IQWiG Reports – Commission No. A22-11

Burosumab (X-linked hypophosphataemia) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Burosumab (X-chromosomale Hypophosphatämie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 2022). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Monika Helfert and Martha Kirchhoff.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
6MWT	6-minute walk test
ACT	appropriate comparator therapy
AE	adverse event
CHQ	Child Health Questionnaire
CTCAE	Common Terminology Criteria for Adverse Events
FPS-R	Faces Pain Scale - Revised
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PROMIS	Patient Reported Outcomes Measurement Information System
RCT	randomized controlled trial
RGI-C	Radiographic Global Impression of Change
RSS	Rickets Severity Score
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
XLH	X-linked hypophosphataemia

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug burosumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 February 2022.

Research question

The aim of the present report is to assess the added benefit of burosumab in comparison with phosphate substitution as the appropriate comparator therapy (ACT) for the treatment of X-linked hypophosphataemia (XLH) in patients aged 1 to 17 years with radiographic evidence of bone disease.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of burosumab

Therapeutic indication	ACT[a]
XLH treatment in patients aged 1 to 17 years with radiographic evidence of bone disease	Phosphate substitution[b]
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The UX023-CL301 study was used for the benefit assessment. The UX023-CL301 study is an open-label RCT comparing burosumab with oral phosphate substitution and active vitamin D. The study included paediatric patients aged 1 to 12 years with radiographic evidence of XLH and a minimum Rickets Severity Score (RSS) total score of 2.

At baseline, patients had to have a (fasting) serum phosphate level below 3.0 mg/dL. The patient or a directly related family member with appropriate X-linked inheritance had to exhibit a PHEX mutation or variant of uncertain significance. Before enrolment, all patients received conventional therapy with oral phosphate and active vitamin D for a minimum of

12 consecutive months (children ≥ 3 years of age) or a minimum of 6 consecutive months (children < 3 years of age) up to 7 days prior to randomization (wash-out phase).

Following the screening phase, patients were randomized to the study arms, stratified by rickets severity (RSS total score ≤ 2.5 versus > 2.5), age (< 5 versus ≥ 5 years), and region (Japan versus rest of the world). A total of 29 patients were randomized to the intervention arm (burosumab) and 32 patients to the comparator arm (phosphate substitution).

The planned treatment duration was 64 weeks. After the end of the study, patients enrolled at study sites in Europe, United States, Canada, and Australia were invited to participate in an extension phase of a maximum of 76 weeks, during which all patients received burosumab. This single-arm extension phase is irrelevant for the present benefit assessment.

Burosumab treatment in the intervention arm was largely in compliance with the specifications of the Summary of Product Characteristics (SPC). However, the UX023-CL301 study allowed a burosumab dose increase up to a maximum of 1.2 mg/kg body weight, rather than to 2 mg/kg body weight as specified in the SPC. Eight children (28%) received a burosumab dose increase in the course of the UX023-CL301 study. Two of these 8 children received the dose increase only in Week 64. It is unclear how many of the other 6 children would have received another dose increase had they been treated in accordance with the SPC. Also unclear are the consequences of this discrepancy between the maximum doses allowed in the UX023-CL301 study versus those specified by the SPC on the study's observed effects on patient-relevant outcomes. This remaining uncertainty was taken into account in the assessment of the certainty of results.

The primary outcome of the study was the evaluation of the change in rickets measured using the Radiographic Global Impression of Change (RGI-C) score. Patient-relevant secondary outcomes were morbidity, health-related quality of life, and adverse events (AEs) outcomes.

No data available for XLH patients aged 1 to 12 years with an RSS total score below 2

The UX023-CL301 study enrolled only paediatric patients aged 1 to 12 years with an RSS total score of 2 or above.

Hence, no data are available for the present benefit assessment regarding patients in this age group (1 to 12 years) with an RSS total score below 2.

No data available for XLH patients aged 13 to 17 years

Patients aged 13 to 17 years were excluded from the UX023-CL301 study.

Hence, no data for use in the present benefit assessment are available for patients in this age group (13 to 17 years).

Implementation of the ACT

The present benefit assessment of burosumab was carried out using the ACT of phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

In the UX023-CL301 study, the dosage of both oral phosphate and active vitamin D was individualized upon the physician's discretion. For this purpose, investigators were provided with treatment recommendations, one written by experts from the EU and the other by experts from the United States. The 2 guidelines differ in the recommended oral phosphate dosages. For instance, the US guideline recommends oral phosphate doses of 20 to 40 mg/kg/day, split into 2 to 5 daily doses, while the EU guideline recommends 45 to 70 mg/kg/day, split into 3 to 4 daily doses.

According to the SPC of a product approved for oral phosphate substitution in this therapeutic indication in Germany, children should not receive more than 50 mg phosphate per kg body weight. The S1 guideline on hereditary hypophosphataemic rickets recommends 20 to 40 mg phosphate/kg/day, split into multiple daily doses. According to Haffner 2019, starting doses of 20 to 60 mg/kg/day are recommended for the treatment of hypophosphataemia. This makes the recommendation from EU experts (45 to 70 mg/kg/day), on which the study relied, seem relatively high.

According to the information provided in Module 4 A, the average oral phosphate doses actually administered in the study were 20 to 60 mg/kg/day. About 25% of the patients received a phosphate dose > 50 mg/kg. Common potential side effects of phosphate substitution (e.g. hyperparathyroidism, hypocalcaemia, nephrocalcinosis) were closely monitored in the UX023-CL301 study through periodic laboratory and physical examinations, and dose adjustments were possible where needed. The phosphate dosage therefore remains without consequence for the present benefit assessment.

Risk of bias and certainty of conclusions

The risk of bias across outcomes for the UX023-CL301 study is rated as low. The risk of bias on the outcome level is deemed high for the results of all outcomes except overall survival, serious adverse events (SAEs), and severe AEs. This is due to lack of blinding in subjective recording of outcomes. In addition, all outcomes with usable data suffer from uncertainties regarding the maximum possible dosage in the UX023-CL301 study's burosumab arm. Therefore, any effects demonstrated on the basis of the UX023-CL301 study can be used to derive at most hints, e.g. of added benefit, for all outcomes.

Results

Mortality

All-cause mortality

Deaths were recorded under AEs. There was no statistically significant difference between treatment arms. This resulted in no hint of an added benefit of burosumab in comparison with

phosphate substitution for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Walking ability (6-minute walk test [6MWT])

For the outcome of walking ability, there was a statistically significant difference in absolute walking distance between treatment arms (improvement in walking distance by 43.2 meters in the burosumab arm compared to the control arm). However, the lower limit of the 95% confidence interval is 2.3 m, which seems too low to rate the observed effect as clinically relevant. In addition, baseline values markedly differ between the 2 treatment arms. These differences are relevant despite adjustment in the analyses, e.g. for the respective baseline value: The children in the burosumab arm walked 365.9 m at baseline (about 62% of the expected distance), compared to 450.5 m for the children in the control arm (about 76% of the expected distance). Due to these different baseline conditions, it is safe to assume that the children in the burosumab had a higher potential for improvement in walking ability than those in the control arm. For the change in walking ability, operationalized as percent of the expected distance, no statistically significant difference between the 2 treatment arms was found.

