Prospective) Safety Analysis Set