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 6.0
Date of last version of the progress report	22 April 2024
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 Immunoglobulin G1 (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 mg/0.33mL, 20 mg/0.67mL and 30 mg/mL solution in prefilled syringe
Product reference	EU/1/17/1262/001 EU/1/17/1262/002 } 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).

	EU/1/17/1262/003 EU/1/17/1262/004 EU/1/17/1262/005 EU/1/17/1262/006 } prefilled syringes
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, treated with burosumab for X-linked Hypophosphataemia (XLH), including but not limited to: long-term safety (as evidenced by death, hospitalisations, cardiovascular disease (CVD), 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 (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 (MAH)

MARKETING AUTHORISATION HOLDER(S)

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PASS PROGRESS INFORMATION

Protocol version and date	Version 2.0; 12 January 2021 (Sub-study to the parent XLH Registry Protocol Version 4.0; 27 October 2021) **N.B.:** This annual progress report is based on Version 2.0 of the post-authorisation safety study (PASS) protocol dated 12 January 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 2.0), in which the study population comprises of patients who are on burosumab. Patients who are on alternative XLH treatments only (not exposed to burosumab) are assessed for the secondary objective of the PASS and are not included in this progress report. Protocol Version 2.0 is approved in all countries participating to the study but one: Ireland, where approval is pending for 1 site. Adult subjects need to provide additional consent via local versions of the master Informed Consent Form Version 4.0 dated 14 February 2022 to participate in the PASS. At the time of data cut-off, 149 adults, 375 children, and 136 adolescents have consented to PASS protocol Version 2.0. 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 December 2018
Study initiated (FPI)	24 April 2019
Data cut-off date	18 February 2025
Country(-ies) of study	**Planned:** Belgium, Bulgaria, Czech Republic, Germany, Denmark, France, Hungary, Ireland, Italy, Latvia, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom (UK).

Currently enrolling: Belgium, Bulgaria, Czech Republic, Denmark, France, Hungary, Italy, Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, UK.

Subject disposition

A total of 660 subjects were included in the safety analysis set (SAF) as of 18 February 2025. Since the process of reconsenting the subjects who were initially enrolled under PASS protocol Version 1.0 is still ongoing, the population considered for this report comprises of subjects consented under PASS Version 1.0 and PASS Version 2.0. Subjects consented under PASS Version 2.0 will include only subjects who have been treated at least once with burosumab with or without other XLH treatment either concomitantly, before and/or after other XLH treatments (SAF). Patients who have received only other XLH treatments during the study period are included in the cohort safety analysis set (CSAF). It is to be noted that this report considers only subjects treated at least once with burosumab during the study period (SAF), either under PASS protocol Version 1.0 or under PASS protocol Version 2.0.

	Belgium	Bulgaria	Czech Republic	Denmark	France	Hungary	Ireland	Italy	Netherlands	Norway	Portugal	Slovakia	Slovenia	Spain	Sweden	United Kingdom	Latvia	Total
PASS	14	14	5	5	217	15	9	85	29	16	5	4	3	42	12	181	4	660

PASS = post-authorisation safety study

Note that, because confirmation of signed consent of informed consent form (ICF) for Protocol Version 3.0 or Protocol Version 4.0 to participate in the PASS is a requirement for being included in the SAF, subjects who are participating in the PASS can be excluded from the SAF if they are missing a record of which ICF version was signed. This could result in some subjects who are participating in the PASS having a flag for PASS participation in the electronic data capture (EDC) system but being excluded from the SAF and the current annual progress safety report.