Overall, this resulted in no hint of an added benefit of burosumab in comparison with phosphate substitution for walking ability (6MWT); an added benefit is therefore not proven.

Physical functioning / mobility (Patient Reported Outcomes Measurement Information System [PROMIS] Paediatric Physical Function Mobility)

For the outcome of physical functioning / mobility, surveyed using the Paediatric Physical Function Mobility domain score, no statistically significant difference between treatment arms was found.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Fatigue (PROMIS Paediatric Fatigue)

No statistically significant difference between treatment arms was found for the outcome of fatigue.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Pain (PROMIS Paediatric Pain Interference)

No statistically significant difference between treatment arms was shown for the outcome of pain.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Pain intensity (surveyed using Faces Pain Scale – Revised [FPS-R])

There was no statistically significant difference between treatment arms for the outcome of pain intensity. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Dental events

No statistically significant difference between treatment arms was found for the outcome of dental events. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Health-related quality of life

No patient-relevant outcomes in the category of health-related quality of life were recorded in the UX023-CL301 study. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

No statistically significant difference between treatment arms was found for the outcomes of SAEs and severe AEs. Consequently, there is no hint of greater or lesser harm from burosumab in comparison with phosphate substitution for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

No statistically significant difference between treatment arms was found for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from burosumab in comparison with phosphate substitution; greater or lesser harm is therefore not proven.

Specific AEs

General disorders and administration site conditions (AEs), injury, poisoning and procedural complications (AEs), respiratory, thoracic, and mediastinal disorders (AEs)

For each of the outcomes of general disorders and administration site conditions (AEs), injury, poisoning, and procedural complications (AEs) as well as respiratory, thoracic, and mediastinal disorders (AEs), a statistically significant difference was found to the disadvantage of burosumab in comparison with phosphate substitution. This results in a hint of greater harm from burosumab in comparison with the ACT for each of them.

Constipation (AEs)

For the outcome of constipation (AEs), a statistically significant difference was found to the disadvantage of burosumab in comparison with the ACT. This difference was no more than marginal, however. This results in no hint of greater or lesser harm from burosumab in comparison with phosphate substitution; greater or lesser harm is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of added benefit of the drug burosumab in comparison with the ACT is assessed as follows:

For assessing the added benefit of burosumab in comparison with the ACT, the company submitted data only on XLH patients aged 1 to 12 years with a minimum RSS total score of 2. No data are available for XLH patients aged 13 to 17 years and/or those with an RSS total score below 2. For this reason, the added benefit of burosumab is derived separately for these patient groups.

XLH patients aged 1 to 12 years with a minimum RSS total score of 2

All things considered, only unfavourable effects were found in the outcome category of side effects, each with the probability of hint and the extent of considerable. These unfavourable effects each concern specific AEs.

The unfavourable effects of burosumab are deemed insufficient for deriving a lesser benefit of burosumab in comparison with phosphate substitution. This rating is based on the results for the morbidity outcomes (e.g. 6MWT) as well as the fact that unfavourable effects are found only for outcomes from the non-serious/non-severe side effects category.

In summary, there is no hint of added benefit of burosumab in comparison with the ACT for XLH patients aged 1 to 12 years with a minimum RSS total score of 2; an added benefit is therefore not proven.

XLH patients aged 1 to 12 years with an RSS total score below 2

No data relevant for the present benefit assessment are available for XLH patients aged 1 to 12 years with an RSS total score below 2. For these patients, no added benefit is therefore proven.

XLH patients aged 13 to 17 years

For XLH patients aged 13 to 17 years, no data relevant for the present benefit assessment are available. For these patients, no added benefit is therefore proven.

Table 3 shows a summary of the probability and extent of added benefit of burosumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Burosumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
XLH treatment in patients aged 1 to 17 years with radiographic evidence of bone disease	Phosphate substitution[b]	Children with XLH aged 1 to 12 years: RSS total score ≥ 2.0 ▪ Added benefit not proven RSS total score < 2.0[c] ▪ Added benefit not proven
		Adolescents with XLH aged 13 to 17 years[c] ▪ Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. c. No data are available for this patient group. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RSS: Rickets Severity Score; XLH: X-linked hypophosphataemia		

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2018, where the G-BA had determined a non-quantifiable added benefit of burosumab. In said assessment, however, the added benefit had been regarded as proven by the approval, irrespective of the underlying data, due to orphan drug status.

2.2 Research question

The aim of the present report is to assess the added benefit of burosumab in comparison with phosphate substitution as the ACT in the treatment of XLH in patients aged 1 to 17 years with radiographic evidence of bone disease.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of burosumab

Therapeutic indication	**ACT**[a]
XLH treatment in patients aged 1 to 17 years with radiographic evidence of bone disease	Phosphate substitution[b]
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; XLH: X-linked hypophosphataemia	

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company’s inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on burosumab (status: 2 November 2021)
- bibliographical literature search on burosumab (last search on 2 November 2021)
- search in trial registries / trial results databases for studies on burosumab (last search on 2 November 2021)
- search on the G-BA website for burosumab (last search on 5 November 2021)

To check the completeness of the study pool:

- search in trial registries for studies on burosumab (last search on 17 February 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant studies.

2.3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: burosumab versus phosphate substitution

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
UX023-CL301	Yes	Yes	No	Yes [3]	Yes [4,5]	Yes [6-15]

a. Study sponsored by the company.
b. References of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The benefit assessment used the UX023-CL301 study, with the study phase from Week 0 to 64 being analysed. The subsequent optional single-arm extension phase (Weeks 65 to 140) is irrelevant for the present benefit assessment (see Section 2.3.2). The approach and study pool concur with those used by the company.

