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Committee for Orphan Medicinal Products

# Orphan Maintenance Assessment Report

Crysvita (burosumab)
Treatment of phosphaturic mesenchymal tumour
EU/3/18/2011
Sponsor: Kyowa Kirin Holdings B.V.

**Note**

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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# Table of contents

# 1. Product and administrative information

| **Product** | |
|---|---|
| Designated active substance(s) | Burosumab |
| Other name(s) | - |
| International Non-Proprietary Name | Burosumab |
| Tradename | Crysvita |
| Orphan condition | Treatment of phosphaturic mesenchymal tumour |
| Sponsor's details: | Kyowa Kirin Holdings B.V.<br>Bloemlaan 2<br>2132 NP Hoofddorp<br>Noord-Holland<br>Netherlands |
| **Orphan medicinal product designation procedural history** | |
| Sponsor/applicant | Ultragenyx Germany GmbH |
| COMP opinion | 15 March 2018 |
| EC decision | 16 April 2018 |
| EC registration number | EU/3/18/2011 |
| **Post-designation procedural history** | |
| Transfer of sponsorship | From Ultragenyx Germany GmbH to Kyowa Kirin Holdings B.V. – EC decision of 12 February 2019 |
| COMP opinion on review of orphan designation at the time of marketing authorisation | 15 January 2018 |
| **Marketing authorisation type II variation procedural history** | |
| Rapporteur / Co-rapporteur | Kristina Dunder/ Jayne Crowe |
| Applicant | Kyowa Kirin Holdings B.V. |
| Application submission | 17 December 2020 |
| Procedure start | 23 January 2021 |
| Procedure number | EMA/H/C/004275/II/0023 |
| Invented name | Crysvita |
| Proposed therapeutic indication | Extension of indication to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over, based on data from two ongoing open-label clinical studies, UX023T-CL201 and KRN23-002, in adults with TIO (144-week data and 88-week data are available, respectively)<br><br>Further information on Crysvita can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/en/medicines/human/EPAR/crysvita |
| CHMP opinion | 23 June 2022 |

| COMP review of orphan medicinal product designation procedural history | |
|---|---|
| COMP rapporteur(s) | Bozenna Dembowska-Baginska / Elisabeth Johanne Rook |
| Sponsor's report submission | 19 February 2021 |
| COMP discussion | 14-16 June 2022 |
| COMP opinion (adoption via written procedure) | 24 June 2022 |

# 2. Grounds for the COMP opinion

## *2.1. Orphan medicinal product designation*

The COMP opinion that was the basis for the initial orphan medicinal product in designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing burosumab was considered justified based on preliminary clinical data demonstrating that treatment increased serum phosphorus leading to improvements in fatigue and pain in patients affected by tumour-induced osteomalacia associated with the condition;
- the condition is chronically debilitating due to severe osteomalacia and low bone density leading to severe symptoms of musculoskeletal pain, fractures, muscle weakness, fatigue, and difficulty with ambulation. In rare cases tumours can be malignant that may metastasise and cause death;
- the condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing burosumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data to support significant benefit. Patients were affected by the condition and had tumour-induced osteomalacia that was not curable by surgical resection and was inadequately managed by the currently authorised products for rickets and osteomalacia. Treatment with the product increased serum phosphorus leading to improvements in fatigue and pain. The Committee considered that this constitutes a clinically relevant advantage for patients affected by tumour-induced osteomalacia associated with the condition.

# 3. Review of criteria for orphan designation at the time of type II variation

## Article 3(1)(a) of Regulation (EC) No 141/2000

***Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made***

**Condition**

Phosphaturic mesenchymal tumours (PMT), also described in the literature as phosphaturic mesenchymal tumour of mixed connective tissue type (PMTMCT), are a mesenchymal tumour distinguished by a distinctive morphology. This is the only orphan designation for the condition.

Most phosphaturic mesenchymal tumours present as nonspecific soft tissue or bone masses, often with a component of fat. Some may be highly calcified.

