IQWiG Reports – Commission No. A22-88

Burosumab (hypophosphataemia in tumour-induced osteomalacia) –

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

Extract

[1] Translation of Sections I 1 to I 5 of the dossier assessment *Burosumab (Hypophosphatämie bei tumorinduzierter Osteomalazie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 17 November 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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ENS	epidermal nevus syndrome
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TIO	tumour-induced osteomalacia

I 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 22 August 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) in patients aged 1 year and older with FGF23-related hypophosphataemia in tumour-induced osteomalacia (TIO) associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized.

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

Table 2: Research question for the benefit assessment of burosumab

Therapeutic indication	**ACT**[a]
Treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized in patients aged 1 year and older	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; FGF23: fibroblast growth factor 23; G-BA: Federal Joint Committee	

The company did not follow the G-BA's specification of the ACT. In the company's opinion, a large percentage of the target population exhibits an inadequate response to phosphate substitution. Because of the lack of treatment response and potential treatment-associated sequelae, the company therefore deems further phosphate substitution not to be indicated for these patients. Hence, the company defines the ACT as individualized therapy, comprising measures such as radiotherapy and tumour ablation as well as best supportive care to alleviate the disease's concomitant complications and sequelae.

The company's justification for deviating from the G-BA's ACT is not plausible. However, the company's approach did not have any technical repercussions for the present benefit assessment, because no studies were available comparing burosumab with either of the comparator therapies, i.e. the one chosen by the company or the one specified by the G-BA.

The present benefit assessment was thus carried out using the ACT specified by the G-BA, phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

The check for completeness of the study pool for the present benefit assessment identified no randomized controlled trial (RCT) which would allow a direct comparison of burosumab versus phosphate substitution.

Under "Other investigations", the company's dossier presents data from the 2 single-arm studies UX023T-CL201 and KRN23-002, based on which the marketing authorization was granted for the present therapeutic indication. The company did not present data on the ACT.

Evidence presented by the company – UX023T-CL201 study

The UX023T-CL201 study is a single-arm study enrolling, according to its inclusion criteria, patients (≥ 18 years) with TIO as well as patients with osteomalacia associated with epidermal nevus syndrome (ENS). The company reports that among the total of 17 patients included in the study, 14 patients exhibited TIO.

The UX023T-CL201 study involved a 48-week treatment phase as well as a subsequent extension phase of up to 252 weeks. Hence, patients were treated, at maximum, until Week 300.

Patients in the UX023T-CL201 study received burosumab subcutaneously every 4 weeks.

Evidence presented by the company – KRN23-002 study

The KRN23-002 study is a single-arm study enrolling 14 patients (≥ 18 years) with TIO, with 1 patient withdrawing consent for study participation before receiving the 1st dose of the study medication.

The KRN23-002 study involved a 48-week treatment phase as well as a subsequent extension phase of up to 96 weeks. Hence, patients were treated, at maximum, until Week 144.

Thirteen patients in the KRN23-002 study received burosumab subcutaneously every 4 weeks.

Submitted data unsuitable for drawing conclusions on added benefit

The data presented by the company from the 2 single-arm studies UX023T-CL201 and KRN23-002 allow no comparison with the ACT and are therefore unsuitable for the benefit assessment.

Results on added benefit

Since no usable data are available for the benefit assessment, there is no hint of an added benefit of burosumab in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3: Burosumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of FGF23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized in patients aged 1 year and older	Phosphate substitution[b]	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. ACT: appropriate comparator therapy; FGF23: fibroblast growth factor 23; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[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 [5,6].

I 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 patients aged 1 year and older with FGF23-related hypophosphataemia in TIO associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized.

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]
Treatment of FGF 23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized in patients aged 1 year and older	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; FGF23: fibroblast growth factor 23; G-BA: Federal Joint Committee	

The company did not follow the G-BA's specification of the ACT. In the company's opinion, a large percentage of the target population exhibits an inadequate response to phosphate substitution. Because of the lack of treatment response and potential treatment-associated sequelae, the company therefore deems further phosphate substitution not to be indicated for these patients. Hence, the company defines the ACT as individualized therapy, comprising measures such as radiotherapy and tumour ablation as well as best supportive care to alleviate the disease's concomitant complications and sequelae.

The company's justification for deviating from the G-BA's ACT is not plausible. However, the company's approach did not have any technical repercussions for the present benefit assessment, because no studies were available comparing burosumab with either of the comparator therapies, i.e. the one chosen by the company or the one specified by the G-BA.

The present benefit assessment was thus carried out using the ACT specified by the G-BA, phosphate substitution in conjunction with vitamin D substitution (calcitriol or alfacalcidol).

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

I 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: 8 August 2022)
- bibliographical literature search on burosumab (last search on 7 July 2022)
- search in trial registries / trial results databases for studies on burosumab (last search on 7 July 2022)
- search on the G-BA website for burosumab (last search on 7 July 2022)
- bibliographical literature search on the ACT (last search on 7 July 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 7 July 2022)

To check the completeness of the study pool:

- search in trial registries for studies on burosumab (last search on 13 September 2022); for search strategies, see I Appendix A of the full dossier assessment

Having deviated from the ACT specified by the G-BA (see Section I 2), the company searched for studies comparing burosumab versus the company-defined ACT. For the sake of completeness, the company reports having also searched for studies comparing burosumab versus the ACT specified by the G-BA. According to information provided in Module 4 A, the company found no relevant RCT for either constellation.

The check for completeness of the study pool for the present benefit assessment identified no RCT which would allow a direct comparison of burosumab versus phosphate substitution.