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: burosumab versus phosphate substitution

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
UX023-CL301	RCT, open-label, parallel-group	XLH patients aged 1 to 12 years with ▪ radiographic evidence of rickets with an RSS total score ≥ 2.0 ▪ Serum phosphate < 3.0 mg/dL (0.97 mmol/L)[b] ▪ Confirmed PHEX mutation (patient or directly related family member) ▪ Prior therapy with both oral phosphate and active vitamin D	Burosumab N = 29 Phosphate substitution[c] N = 32	Screening: up to 8 weeks including wash-out phase[d] Treatment: 64 weeks, followed by voluntary participation in a single-arm extension phase up to Week 140[e] Follow-up observation: 5 weeks; 12 weeks for patients not participating in the extension phase[f]	16 study centres in Australia, Canada, Japan, South Korea, Sweden, United Kingdom, United States 9/2016–7/2019 Data cut-offs ▪ Week 40 ▪ Week 64	Primary: change in rickets (RGI-C global score) Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Based on fasting levels (at least 4 hours) at screening and/or study start
c. Additionally, patients received substitution with active vitamin D (alfacalcidol or calcitriol).
d. Patients were to have received no oral phosphate or active vitamin D therapy for 7 days prior to randomization.
e. The extension phase for patients in Europe, the United States, Canada, and Australia was introduced with the study protocol's Amendment 1. Patients in Japan and South Korea were ineligible for participation in the extension phase. These patients did not receive any burosumab in Week 64. The extension phase is irrelevant for the present benefit assessment and is not presented below.
f. The original protocol provided for a follow-up phase for side effects outcomes with a duration of 12 weeks after the last dose of the study drug. From Amendment 1 onward, this follow-up period applied only to patients who, after Week 64, did not receive burosumab therapy in the extension phase or outside the study. Follow-up was 5 weeks for patients who continued burosumab therapy outside the extension phase.

AE: adverse event; N: number of randomized patients; RCT: randomized controlled trial; RGI-C: Radiographic Global Impression of Change; RSS: Rickets Severity Score

Table 7: Characteristics of the intervention – RCT, direct comparison: burosumab versus phosphate substitution

Study	Intervention	Comparison
UX023-CL301	Burosumab 0.8 mg/kg body weight, s.c. every 2 weeks	Oral phosphate[a]: individualized dosage upon the physician's discretion [b]
	Dose adjustment: ▪ Burosumab: based on fasting serum phosphate levels, dose increases (to 1.2 mg/kg body weight; maximum of 90 mg) [c] or decreases[d] were allowed. ▪ Oral phosphate/active vitamin D: Individualized dose adjustment on the basis of clinical and laboratory parameters was allowed at any time. **Pretreatment** Oral phosphate and active vitamin D up to 7 days prior to randomization ▪ In children aged ≥ 3 years: for ≥ 12 consecutive months ▪ In children aged < 3 years: for ≥ 6 consecutive months **Non-permitted prior and concomitant treatment** ▪ Leuprorelin, triptorelin, goserelin, or other drugs delaying puberty ▪ Growth hormones ≤ 12 months prior to screening visit ▪ PTH suppressors ≤ 2 months prior to screening visit ▪ Monoclonal antibodies ≤ 90 days prior to screening visit ▪ Aluminium hydroxide antacids ≤ 7 days prior to screening visit ▪ Systemic cortisone ≤ 7 days prior to screening visit ▪ Acetazolamide ≤ 7 days prior to screening visit ▪ Thiazide ≤ 7 days prior to screening visit **Non-permitted concomitant treatment for patients in the intervention arm** ▪ Oral phosphate and active vitamin D	

a. Additionally, patients received substitution with active vitamin D (alfacalcidol or calcitriol).
b. The company made available dosing recommendations from EU and US experts [16,17].
c. Dose increases were allowed, provided 3 criteria were met:
- 2 consecutive serum phosphate levels < normal range and
- serum phosphate increase ≤ 0.5 mg/dL from baseline and
- serum phosphate decrease not due to burosumab dose interruption.

d. At serum phosphate levels above the ULN for age, treatment initially had to be interrupted. After other causes for the serum phosphate increase had been ruled out, patients were allowed to continue treatment with half of the prior dose (maximum dose: 40 mg). Following a dose decrease, patients were allowed to continue their prior dose, provided the 3 above criteria for dose increase were met.

PTH: parathyroid hormone; RCT: randomized controlled trial; s.c.: subcutaneous; ULN: upper limit of normal

The UX023-CL301 study is an open-label RCT comparing burosumab with oral phosphate substitution and active vitamin D. The study included paediatric patients aged 1 to 12 years with radiographic evidence of XLH and a minimum RSS total score of 2.

At baseline, patients had to have a (fasting) serum phosphate level below 3.0 mg/dL. The patient or a directly related family member with appropriate X-linked inheritance had to exhibit a PHEX mutation or variant of uncertain significance. Before enrolment, all patients received conventional therapy with oral phosphate and active vitamin D for a minimum of

12 consecutive months (children ≥ 3 years of age) or a minimum of 6 consecutive months (children < 3 years of age) up to 7 days prior to randomization (wash-out phase).

Following the screening phase, patients were randomized to the study arms, stratified by rickets severity (RSS total score ≤ 2.5 versus > 2.5), age (< 5 versus ≥ 5 years), and region (Japan versus rest of the world). A total of 29 patients were randomized to the intervention arm (burosumab) and 32 patients, to the comparator arm (phosphate substitution).

The planned treatment duration was 64 weeks. After the end of the study, patients enrolled at study sites in Europe, United States, Canada, and Australia were invited to participate in an extension phase of a maximum of 76 weeks, during which all patients received burosumab. This single-arm extension phase is irrelevant for the present benefit assessment.

Burosumab treatment in the intervention arm was largely in compliance with the specifications of the SPC [18]. However, the UX023-CL301 study allowed a burosumab dose increase only to a maximum of 1.2 mg/kg body weight, rather than to 2 mg/kg body weight as specified in the SPC. Eight children (28%) received a burosumab dose increase in the course of the UX023-CL301 study. Two of these 8 children received the dose increase only in Week 64. It is unclear how many of the other 6 children would have received another dose increase had they been treated in accordance with the SPC. Also unclear are the consequences of this discrepancy between the maximum doses allowed in the UX023-CL301 study versus those specified by the SPC on the effects observed in patient-relevant outcomes [18]. Due to this uncertainty, only hints, e.g. of an added benefit, can be derived on the basis of the UX023-CL301 study (see Section 2.4.2).

The primary outcome of the study was the evaluation of the change in rickets measured using the RGI-C score. Patient-relevant secondary outcomes were morbidity, health-related quality of life, and adverse events (AEs) outcomes.

No data available for XLH patients aged 1 to 12 years with an RSS total score below 2

The UX023-CL301 study enrolled only paediatric patients aged 1 to 12 years with a minimum RSS total score of 2. However, the patient population of this age (1 to 12 years) may conceivably include a relevant percentage of patients with an RSS total score under 2 [19,20]. The company has not submitted any data on the percentage of the patient population to which this applies. Likewise, the company did not explain the extent to which the data from the UX023-CL301 study are transferable to the patient group with an RSS total score below 2.

Hence, no data are available for the present benefit assessment regarding patients in this age group (1 to 12 years) with an RSS total score below 2.

No data available for XLH patients aged 13 to 17 years

Patients aged 13 to 17 years were excluded from the UX023-CL301 study. Hence, no usable data are available for this patient group.