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	This PASS is a 10-year, non-interventional, prospective, observational cohort study using data collected in the International XLH Registry (non-EU countries, i.e., Switzerland and Israel, do not participate in the PASS) that collects data on subjects with XLH. For the XLH Registry, enrolment of new subjects was closed on 10 February 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 the XLH Registry to receive burosumab (Belgium and Switzerland for the XLH Registry and Belgium for the PASS). Additionally, for the XLH Registry, secondary data from subjects enrolled in Germany (investigator-initiated study) and in the Netherlands (ORPHOS-NED project) can still be added to the Registry. These subjects do not participate in the PASS.
Adverse event (AE)	An 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. As a note, assessments of events (including causality, seriousness, severity, etc.) reported in this annual progress report are based on investigator assessment, unless otherwise stated. Cumulatively from the start of the PASS up to the cut-off date: • Of the 660 subjects considered in this report, a total of 1441 AEs were reported in 371 subjects (56.2%) who reported at least 1 AE. Adverse events (AEs) led to death in 1 subject (0.2%) (039015-013) and AEs leading to XLH treatment withdrawal were reported in 3 subjects (0.5%) (033002-032, 033004-009, 044009-003). In total, 31 subjects (4.7%) (033001-018, 033001-020, 033002-010, 033002-011, 033002-038, 033002-040, 033003-001, 033003-019, 033004-036, 033005-008, 033006-002, 033010-004, 034009-003, 039003-007, 039006-008, 039015-013, 044003-004, 044003-005, 044003-008, 044009-004, 044009-007, 044009-010, 044009-014, 044009-016, 044013-003, 044015-001, 044028-002, 047001-003, 047001-004, 047001-005, 047001-007) reported at least one severe AE in the study and 3 subjects (0.5%) (033002-010, 033005-008, 044003-005) reported at least one severe event possibly related to burosumab. • A total of 39 serious adverse events (SAEs) were reported in 32 subjects (4.8%) (031001-025, 033002-010, 033002-049, 033002-115, 033003-018, 033005-002, 033005-006, 033005-008, 033006-001, 033006-002, 033010-004, 039003-007, 039006-008, 039007-004, 039012-001, 039013-007, 039015-013, 044001-006, 044001-014, 044009-010, 044015-001,

	044017-002, 044017-018, 044026-001, 044026-007, 044026-009, 044028-001, 047001-003, 047001-004, 047001-005, 047001-007, 047002-004). • A total of 14 SAEs reported in 11 subjects were severe in intensity. The details are as follows: o Subject 033002-010 reported a severe SAE of Intercranial hypertension. This event was assessed as "possibly related" to burosumab treatment and was considered as recovered during data cut-off. o Subject 033005-008 reported a severe SAE of Nephrocalcinosis. This event was assessed as "possibly related" to burosumab treatment and was continuing during data cut-off. Dose reduction of burosumab was recommended. o Subject 044009-010 reported 2 severe SAEs: Foramen magnum decompression for Chiari malformation which was assessed as "unlikely related" to burosumab treatment and was considered as recovered during data cut-off; Knee problems, requiring hospital admission which was assessed as "not related" to burosumab treatment and was considered as recovered during data cut-off. o Subject 047001-003 reported 2 severe SAEs: Drug intoxication which was assessed as "unlikely related" to burosumab treatment and was considered as recovered during data cut-off; Suicide attempt which was assessed as "not related" to burosumab treatment and was considered as recovered during data cut-off; however, burosumab treatment was interrupted. o Subject 047001-004 reported a severe SAE of Right-side femur fracture. This event was assessed as "unlikely related" to burosumab treatment and was continuing during data cut-off and dose change was not recommended. o Subject 047001-005 reported a severe SAE of Infection in surgical wound, left leg. This event was assessed as "unlikely related" to burosumab treatment and was considered as recovered during data cut-off and dose change was not recommended. o Subject 039003-007 reported severe SAE of Intercranial hypertension twice. The event was first reported to have started on 10 January 2024 and second time the event start date was reported as 03 February 2024. Both

	events were assessed as "not related" to burosumab treatment and were considered as recovered during data cut-off, dose change was not recommended. o Subject 039006-008 reported a severe SAE of Arthrosis-like changes in both feet due to tibial varus. This event was assessed as "not related" to burosumab treatment and was continuing during data cut-off, dose change was not recommended. o Subject 044015-001 reported a severe SAE of Left uncemented total hip replacement. This event was assessed as "not related" to burosumab treatment and was considered as recovered during data cut-off, dose change was not recommended. o Subject 047001-007 reported a severe SAE of Removal of osteosynthesis left femur (elective surgery, hospitalisation). This event was assessed as "not related" to burosumab treatment and was considered as recovered during data cut-off, dose change was not recommended. o One severe SAE resulted in death (039015-013) (AE term: Unknown event resulting in death); however, this event was unlikely to be related to burosumab treatment, dose change was not recommended. • Of the 39 SAEs reported in 32 subjects, 29 SAEs (reported in 23 subjects) were assessed as "not related" or "unlikely related" to burosumab. The relationship to XLH treatment was not reported for 6 SAEs. • A total of 4 SAEs reported among 4 subjects were probably or possibly related to burosumab and the details are as follows: o Subject 033005-002 reported Mild nephrocalcinosis Grade I which was mild in severity. This event was assessed as "possibly related" to burosumab and was continuing during data cut-off. No change in burosumab treatment was recommended. o Subject 033005-008 reported Nephrocalcinosis which was characterised as severe. This event was assessed as "possibly related" to burosumab and was continuing during data cut-off. Dose reduction in burosumab treatment was recommended.

