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 4.0
Date of last version of the progress report	06-Apr-2022
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 mineralization
Medicinal product	Invented name: Crysvita Pharmaceutical form and strength: 10, 20 and 30 mg/mL solution for injection in vials

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
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, hospitalizations, cardiovascular disease, cancer [all sites]), hypophosphataemia and its complications, ectopic mineralization, 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:** 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)

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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 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 1.28.1) are based on primary and secondary objectives of the PASS protocol (version 2), which includes as the study population those patients who are on burosumab (primary objectives) and those patients who are on alternative XLH treatments (secondary objective). While protocol version 2 includes adults in the study population and has been approved by PRAC, it is not yet implemented at all sites that participate in the post-authorization safety study (PASS). The PASS protocol version 2 is currently being submitted to the respective countries' ethics committees and individual participating hospital sites - approvals pending (expected June 2023) for Belgium, France, Ireland and Sweden. Additionally, adult subjects need to provide additional consent via the Informed Consent Form Version 4.0 dated 14-Feb-2022 to participate in the PASS. At the time of data cut-off, no adults have consented to PASS protocol V2 and minors participating to the PASS protocol V1 are being reconsented to Protocol V2. This report therefore includes only children and adolescents with an expanded sample size over previous years, with adults expected to qualify for inclusion from Q2 in 2023.
Approval date/s (approved by Committee for Medicinal Products for Human Use [CHMP])	13-DEC-2018
Study initiated (FPI)	24-APR-2019
Data cut-off date	17-FEB-2023

<table>
<tr><td>Country(-ies) of study</td><td>Planned: Belgium, Bulgaria, Czech Republic, Denmark, France, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, UK

Currently enrolling: Belgium, Czech Republic, Denmark, France, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, UK</td></tr>
<tr><td>Subject disposition</td><td>402 subjects enrolled as of 17-Feb-2023 (including 321 under burosumab (invented name Crysvita), alone or in combination with alternative XLH treatment). Because the reconsent of subjects enrolled under PASS protocol V1 at time of data cut-off is ongoing, the population considered for this report contains both subjects consented under PASS V1 and PASS V2. Differently from PASS protocol V1, subjects consented under PASS V2 will only be under burosumab treatment.

<table>
<tr><th></th><th>Belgium</th><th>Czech Republic</th><th>Denmark</th><th>France</th><th>Hungary</th><th>Ireland</th><th>Italy</th><th>Netherlands</th><th>Norway</th><th>Portugal</th><th>Slovenia</th><th>Spain</th><th>Sweden</th><th>United Kingdom</th><th>Totals</th></tr>
<tr><td>PASS</td><td>6</td><td>6</td><td>3</td><td>146</td><td>8</td><td>1</td><td>32</td><td>23</td><td>10</td><td>4</td><td>3</td><td>28</td><td>4</td><td>128</td><td>402</td></tr>
<tr><td>PASS under burosumab</td><td>2</td><td>5</td><td>1</td><td>108</td><td>6</td><td>1</td><td>16</td><td>20</td><td>9</td><td>4</td><td>3</td><td>19</td><td>3</td><td>124</td><td>321</td></tr>
</table>
PASS = post-authorization safety study

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 XLH Treatment, Gender and Country (All Screened Subjects).</td></tr>
<tr><td>Recruitment</td><td>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).</td></tr>
<tr><td>Adverse event (AE)</td><td>A summary overview of all adverse events (AEs) by age group and treatment for XLH (burosumab/Crysvita and alternative treatment) is provided in the end-of-text Table 1.28.1 Summary Overview of All Adverse Events by XLH Treatment and Age Group (Prospective) Safety Analysis Set.</td></tr>
</table>

	Cumulatively from the start of the PASS up to the cut-off date: • Of the total 402 subjects, there were 135 subjects (33.6%) with at least 1 AE reported. There was a total of 446 AEs reported for these subjects. No AEs lead to death in the study, however, AEs leading to XLH treatment withdrawal, were reported in 2 subjects (0.5%). In total, 11 subjects (2.7%) reported at least one severe AE in the study. • There were 10 subjects (2.5%) who collectively reported 15 serious adverse events [SAEs] (044001-006, 044001-014, 044009-010, 033002-010, 033006-001, 047001-003, 047001-004, 047001-005, 044026-009, and 044026-001). • A total of 7 SAEs reported in 5 subjects were severe in intensity, which include 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 one severe SAE was ongoing (of femur fracture of right side), with the remaining severe SAEs having recovered at the data cut-off date. • Of the 15 SAEs reported among 10 subjects, 13 (among 9 subjects) were assessed as 'not related' or 'unlikely related' to burosumab. One subject (033002-010) had a SAE of intracranial hypertension which was assessed by the Investigator as 'possibly related' to burosumab. The subject's burosumab dose was not altered following the event. Another subject (044001-014) reported with an SAE of tertiary hyperparathyroidism which was assessed by the Investigator as 'probably related' to burosumab. The subject's burosumab was interrupted following the event. The event of intracranial hypertension was considered as recovered and tertiary hyperparathyroidism was considered as ongoing at the data cut-off date. • Of the 15 reported SAEs, 12 SAEs (8 of the 10 subjects) had recovered and 3 SAEs (3 of the 10 subjects) were ongoing at the data cut-off date (including 1 subject with 2 SAEs, 1 recovered and 1 ongoing). Details are as follows: o Subject 044001-006 reported craniosynostosis and this event was assessed as 'not related' to burosumab.