From the company's perspective, it is safe to assume that the effect on serum phosphate homoeostasis and bone metabolism which was observed in the UX023-CL301 study for the patient population of 1 to 12 years remains in place in the age group of patients 13 to 17 years. Firstly, bone growth is complete in only a small percentage of children in this age group, and secondly, other data show that the favourable effect of burosumab treatment continues even after the closure of epiphyseal plates. In this regard, the company cites the single-arm study UX023.-CL201 [3], which investigated burosumab administration in children with XLH. According to the company, 11 of the 52 children with XLH who participated in this study reached adolescence in the course of the study; this was defined as participants experiencing partial or complete closure of the distal femoral and proximal tibial epiphyseal plates during the study. Based on serum phosphate and rickets data, the company deems these study participants – like the total population – to show response to burosumab therapy. In addition, the company cites as supplementary information a British early access programme [21] which, in the company's view, investigates the effectiveness of burosumab in adolescents with closed epiphyseal plates. In the company's opinion, the transferability of evidence to the age group 13 to 17 years was confirmed in the context of the EMA approval [15].

The company's reasoning refers exclusively to results on burosumab. However, it is insufficient to merely describe results. A comparison with the ACT is always required for the benefit assessment. The company has not submitted any corresponding results on the ACT. It is therefore unclear to what extent the results from the UX023-CL301 study for paediatric patients (with an RSS total score of at least 2) are transferable to the patient population aged 13 to 17 years.

Hence, no data for use in the present benefit assessment are available for patients in this age group (13 to 17 years).

Implementation of the ACT

The present benefit assessment of burosumab was carried out using the ACT of phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

In the UX023-CL301 study, the dosage of both oral phosphate and active vitamin D was individualized upon the physician's discretion. For this purpose, the investigators were provided with treatment recommendations, one by experts from the EU and the other by experts from the United States [16,17]. The 2 guidelines differ in the recommended oral phosphate dosages. For instance, the US guideline recommends oral phosphate doses of 20 to 40 mg/kg/day, split into 2 to 5 daily doses, while the EU guideline recommends 45 to 70 mg/kg/day, split into 3 to 4 daily doses.

According to the SPC of the product approved for oral phosphate substitution in this therapeutic indication in Germany, 50 mg phosphate per kg body weight should not be exceeded in children [22]. The S1 guideline on hereditary hypophosphataemic rickets recommends 20 to 40 mg phosphate/kg/day, split into multiple daily doses [23]. According to Haffner 2019, starting

doses of 20 to 60 mg/kg/day are recommended for the treatment of hypophosphataemia [24]. The expert recommendation from the EU (45 to 70 mg/kg/day [17]), on which the study relied, therefore seems relatively high.

According to the information provided in Module 4 A, the average oral phosphate doses actually administered in the study were 20 to 60 mg/kg/day. About 25% of the patients received a phosphate dose > 50 mg/kg. Common potential side effects of phosphate substitution (e.g. hyperparathyroidism, hypocalcaemia, nephrocalcinosis) were closely monitored in the UX023-CL301 study through periodic laboratory and physical examinations, and dose adjustments were possible where needed [24]. The phosphate dosage therefore remains without consequence for the present benefit assessment.

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population – RCT, direct comparison: burosumab vs. phosphate substitution

Study Characteristic Category	Burosumab N[a] = 29	Phosphate substitution N[a] = 32
UX023-CL301		
Age [years]		
Mean (SD)	6 (3)	6 (3)
< 5 years, n (%)	14 (48)	12 (38)
≥ 5 years, n (%)	15 (52)	20 (63)
Age at initiation of substitution therapy[b] [years], mean (SD)	3 (3)	2 (2)
Duration of substitution therapy[a] [years], mean (SD)	3.3 (3.1)	4.3 (3.0)
Sex [f/m], %	55/45	56/44
Ancestry, n (%)		
Asian	2 (7)	6 (19)
White	25 (86)	25 (78)
Other	2 (7)	1 (3)
Geographical region, n (%)		
USA/Canada	18 (62)[c]	22 (69)[c]
Europe	2 (7)	3 (9)
Japan/Korea	2 (7)[c]	5 (16)[c]
Australia	7 (24)	2 (6)
BMI [kg/m²], mean (SD)	18.0 (2.5)	18.2 (2.2)
Height [z-score], mean (SD)	−2.1 (0.9)	−2.3 (1.2)
RSS total score		
Mean (SD)	3.2 (1.0)	3.2 (1.1)
≤ 2.5, n (%)	10 (34)	12 (38)
< 2.5, n (%)	19 (66)	20 (63)
Serum phosphate [mg/dL], mean (SD)	2.4 (0.2)	2.3 (0.3)
Serum 1,25$(OH)_2$ vitamin D [pg/mL], mean (SD)	46.0 (20.1)	40.2 (14.9)
Alkaline phosphatase [U/L], mean (SD)	510.8 (124.9)	523.4 (154.4)
Treatment discontinuation, n (%)[d]	0 (0)	0 (0)
Study discontinuation, n (%)[d]	0 (0)	0 (0)

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. Consisting of the oral administration of phosphate and active vitamin D.
c. IQWiG calculation.
d. With regard to the part of the study which is relevant for the present benefit assessment (treatment phase Week 0–64 without extension phase).

BMI: body mass index; f: female; m: male; n: number of patients in the category; MD: mean difference; N: number of randomized patients; RCT: randomized controlled trial; RSS: Rickets Severity Score; SD: standard deviation

In view of the relatively small case numbers, patient characteristics are largely comparable between the treatment arms. This applies to both demographic and disease characteristics. In both study arms, the mean patient age was 6 years, with the sex ratio being almost balanced. More than half of patients (about 65%) were examined in study centres in the United States or Canada. Slightly more children under 5 years of age were included in the intervention arm than in the control arm (48% versus 38%).

Neither of the 2 study arms included cases of treatment discontinuation or premature study discontinuation.

Transferability to the German health care context

In the company's opinion, the results of the UX023-CL301 study are transferable to the German health care context. The company bases this conclusion on (1) most patients being white and (2) XLH being a genetic disorder which is independent from external influences.

The company provided no further information on the transferability of study results to the German health care context.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: burosumab versus phosphate substitution

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
UX023-CL301	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the UX023-CL301 study.

Limitations resulting from the open-label study design are described in Section 2.4 with the outcome-specific risk of bias.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality

- all-cause mortality

- Morbidity
  - walking ability, surveyed using the 6MWT
  - physical functioning / mobility surveyed using the Patient Reported Outcomes Measurement Information System (PROMIS) Paediatric Physical Function Mobility
  - fatigue surveyed using the PROMIS Paediatric Fatigue Domain Score
  - pain surveyed with the PROMIS Paediatric Pain Interference
  - pain intensity surveyed using the FPS-R
  - dental events
- health-related quality of life
- Side effects
  - SAEs
  - severe AEs, operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)
  - discontinuation due to AEs
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that taken by the company, which used further outcomes in the dossier (Module 4 A).