Under “Other investigations”, the company’s dossier presents data from the 2 single-arm studies UX023T-CL201 [1,2] and KRN23-002 [3,4], based on which marketing authorization was granted in the present therapeutic indication.

A check for completeness of the study pool presented by the company for other investigations was foregone because the data submitted by the company under “Other investigations” are unsuitable for the benefit assessment due to the lack of comparison with the ACT. This is explained below.

Evidence presented by the company – UX023T-CL201 study

The UX023T-CL201 study is a single-arm study enrolling, according to its inclusion criteria, patients (≥ 18 years) with TIO as well as patients with osteomalacia associated with ENS. The company reports that among the total of 17 patients included in the study, 14 patients exhibited TIO. Patients had to discontinue any existing phosphate substitution or substitution with

vitamin D metabolites or their analogues at the latest 2 weeks prior to screening. However, the interval prior to study start during which the patient received no phosphate substitution or substitution with vitamin D metabolites or their analogues was longer because the period between screening and study start differed among patients.

The UX023T-CL201 study involved a 48-week treatment phase as well as a subsequent extension phase of up to 252 weeks. Hence, patients were treated, at maximum, until Week 300.

Patients in the UX023T-CL201 study received burosumab subcutaneously every 4 weeks. Proceeding from a burosumab starting dose of 0.3 mg/kg burosumab at Week 0, patients were allowed to receive incrementally increased or reduced burosumab doses in the course of the study in an effort to reach a target fasting serum phosphate level in the range of 2.5 to 4.0 mg/dL.

Primary outcomes of the UX023T-CL201 study are serum phosphate concentration as well as histomorphometric parameters. Secondary patient-relevant outcomes are morbidity, health-related quality of life, and adverse events (AEs).

Evidence presented by the company – KRN23-002 study

The KRN23-002 study is a single-arm study enrolling 14 patients (≥ 18 years) with TIO, with 1 patient withdrawing consent for study participation before receiving the 1st dose of the study medication. At the latest 2 weeks prior to screening, patients had to discontinue any existing substitution with oral phosphate or vitamin D metabolites or their analogues. The time before study start during which the patient received no phosphate substitution or substitution with vitamin D metabolites or their analogues, however, was longer due to the individually differing periods between screening and study start.

The KRN23-002 study involved a 48-week treatment phase as well as a subsequent extension phase of up to 96 weeks. Hence, patients were treated, at maximum, until Week 144.

Thirteen patients in the KRN23-002 study received burosumab subcutaneously every 4 weeks. Proceeding from a burosumab starting dose of 0.3 mg/kg burosumab at Week 0, patients were allowed to receive incrementally increased or reduced burosumab doses in the course of the study in an effort to reach a target fasting serum phosphate level in the range of 2.5 to 4.0 mg/dL.

The primary outcome of the KRN23-002 study is serum phosphate concentration. Secondary patient-relevant outcomes are morbidity, health-related quality of life, and AEs.

The company's approach

Under "Other investigations", the dossier's Module 4 C presents the results of the 2 single-arm studies UX023T-CL201 and KRN23-002. The company presents no data on the ACT.

The company reports that the presented data on burosumab are unsuitable for proving the added benefit of burosumab or for quantifying its extent.

Thereafter, however, the company cites a reportedly high therapeutic need in the therapeutic indication, symptom improvement, improvement in the quality of life of patients treated with burosumab as well as good tolerability of burosumab. Despite the fact that both studies included only adult patients, the company additionally assumes – on the basis of the similarity of the disease, the burosumab mechanism of action, and the patient population – that the results are transferable to patients aged 1 to 17 years.

In conflict with its prior evaluation, the company therefore derives a hint of non-quantifiable added benefit for patients aged 1 year and older with FGF23-related hypophosphataemia in TIO associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized.

Submitted data unsuitable for drawing conclusions on added benefit

The company's approach was inappropriate because the data presented by the company from the 2 single-arm studies UX023T-CL201 and KRN23-002 do not allow any comparison with the ACT, and overall, no suitable data are therefore available for assessing the added benefit of burosumab in the therapeutic indication.

I 4 Results on added benefit

No suitable data are available for assessing burosumab in the treatment of FGF 23-related hypophosphataemia in TIO associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized in patients aged 1 year and older. This results in no hint of added benefit of burosumab in comparison with phosphate substitution; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of burosumab in comparison with the ACT.

Table 5: Burosumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of FGF 23-related hypophosphataemia in tumour-induced osteomalacia associated with phosphaturic mesenchymal tumours which cannot be curatively resected or localized in patients aged 1 year and older	Phosphate substitution[b]	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. ACT: appropriate comparator therapy; FGF23: fibroblast growth factor 23; G-BA: Federal Joint Committee		

The assessment described above deviates from the company's, which derived a hint of non-quantifiable added benefit in the present therapeutic indication on the basis of the data it presented from the 2 single-arm studies UX023T-CL201 and KRN23-002.

The G-BA decides on the added benefit.

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.

1. Ultragenyx Pharmaceutical. UX023T-CL201: A Phase 2 Open-Label Trial to Assess the Efficacy and Safety of KRN23, an Antibody to FGF23, in Subjects With Tumor-Induced Osteomalacia (TIO) or Epidermal Nevus Syndrome (ENS)-Associated Osteomalacia - ClinicalTrials.gov (NCT02304367). Stand des Eintrags: 21.02.2022 [online]. 2014 [Accessed: 17.08.2022]. URL: https://clinicaltrials.gov/ct2/show/NCT02304367.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-88.html.