	○ Subject 047001-004 reported right side femur fracture and this event was– assessed as 'unlikely related' to burosumab. ○ Subject 044001-014 reported tertiary hyperparathyroidism and this event was assessed as 'probably related' to burosumab. • There were 130 AEs among 72 subjects ongoing at the data cut-off date. • Out of the 72 subjects with ongoing AEs, 9 subjects (034005-003, 044016-006, 031001-001, 034002-002, 044001-014, 031001-009, 034007-001, 033002-014, 033005-001) had 12 AEs which were assessed by the Investigator as 'probably related' to burosumab. Among these 9 subjects, burosumab dose was altered following the event for 4 subjects (dose increased for 031001-001 and 031001-009, dose reduced for 034002-002, and dose interrupted for 044001-014). Among these same 9 subjects: ○ Subject 034005-003 reported kidney stone (mild AE). ○ 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 031001-001 reported more waddling gate (mild AE) and pain in the back (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 034007-001 reported hyperparathyroidism (mild AE).

	○ Subject 033002-014 reported painful injection.(severity not reported) ○ Subject 033005-001 reported nephrocalcinosis (moderate AE). • Of the total 81 subjects who were treated with alternative XLH treatment only, there were 17 (21%) with at least 1 AE reported. Of the 17 subjects with AE reported, 5 AE (6.2%) were assessed by the Investigator as "possibly/probably related" to XLH treatment.
Protocol deviation/s	There were 55 protocol deviations reported for subjects participating in the PASS, cumulatively up to the data cut-off date: • Of the 55 total deviations, 27 were assessed as 'major' severity meaning a deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects – 21 of the 27 were related to the informed consent forms (ICFs) and informed consent process, 3 were related to study-related procedures and criteria, and 3 were related to SAE criteria. • Of the 55 total deviations, 13 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 09-Apr-2021, it was noted by the Monitor that the study coordinator (SC) had taken an ICF from the subject and entered this subject into the electronic data capture (while providing XLH family history details - retrospective data), not realizing she was not on delegation log to take an informed consent and to obtain medical/concomitant medication history. Principal Investigator (PI) noted the error and informed the site manager (SM) about this event by email on 09-Apr-2021. SM discussed the deviation with PI and reminded the importance of following consent process. Subject will be reconsented to ICF (version 2.0 dated 14-Jan-2019) following incorrect consent process. PI to add comment to new ICF explaining that due to issues identified a new form needs to be completed. PI to ensure that Study Nurse (SN) is re-trained on correct ICF management following the

	deviation identified on 09-Apr-2021. Training to be recorded on study specific training log. A scan copy to be provided to SM. 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 initiated 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. 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 initiated the boxes of the ICF at the time of consent. The Monitor discussed the deviation with the PI and Research Nurse 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 Research Nurse on the ICF process. o Subject 034005-003 - On 27-Mar-2020, it was noted by the Monitor that the original signed ICF and subsequent reconsent were missing from site records. The correction item was to retrain the PI and the subject to be reconsented. o Subject 034005-004 - On 27-Mar-2020, it was noted by the Monitor that the original ICF was missing from site records. The correction item was to retrain the PI on ICFs. o Subject 044008-009 - On 09-Sep-2021, it was noted by the Monitor that the parent of the subject had not initiated the final 2 boxes of the ICF (version 2.0 dated 14-Jan-2019) in error. The Monitor reviewed the requirements of data to be added to the ICF with the site staff and they were reminded to review the ICF and make sure that all required data is added. The format of the ICF will be updated to make it clearer for the subjects where to sign. The parent of the subject will be asked to correct the ICF at the next visit.