Table 10 shows the outcomes for which data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: burosumab vs. phosphate substitution

Study	Outcomes														
	All-cause mortality[a]	Walking ability (6MWT)[b]	Physical functioning / mobility (PROMIS Paediatric Physical Function Mobility)[b]	Fatigue (PROMIS Paediatric Fatigue)	Pain (PROMIS Paediatric Pain Interference)[b]	Pain intensity (FPS-R)[b]	Dental events[c]	Health-related quality of life	SAEs	Severe AEs[d]	Discontinuation due to AEs	Constipation (PT, AEs)	General disorders and administration site conditions (SOC, AEs)	Injury, poisoning, and procedural complications (SOC, AEs)	Respiratory, thoracic, and mediastinal disorders (SOC, AEs)
UX023-CL301	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. Deaths were surveyed under AEs.
b. Outcome surveyed only in children 5 years and older.
c. Surveyed by the company under the side effects category. In the present benefit assessment, this outcome was categorized under morbidity.
d. Severe AEs are operationalized as CTCAE grade 3–4.
e. No usable data available; see below for reasoning.

6MWT: 6-minute walk test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FPS-R: Faces Pain Scale – Revised; PROMIS: Patient-Reported Outcomes Measurement Information System; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; SAE: serious adverse event

Notes on analyses of the morbidity outcome category

- Dental events: The company's dossier listed this outcome under side effects. The present benefit assessment, in contrast, allocated this outcome to the morbidity outcome category. In the UX023-CL301 study, dental events were surveyed using 2 different methods:
  - Firstly, dental events were recorded using an oral survey, where patients were periodically asked by the investigator during their respective hospital visits whether one of the following dental events had occurred: caries, tooth extraction, root canal treatment, dental abscesses, or gingivitis.
  - Secondly, dental events were surveyed as AEs if they were identified by the investigator during an oral examination.

  In Module 4 A, the company reports that all children who, according to the oral dental survey, suffered from dental symptoms also had dental events documented as AEs. According to the company, dental events also occurred in other children who reported no dental complaints in the oral dental survey. The dental AE of teething, which occurred in

one child in the burosumab group, was disregarded. Therefore, it is safe to assume that the percentage of patients with any dental event as presented in dental AEs is complete.

However, the study did not ensure that the dental examinations were performed by a specialist or adequately trained healthcare staff. The resulting uncertainty was taken into account when determining the certainty of results for this outcome (see Section 2.4.2).

- Pain, fatigue, and physical functioning: The study surveyed pain, fatigue, and physical functioning using the Patient Reported Outcomes Measurement information System (PROMIS). For children 5 to 7 years of age, the study used a version of the questionnaire which was to be completed by parents or guardians (proxy report). Children 8 years and older received a version to be completed by the children themselves (self-report). In children turning 8 years old during the study, proxy reporting was continued.

  PROMIS is a valid, generic system consisting of domain-specific instruments for the self-reported and proxy-reported assessment of physical, mental, and social health.

  In general, the PROMIS system allows generating user-defined short forms for each domain by selecting items from the PROMIS item database. The UX023-CL301 study used such a user-defined short form tailored to the paediatric patient population. According to the company, the study surveyed, e.g. a selection consisting a total of 22 items from the 3 domains of pain (consisting of 20 items), mobility (consisting of 24 items), and fatigue (consisting of 25 items) on the basis of the main symptoms of XLH patients as established in the pivotal study UX023-CL201. In accordance with the PROMIS recommendation, scoring was performed separately for each domain, with the raw data being transformed into T-values. However, it is unclear which reference population was used for the transformation.

  The study protocol predefined the surveying of the items in the questionnaire submitted by the company for the domains of pain, fatigue, and physical functioning / mobility. In addition, content validity was examined with regard to the symptoms surveyed in the UX7575A study [25] and deemed adequate. While the study documents do not include any rationale regarding the item selection for the domains of pain, fatigue, and physical functioning / mobility, the items selected by the company were rated as relevant and comprehensible by affected people in cognitive interviews conducted in the UX7575A study. While overall, it is unclear whether the list of items selected by the company is complete, this issue is not deemed sufficiently serious for the results not to be usable.

- Not included: change in rickets, surveyed by means of the RGI-C score and RSS since the assessment of these outcomes is based solely on a radiological evaluation. The company did not provide adequate evidence for these outcomes representing valid surrogates for patient-relevant outcomes.
- Not included: change in serum phosphate level. No evidence suitable for establishing a sufficient correlation or validation of the surrogate marker to patient-relevant outcomes was presented.

- Presented as supplementary information: body height (surveyed via z-score): In the present therapeutic indication, body height is a highly relevant treatment goal. Any impairments presumably result in reduced longitudinal growth and are depicted in health-related quality of life and/or health status. The results are presented as supplementary information in Appendix B of the full dossier assessment.

Notes on analyses of the outcome category of health-related quality of life

- Health-related quality of life: The company used the SF-10 questionnaire for surveying health-related quality of life. In children 5 years or older, the questionnaire was completed by a caregiver or parent.

  The SF-10 containing 10 items was developed from an instrument with 50 items (Child Health Questionnaire-PF50 [CHQ-PF50]). Based on these 10 items of the SF-10, two components are formed.

  - Physical Health Score (PHS-10): items 1, 2a, 2b, 3, and 5 ask about general health status, physical limitations due to health problems and pain.
  - Psychosocial Health Score (PSS-10): items 4 and 6 through 9 reflect limitations due to mental problems, behavioural abnormalities, satisfaction, and friendship.

  No children were involved in the development of the SF-10. Therefore, it is unclear whether after eliminating 40 items from the original instrument (CHQ-PF50), the resulting questionnaire still depicts all relevant aspects concerning the health-related quality of life in children – particularly children with XLH. In addition, children aged 5 and older can and should self-rate their health-related quality of life [26,27]. According to the EMA's Reflection Paper, there is generally no overlap between self-rated and proxy-rated patient-reported outcomes [28].

  Therefore, the SF-10 results on health-related quality of life as presented by the company were excluded from the benefit assessment.

