POST-AUTHORISATION SAFETY STUDY (PASS)

Annual Progress Report

STUDY OVERVIEW

Title	Non-interventional Post-Authorisation Safety Study of Burosumab in the Treatment of Children with X-linked Hypophosphataemia (XLH)
Version of the progress report	Version 3.0
Date of last version of the progress report	15 Oct 2020
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 paediatric subjects with XLH and radiographic evidence of bone disease who are aged 1 year of age and older and adolescents with growing skeletons, treated with burosumab, including but not limited to: 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 study using data from the 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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***Note:** The European Qualified Person for Pharmacovigilance for Kyowa Kirin has changed to Beatriz Mengotti, effective from 12 Aug 2021

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PASS PROGRESS INFORMATION

Protocol version and date	Version 1.0; 15-August-2018 (Sub-study to the parent XLH Registry Protocol-Version 3.0; 15-February-2019) **N.B.:** This annual progress 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. The PASS protocol version 2 is in process of being submitted to the respective countries ethics committees and individual participating hospital sites-approvals pending (expected June 2022).
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	18-FEB-2022
Country(-ies) of Study	**Planned:** EU countries, Norway, and United Kingdom **Currently enrolling:** Belgium, Czech Republic, France, Hungary, Ireland, Italy, Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, United Kingdom

Subject Disposition

359 subjects enrolled as of 18-February-2022

	Belgium	Czech Republic	France	Hungary	Italy	Ireland	Netherlands	Norway	Portugal	Slovenia	Spain	Sweden	United Kingdom	Totals
PASS	5	4	129	1	34	1	25	9	**3**	**3**	**25**	**4**	**116**	**359**
PASS under Burosumab	0	3	90	1	17	1	20	9	**3**	**3**	**16**	**3**	**111**	**277**

The overall subject disposition (till date) can be found in the End-of-text SAP Table 1.1.1 Subject Disposition by XLH Treatment, Gender and Country (All Screened Subjects)

Recruitment

Active, recruiting

Adverse event (AE)

Table from SAP, End-of-text **Error! Reference source not found.** provides the summary overview of All Adverse Events (AEs) by Age Group and treatment for XLH (Burosumab and alternative treatment)

Cumulatively from the start of the PASS up to the cut-off date (18-February-2022):

- There are 101 subjects with at least 1 adverse event reported. There are a total of 282 adverse events reported for these 101 subjects.
- There were 8 subjects who reported 10 Serious Adverse Events (033002-010, 033006-001, 044001-006, 044001-014, 044009-010, 047001-003, 047001-004, 047001-005). Of the 10 SAEs reported, 1 subject (033002-010) had 1 SAE [Intracranial pressure increased] which was assessed by the Investigator as 'possibly related' to burosumab. The subject's burosumab dose was not altered following the event.

	• Out of the 8 subjects, 7 subjects had recovered from the SAEs and 3 subjects (see below) SAEs were ongoing at the cut-off date. o Subject 044001-006 reported craniosynostosis [Craniosynostosis] – (Investigator assessed relatedness as 'not related' and Company assessed relatedness to 'not related' to burosumab) o Subject 033002-010 reported intracranial hypertension [Intracranial pressure increased] – (Investigator assessed relatedness as 'possibly related' and company assessed relatedness as 'related' to burosumab) o Subject 047001-004 reported right side femur fracture [Femur fracture] – (Investigator assessed relatedness as 'unlikely related' and Company assessed relatedness as 'not related' to burosumab) • There were 111 AEs ongoing at the cut-off date. • Out of the 50 subjects with ongoing AEs, 6 subjects (031001-009, 033001-011, 033005-001, 033006-005, 034007-001, 044016-006) had 9 AEs which were assessed by the Investigator as 'probably related' to burosumab. Only 1 subject's burosumab dose was altered following the event (031001-009, dose increased). o Subject 031001-009 reported pain in the legs [Pain in extremity] (mild AE) o Subject 033001-011 reported pruritus on the injection site [Injection site pruritus] (moderate AE) and cutaneous rash on the injection site [Injection site erythema] (mild AE) o Subject 033005-001 reported nephrocalcinosis [Nephrocalcinosis] (moderate AE) o Subject 033006-005 reported pain due to injection [Injection site pain] (mild AE) o Subject 034007-001 reported hyperparathyroidism [Hyperparathyroidism] (mild AE)