	○ Subject 044001-014 reported Tertiary hyperparathyroidism which was moderate in severity. This event was assessed as "probably related" to burosumab and was continuing during data cut-off, and drug interruption was recommended. ○ Subject 033002-010 reported Intracranial hypertension which was characterised as severe. This event was assessed as "possibly related" to burosumab and was recovered at data cut-off (SAE start date: 25 September 2020, SAE end date:2022-05-UNK). No changes in burosumab treatment was recommended. • Of the 39 SAEs, 30 SAEs (reported in 25 of the 32 subjects) had recovered, and 6 SAEs (reported in 6 of the 32 subjects) were continuing at the data cut-off date (including 1 subject with 2 SAEs). Details of ongoing SAEs are as follows: ○ Subject 044001-014 reported Tertiary hyperparathyroidism which was moderate in severity and this event was assessed as "probably related" to burosumab. Burosumab treatment was interrupted for this subject. ○ Subject 033005-002 reported Mild nephrocalcinosis Grade I which was mild in severity and this event was assessed as "possibly related" to burosumab. No dose change was recommended for this subject. ○ Subject 033005-008 reported Nephrocalcinosis which was categorised as severe, and this event was assessed as "possibly related" to burosumab. Dose reduction was recommended for this subject. ○ Subject 044001-006 reported Craniosynostosis and this event was assessed as "not related" to burosumab. ○ Subject 039006-008 reported Arthrosis-like changes in both feet due to tibial varus 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. • There were 499 ongoing AEs reported in 232 subjects at the data cut-off date.

	○ Out of the 232 subjects with ongoing AEs, 8 subjects (031001-009, 032006-002, 033003-001, 033005-001, 044001-014, 044015-001, 044016-006, 044028-006) had 10 AEs which were assessed as "probably related" to burosumab. • Among these 8 subjects: ○ Subject 031001-009 reported Pain in the legs (mild AE) and was recommended an increase in burosumab dose. Pain was reported after osteotomy on January 2020, and it was continuing at data cut-off time. ○ Subject 032006-002 reported Intermittent increased pain in legs one week and a half after each burosumab injection (mild AE). No burosumab dose change was recommended. ○ Subject 033003-001 reported Lower limbs pain (severity not reported). No burosumab dose change was recommended. ○ Subject 033005-001 reported Nephrocalcinosis (moderate AE). This event was assessed as "probably related" to burosumab treatment; however, no burosumab dose change was recommended. ○ Subject 044001-014 reported Tertiary hyperparathyroidism (moderate AE) and treatment with burosumab was interrupted. ○ Subject 044015-001 reported Restless leg syndrome (mild AE). No burosumab dose change was recommended. ○ 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). No burosumab dose change was recommended. ○ Subject 044028-006 reported Fatigue (moderate AE). No burosumab dose change was recommended. • One subject (044002-006), a 58-year-old male from the UK, reported having history of mild renal impairment (unknown glomerular filtration rate [GFR] status categorised as CKD) at baseline. At the time of data cut-off, the event was ongoing.

	• One subject (044017-002), a 32-year-old female from the UK, reported an event of Pregnancy (AE start date: November 2021 - AE end date: 05 October 2022). The subject was receiving the XLH treatment Calcitriol during the event and no dose change of Calcitriol was recommended. The subject started receiving burosumab on 08 November 2021 and stopped the treatment in January 2022 because of the pregnancy.
Protocol deviations	There were 228 protocol deviations reported for 145 subjects participating in the PASS and exposed to burosumab, cumulatively up to the data cut-off date: • Of the 228 protocol deviations, 68 were assessed as 'critical' in terms of severity (a deviation from protocol-related procedures that threatens the integrity of data, adversely affects subjects and/or could invalidate acceptability of a project (or part of it)). Of these 68 critical protocol deviations, 50 were considered as important. Forty-nine of these 50 protocol deviations were related to 'Informed Consent and Process'. o The remaining one deviation (Patient ID: 039007-004) was related to 'safety'. The deviation was described as follows: Subject was hospitalised from 18 December 2020 to 22 December 2020 due to Headache and Flush; however, due to an oversight, Principal Investigator (PI) did not report the SAE in EDC within 1 day from acknowledgement. As a corrective action the Clinical Research Associate (CRA) retrained PI on safety reporting procedures for patients enrolled into the PASS sub-study, the PI was requested to report the SAE to MAH, Ethics Committee (EC), and Regulatory Authority (RA) as per country requirements, and to enter the SAE into the EDC as per protocol. • Of the 228 total deviations, 133 were assessed as 'major' severity (a deviation from protocol-related procedures that could affect the integrity of the data or adversely affect subjects). Of these 133 major protocol deviations, 75 were considered as important. Sixty-seven of these 75 protocol deviations were related to the 'Informed Consent and Process' and 8 were related to 'safety'. • The 8 safety related protocol deviations are as follows: o Subject 039007-004 experienced an AE "Urticaria in the site of burosumab injection"; however, due to an oversight, PI did not report the event in EDC within the protocol mandated timeline of 4 days. As a corrective