2.4.2 Risk of bias

Table 11 presents the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: burosumab versus phosphate substitution

Study	Outcomes															
	Study level	All-cause mortality[a]	Walking ability (6MWT)	Physical functioning / mobility (PROMIS Paediatric Physical Function Mobility)	Fatigue (PROMIS Paediatric Fatigue)	Pain (PROMIS Paediatric Pain Interference)	Pain intensity	Dental events	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Constipation (PT, AEs)	General disorders and administration site conditions (SOC, AEs)	Injury, poisoning, and procedural complications (SOC, AEs)	Respiratory, thoracic, and mediastinal disorders (SOC, AEs)
UX023-CL301	L	L	H[c]	H[c]	H[c]	H[c]	H[c]	H[c]	–[d]	L	L	H[c]	H[c]	H[c]	H[c]	H[c]

a. Deaths were surveyed under AEs.
b. Severe AEs are operationalized as CTCAE grades 3–4.
c. Lack of blinding with subjective recording of outcomes.
d. No usable data available; for the reasoning, see Section 2.4.1 of the present dossier assessment.

6MWT: 6-minute walk test; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FPS-R: Faces Pain Scale – Revised; H: high; MedDRA: Medical Dictionary for Regulatory Activities; L: low; PROMIS: Patient-Reported Outcomes Measurement Information System; PT: Preferred Term; RCT: randomized controlled study; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: System Organ Class

The risk of bias is deemed high for the results of all outcomes except all-cause mortality, SAEs, and severe AEs. This is due to lack of blinding in subjective recording of outcomes.

Summary assessment of the certainty of conclusions

The certainty of conclusions in the UX023-CL301 study is deemed limited due to the uncertainties regarding the maximum possible dosage in the intervention arm as described in Section 2.3.2. Irrespective of the low outcome-specific risk of bias in some cases, at most hints, e.g. of added benefit, can therefore be derived on the basis of the available information for all outcomes. For the outcome of dental events, other factors further limit the certainty of conclusions (see Section 2.4.1).

2.4.3 Results

Table 12 and Table 13 summarize the results on the comparison of burosumab with phosphate substitution in XLH patients. Where necessary, IQWiG calculations are provided in addition to the data from the company's dossier.

Height results are presented as supplementary information in Appendix B of the full dossier assessment. The results on common AEs, SAEs, and severe AEs are presented in Appendix C of the full dossier assessment. Discontinuation due to AEs did not occur in any of the study arms.

Table 12: Results (mortality, morbidity, side effects) – RCT, direct comparison: burosumab versus phosphate substitution

Study Outcome category Outcome	Burosumab		Phosphate substitution		Burosumab vs. phosphate substitution
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
UX023-CL301 (week 64)					
Mortality					
All-cause mortality[b]	29	0 (0)	32	0 (0)	NC
Morbidity					
Dental events[c]	29	15 (51.7)	32	10 (31.3)	1.66 [0.89; 3.09]; 0.122
Health-related quality of life					
No usable data available[d]					
Side effects					
AEs (supplementary information)	29	29 (100)	32	27 (84.4)	–
SAEs	29	3 (10.3)	32	3 (9.4)	1.10 [0.24; 5.04][e]; 0.971
Severe AEs[f]	29	4 (13.8)	32	3 (9.4)	1.47 [0.36; 6.03][e]; 0.637
Discontinuation due to AEs	29	0 (0.0)	32	0 (0.0)	NC
Constipation (PT, AEs)	29	5 (17.2)	32	0 (0.0)	12.10 [0.70; 209.71]; 0.016
General disorders and administration site conditions (SOC, AEs)[g]	29	25 (86.2)	32	8 (25.0)	3.45 [1.86; 6.39]; < 0.001
Injury, poisoning, and procedural complications (SOC, AEs)[h]	29	10 (34.5)	32	2 (6.3)	5.52 [1.32; 23.12]; 0.006
Respiratory, thoracic, and mediastinal disorders (SOC, AEs)	29	21 (72.4)	32	9 (28.1)	2.57 [1.42; 4.68]; < 0.001

a. IQWiG calculation, unconditional exact test (CSZ method according to [29]).
b. Deaths were recorded within the framework of AEs.
c. Key underlying events are caries and dental abscess.
d. See Section 2.4.1 of the present dossier assessment for the reasoning.
e. IQWiG calculation of RR and 95% CI (asymptotic).
f. Operationalized as CTCAE grades 3 to 4.
g. Key underlying events are injection site erythema (burosumab: 9 [31.0%] versus phosphate substitution: 0 [0.0%]; RR: 20.90; 95% CI: [1.27; 343.87]; p < 0.001) and fever (burosumab: 16 [55.2%] versus phosphate substitution: 6 [18.8%]; RR: 2.94; 95% CI: [1.33; 6.50]; p = 0.003).
h. Key underlying events are contusion (burosumab: 4 [13.8%] versus phosphate substitution: 0 [0.0%]; RR: 9.90; 95% CI: [0.56; 176.29]; p = 0.030) and falls (burosumab: 3 [10.3%] versus phosphate substitution: 0 [0.0%]; RR: 7.70; 95% CI: [0.41; 143.00]; p = 0.072.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: burosumab versus phosphate substitution (multipage table)

Study Outcome category Outcome	Burosumab			Phosphate substitution			Burosumab vs. phosphate substitution
	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SE)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SE)	MD[c] [95% CI]; p-value
UX023-CL301 (Week 64)							
Morbidity							
Walking ability (6MWT)[d]	15	365.9 (118.1)	97.9 (19.3)	20	450.5 (106.4)	30.8 (18.1)	43.20 [2.33; 84.07]; 0.038
Physical functioning / mobility (PROMIS Paediatric Physical Function Mobility Domain Score)[e, f]							
Proxy rated, age 5–7 years[g]	7	42.9 (9.5)	2.6 (3.8)	9	41.9 (11.3)	1.1 (1.6)	0.93 [-5.32; 7.17]; 0.771
Self-rated, age 8–12 years[g]	8	47.7 (8.4)	3.0 (1.2)	11	48.4 (7.9)	0.7 (1.3)	2.09 [-0.76; 4.94]; 0.150
Fatigue (PROMIS Paediatric Fatigue Domain Score)[e, h]							
Proxy rated, age 5–7 years[g]	7	51.9 (10.7)	-5.2 (3.7)	9	53.0 (16.2)	-3.3 (3.1)	-1.85 [-9.48; 5.77]; 0.634
Self-rated, age 8–12 years[g]	8	45.2 (7.3)	-2.1 (3.1)	11	42.1 (9.4)	-1.0 (2.3)	0.57 [-5.36; 6.49]; 0.852
Pain (PROMIS Paediatric Pain Interference Domain Score)[e, h]							
Proxy rated, age 5–7 years[g]	7	55.9 (12.7)	-4.8 (4.9)	9	52.3 (12.3)	-0.8 (1.7)	-1.52 [-7.56; 4.52]; 0.622
Self-rated, age 8–12 years[g]	8	50.0 (8.3)	-3.0 (2.6)	11	47.9 (12.1)	-0.2 (2.6)	-1.64 [-7.06; 3.79]; 0.554
Pain intensity (FPS-R)[h,i]							
Self-rated, age ≥ 5 years	15	0.4 (1.1)	0.1 (0.4)	20	0.7 (1.2)	-0.1 (0.3)	0.05 [-0.58; 0.68]; 0.879