	○ Subject 044008-008 - On 09-Sep-2021, it was noted by the Monitor that the parent of the subject had not initiated the final 2 boxes of the ICF (version 2.0 dated 14-Jan-2019) in error. The Monitor reminded the site staff to review and check the full ICF to confirm that all data have been entered into the ICF. ○ Subject 044012-005 - On 29-Jul-2021, during a review of the ICF (version 2.0 dated 14-Jan-2019), the Monitor noted the parent of subject did not sign the ICF due to an error in the formatting of the ICF. The ICF was also not printed on the site letter headed paper. Study team were informed of the error and re-trained on completion of ICFs and ICF process. Formatting of the template ICF (version 2.0 dated 14-Jan-2019) was updated to confirm that the letter header is present and that it is clear where the subject should sign. Study team were reminded to review completed ICFs at the subject visit to confirm that no information is missing. Parent of the subject will complete a new ICF at their next clinic visit, planned for 24-Aug-2021. ○ Subject 044026-006 – On 25-May-2021, it was noted by the Monitor that the parent of the subject did not add all required information to the signature section of the ICF (version 2.0 dated 14-Jan-2019). Name of child, name of parent, date, and relationship were all added to the ICF; however, the parent did not add their signature in error. The Monitor re-trained the PI on ICF completion and collected a copy of the training log to document this. The Monitor requested that PI ask the parent to reconsent using a new ICF (version 2.0 dated 14-Jan-2019) to ensure all data is 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 that the study team document this in the subject's medical records. ○ Subject 044026-005 - On 25-May-2021, it was noted by the Monitor that the parent of the subject did not add all required information to the signature section of the ICF (version 2.0 dated 14-Jan-2019). Name of child, name of parent, date, and relationship were all added to the ICF; however, the parent did not add their signature in error. The Monitor re-trained the PI on ICF completion and collected a copy of the training log to document this. The Monitor requested that PI ask the parent to reconsent using a new ICF (version 2.0 dated 14-Jan-2019) to ensure all

	data is 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 that the study team document this in the subject's medical records. o Subject 044026-004 - On 25-May-2021, it was noted by the Monitor that the parent of the subject did not add all required information to the signature section of the ICF (version 2.0 dated 14-Jan-2019). Name of child, name of parent, date, and relationship were all added to the ICF; however, the parent did not add their signature in error. The Monitor re-trained the PI on ICF completion and collected a copy of the training log to document this. The Monitor requested that PI ask the parent to reconsent using a new ICF (version 2.0 dated 14-Jan-2019) to ensure all data is 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 that the study team document this in the subject's medical records. o Subject 044005-005 - After the on-site monitoring visit on 26-Sep-2022 it was noted by the Monitor that ICF (version 2.0 dated 14-Jan-2019) was available in the Site File for 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 the ICF signed on 07-Jul-2020 was misplaced. The subject had already been reconsented using ICF (version 2.0 dated 14-Jan-2019) signed on 16-Nov-2021. The Monitor will provide re-training to the study team, and this will be 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 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 07-Jul-2020 was misplaced. The subject had already been reconsented using ICF (version 2.0 dated 14-Jan-2019) signed on 24-Nov-2021. The Monitor will provide re-training to the study team, and this will be documented on the study specific training log.
Problems/ bottlenecks encountered	• Since summer 2021, most of the COVID-19 restrictions have been lifted in the EU; nevertheless, subjects tend to go to clinical sites only when it is strictly necessary (clinical visits). Ethical approval of the XLH Registry Protocol Amendment 3 with embedded PASS (Version 4 dated 27-Oct-2021) protocol and the associated additional consenting process has taken considerable time. There are 129 adult subjects that still require additional consenting to participate in the PASS (UK, France, Italy, Spain, Norway and Germany). The option of remote consenting for the PASS has been proposed and some sites in the UK are using it, however many sites wanted to have a face-to-face visit with their subjects to consent them. • Considering that this report includes only children and adolescents, no pregnancies in female subjects treated with burosumab have been detected up to data cut-off date. • 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, on 11 January 2023 a middle study update of the electronic case report form (eCRF) to include the CKD variable was implemented. 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: First interim report of study results was submitted after 50 paediatric subjects under 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 interim report of study results was submitted on 04-Oct-2021. Second interim report of study results to be submitted 5 years after initiation of the PASS in paediatric populations (estimated submission 2024) Final report of study results to be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029). Adults: First interim report of study results to be submitted after 50 adult subjects under burosumab have achieved at least 6 months of time in the PASS. To date there are no adult subjects enrolled in the PASS It is estimated that the first interim report will be submitted in 2024, subject to adult subjects on burosumab treatment included in the registry consenting to participate in the PASS. Second interim report of study results to be submitted 5 years after initiation of the PASS in paediatric populations, i.e. a report covering use in all populations (estimated submission 2024)

APPENDIX: END-OF-TEXT TABLES

Table 1.1.1: Subject Disposition by XLH Treatment, Gender and Country (All Screened Subjects)

Table 1.28.1: Summary Overview of All Adverse Events by XLH Treatment and Age Group (Prospective) Safety Analysis Set