	○ Subject 044016-006 reported 1. localised reaction around both injection sites, the size of a 20p coin [Injection site reaction]; 2. itchy injection sites, the size of a 20p coin, lasted around 24 hours [Injection site pruritus]; and 3. Sore around both injection sites, the size of a 20p coin, lasted around 24 hours [Injection site pain] (mild AEs)
Protocol deviation/s	There were 46 protocol deviations reported for subjects participating in the PASS, cumulatively up to the cut-off date (18-February-2022): • Of the 46 deviations; 30 deviations were assessed as 'major' severity meaning a deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects – 27 deviations were related to the informed consent forms (ICFs) and study-related procedures, and 3 deviations were related to adverse event reporting. • Of the 46 deviations, 10 deviations 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 034005-003 – During an on-site monitoring visit on 27-Mar-2020 it was noted by the Monitor that the original signed informed consent form (ICF) and subsequent re-consent were missing from site records. This was corrected on 20-May-2020 where the subject was required to sign a new copy of the study informed consent form. ○ Subject 034005-004- During an on-site monitoring visit on 27-Mar-2020 it was noted by the Monitor that the original signed informed consent form (ICF)was missing from site records. This was corrected on 01-Sep-2020 where the subject was required to sign a new copy of the study informed consent form. ○ Subject 044009-017 - During a review of the ICF (Version 2.0 dated 14Jan2019) on 27-Nov-2020, the Monitor noted that the subject's parent had initialed all the relevant boxes and printed their name, however, they had not added their signature to the ICF in error. ○ Subject 044012-005 - During a review of the ICF (Version 2.0 dated 14Jan2019) on 29-Jul-2021, 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. Formatting of the template ICFs was updated to confirm that the letter header is present and that it is clear where the subject should sign. Study teams 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 on 23-Nov-2021. o Subject 044015-002 - Subject 044015-002 to be reconsented to ICF (Version 2.0 dated 14Jan2019) following incorrect completion of the consent form - the subject's parent did not add subjects name, print name and sign in the correct boxes. Subject's parent to complete ICF correctly ensuring correct boxes completed. Subject's parent to add comment to new ICF that they consented for their child to take part in the study when the original consent form was signed but due to issues identified a new form is to be completed. A comment should be added to the subject's medical record by the PI or delegate to document the same. Corrective actions completed on 18-Jun-2021. o Subject 044015-004 - Subject 044015-004 to be reconsented following incorrect completion of the ICF (Version 2.0 dated 14Jan2019) where the subject's parent did not sign the ICF. Subject to be reconsented and parent to sign a new copy of the ICF ensuring that it is completed properly. Parent to add comment to state that they consented for their child to take part in the study when the original ICF was signed but due to issues noted on the ICF they have reconsented. A comment is to be added to the subject's medical record to document the same. Corrective actions completed on 18-Jun-2021. o Subject 044015-011 - Parent of subject 044015-011 did not write their relationship to the subject and date on the ICF (Version 2.0 dated 14Jan2019). Relationship and date were added to ICF by PI instead of the subject's parent. Parent of subject 044015-011 to add comment to ICF to confirm relationship to subject. A note in the medical records should be made to document the issue and confirm it has now been rectified. On 4-Mar-21 it was confirmed that the ICF had been signed by PI and note added to ICF to document that the ICF was not signed at the time of the subject visit.

	○ Subject 044015-011 - Parent of subject had completed ICF version 1.0 31Jul2017 on 27-Feb-2019 however the ICF has not been signed off by the PI or delegate. At the time of consenting the new version of the ICF version 2.0 14Jan2019 was current. Therefore, the Subject did not sign the current version of the ICF. The PI and study coordinators were retrained on the informed consent process and correct ICF management. On 4-Mar-21 it was confirmed that the ICF had been signed by PI and note added to ICF to document that the ICF was not signed at the time of the patient visit. ○ Subject 044026-005 - Site are currently enrolling subjects remotely to avoid any impact of COVID-19 pandemic. Parent of subject 044026-005 did not complete the ICF (Version 2.0 dated 14Jan2019) correctly. Parent added all information to the ICF but did not add their signature as the signature box was missing from the bottom of the page due to a formatting error. Subject to be re-consented using a new copy of the ICF at their next clinic visit on 22-Oct-2021. ○ Subject 044026-006 - Site are currently enrolling subjects remotely to avoid any impact of COVID-19 pandemic. Parent of subject 044026-006 did not complete the ICF (Version 2.0 dated 14Jan2019) correctly. Parent added all information to the ICF but did not add their signature as the signature box was missing from the bottom of the page due to a formatting error. Subject to be re-consented using a new copy of the ICF at their next clinic visit on 23-Nov-2021.
Problems/ Bottlenecks encountered	**Bottlenecks:** Since 11th March 2020, the XLH Registry and the PASS have been impacted by the COVID-19 Pandemic restrictions: ▪ COVID-19 restrictions and staff redeployment to support the global vaccine effort may have prevented sites from entering data in the electronic case report forms in a timely manner. ▪ Subject contact during COVID-19 may have been limited which may have impacted soliciting AEs.

	COVID-19 may have prevented sites from reporting safety events in a timely fashion (e.g., serious adverse events (SAEs) should be reported within 24 hours of becoming aware). This may result in an increased number of Protocol Deviations. This may also contribute to an increase in missing data on safety events due to limited contact with subjects because of local restrictions. • The re-consenting process for the subjects who were initially enrolled into the XLH Registry in a participating country where burosumab is available (UK, France, Italy, Sweden) has taken considerable time and 10 subjects still require having this re-consent in place to allow participation in the PASS. The option of remote re-consenting has been proposed, however many sites wanted to have a face-to-face visit with their subjects to re-consent them. COVID-19 restrictions have limited these face-face visits.
Planned interim/ final Analysis report	First interim report of study results to be submitted after 50 paediatric subjects under burosumab have achieved at least 6 months of time in the PASS. This milestone was achieved on 28-February-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 4-October-2021.Second interim report of study results to be submitted 5 years after initiation of the PASS in paediatric populations Final report of study results to be prepared 10 years from the start of data collection in the paediatric population (estimated submission 2029)

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