a. Number of patients taken into account in the analysis for the calculation of the effect estimation; the baseline values may be based on different patient numbers.
b. Refers to the change from baseline to Week 64.
c. Generalized Estimation Equation (GEE) model at Week 64, taking into account the treatment arm, prior visits, interaction between treatment arm and visit, RSS total score (≤ 2.5 / > 2.5), and baseline value at study start.
d. Measured in meters. The 6MWT was surveyed only in patients 5 years and older.
e. PROMIS scores are presented as T-scores. The T-score scales the domain raw data to a standardized score with a mean of 50 and a standard deviation (SD) of 10.
f. Higher (increasing) values indicate better symptoms; positive effects (burosumab minus phosphate substitution) indicate an advantage for the intervention.
g. Age at enrolment; in the proxy-reported assessment, the case number decreases from 8 to 7 (from study start to end). When using self-reported assessment, in contrast, the case number increases from 7 to 8. This is inexplicable because in children turning 8 years old during the study, parents were to continue proxy reporting.
h. Lower (decreasing) values indicate better symptoms; negative effects (burosumab minus phosphate substitution) indicate an advantage for the intervention.

Table 13: Results (morbidity, health-related quality of life) – RCT, direct comparison: burosumab versus phosphate substitution (multipage table)

Study Outcome category Outcome	Burosumab			Phosphate substitution			Burosumab vs. phosphate substitution
	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SE)	N[a]	Values at baseline mean (SD)	Change at end of study[b] mean (SE)	MD[c] [95% CI]; p-value
6MWT: 6-minute walk test; CI: confidence interval; FPS-R: Faces Pain Scale – Revised; GEE: Generalized Estimation Equation; MD: mean difference; N: number of analysed patients; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial; RSS: Rickets Severity Score; SD: standard deviation; SE: standard error							

Based on the available data, at most hints, e.g. of an added benefit, can be determined for all outcomes (see Section 2.3.2 and Section 2.4.2).

Mortality

All-cause mortality

Deaths were recorded within the framework of AEs. There was no statistically significant difference between treatment arms. This resulted in no hint of an added benefit of burosumab in comparison with phosphate substitution for the outcome of all-cause mortality; an added benefit is therefore not proven.

Morbidity

Walking ability (6MWT)

Walking ability was surveyed using the 6MWT in children aged 5 years and older. For the outcome of walking ability, there was a statistically significant difference in absolute walking distance between treatment arms (improvement in walking distance by 43.2 meters in the burosumab arm compared to the control arm). However, the lower limit of the 95% confidence interval is 2.3 m, which seems too low to rate the observed effect as clinically relevant. In addition, baseline values markedly differ between the 2 treatment arms. These differences are relevant despite adjustment in the analyses, e.g. for the respective baseline value: The children in the burosumab arm walked 365.9 m at baseline (about 62% of the expected distance), compared to 450.5 m for the children in the control arm (about 76% of the expected distance). Due to these different baseline conditions, it is safe to assume that the children in the burosumab had a higher potential for improvement in walking ability than those in the control arm. In the change in walking ability, presented as percentage of the expected walking distance, no statistically significant difference between the 2 treatment arms is found (see Appendix D of the full dossier assessment).

Overall, this resulted in no hint of an added benefit of burosumab in comparison with phosphate substitution for walking ability (6MWT); an added benefit is therefore not proven.

Physical functioning / mobility (PROMIS Paediatric Physical Function Mobility)

For the outcome of physical functioning / mobility, surveyed in children aged 5 years and older using the PROMIS Paediatric Physical Function Mobility Domain Score, no statistically significant difference between treatment arms was found.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Fatigue (PROMIS Paediatric Fatigue)

There was no statistically significant difference between treatment arms for the outcome of fatigue, surveyed in children aged 5 years and older.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Pain (PROMIS Paediatric Pain Interference)

There was no statistically significant difference between treatment arms for the outcome of pain, surveyed in children aged 5 years and older.

This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Pain intensity (surveyed using the FPS-R)

Children aged 5 years and older self-reported pain intensity using the FPS-R.

There was no statistically significant difference between treatment arms for the outcome of pain intensity. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Dental events

No statistically significant difference between treatment arms was found for the outcome of dental events. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Health-related quality of life

The UX023-CL301 study did not survey any usable data on outcomes from the health-related quality of life category. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs

There was no statistically significant difference between treatment arms for the outcomes of serious AEs (SAEs) or severe AEs. Consequently, there is no hint of greater or lesser harm from

burosumab in comparison with phosphate substitution for either of them; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

There was no statistically significant difference between treatment arms for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm from burosumab in comparison with phosphate substitution; greater or lesser harm is therefore not proven.

Specific AEs

General disorders and administration site conditions (AEs), injury, poisoning and procedural complications (AEs), respiratory, thoracic, and mediastinal disorders (AEs)

For each of the outcomes of general disorders and administration site conditions (AEs), injury, poisoning, and procedural complications (AEs) as well as respiratory, thoracic, and mediastinal disorders (AEs), a statistically significant difference was found to the disadvantage of burosumab in comparison with phosphate substitution. In each case, this results in a hint of greater harm from burosumab in comparison with phosphate substitution.

Constipation (AEs)

For the outcome of constipation (AEs), a statistically significant difference was found to the disadvantage of burosumab in comparison with phosphate substitution. This difference was no more than marginal, however (see Section 2.5.1). This results in no hint of greater or lesser harm from burosumab in comparison with phosphate substitution; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- Age (< 5 years versus ≥ 5 years)
- Sex (female versus male)
- Rickets severity at baseline (RSS total score ≤ 2.5 versus RSS total score > 2.5).

All mentioned subgroup characteristics and cut-off values were prespecified. The company submitted subgroup analyses for all outcomes listed in the dossier, except the SOC of injury, poisoning, and procedural complications, without providing any reasoning for this omission.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

When applying the above-described methods, the available subgroup results show no effect modifications.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 14).