PMTs are fundamentally composed of a hypocellular proliferation of bland neoplastic spindled cells growing in a highly vascular, hyalinized, partially calcified basophilic matrix. Individual PMT, however, show significant differences in cellularity, vascularity, and matrix composition, and thus, the morphological spectrum of PMT is broad, undoubtedly accounting for historical confusion of PMT with other mesenchymal tumour types.

PMTs may occur in any soft tissue or bone location. In soft tissues, PMTs often involve the extremities and acral sites, whereas bone tumours commonly involve the appendicular skeleton, cranial bones, and paranasal sinuses. They are extremely rare in the retroperitoneum, viscera and mediastinum.

The vast majority of PMTs are benign mesenchymal neoplasms and not considered sarcomas. A few cases of malignant tumours have been reported, which are considered sarcomas. Malignant tumours may metastasise and cause death from disease.

Expression of FGF23 protein has been documented in some tumours. FGF23 is a phosphaturic hormone that inhibits renal proximal tubule phosphate re-uptake. Elevated serum levels of FGF23 can be demonstrated in patients with phosphaturic mesenchymal tumour associated (TIO).

The World Health Organization in the 2013 Classification of Tumours of Soft Tissue and Bone define PMT as "morphologically distinctive neoplasms that produce tumour-inducted osteomalacia (TIO) in most affected patients, usually through production of fibroblast growth factor 23 (FGF23)". Historically, it was felt that any mesenchymal tumour type could occasionally cause TIO. However, over time it was recognised that most TIO-associated tumours represented examples of this single histopathologic entity also recognised since 2013 by the WHO. The literature also describes soft tissue and bone tumours showing morphological features of PMT with demonstrable expression of FGF23 but without known TIO. Such tumours have been referred to by some as the "non-phosphaturic" variant of PMT. Also, there are PMT with known TIO, which are FGF23-negative, reflecting production of other phosphaturic hormones.

The approved therapeutic indication "*CRYSVITA is indicated for the treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised in patients aged 1 year and over*" falls within the scope of the designated orphan condition "Treatment of phosphaturic mesenchymal tumour".

**Intention to diagnose, prevent or treat**

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

**Chronically debilitating and/or life-threatening nature**

The sponsor discusses PMT to be chronically debilitating due to very severe osteomalacia (often extremely low bone density) and severe symptoms of musculoskeletal pain, fractures, muscle weakness, fatigue, and difficulty with ambulation. This profoundly impacts the affected individual's day-to-day functioning and quality of life. In adults, due to the latency of diagnosis, PMTs typically present with severe progressive fatigue, profound muscle weakness, and bone pain caused by severe osteomalacia/rickets that leads to fractures of the long bones, vertebra, and ribs.

Tumour-inducted osteomalacia (TIO) is a major clinical manifestation of PMT. TIO is characterized by high FGF23 levels caused by the PMT that results in hypophosphatemia due to renal phosphate wasting and low or inappropriately normal 1,25-dihydroxy vitamin D levels. In children, in whom TIO (major clinical manifestation of PMT) is rarer than in adults, the condition may present with generalized osteopenia, rickets, pseudo fractures, bowing of the extremities, gait abnormalities, growth retardation, and pain in the bones, joints, and muscles.

The sponsor does not discuss the condition to be life-threatening. Nevertheless, it can be found in the literature that malignant tumours may metastasise and cause death from the disease.

The sponsor has provided an adequate discussion on the morbidity of the condition. The COMP deems the condition to be chronically debilitating due to severe osteomalacia and low bone density leading to severe symptoms of musculoskeletal pain, fractures, muscle weakness, fatigue, and difficulty with ambulation. In rare cases tumours can be malignant that may metastasise and cause death

**Number of people affected or at risk**

The sponsor has assumed that most cases of PMT will have tumour-inducted osteomalacia (TIO). This assumption is used as the basis for the prevalence estimate for the maintenance report. Those patients with PMT that don't present with TIO have not been considered as it is assumed that they will not make a significant difference to the overall prevalence estimate.