	action site manager (SM) retrained the PI on AE management and supported the PI with the case report form (CRF) data entry. o Subject 039006-008 experienced a SAE (Arthrosis-like changes in both feet due to tibial varus) but was not reported within 24 hours of site's awareness as per protocol. As a corrective action SM retrained sub-Investigator (Sub-I) on SAE management and supported the Sub-I with the CRF data entry and Kyowa Kirin International (KKI) safety reporting. o Subject 039013-001 experienced 6 non-serious AEs including COVID infection, Hip joint pain, Knee joint pain, Tooth abscess, Devitalised molar, and Vertigo. Due to lack of dedicated personnel for completion of data entry in CRF at site, the timelines for reporting these above mentioned non-serious AEs (within 4 business days) was missed. On 20 December 2023, the PI appointed a new Study Coordinator (SC) who was responsible for data entry. Once SC noticed the missed AEs, she reported them immediately in the CRF under AE tab. As a corrective action SM retrained the PI on safety reporting requirements for the study. o Subject 039013-002 experienced 4 non-serious AEs including Joint bone pain, Joint bone pain, Vitamin D decrease, and COVID infection. Due to lack of dedicated personnel for completion of data entry in CRF at site, the timelines for reporting these above mentioned non-serious AEs (within 4 business days) was missed. As a corrective action, on 20 December 2023, the PI appointed a new SC who was responsible for data entry. Once SC noticed the missed AEs, she reported them immediately in the CRF under AE tab. As a corrective action SM retrained the PI on safety reporting requirements for the study. o Subject 039013-004 experienced several AEs and due to lack of dedicated personnel appointed by PI for completion of data entry in the CRF, the AEs were not reported in the CRF. On 20 December 2023, PI appointed a new SC who was responsible for data entry. Once SC noticed the missed AEs, she reported them immediately in the CRF under the AE tab. As a corrective action SM retrained the PI on safety reporting requirements for the study. o Subject 039013-006 experienced 2 non-serious AEs including Dysmenorrhoea and Anaemia. Due to lack of personnel dedicated to the completion of data entry in CRF at site, the timelines for reporting these 2 non-serious

	AEs (within 4 business days) were missed. On 20 December 2023, PI appointed a new SC who was responsible for data entry. Once she noticed the missed AEs, she reported them immediately in the CRF under AE tab. As a corrective action SM retrained the PI on safety reporting requirements and PI's responsibilities related to the study. o Subject 044014-001 had an SAE of Vomiting but was not entered in the EDC. This SAE was entered into the EDC during the Data Abstraction Visit by the Data Abstractor. The PI was asked to review the SAE, assign causality and severity, review the event and enter the data into EDC. As a corrective action, to prevent AEs from not being entered into the EDC within the protocol specified timelines again, training for all delegated members of the team was provided and the training was documented on the training logs. o Subject 039012-001 had an SAE "Acute appendicitis" on 25 July 2022 but was not reported in the EDC by Sub-I within 24 hours of awareness. As a corrective action, CRA retrained the study staff and supported the Sub-I to document the SAE in the EDC.
Problems/ bottlenecks encountered	• Ethics approval of the XLH Registry Protocol Amendment 3 with the embedded PASS protocol (Version 4.0 dated 27 October 2021) and the associated additional consenting process has taken considerable time. There are about 200 adult subjects that still require additional consenting to participate in the PASS. Remote consenting for the PASS has been proposed and while some sites in the UK have adopted this process, many sites still prefer in-person clinic visits to obtain consent from their subjects. • Pregnancies are currently captured in the EDC in the AE page of the CRF. To better identify a pregnancy, a specific pregnancy form will be developed during the next update of the EDC. One pregnancy in a female subject treated with burosumab has been detected up to the 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 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 CSR of paediatric results was submitted on 26 October 2021. The second interim CSR of paediatric results was submitted on 23 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 results in adult population was submitted on 29 January 2025, after 50 adult subjects on burosumab had achieved at least 6 months of time in the PASS. 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

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).