Table 14: Extent of added benefit at outcome level: burosumab versus phosphate substitution (multipage table)

Outcome category **Outcome**	**Burosumab vs. phosphate substitution** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	Event rates: 0.0% vs. 0.0% RR: NC p = NC	Lesser/added benefit not proven
Morbidity		
Walking ability (6MWT)[c]	Mean: 97.90 vs. 30.8 MD: 43.20 [2.33; 84.07] p = 0.038	Lesser/added benefit not proven[d]
Physical functioning / mobility (PROMIS Paediatric Physical Function Mobility Domain Score)		
Self-report, age 5–7 years[e]	Mean: 2.6 vs. 1.1 MD: 0.93 [-5.32; 7.17] p = 0.771	Lesser/added benefit not proven
Self-report, age 8–12 years[e]	Mean: 3.0 vs. 0.7 MD: 2.09 [-0.76; 4.94] p = 0.150	Lesser/added benefit not proven
Fatigue (PROMIS Paediatric Fatigue Domain Score)		
Proxy report, age 5–7 years[e]	Mean: -5.2 vs. -3.3 MD: -1.85 [-9.48; 5.77] p = 0.634	Lesser/added benefit not proven
Self-report, age 8–12 years[e]	Mean: -2.1 vs. -1.0 MD: 0.57 [-5.36; 6.49] p = 0.852	Lesser/added benefit not proven
Pain (PROMIS Paediatric Pain Interference Domain Score)		
Proxy report, age 5–7 years[e]	Mean: -4.8 vs. -0.8 MD: -1.52 [-7.56; 4.52] p = 0.622	Lesser/added benefit not proven
Self-report, age 8–12 years[e]	Mean: -3.0 vs. -0.2 MD: -1.64 [-7.06; 3.79] p = 0.554	Lesser/added benefit not proven
Pain intensity (FPS-R) Self-report, age ≥ 5 years [e]	Mean: 0.1 vs. -0.1 MD: 0.05 [-0.58; 0.68] p = 0.879	Lesser/added benefit not proven
Dental events	Event rates: 51.7% vs. 31.3% RR: 1.66 [0.89; 3.09] p = 0.122	Lesser/added benefit not proven
Health-related quality of life		
No usable data available[f]		

Table 14: Extent of added benefit at outcome level: burosumab versus phosphate substitution (multipage table)

Outcome category **Outcome**	**Burosumab vs. phosphate substitution** **Proportion of events (%) or mean change** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	Event rates: 10.3% vs. 9.4% RR: 1.10 [0.24; 5.04] p = 0.971	Greater/lesser harm not proven
Severe AEs	Event rates: 13.8% vs. 9.4% RR: 1.47 [0.36; 6.03] p = 0.637	Greater/lesser harm not proven
Discontinuation due to AEs	Event rates: 0.0% vs. 0.0% RR: NC p = NC	Greater/lesser harm not proven
Constipation	Event rates: 17.2% vs. 0.0% RR: 12.10 [0.70; 209.71] RR: 0.08 [0.00; 1.43][g] p = 0.016	Outcome category: non-serious/non-severe side effects Greater/lesser harm not proven[h]
General disorders and administration site conditions	Event rates: 86.2% vs. 25.0% RR: 3.45 [1.86; 6.39] RR: 0.29 [0.16; 0.54][g] p < 0.001	Outcome category: non-serious/non-severe side effects Greater harm, extent: considerable
Injury, poisoning, and procedural complications	Event rates: 34.5% vs. 6.3% RR: 5.52 [1.32; 23.12] RR: 0.18 [0.04; 0.76][g] p = 0.006	Outcome category: non-serious/non-severe side effects Greater harm, extent: considerable
Respiratory, thoracic, and mediastinal disorders	Event rates: 72.4% vs. 28.1% RR: 2.57 [1.42; 4.68] RR: 0.39 [0.21; 0.70][g] p < 0.001	Outcome category: non-serious/non-severe side effects Greater harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u)
c. Measured in meters. The 6MWT was surveyed only in patients 5 years and older.
d. See Section 2.4.3 of the present dossier assessment for the reasoning.
e. Age at enrolment.
f. See Section 2.4.1 of the present dossier assessment for the reasoning.
g. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
h. Discrepancy between CI (asymptotic) and p-value (unconditional exact test, CSZ method) due to different calculation methods; derivation through p-value. The extent of the effect in this non-serious / non-severe outcome was rated as no more than marginal.

6MWT: 6-minute walk test; AE: adverse events; CI: confidence interval; CI_u: upper limit of CI; FPS-R: Faces Pain Scale - Revised; MD: mean difference; NC: not calculable; PROMIS: Patient-Reported Outcomes Measurement Information System; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 15: Favourable and unfavourable effects from the assessment of burosumab in comparison with phosphate substitution

Favourable effects	Unfavourable effects
–	Non-serious / non-severe side effects ▪ General disorders and administration site conditions (AEs): hint of greater harm – extent: considerable ▪ Injury, poisoning, and procedural complications (AEs): hint of greater harm – extent: considerable ▪ Respiratory, thoracic, and mediastinal disorders (AEs): hint of greater harm – extent: considerable
No usable data were available for the outcome of health-related quality of life.	
AE: adverse event	

For assessing the added benefit of burosumab in comparison with the ACT, the company submitted data only on XLH patients aged 1 to 12 years with a minimum RSS total score of 2. No data are available for XLH patients aged 13 to 17 years and/or those an RSS total score below2 (also see Section 2.3.2). For this reason, the added benefit of burosumab is derived separately for these patient groups.

XLH patients aged 1 to 12 years with a minimum RSS total score of 2

All things considered, only unfavourable effects were found in the outcome category of side effects, each with the probability of hint and the extent of considerable. These unfavourable effects each concern specific AEs.

The unfavourable effects of burosumab are deemed insufficient for deriving a lesser benefit of burosumab in comparison with phosphate substitution. This rating is based on the results for the morbidity outcomes (e.g. 6MWT) as well as the fact that unfavourable effects are found only for outcomes from the non-serious/non-severe side effects category.

In summary, there is no hint of added benefit of burosumab in comparison with the ACT for XLH patients aged 1 to 12 years with a minimum RSS total score of 2; an added benefit is therefore not proven.

XLH patients aged 1 to 12 years with an RSS total score below 2

No data relevant for the present benefit assessment are available for XLH patients aged 1 to 12 years with an RSS total score below 2. For these patients, no added benefit is therefore proven.

XLH patients aged 13 to 17 years

For XLH patients aged 13 to 17 years, no data relevant for the present benefit assessment are available. For these patients, no added benefit is therefore proven.

Table 16 summarizes the result of the assessment of added benefit of burosumab in comparison with the ACT.

Table 16: Burosumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
XLH treatment in patients aged 1 to 17 years with radiographic evidence of bone disease	Phosphate substitution[b]	Children with XLH aged 1 to 12 years: RSS total score ≥ 2.0 ▪ Added benefit not proven RSS total score < 2.0[c] ▪ Added benefit not proven
		Adolescents with XLH aged 13 to 17 years[c] ▪ Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In accordance with the G-BA, vitamin D substitution (calcitriol or alfacalcidol) is presumed to be in place. c. No data are available for this patient group. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; RSS: Rickets Severity Score; XLH: X-linked hypophosphataemia		

The assessment described above deviates from that by the company, which derived proof of considerable added benefit for the entire target population.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2018, where the G-BA had determined a non-quantifiable added benefit of burosumab. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data due to orphan drug status.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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