The sponsor provided the result obtained from a Danish Registry where the epidemiological results of a survey for the incidence and prevalence of TIO are reported. (*Abrahamsen B et al, Calcified Tissue International, published on line 5 April 2021*). The incidence is 0.13 in 100,000 and the prevalence is reported to be 0.09 in 100,000.

A literature search has also been conducted. The sponsor notes that in Florenzano et al 2020 just over 1000 cases have been reported worldwide of which 10% are in Europe.

Using the 111 total reported EU cases from 2006-2020 and an EU Community population estimated at 513,471,676 (Eurostat 2019), the prevalence of TIO is approximately 0.0022 per 10,000 individuals (i.e., [111 cases ÷ 513,471,676] x 10,000). The sponsor thinks that these numbers are likely to underestimate prevalence, since some cases may go unreported and unpublished, although this calculation also assumes that all patients reported during the period 2006-2017 were still alive at the end of the reporting period.

Results from the observational, open cohort epidemiology study carried out in Denmark estimate the prevalence of TIO to be no more than 0.70 per 100,000 persons for the total population and 0.26 per 100,000 persons in adults.

The COMP accepted the Danish estimate of 0.07 in 10,000 for the purpose of Maintenance of the Orphan Designation.

## Article 3(1)(b) of Regulation (EC) No 141/2000

***Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.***

**Existing methods**

There are currently no products authorised specifically for PMT. Conventional chemotherapeutics that are authorised for the treatment of soft tissue sarcoma, are also considered to be authorised for PMT.

The current best standard of care for PMT includes surgery when the PMT is limited and localised. Surgery with wide margins can be performed, which usually cures PMT. After tumour removal, bone healing starts immediately, and most patients experience symptomatic improvement within days to weeks. Within 72 hours phosphate homeostasis normalises, though it can take many months for resolution of osteomalacia. Hence, curative surgery is a satisfactory method.

The proposed treatment for designation is not considered to be disease modifying but treat TIO as a major manifestation. The conventional therapy regimen is the same as that used for treatment of X-linked hypophosphatemia. Experts recommend multiple high daily doses of supplemental oral phosphate and/or active vitamin D therapy (e.g., calcitrol or alfacalcidiol) that are individualized to each patient. If the causative tumour/lesion is subsequently found and successfully resected, drug therapy can be discontinued. Calcium supplementation may also be added at the beginning of conventional therapy to aid in bone healing.

No treatments are specifically authorised for the treatment of TIO, nevertheless symptomatic treatments that are authorised and indicated for hypophosphatemia vitamin D resistant rickets (also referred to as hypophosphatemia rickets), rickets and osteomalacia are available including active forms of Vitamin D (alfacalcidol and calcitrol) and phosphate.

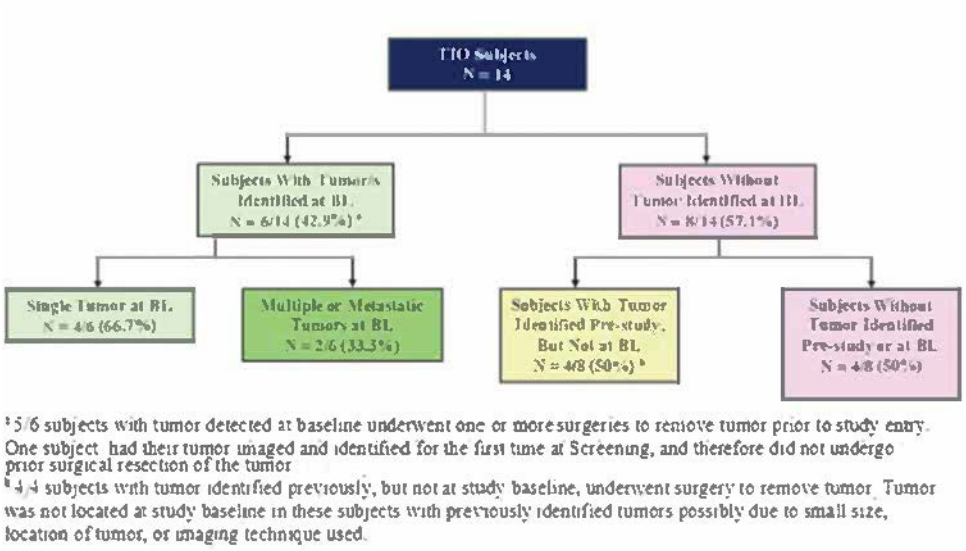
**Significant benefit**

The sponsor believes that their product could offer significant benefit in patients in unresectable PMTs or who have had an inadequate response to surgery. The sponsor did not come for protocol assistance regarding significant benefit.

Two trials were used to support significant benefit.

1. Study UX023T-CT201. This was an open-label, multicentre, Phase II study designed to assess the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of burosumab in adult subjects with TIO or epidermal naevus syndrome (ENS) associated osteomalacia based on evidence of excessive FGF23 that is not amendable to cure by surgical excision of the tumour/lesion. This was a 48-week treatment period followed by a treatment extension period of up to 300weeks. All subjects received SC burosumab at a starting dose of 0.3mg/kg Q4w.

**Figure 1.** Tumour Disposition at Study Baseline (UX023T-CL201)




[a] 5/6 subjects with tumor detected at baseline underwent one or more surgeries to remove tumor prior to study entry. One subject had their tumor imaged and identified for the first time at Screening, and therefore did not undergo prior surgical resection of the tumor

[b] 4/4 subjects with tumor identified previously, but not at study baseline, underwent surgery to remove tumor. Tumor was not located at study baseline in these subjects with previously identified tumors possibly due to small size, location of tumor, or imaging technique used.

2. Study KRN23-002 an open label, multicentre, Phase 2 study designed to assess the efficacy, safety, PK and PD of burosumab in adult subjects with TIO or ENS-associated osteomalacia based on evidence of excessive FGF23 that is not amenable to cure by surgical excision of the tumour/lesion.

In Study KRN023-002, the tumour location and type had been identified prior to the study for nine of 13 subjects (69%). Tumours had never been located in 4/13 subjects (31%), and TIO had been diagnosed based on clinical symptoms and biochemical evidence. The planned study treatment is 144 weeks or until the study drug is commercially available in the subject's local territory. The study was ongoing as of the data cut-off date for week 88 CSR.

In total, not more than 27 subjects were enrolled in the two studies in the application to extend the indication for Crysvita to include treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours that cannot be curatively resected or localised, in patients aged 1 year and over.

In total, 50% of the subjects in UX023T-CL201 and 69% in KRN023-002 reached the endpoint of achieving mean serum phosphorus levels above the lower limit of normal at the mid-point of the dose interval. The two TIO-studies also showed an increase in serum phosphate compared to the baseline level. This increase is of clinical relevance. The number of new fractures/pseudofractures decreased over time in Study UX023T-CL201. This is also considered clinically relevant. The mobility data as assessed by the 6-minute walking test and the sit-to-stand test offers some support also to the clinical data.

As the patients recruited into both these studies comprised primarily of patients with phosphaturic mesenchymal tumours which could not be resected surgically, the COMP considered that the results of these two studies could be used to support a clinically relevant advantage for significant benefit over surgery.

# 4. COMP position adopted on 24 June 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of phosphaturic mesenchymal tumour (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.07 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to severe osteomalacia and low bone density leading to fractures, severe symptoms of musculoskeletal pain, muscle weakness, fatigue, and difficulty with ambulation. In rare cases tumours can be malignant that may metastasise and cause death;
- although satisfactory methods for the Treatment of the condition have been authorised in the European Union, the assumption that Crysvita may be of potential significant benefit to those affected by the orphan condition. Clinical trial data showed an increase in serum phosphate compared to the baseline level and a reduction in the spontaneous fractures in patients who had tumours which were not surgically resectable.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Crysvita, burosumab, for treatment of phosphaturic mesenchymal tumour (EU/3/18/2011) is not removed from the Community Register of Orphan Medicinal Products.